

Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis

K Dalziel, A Round, K Stein, R Garside and
A Price



July 2004

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Abstract

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Objectives: To evaluate the effectiveness of imatinib as first-line treatment for chronic myeloid leukaemia (CML) compared with interferon-alpha (IFN- α), hydroxyurea and bone marrow transplantation (BMT), and the cost-effectiveness of imatinib compared with IFN- α and hydroxyurea.

Data sources: Electronic databases.

Review methods: Selected studies and full-text articles were screened and rigorously selected. Survival was the key outcome measure. Surrogate outcome measures included haematological (blood) response and cytogenetic (bone marrow) response (CR). As no published cost-effectiveness studies were found that compared imatinib and IFN- α , an independent Markov model was constructed and this was compared with models submitted to the National Institute for Clinical Excellence by the manufacturer of imatinib.

Results: Intention-to-treat analysis showed that imatinib was associated with complete CR at 12 months follow-up of 68% compared with 20% for the IFN- α plus Ara-C group. The estimated proportion of people taking imatinib who had not progressed to accelerated or blast phases at 12 months was 98.5%, and 93.1% for IFN- α plus Ara-C. Overall survival was not statistically significantly different. Withdrawal due to side-effects was 2% for imatinib and 5.6% for IFN- α plus Ara-C. Cross-over due to intolerance was 0.7% and 22.8% for imatinib and for IFN- α plus Ara-C, respectively. Quality of life was better in the imatinib group than the IFN- α group when assessed at 1, 3 and 6 months. Median survival across the four IFN- α versus hydroxyurea studies was 66 and 56.2 months, respectively. Median complete CR was 6% for IFN- α and 0 for hydroxyurea. Median withdrawal due to side-

effects was 24% and 4% for IFN- α and hydroxyurea, respectively. Four out of the five studies comparing BMT and IFN- α showed a long-term survival advantage for BMT over IFN- α , but a short-term disadvantage. In four of the five studies comparing BMT and IFN- α , median survival had not yet been reached in the BMT groups in 6–10 years. Median survival in the IFN- α arms ranged from 5.2 to 7 years. The BMT group gained a survival advantage over IFN- α at 3–5.5 years. In the BMT group death due to transplant-related complications ranged from 36 to 45%. The incremental cost-effectiveness ratio (ICER) of imatinib compared with IFN- α from the independent model was £26,180 per quality-adjusted-life-years (QALY) gained and was relatively robust. Imatinib was less cost-effective than hydroxyurea with an ICER of £86,934.

Conclusions: Imatinib appears to be more effective than current standard drug treatments in terms of cytogenetic response and progression-free survival, with fewer side-effects. However, there is uncertainty concerning longer term outcomes, the development of resistance to imatinib, the duration of response and the place of imatinib relative to BMT. New issues are continually arising, such as optimal management pathways and combination therapies.

Recommendations for research include: long-term follow-up data from the first- and second-line imatinib trials; investigation into specific subgroups, e.g. high-risk patients, the elderly, children or those eligible for BMT; long-term comparisons of imatinib with BMT performed in early stages of CML; the use of imatinib in combination with other therapies, and further detailed economic studies. Investigation of the impact of CML and imatinib on quality of life is also important.



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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Abelson oncogene An oncogene is a cancer-causing gene. The Abelson oncogene is located on that part of chromosome 9 that translocates to chromosome 22 in chronic myeloid leukaemia.

Allogeneic transplant A bone marrow or stem cell transplant using marrow from another person. If the marrow is from an identical twin, it is termed syngeneic.

Allopurinol A drug used to control excessive white blood cells and to minimise the build-up of blood uric acid.

Autologous transplant A bone marrow or stem cell transplantation using the patient's own marrow which is removed, treated and stored before administration.

Basophilia An excess number of basophils, a rare type of white cell, found in the peripheral blood.

Blast cells Immature cells found in and produced by the bone marrow. Not normally found in the peripheral blood.

Bone marrow The soft substance that fills bone cavities. It is composed of mature and immature blood cells and fat. Red and white blood cells and platelets are formed in the bone marrow.

Bone marrow transplant A procedure where a patient's bone marrow is replaced by healthy bone marrow. The bone marrow to be replaced may be deliberately destroyed by high doses of chemotherapy and/or radiation therapy. The replacement marrow may come from another person, or it may be previously harvested from the patient's own marrow.

Breakpoint cluster region The region of a chromosome where breaks cluster. In the case of chronic myeloid leukaemia, the narrow part

of chromosome 22 where the translocation to chromosome 9 occurs which includes the Abelson oncogene (BCR-ABL). The BCR-ABL protein product results in the excessive proliferation of a tyrosine kinase.

Chemotherapy The treatment of a disease by chemicals to destroy cancer cells. Chemotherapy can affect the whole body.

Cyclophosphamide Preconditioning treatment for bone marrow transplantation.

Cytogenetic response A response to treatment at a level of chromosomal abnormalities. In the case of chronic myeloid leukaemia, assessed by counting the number of Philadelphia-positive (Ph+) cells in metaphase (usually 20 metaphases are analysed). A complete response reveals no Ph+ cells, a partial response leaves up to 35% Ph+ cells evident and with a minor response from 35% to 95% Ph+ cells are still evident.

Cytopenia A reduction in the number of cells circulating in the blood.

CRKL An adapter protein that becomes tyrosine phosphorylated by BCR-ABL.

EQ-5D A European quality of life questionnaire containing five physical and psychological dimensions.

Erythrocytes Red blood cells which carry oxygen around the body and carbon dioxide back to the lungs.

Extramedullary disease Disease occurring outside the bone marrow.

Fibroblasts Connective tissue cells.

Gompertz function A function used to estimate survival curves.

continued

Glossary continued

Graft-versus-host disease A complication of bone marrow transplantation where there is a reaction of donated bone marrow against a patient's own tissue. It can be fatal and is due to the donor's immune cells recognising the host cells as foreign.

Haematological response Refers to the normalisation of blood cell counts. Chronic myeloid leukaemia causes overproliferation of white blood cells and treatments aim to lower these. Typically, the response is classified as complete (WBC $<10 \times 10^9/l$, platelets $<450 \times 10^9/l$, no immature cells in the peripheral blood with normal differential count, and disappearance of symptoms and signs).

Hydroxyurea A drug used in the treatment of chronic myeloid leukaemia that inhibits DNA synthesis.

Incremental cost-effectiveness ratio Demonstrates the total additional cost per quality-adjust-life-year gained of one alternative over another. There is no particular point at which an alternative is said to be cost-effective as this will be a policy decision. The larger the incremental cost-effectiveness ratio the less likely it is to be cost effective.

Interferon- α Interferon is a protein derived from human cells. It has a role in fighting viral infections by preventing virus multiplication in cells. Interferon- α is made by leucocytes. It is often used as first line therapy in chronic myeloid leukaemia.

Landmark analysis A form of survival analysis where only patients who have survived for a specified period are included in the analysis.

Leucocytes White blood cells that are responsible for fighting infections.

Leucopenia A reduced number of white blood cells in the blood. It may affect a single cell type or all white cells.

Leucopheresis A process of removing excess white blood cells from the peripheral blood.

Matched unrelated donor Unrelated allogeneic transplant: the person donating marrow is unrelated to the patient. The chances of finding an unrelated compatible donor from the general population depend on the rarity of the individual's tissue type.

Genetic and ethnic background can also affect the likelihood of finding a donor.

Metaphase The second phase of mitosis (cell division). Cells in this phase of division are used for cytogenetic analysis in chronic myeloid leukaemia to identify the proportion of Ph+ chromosomes.

Mitosis A division of cells which consists of four phases - prophase, metaphase, anaphase and telophase.

Myelocytes Committed progenitor cells produced by, and found in, the bone marrow, which develop into mature leucocytes.

Neurotoxic Poisonous to the nervous system.

Neutropenia A decrease in neutrophils (white blood cells) circulating in the blood.

Peripheral blood In this report, peripheral blood refers to blood in the circulatory system.

Promyelocytes Committed progenitor cells produced by and found in the bone marrow, which develop into myelocytes.

Radiation therapy Treatment using high-energy radiation from X-rays or other rays intended to damage cancer cells and stop them multiplying.

Stem cells Very early progenitor cells which divide and mature to become all the types of cells that make up the blood and immune system.

Thrombocytes Platelets (fragments of bone marrow cells) found in the blood which help to form clots and control bleeding.

Thrombopenia A reduced number of thrombocytes (platelets) in the blood.

Toxicity The quality of being poisonous. The National Cancer Institute grades toxicity levels of treatments as 1, mild; 2, moderate; 3, severe; and 4, life-threatening.

Tyrosine kinase An enzymic protein that adds phosphate residues to other proteins in the cell. In chronic myeloid leukaemia the abnormal tyrosine kinase, BCR-ABL, phosphorylates proteins which cause cellular proliferation.

Weibull curve A mathematical function that is often used in modelling to describe survival times, and in which the chance of survival varies with time.

List of abbreviations

ABL	Abelson oncogene	IRIS	International Randomised Study of Interferon + Ara-C vs STI-571 in CML
Ara-C	cytosine arabinoside	ITT	intention-to-treat
BCR	breakpoint cluster region	M:F	male to female
BMT	bone marrow transplantation	MU	mega-units
BNF	British National Formulary	NA	not applicable
BU	busulfan	NICE	National Institute for Clinical Excellence
CI	confidence interval	NP	not possible
CML	chronic myeloid leukaemia	NR	not reported
CR	cytogenetic response	NS	not significant
CRD	Centre for Reviews and Dissemination	PBSC	peripheral blood stem cells
CRKL	CRK oncogene-like protein	PEG	pegylated
CT	computed tomograph	PFS	progression-free survival
ECOG	Eastern Co-operative Oncology Group	Ph+	Philadelphia-positive cell
EMA	European Agency for the Evaluation of Medicinal Products	PHR	partial haematological response
EQ-5D	European Quality of Life Instrument	PISCES	PEGIntron and imatinib/STI-571 Combination Evaluation Study
FACT-BRM	Functional Assessment of Cancer Therapy–Biological Response Modifier	QALY	quality-adjusted life-year
FCE	finished consultant episode	QoL	quality of life
FDA	Food and Drug Administration (USA)	RCT	randomised controlled trial
FISH	fluorescence <i>in situ</i> hybridisation	RR	relative risk
GRC	Global rating of change	RT-PCR	reverse transcriptase–polymerase chain reaction
GVHD	graft-versus-host disease	SCT	stem cell transplantation
HLA	human-leucocyte antigen	S.C.	subcutaneous
HR	haematological response	SD	standard deviation
HU	hydroxyurea	SE	standard error
ICER	incremental cost-effectiveness ratio	SPIRIT	STI-571 Prospective International Randomized Trial
IFN- α	interferon-alpha	STI-571	imatinib
IM	imatinib	SUHT	Southampton University Hospitals NHS Trust
Int	intermediate	WBC	white blood cell

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Background

Chronic myeloid leukaemia (CML) is a rare blood cancer with an incidence of 1.0 per 100,000 for men and 0.8 per 100,000 for women. In CML, excessive numbers of leukaemic white blood cells are produced that suppress the production of normal white blood cells. In 95% of cases a specific chromosomal abnormality, the Philadelphia chromosome, is present. This is a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9. The consequent molecular abnormality is a fusion protein, BCR-ABL, which is a tyrosine kinase. There are three identifiable phases of chronic myeloid leukaemia: chronic, accelerated and blast phase, with blast phase being fatal within 3–6 months.

CML is not currently curable with conventional chemotherapy or immunotherapy. Patients diagnosed in the chronic phase may expect a median of 3–5 years' survival. Bone marrow transplantation (BMT) offers a cure but is only available to a minority of people.

Current drug treatments include interferon-alpha (IFN- α) and hydroxyurea. Imatinib is a new treatment that works by blocking the ATP binding site on the BCR-ABL tyrosine kinase. Imatinib has already been recommended for treatment of patients in all phases of the disease who have failed treatment with IFN- α .

Objectives

This assessment evaluates the effectiveness of imatinib as first-line treatment for those with CML in chronic phase compared with IFN- α , hydroxyurea and BMT, and the cost-effectiveness of imatinib compared with IFN- α and hydroxyurea.

Methods

A systematic review of the literature was undertaken. Searches of electronic databases, websites and reference lists were made to identify relevant studies. All studies of imatinib were included, along with randomised controlled trials

(RCTs) of IFN- α compared with hydroxyurea and comparative studies of BMT compared with IFN- α . Studies were only included if they were on adults in chronic phase and were published in English.

The titles and abstracts of studies and full text articles were screened independently by two reviewers for inclusion. Using a structured form, the quality (internal and external validity) of the included studies was assessed by one reviewer and checked by a second reviewer.

Owing to the lack of homogeneous RCTs, meta-analyses were not performed but comparative data were provided where available. The assessment includes all patient relevant outcome measures reported by the studies.

Survival is the key outcome measure. Surrogate outcome measures include haematological (blood) response (HR) and cytogenetic (bone marrow) response (CR). Based on the current evidence and knowledge of the effect of imatinib, it is generally considered that the relationship between CR and survival is sufficiently strong to support the use of CR as a surrogate outcome measure.

Results

One RCT comparing imatinib with IFN- α plus Ara-C was identified. Four RCTs comparing IFN- α with hydroxyurea were included, along with five studies comparing BMT and IFN- α . The study comparing IFN- α plus Ara-C to imatinib was of reasonable quality, with the main potential biases being the lack of blinding (patient, physician, outcome measurement and data analysis), the potential for bias in the assessment of quality of life, and the high cross-over and attrition rates. The study reports on relatively short-term outcomes (12 months for the majority of this analysis). The studies comparing IFN- α and hydroxyurea were of reasonable quality, with lack of blinding and allocation concealment being the main potential biases. The BMT trials were of variable quality, with lack of randomisation, blinding, power calculation and groups that differed at baseline.

Intention-to-treat analysis showed that imatinib was associated with complete CR at 12 months follow-up of 68% compared with 20% for the IFN- α plus Ara-C group ($p < 0.001$). The estimated proportion of people taking imatinib who had not progressed to accelerated or blast phases at 12 months was 98.5% and 93.1% for IFN- α plus Ara-C ($p < 0.001$). Overall survival was not statistically significantly different between the two groups, with death rates of 2% and 3.8% for imatinib and IFN- α , respectively. Withdrawal due to side-effects was 2% for imatinib and 5.6% for IFN- α , and cross-over due to intolerance was 0.7% for imatinib and 22.8% for IFN- α plus Ara-C. Quality of life was better in the imatinib group than the IFN- α group when assessed at 1, 3 and 6 months using the Functional Assessment of Cancer Therapy – Biological Response Modifier instrument.

Median survival across the four IFN- α versus hydroxyurea studies was 66 months (range 61–76 months) for IFN- α and 56.2 months (range 52–66 months) for hydroxyurea. Median complete CR was 6% (range 4–9%) for IFN- α and 0 (range 0–1%) for hydroxyurea. Median withdrawal due to side-effects was 24% (range 18–25%) for IFN- α and 4% (range 1–4%) for hydroxyurea.

Four out of the five studies comparing BMT and IFN- α showed a long-term survival advantage for BMT over IFN- α , but a short-term (0–4 years approximately) disadvantage. In four of the five studies comparing BMT and IFN- α , median survival had not yet been reached in the BMT groups in 6–10 years. Median survival in the IFN- α arms ranged from 5.2 to 7 years. The BMT group gained a survival advantage over IFN- α at 3–5.5 years. In the BMT group death due to transplant-related complications ranged from 36 to 45% (median 38%).

Cost-effectiveness

A search of the economic literature revealed no published cost-effectiveness studies comparing imatinib and IFN- α . An independent Markov model was constructed and this was compared with models submitted to the National Institute for Clinical Excellence by the manufacturer of imatinib, Novartis. The incremental cost-effectiveness ratio (ICER) of imatinib compared with IFN- α from the independent model was £26,180 per quality-adjusted-life-years (QALY) gained (ranging from £13,555 to £51,870) and was relatively robust when subjected to a number of sensitivity analyses. This figure is similar to

industry estimates of between £18,000 and £26,000. Imatinib was less cost-effective than hydroxyurea with an ICER of £86,934. Probabilistic analysis showed that if the decision-maker was willing to pay £27,000 per QALY, then imatinib had a greater probability of being cost-effective than IFN- α . With three comparators, hydroxyurea, IFN- α and imatinib, hydroxyurea is most likely to be cost-effective until willingness to pay is greater than £86,000. However, this may be appropriate first-line treatment only in occasional circumstances, such as frail or very elderly people. The ICER between hydroxyurea and imatinib is high, predominantly owing to large cost differences between the treatments.

Conclusions

Imatinib appears to be more effective than current standard drug treatments in terms of cytogenetic response and progression-free survival, with fewer side-effects. However, there is uncertainty concerning longer term outcomes, the development of resistance to imatinib, the duration of response and the place of imatinib relative to BMT. New issues are continually arising, such as optimal management pathways and combination therapies.

Recommendations for research (in priority order)

- Long-term follow-up data from the first- and second-line imatinib trials are critical to determine the effect on survival, duration of response and development of resistance.
- Research is also needed into specific subgroups such as high-risk patients, the elderly, children or those eligible for BMT.
- Long-term comparisons of imatinib with BMT performed in early stages of CML are important to identify whether and when a survival advantage shifts from imatinib to BMT.
- Imatinib is likely to be used in combination with other therapies, and detailed research is necessary to determine optimal treatment pathways.
- More detailed economic studies are also required to aid appraisal of imatinib compared with BMT, and in high-risk patients.
- Further investigation of the impact of CML and imatinib on quality of life is important. Preference-based measures that yield an estimate of societal values are needed.

Chapter I

Aim of the review

The aim was to assess the effectiveness of imatinib as first-line treatment for those with chronic myeloid leukaemia (ML) in chronic phase compared with interferon-alpha (IFN- α),

hydroxyurea and bone marrow transplantation (BMT), and the cost-effectiveness of imatinib compared with IFN- α and hydroxyurea.

Chapter 2

Background

Description of the underlying health problem

Natural history and clinical presentation of CML

Leukaemia is a rare type of cancer affecting the blood. CML is the third most common type of leukaemia. In CML the bone marrow produces an excessive number of abnormal stem cells (the precursor cells of white cells, red cells and platelets). The abnormal cells eventually suppress the production of normal white blood cells (WBCs) that act to protect the body against infection.

Three phases of CML are usually identifiable: the chronic phase, an accelerated phase and the blast phase. The accelerated phase is seen in about two-thirds of patients, whereas others progress directly to the blast phase. Transition between the phases may be gradual or rapid. Typically, the annual progression from chronic to blast phase is 5–10% in the first 2 years and 20% in subsequent years.¹

Chronic phase

The chronic phase is the initial, usually relatively stable and benign phase of CML and generally lasts for 3–5 years from diagnosis. During this period malignant progenitor cells proliferate rapidly but retain their ability to differentiate. Progression of CML is due to the gradual loss of differentiation potential of malignant cells.

In the chronic phase there is less than 10% blasts and promyelocytes (immature cells) in the bone marrow. There is an elevated WBC count, including basophilia, and often an elevated platelet count in the peripheral blood. Because the disease progresses slowly, it is difficult to detect in its early stages. In 40% of sufferers, CML is only discovered when a routine blood test or examination for an unrelated disorder is performed.¹

The majority of patients are in chronic phase at presentation. The main clinical findings are:

- fatigue or pale appearance due to anaemia: this is often the symptom that leads people with CML to seek medical advice

- a feeling of ‘fullness’ or a tender lump on the left side of their abdomen due to enlargement of the spleen (half of all patients have splenomegaly); sometimes the liver is also enlarged
- fever and/or night sweats
- weight loss may also be apparent.

Accelerated phase

The accelerated phase marks the transition to the blast phase, typically lasting for up to 18 months,² but sometimes leading to a rapidly fatal blast crisis within 6 months. No single set of criteria for its onset is accepted. However, in some cases the accelerated phase is defined as between 5 and 30% blasts in the peripheral blood and bone marrow. Other authors use greater than 15% blasts as a definition.³ Symptoms in the accelerated phase may include feeling fatigue (due to anaemia), infections, bruising or bleeding.

Blast phase

The blast phase is usually fatal within 3–6 months of onset. The presence of 30% or more blast cells in the marrow or any blast cells within the peripheral blood defines the blast phase. Clinically, it is characterised by signs and symptoms such as fever, sweats, pain, weight loss, and enlarged lymph nodes, liver or spleen.

Epidemiology

All types of leukaemia account for 2.1% of all cancers in England and Wales⁴ and the gender ratio for men:women is 1.7:1. In 1997, 531 new cases of CML were diagnosed in England: an annual rate of 1.0 per 100,000 for men and 0.8 per 100,000 for women.

Although CML is rare below the age of 20 years, it does occur in all age groups. People registered in trials of interferon treatment for CML have median ages between 47 and 56 years at study commencement.^{5–7} A trial of imatinib reports median age at commencement of 51 years⁸ and trials of BMT report lower median ages of 31–36 years.^{9–12}

Academic publications tend to report younger populations than population registries. This may reflect selection practices in clinical trials and bias

arising from studies being carried out in tertiary care institutions.

National cancer registers may not be notified of all cases, but are likely to be more representative of all people with CML than those enrolled in clinical trials. A local registry of patients in north-east England gives a median age at onset of between 60 and 69 years.¹³ A population-based survey of CML patients in Norway found a median age at onset of 62 years.¹⁴

Prevalence is difficult to estimate given varying estimates of survival. Based on 3–5-year median survival times, there are probably about 3000–3500 people with CML in England and Wales, or approximately 90–105 people per Strategic Health Authority area of 1.5 million people.

Aetiology, pathology and prognosis

Molecular mechanisms

In 95% of cases of CML, patients have a genetic abnormality caused by a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9 (the Philadelphia chromosome).¹⁵ This is not an inherited abnormality but is acquired by individual stem cells. As a result, proliferation of both mature and immature WBCs occurs in the bone marrow and the blood.

The Abelson oncogene (ABL) is located on chromosome 9. In CML this translocates to the breakpoint cluster region (BCR) gene on chromosome 22. As a consequence, an abnormal protein, a tyrosine kinase, is formed. Patients with CML who do not have the Philadelphia chromosome have complex or different translocations which still result in the formation of the BCR-ABL gene and its product.

Tyrosine kinases function as part of the internal communication network of the cell, regulating processes such as proliferation, differentiation and survival.¹⁶ In CML, the BCR-ABL protein product results in the production of a tyrosine kinase which is not controlled by normal cellular mechanisms. The cells containing the abnormal gene and protein replicate quickly, and may be protected from programmed cell death (apoptosis). They therefore come to predominate, initially in the bone marrow and subsequently in the bloodstream. By the time these cells are detected in the bloodstream, the disease process is well underway. Patients with CML at presentation or relapse usually have a total burden of more than

10¹² malignant cells.¹⁷ Several additional complex genetic abnormalities are acquired during progression of CML and are implicated in progression of disease. However, molecular mechanisms underlying the development of CML and the inevitable transformation to blast crisis are not completely understood.¹⁸ For example, the BCR-ABL abnormality can be detected in people who have not developed CML.¹⁹

Survival

A study in 1924 by Minot and colleagues reported an average survival in untreated patients of 36.6 months.²⁰ In 1998, a population-based survey in Norway also described a median survival of 36 months, with an estimated 5-year survival rate of 33%.¹⁴ Survival is also dependent on other medical conditions, which are prevalent in the elderly population, such as heart and respiratory disease. A significant proportion (30%) of people with chronic phase CML die from an unrelated condition.¹⁴

However, in the literature, IFN- α trials report a median survival of 63–76 months.^{5,7,21} This is likely to refer to a younger and more selected population than is seen in routine clinical practice. Changes in the availability of blood testing and, possibly, earlier presentation and diagnosis over time, suggest that length of survival is not comparable between cohorts established at different times. This may be due to lead-time bias²² and developments in adjunctive treatment, such as more effective anti-infective agents.

Risk scores

Several risk-scoring systems have been developed which categorise people with chronic phase CML into risk groups that reflect their survival prognosis. The most common is the Sokal score, although other prognostic scores have also been developed (see Appendix 1). In clinical practice, knowledge of individual risk scores may inform treatment decisions. The three Sokal categories represent those with good prognosis (low risk), those with intermediate prognosis (intermediate risk) and those with poor prognosis (high risk). Expected median survival for CML patients treated with chemotherapy at high, intermediate and low risk has been estimated at 2.5, 3.5 and 5 years, respectively.²³

The Sokal score has been shown to perform less well as a prognostic indicator among people receiving IFN- α treatment than among those treated with hydroxyurea or busulfan chemotherapy. In response to this, a newer

prognostic score (the Hasford or IFN- α score) was developed (see Appendix 1).²⁴

Both Sokal and Hasford scores have been shown to be predictors of survival.^{5,25–26} The Benelux CML Study Group reports that the Sokal score is discriminatory for survival in patients receiving hydroxyurea, but not for patients receiving IFN- α .⁵ Hehlmann and colleagues report that stratification according to risk group has a greater effect on survival than treatment allocation in patients receiving IFN- α , hydroxyurea or busulfan.²⁶ This suggests that risk profile is an important potential confounder in comparisons of treatment and should be taken into account, preferably through the use of randomisation in the context of direct comparisons.

Both risk score systems have shown a significant association with haematological and cytogenetic response, with low-risk patients responding more quickly and keeping their response for longer [for definitions of haematological and cytogenetic response see 'Outcome measures' (p. 8)].²⁵ Risk category and haematological response in particular are strongly associated ($p = 0.002$ for the Hasford score and $p = 0.005$ for Sokal). For both, the association is less strong for cytogenetic response, and the new score has a weaker association than the Sokal score ($p = 0.061$ for the Hasford score and $p = 0.01$ for Sokal).²⁸

It has not been possible to validate the Hasford measure in people treated with imatinib because of the lack of longer term survival data, but clinical consensus is that the Hasford score will also be applicable to this treatment group.

Significance in terms of ill-health

Little published evidence is available about the quality of life in people with CML or those who are taking various treatments for CML. People diagnosed with CML may not have any symptoms. Others may present with fatigue, a tender abdomen, a temperature, night sweats or weight loss. As the disease progresses symptoms worsen and it may be difficult to differentiate the symptoms of disease from the side-effects of treatment.

The side-effects of IFN- α and chemotherapy have been well documented. A substantial minority of people cease treatment with IFN- α owing to intolerance or have their doses adjusted.²⁹ Clinical consensus is that the adverse effects of IFN- α have a major impact on quality of life. The psychological benefits of taking a drug in a trial

situation with the possibility of long-term gain may, however, be sufficient to outweigh the effect of the symptoms on quality of life.³⁰

Quality of life is not solely determined by the adverse effects of therapy; the physical consequences of the disease itself and the psychological effects of knowing the poor prognosis with CML may be important determinants.³¹ It has also been suggested that a strong determinant of quality of life in chronic leukaemia is reaction to the uncertainty of living with this disease.³¹ In these circumstances, the adverse effects of treatment may play a relatively small part for some patients, although individuals' experiences will differ. Taking all these factors into account, CML is likely to have a significant and increasing impact on quality of life throughout its course.

Current service provision

CML is not currently curable with conventional chemotherapy or immunotherapy. Most treatments aim to return the patient to the chronic phase of the disease. Treatment depends on the overall health and age of the patient and, for BMT, the availability of a suitable matched bone marrow donor. Clinicians suggest that older, frailer patients are offered much more limited treatment alternatives and may, in practice, be restricted to hydroxyurea. More detailed information on treatment options is shown in the section 'Description of the new intervention' (p. 7).

There were 7366 finished consultant episodes (FCEs) for CML (4322 male) in 1999–2000. FCEs count each episode of care delivered under a single consultant during each period of hospital stay (as a day-case or inpatient). This means that each patient may be counted a number of times. The median age of consultation was 51 from this data source. The age distribution is shown in *Table 1*. This difference from cancer registries may be due to more intensive hospital-based therapy,

TABLE 1 Number of FCEs for CML in England, 1999–2000

Age (years)	n (%)
0–14	189 (3)
15–59	4541 (62)
60–74	1798 (24)
75+	838 (11)
Total	7366

such as BMT, among younger CML patients, which accounts for greater numbers of FCEs among this age group. These FCEs represent 7133 hospital admissions, 5317 of which were day-cases. In total, 18,206 bed-days were accounted for by CML. Much of CML therapy is given on an outpatient basis, and hence will not be recorded in these statistics.

Current options for treatment

This subsection gives a brief overview of the main current treatments for CML, other than imatinib, which is discussed under 'Description of the new intervention' (p. 7).

Interferons

Interferons are a complex group of naturally occurring proteins with potent multiple effects on immunity and cell function. IFN- α therapy was introduced in the 1980s, and regulates cytokine expression and inhibits haematological growth factors. It is also an immunomodulator (alters T-cell reactivity) and is directly cytotoxic to some tumour cells.^{29,32} However, the exact basis for the effects of IFN- α in CML is not known, and may vary from person to person.²⁵ Throughout this report interferon refers to IFN- α .

Daily injections are needed and relatively high doses have to be given to induce a cytogenetic response. Most people experience adverse effects, at least initially. These factors reduce treatment adherence. IFN- α has a toxic profile producing both acute and chronic adverse effects. Because of this, clinician consensus is that many older or frailer patients are not suitable for treatment with IFN- α . Such patients may make up a significant proportion of the CML population.

Combining IFN- α with other agents such as cytarabine arabinoside (Ara-C) has been shown to improve cytogenetic response and survival compared with IFN- α alone, but to increase toxicity.^{18,33–35} However, this combination is not currently licensed in the UK.³⁶ There are reports that IFN- α is now being used in combination with imatinib.³⁷

More recently, pegylated (PEG) IFN- α has been used for CML. The addition of a polyethyleneglycol molecule to IFN produces a molecule with a longer half-life and more favourable pharmacokinetics. These characteristics permit injection once a week. Pegylated IFN- α has been used in combination with imatinib and it is thought that it may have a synergistic effect. High rates of grade 3 and 4 haematopoietic toxicity (77%) have been reported with pegylated IFN- α , although non-haematological

events appear minimal and results are still in the very early stages.^{38,39}

Hydroxyurea

Until the advent of IFN- α therapy, hydroxyurea was considered the standard treatment for newly diagnosed patients. Hydroxyurea suppresses the excessive multiplication of the myeloid peripheral cells by inhibiting one of the enzymes involved in DNA replication. Hydroxyurea relieves symptoms with few adverse effects and produces haematological remission in over 90% of patients. However, it has little or no effect on cytogenetic response. It is generally accepted that hydroxyurea can modestly prolong survival compared with busulfan, which is associated with more adverse effects.²² Hydroxyurea is often used in combination with IFN- α , when IFN- α fails, when IFN- α is not tolerated, or in very elderly or frail people.

BMT or stem cell transplantation

Allogenic BMT is an appropriate comparative treatment for imatinib in only a small number of patients (less than one-fifth of those eligible for drug treatments). It is currently the favoured treatment for young patients with CML in the chronic phase who have an available donor. BMT is associated with a high early mortality rate (20–40%) and therefore is only suitable for healthy people in relatively early stages of disease. It is not possible to receive a transplant unless a suitable donor is available, as it is likely that the transplant will be rejected. In this report BMT is briefly compared with imatinib through indirect comparisons of effectiveness. BMT is not, however, modelled in cost-effectiveness analysis owing to the differences in eligible populations.

BMT and stem cell transplantation (SCT) have traditionally been the only potentially curative treatments for CML. Some 50–55% of patients under 40 years receiving BMT may remain disease free at 10 years.⁴⁰ Autologous BMT involves aspirating the person's own marrow when they are in remission, treating the marrow with myeloablative therapy and then reinfusing intravenously. Allogenic BMT involves donated marrow from a human leucocyte antigen (HLA)-identical sibling or a matched unrelated donor. The process involves aspirating marrow from the donor and infusing into the recipient. Autologous transplants are thought to be associated with the lowest mortality. Effectiveness is thought to be greatest for HLA-identical sibling transplants, although advancing experience with techniques has led to reports that matched unrelated donor transplants can have equivalent outcomes.⁴¹

Newer BMT techniques and preconditioning regimens are continually emerging.

There is a substantial transplant-related mortality of 20–40%, with the main causes of death being infection, cytomegalovirus pneumonitis and graft-versus-host disease (GVHD).⁴² Currently fewer than one-fifth of patients are both suitable for a BMT (are in good general condition and aged under 55) and have access to a donor.¹ The most favourable timing of the transplant is controversial, but is generally thought to be more successful if offered relatively early in the disease process.^{1,43}

With the introduction of imatinib, more options have become available for people in whom BMT is possible. There may be a role for imatinib as part of a preconditioning regimen, following BMT, or as a direct alternative. There is currently no published evidence to guide management in this area.

Other possible treatments not included in this assessment report

Peripheral blood stem cell transplantation

This is a newer technique which involves obtaining and infusing peripheral blood stem cells (PBSCs) rather than marrow cells. The procedure can be autologous or allogeneic. The advantage is thought to be faster haematopoietic cell reproduction than with marrow owing to the cells from peripheral blood being more differentiated. The treatment may also be safer owing to the shorter duration of neutropenia.⁴⁴ A published randomised trial reports that PBSC transplantations using HLA-identical sibling donors are superior to BMTs, with faster haematopoietic and immune recovery and the potential to reduce disease recurrence.⁴⁵

Busulfan

Busulfan can control the signs and symptoms of CML through controlling blood count, but has little or no effect on the progression of the disease. Busulfan is not usually used regularly for CML as it has less favourable survival and more side-effects than hydroxyurea. For these reasons it is not considered further in this assessment.

Patient diagnosis

CML is diagnosed by the presence of a characteristic blood and bone marrow cellular pattern, together with cytogenetic and molecular diagnostic techniques.

Cytogenetic techniques detect the Philadelphia chromosome, and were originally considered the gold standard. Cytogenetic analysis requires the

examination of at least 20–30 bone marrow cells in mitosis, so that the metaphases can be examined. There are considerable sampling errors because of the relatively small numbers of cells examined and the infrequency of measurement (bone marrow examination is invasive, which precludes frequent testing). The limit of detection is between 1 and 5% (i.e. it cannot detect less than 1% abnormal cells). The definition of minimal residual disease may vary in the literature.

Fluorescence *in situ* hybridisation (FISH) tests for the presence of the BCR-ABL gene, and may be positive in the absence of the Philadelphia chromosome. It uses a fluorescent-labelled DNA probe to determine the presence or absence of a particular segment of DNA. In the case of CML it looks for the BCR-ABL fusion gene in bone marrow or peripheral blood cells. In the FISH test, approximately 200 cells are examined, making it more sensitive than the traditional cytogenetic count of 20–30 metaphases. It is susceptible to false-positive results, and the limit of detection is considered to be between 1 and 5% abnormal cells.⁴⁶ The advantage of this technique is that cells do not need to be cultured or analysed in metaphase.⁴⁷

Southern and Western blotting techniques have a similar sensitivity to FISH, but can be performed on peripheral blood.

Reverse transcriptase–polymerase chain reaction (RT-PCR) is a very sensitive assay which tests for the presence of messenger RNA, the intracellular product that enables proteins to be produced from the DNA gene. Each messenger RNA is specific for the particular protein that it encodes. RT-PCR can detect a single leukaemia cell in 10^5 – 10^6 normal cells.⁴⁸

The CRK oncogene-like protein (CRKL) phosphorylation assay is a functional test that has been developed to detect intracellular activity of the BCR-ABL tyrosine kinase. This CRKL phosphorylation assay is raised in people with CML, drops back to normal levels when the patient has a cytogenetic response, and then becomes elevated again with relapse. The sensitivity and specificity of this test are not yet clear.⁴⁹

Description of the new intervention

Intervention: imatinib

Imatinib mesylate (STI-571, also Gleevec[®] or

Glivec®; Novartis Pharmaceuticals) is a rationally designed competitive inhibitor of the BCR-ABL protein tyrosine kinase. It is taken as a once-daily oral dose.

Imatinib acts by blocking the ATP binding site on the BCR-ABL tyrosine kinase. This inhibition prevents the phosphorylation of the tyrosine residue on the attached substrate, reducing cellular proliferation. BCR-ABL has a long half-life and requires the continuous presence of inhibitors to reduce its function substantially.¹⁸

The recommended dose is 400 mg/day for those in chronic phase CML, escalating to 600 mg/day in those whose disease progresses, those do not haematologically respond within 3 months and those who lose a previously attained haematological response. The dose is administered orally and given once daily with a meal and a large glass of water.

Imatinib has previously been evaluated for the National Institute for Clinical Excellence (NICE) as second-line treatment of CML in chronic phase and as first line treatment in accelerated and blast phases, and the following guidance issued in September 2002:

“Imatinib is recommended as a treatment option for the management of Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in chronic phase in adults who are intolerant of interferon-alpha (IFN- α) therapy or in whom IFN- α is deemed to have failed to control the disease” (NICE Guidance Appraisal No. 50).

The guidance defines IFN- α failure as either (1) failing to achieve a complete haematological response after 3 months of IFN- α treatment as monotherapy or in combination with HU, or (2) failing to achieve major cytogenetic response after 1 year of IFN- α treatment despite haematological response. IFN- α intolerance is defined as the presence of documented grade 3 non-haematological toxicity, persisting for more than 2 weeks, in patients receiving a regimen that contains IFN- α (NICE guidance appraisal no. 50).

Further, the guidance states that

“Imatinib is recommended as an option for the treatment of adults with Philadelphia-chromosome-positive CML in accelerated phase or blast crisis provided they have not received Imatinib treatment at an earlier stage” (NICE Guidance Appraisal No. 50).

Imatinib is a designated orphan drug in the European Union and was first authorised in

November 2001. The current European Agency for the Evaluation of Medicinal Products (EMA) product information states that:

“Glivec (i.e. imatinib) is indicated for the treatment of adult patients with Philadelphia chromosome (bcr-abl) positive chronic myeloid leukaemia (CML) in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.”

In December 2002 the US Food and Drug Administration (FDA) and the EMA issued a licence for imatinib in first-line treatment of CML.

There is little published evidence for imatinib in the following populations: paediatric, before or after BMT, impaired hepatic function, moderate to severe impairment of renal function or overt cardiac disease.

Outcome measures **Cytogenetic and haematological response as intermediate outcomes**

The achievement of a haematological response (HR) and/or a cytogenetic response (CR) has been suggested as an intermediate outcome in CML (i.e. as a proxy for long-term survival). It has been postulated that these responses indicate a reduction in the tumour burden, and therefore a reduction in the number of clonal, genetically unstable cells. This may, in turn, reduce the rate of secondary genetic change and postpone progression of the disease to blast crisis.⁵⁰ However, the effects of IFN- α in increasing cytogenetic abnormalities while prolonging survival suggest that this may not be a straightforward relationship.³² An alternative theory is that the cells destined to produce blast crisis are already present at the time of diagnosis, and time to progression depends on host factors and the doubling time of the blast cells.⁵¹ The former theory, but not the latter, suggests that achievement of an HR and/or a CR is causally associated with prolonged survival.

Classification of CRs is by bone marrow metaphase analysis (*Table 2*).

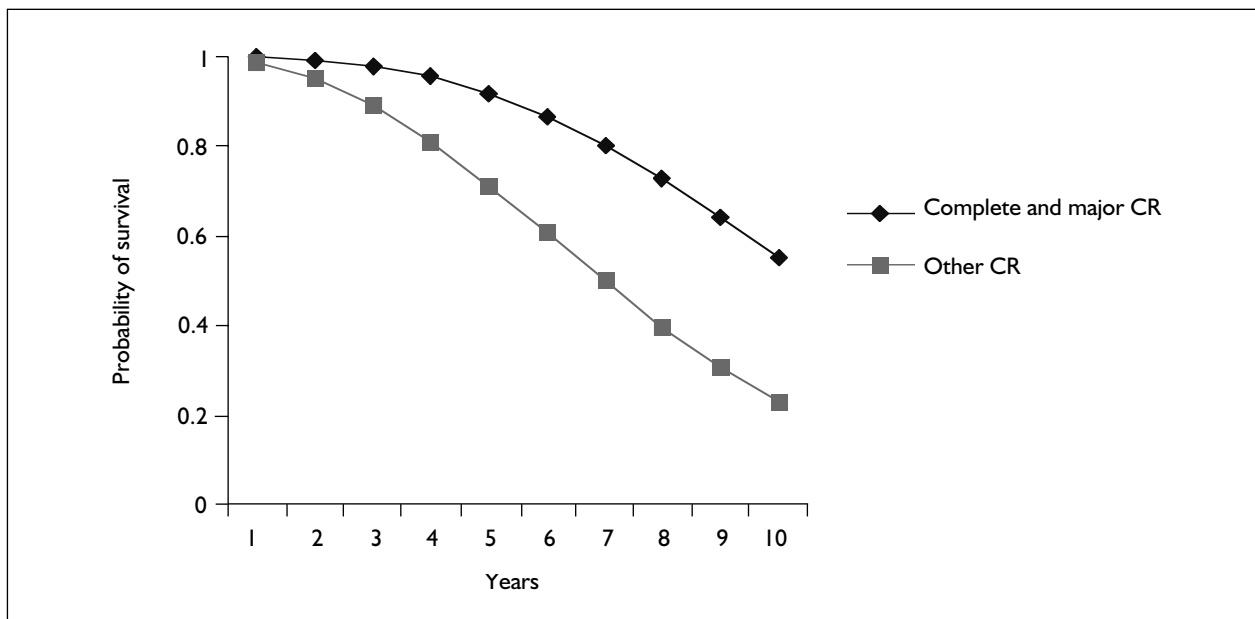
An HR to treatment refers to the normalisation of blood counts. Complete HR is defined as follows:

- WBCs $\leq 10 \times 10^9/l$, platelets $\leq 450 \times 10^9/l$
- no immature cells in peripheral blood
- absence of all signs of disease, including splenomegaly
- resolution of symptoms.

TABLE 2 Classification of CRs by bone marrow metaphase analysis

Degree of CR	Percentage of bone marrow metaphases remaining Philadelphia positive	
	Talpaz et al. (1987) ⁵² criteria	Cortes et al. (1996) ⁵³ criteria
None	>95	>99
Minimal	35–95	35–99
Partial	5–34	1–34
Complete	0	0

NB. Combined partial and complete categories = major.

**FIGURE 1** Overall survival of IFN- α patients who experienced a complete or major CR compared to any other CR. (Figure derived from data presented in the Italian Co-operative Study.²¹)

In most trials, HR is reported as the best response achieved over the length of the trial follow-up.

Evidence relating to IFN- α suggests that a complete HR or CR is indicative of longer survival. For example, the Italian Cooperative Study Group on CML reports that people with a complete CR had approximately 94% survival at 5 years compared with just under 70% in all others (Figure 1).²¹

In the previous NICE appraisal of imatinib for failed IFN- α therapy, it was considered likely "... based on the current evidence and knowledge of the effect of imatinib, that the relationship between cytogenetic response and haematological response and survival is sufficiently strong to support the use of cytogenetic response and haematological response as surrogate measures of efficacy" (Technology Appraisal Guidance No. 50).

There is, however, still reason to be cautious. Responses to therapy may simply represent the identification of subsets of patients with better prognosis. If one therapy delivers prolonged survival compared with the alternative and is associated with higher rates of HR and CR, it is tempting to assume that HR and CR are on the causal pathway by which therapy influences outcome. However, it remains possible that HR and/or CR are an epiphenomenon seen more commonly with a particular therapy, but which may not be produced by an alternative effective therapy. The appearance of CR and/or HR may not be associated with prolonged survival with an alternative therapy such as imatinib. Therefore, the presence of a relationship between CR and HR and survival is not guaranteed to hold for imatinib. In the absence of long-term follow-up data the assessment of such a relationship is not possible.

Even given the general clinical consensus that the relationship between cytogenetic response and survival is causal, there are still uncertainties regarding the duration of response to imatinib and resistance. These issues may impact on the overall survival that is seen with imatinib in the longer term.

Duration of response and resistance

The duration of response to imatinib remains a crucial unanswered question. Recent follow-up data from a Phase II study suggest that survival with imatinib remains above 90% at 2 years.

Imatinib's mechanism of action suggests that continual exposure to the drug is required. It is not known whether imatinib can ever be safely stopped. In contrast, long-standing unmaintained remission has been documented in a small number of people treated with IFN- α and some IFN- α -treated patients remain in remission for 10 years.²⁹ It has been suggested that IFN- α can produce an 'operational cure' even though pathology is still detectable.⁴⁶

Resistance to chemotherapy is a common feature of many cancers, and has been documented with imatinib. Disease progression is at least partly associated with the failure to maintain effective inhibition of BCR-ABL kinase activity⁵⁴ as measured by the CRKL assay. Secondary oncogenic changes that permit malignant proliferation independent of BCR-ABL are also possible, but appear to be less likely as an explanation.⁵⁵ It is probable that resistance will be an important determinant of long-term survival with imatinib, and the mechanism of resistance is discussed further in Appendix 2.

Many aspects of imatinib therapy are still not understood. It is also unclear why some patients fail to achieve a response, but there are several possibilities.

- There is poorer inhibition of BCR-ABL by imatinib in less mature cells (i.e. a high proportion of immature cells is less sensitive to imatinib).
- Relatively resistant stem cells have a proliferation advantage and eventually predominate.
- The percentage of BCR-ABL-positive stem cells may vary considerably between people.³⁶

The ideal method of preventing resistance is to treat disease for as short a time as is needed to eradicate it. Practically, this may be difficult in CML.⁵⁶ Alternatively, studies have indicated that to obtain optimum efficacy and prevent drug resistance, combination therapy with other antineoplastic agents may be necessary.⁵⁶ Recently, studies have reported combining imatinib with other agents such as 2-chlorodeoxyadenosine (2-CdA), fludarabine (F-ara-A),⁵⁷ IFN- α ,³⁷ pegylated recombinant IFN- α 2b,^{38,39} Ara-C,⁵⁸ 17-allylamino-17-demethoxygeldanamycin (17-AAG),⁵⁹ carboplatinum or etoposide,⁵⁶ gamma irradiation and alkylating agents (such as busulfan or treosulfan).⁶⁰

Anticipated costs

Imatinib costs £12.98 per 100 mg. The approximate annual cost per patient for 400 mg/day in the chronic phase is £18,951, and for 600 mg/day in the accelerated or blast phase is £28,426. Doses of 800 mg/day will cost £37,902 per year per patient.

Chapter 3

Methods

Method for reviewing effectiveness

Search strategy

Three separate searches of electronic databases were performed to identify published studies and ongoing research (Appendix 3).

Imatinib

The search performed for the previous NICE assessment report on imatinib as second-line treatment for CML was updated. The previous strategy identified studies assessing first-line treatment of CML. The search was not restricted by study design.

IFN- α versus hydroxyurea

The previous NICE assessment report search for the comparison of hydroxyurea and IFN- α was updated. This search was restricted to randomised comparisons, as high-level evidence is known to exist.

IFN- α versus BMT

Searches were conducted to identify evidence for BMT versus IFN- α . No restrictions by date of publication were applied to these searches.

All searches were restricted to English language publications, and the search terms and strategy are outlined in Appendix 3. Bibliographies of identified publications were searched for further relevant articles, handsearching of conference abstracts (European Haematology Association, American Society of Clinical Oncology, International Society for Experimental Hematology and American Society for Hematology) for imatinib was performed and the manufacturers of imatinib were approached for unpublished studies.

Inclusion and exclusion criteria

Two independent researchers (KD and AR) reviewed titles and abstracts for inclusion. The full texts of articles deemed relevant were obtained and the two researchers independently reviewed each for final inclusion. Disagreements were resolved by consensus.

The following inclusion criteria were applied.

Study design

- Imatinib compared with any other treatment: studies with a control group only

- IFN- α compared with hydroxyurea: randomised controlled trials (RCTs) only
- IFN- α compared with BMT: studies directly comparing IFN- α and BMT in the same study only.

Stricter study design criteria were applied to comparison of IFN- α and hydroxyurea owing to the large number of randomised trials known to be available.

If studies were reported only in abstract form the reviewers tried to obtain the full text article. If a full text article was not available the abstract was excluded.

Population

Adults presenting for first-line treatment of CML in chronic phase were included. Studies of patients in accelerated or blast phase were excluded.

Intervention and comparisons

Studies comparing the following were included:

- imatinib compared with any other treatment
- IFN- α compared with hydroxyurea
- IFN- α compared with BMT.

Studies of hydroxyurea were only included if at least 75% of the control group received hydroxyurea (e.g. at least 75% received hydroxyurea and up to 25% received other agents such as busulfan). Relevant meta-analyses were only included if they reported all relevant outcomes that were present in the original reports of the RCTs, otherwise the original RCTs were included.

Outcomes

Quality of life, overall survival, HR, CR and adverse effects were included.

Data extraction strategy

Data were extracted by one reviewer (KD) and checked by a second reviewer (RG). Response rates and survival were calculated where possible from original data presented in the reports and not from percentages given in the report, which are often adjusted for a variable number of dropouts. In some cases, survival was estimated from survival curves presented in the results.

Quality assessment strategy

Using a structured form, the internal and external validities of the included studies were assessed by one researcher (KD) and checked by a second (RG). The quality assessment of comparative studies was based on the following criteria.

RCTs/comparative studies [Centre for Reviews and Dissemination (CRD) Report No. 4]

- Was the assignment to treatment groups an adequate method of randomisation?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostic factors?
- Were the eligibility criteria specified?
- Were the outcome assessors blinded to the treatment allocation?
- Was the care provided blinded?
- Was the patient blinded?
- Were point estimates and measure of variability presented for the primary outcome measure?
- Was the analysis intention-to-treat (ITT)?

The external validity was reviewed through consideration of patient characteristics, including eligibility and inclusion/exclusion criteria.

Data synthesis

Owing to the lack of suitable randomised evidence, meta-analyses were not performed. Data are described through narrative and summarised in tables.

No direct evidence comparing imatinib with hydroxyurea or BMT was identified. Therefore, outcome measures were calculated directly from the relevant single arms of available trials to enable an approximate assessment of the efficacy of imatinib in relation to these treatments. It cannot be emphasised too strongly that this kind of comparison is potentially biased, particularly in terms of potential differences in the populations studied, the variable completeness of follow-up and publication bias.

A further difficulty arises from the short-term follow-up in the imatinib trial and the consequent reliance on HR and CR as proxy outcome measures for longer term survival.

When 95% confidence intervals (CI) were not described in the original reports, these have been calculated wherever possible using Stata™.

Methods for economic analysis

Systematic review of existing economic literature

Electronic databases were searched for published economic studies. The economic search performed

for the previous NICE assessment report on imatinib as second-line treatment for CML was updated. All economic studies of any treatment for chronic phase CML in adults were included. Economic studies identified have been very briefly described and appraised using the Drummond checklist.⁶¹

Cost-effectiveness and cost utility

A Markov model was developed to determine the incremental cost-effectiveness ratio (ICER) of imatinib compared with hydroxyurea and IFN- α , and of hydroxyurea compared with IFN- α in terms of cost per quality-adjusted life-year (QALY). The model was constructed in Microsoft Excel. The model follows a cohort of 1000 people with CML from the time they commence treatment until death or for a total of 20 years (whichever comes first). Twenty years was selected as a realistic period in which the majority of CML patients' lives could be hypothetically captured. The cycle length for the model is 3 months and costs are calculated based on an NHS perspective.

Basic assumptions

For a person diagnosed with chronic phase CML there is a number of possible treatment pathways. In this economic model, cohorts of 1000 CML patients progress through three alternative treatment pathways. It is assumed that all people in this model are not candidates for BMT and, further, that people will change or stop treatment as a result of disease progression or loss of response.

Figure 2 shows the possible transitions between health states for patients receiving first-line treatment with hydroxyurea in the model. It is not possible to have a CR when being treated with hydroxyurea. It is possible to move to every other state from the chronic phase, but once the accelerated or blast stage has been reached, no return to the chronic phase is possible.

Table 3 shows the three treatment pathways that are compared in the model. The pathways each consist of first-line treatment, treatment when disease progresses to the accelerated phase, treatment when disease progresses to the blast phase and treatment for those who lose their CR.

Once patients are treated following disease progression or loss of CR, assumptions are also made regarding the probabilities of moving from one state to another (transition probabilities). When direct data are not available, relative benefit

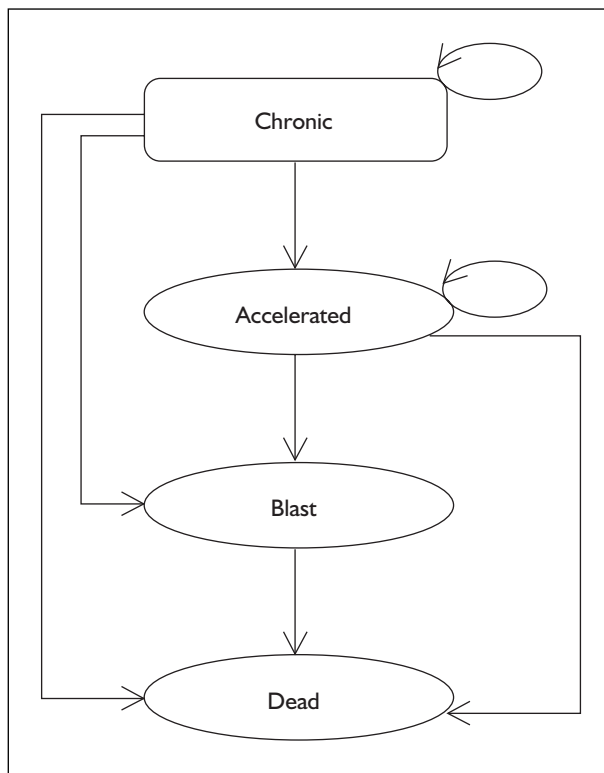


FIGURE 2 Pathway for patients with chronic phase CML treated with hydroxyurea

or disbenefit [relative risk (RR)] of alternative treatments estimated from the literature is applied to available IFN- α data. *Table 4* summarises the derivation of the transition probabilities used. They are calculated from rates reported in studies using the drug in question.

For patients in pathway 1, treatment starts with imatinib and switches to IFN- α treatment on progression or loss of response. Subsequent CR is not permissible.

For patients in pathway 2, treatment starts as IFN- α and switches to imatinib on progression of loss of response. Progression rates from studies of imatinib as second-line treatment are used for those who have lost a CR,⁶² and death rates calculated by applying an RR of survival, estimated from Novartis Study 0106.⁶³

Patients on pathway 3 continue on hydroxyurea until the blast phase, when they receive mercaptopurine.

Each cohort begins in the chronic state, and death is possible from all states. Disease progression is obtained from published progression curves and is

TABLE 3 Treatment pathways for imatinib, IFN- α and hydroxyurea

Treatment pathway	Starting treatment	Treatment when disease progresses to accelerated phase	Treatment when disease progresses to blast phase	Treatment for those who lose their CR
1	Imatinib (400 mg/day)	IFN- α	Mercaptopurine	IFN- α
2	IFN- α	Imatinib (600 mg/day)	Imatinib (600 mg/day)	Imatinib (400 mg/day)
3	Hydroxyurea	Hydroxyurea	Mercaptopurine	NA

TABLE 4 Derivation of transition probabilities used in independent economic model

Treatment pathway	Starting transitions	Transitions when disease progresses to accelerated phase	Transitions when disease progresses to blast phase	Transitions for those who lose their CR
1. Imatinib (400 mg/day)	Imatinib progression rates Imatinib death rates Imatinib response rates	IFN- α progression rates IFN- α death rates	Fixed death rate	IFN- α progression rates IFN- α death rates
2. IFN- α	IFN- α progression rates IFN- α death rates IFN- α response rates	IFN- α progression rates IFN- α death rates \times imatinib RR of survival	Fixed death rate \times imatinib RR of survival	Imatinib following failed IFN- α progression rates IFN- α death rates \times imatinib RR of survival
3. Hydroxyurea	HU progression rates HU death rates	HU progression rates HU death rates	Fixed death rate	NA

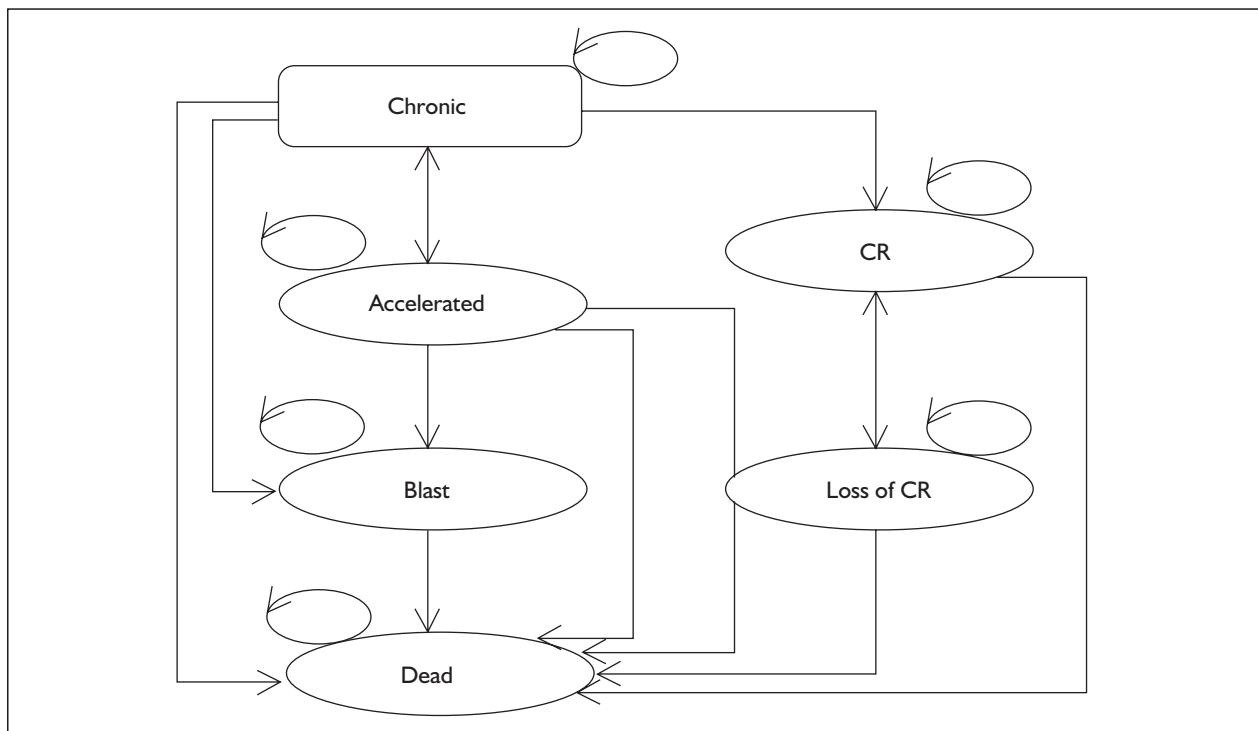


FIGURE 3 Pathway for patients with chronic phase CML treated with imatinib or IFN- α

partitioned in a ratio of 2:1 between progression to accelerated and blast phases (data from Novartis study 0106⁶³).

Figure 3 shows the possible transitions between health states for patients receiving imatinib and IFN- α as first-line treatments in the model (pathways 1 and 2). There are two additional states: CR and loss of CR. A person is permitted to move from chronic phase to all other states except for loss of CR.

Costs

The costs of all the drug treatments were obtained from the British National Formulary (BNF 44, September 2002). Cost such as hospital outpatient visits, inpatient hospital stay, bone marrow tests, blood transfusions and radiology tests were also considered and were obtained from the Southampton University Hospitals NHS Trust (SUHT) databases. Inpatient and outpatient costs were the submitted reference costs for 2001/02 and inpatient visits were assumed to be 3 days in duration. Outpatient visits were assumed to be 50% initial and 50% follow-up. All other costs were direct costs for 2002/03. The cost of radiology tests was composed of one chest X-ray and one basic computed tomography (CT) scan. The cost of a BMT was composed of 20 units of full blood, 10 units of platelets and 2 hours' nursing time (average of grades E and D). Management is

predominantly outpatient in nature and is likely to be very similar between treatments. The number of hospital visits and tests per cycle as used in the model were estimated by haematology consultants. Costs are discounted at 6% per year according to current NICE recommendations.

QALY calculations

Quality of life for those with CML varies with treatment and advancing disease. No empirical studies directly measuring utility values relating to CML were identified, other than the study submitted by Novartis. In the absence of population-derived utilities, values from the Novartis study 0106⁶³ were used. These are patient estimates and to a large extent are likely to capture preference for the treatment as well as a preference for being in a particular health state. Sensitivity analyses using clinician-derived estimates from the Novartis submission⁶³ were performed. QALYs are discounted at 1.5% per year, in line with current NICE recommendations.

Modelling of survival data

Survival data were obtained from published studies of the effectiveness of various drug treatments for CML (see Chapter 4). The economic model was based on survival curves and progression curves.

The following transition probabilities were modelled as being cycle dependent (i.e. the

transition probability changes as the time spent by the cohort in the model increases):

- chronic to accelerated/blast
- chronic/accelerated/CR to death
- chronic to CR.

To obtain the transition probabilities the survival curves were electronically scanned and the program TechDig was used to obtain coordinates for a number of points along the curve. These coordinates were used to estimate a Weibull distribution of the following formula:

$$f(x) = e^{-\lambda x^\gamma}$$

λ and γ were estimated using a least squared method to achieve best fit with data taken from survival and progression curves. Transition probabilities were calculated from the cumulative survival function given a cycle length of 3 months.

The following transition probabilities were constant for each cycle and were derived from the literature (for a description of values and studies see *Table 28*):

- accelerated to blast
- blast to death
- chronic to CR.

When calculating the transition probabilities for imatinib as second-line treatment, data from the published chronic Phase II trial⁶² were used for the first five cycles (1.25 years), after which the IFN- α data derived from the Italian trial²¹ were used as a conservative estimate.

To estimate transition probabilities for hydroxyurea as first-line treatment, a hazard ratio compared with IFN- α was calculated. The scanned survival or progression curves were compared in Stata, assuming an appropriate distribution (Weibull, gamma, exponential or log-normal) to estimate the hazard ratio and standard error (SE). This was used as an estimate of the relative risk. Separate hazard ratios were calculated for mortality, progression and CR. For imatinib, insufficient long-term data were available. A survival function was estimated from point data provided at 6, 9, 12 and 18 months from Novartis study 0106,⁶³ and then a similar procedure as with hydroxyurea was undertaken. It was not possible to estimate the standard error using the point data, so for survival a large standard error was assumed so that the confidence interval crossed 1, to reflect the lack of statistical significance demonstrated so far. Sensitivity analyses were used to explore the effect of uncertainty around all parameters.

Calculation of incremental cost utility

For each treatment the total number of life-years gained, the QALYs gained (i.e. total summed quality of life associated with the numbers of people in each of the possible health states per cycle) and the total costs (i.e. the total summed costs of treating each person in each health state per cycle) were calculated. Each of these sets of three figures was summed over the total life of the model (20 years). The ICER was then calculated for each combination of treatments using the following formula:

$$\text{ICER} = \frac{\text{Total costs drug A} - \text{Total costs drug B}}{\text{QALYs gained drug A} - \text{QALYs gained drug B}}$$

Sensitivity analysis

There is uncertainty concerning many of the data incorporated in the economic model. Extensive one-way sensitivity analyses were performed. The following scenarios were modelled in sensitivity analyses.

- Data from different studies are used for progression and survival with IFN- α .
- Loss of CR or progression on imatinib leads to treatment with an increased dose of imatinib (600 mg/day).
- Loss of CR or progression on imatinib leads to treatment with a combination of imatinib (400 mg/day) and IFN- α (3 MU), and an unchanged progression curve.
- Loss of CR or progression on IFN- α leads to treatment with hydroxyurea.
- Pegylated IFN- α costs are used instead of IFN- α (with no difference in progression or survival).
- Clinician-derived sets of utilities are used.
- All relative risks of imatinib compared to IFN- α are assumed to be 1.

Probabilistic analysis

In addition, to estimate the effect of uncertainty in all parameters simultaneously, a probabilistic analysis was undertaken. Monte Carlo simulation was performed, with 1000 iterations. A graphical representation of uncertainty was generated on a cost-effectiveness plane. A cost-effectiveness acceptability curve was derived to show the probability that imatinib is more cost-effective than other treatments at a range of values that the NHS may be willing to pay per QALY gained.

Comparisons between independent economic analysis and industry submission

The results from the industry model and the independent economic evaluation were compared, and reasons for any differences explored.

Chapter 4

Effectiveness

Research available

Imatinib

No studies of imatinib identified in the previous NICE assessment report were included in this report as they all considered second-line treatment of CML.

The update search identified a total of 213 articles, one of which was included after completing the selection process (*Figure 4*). Twelve of the 213 articles identified were found through handsearching.

IFN- α compared with hydroxyurea

Four RCTs were included from the previous NICE assessment. Two of the RCTs from the previous assessment report were excluded as more than

25% of the control groups received busulfan.^{64,65}

In addition, the one published meta-analysis was excluded as more complete documentation of relevant outcomes was included in individual trial reports.⁶⁶

The additional update search failed to identify any new relevant RCTs. The inclusion process for the update search is illustrated in *Figure 5*.

IFN- α compared with BMT

In total, 339 articles comparing BMT and IFN- α were identified, of which five met the inclusion criteria (*Figure 6, Table 5*).

A list of the full text articles inspected and excluded (along with reasons) is shown in Appendix 4.

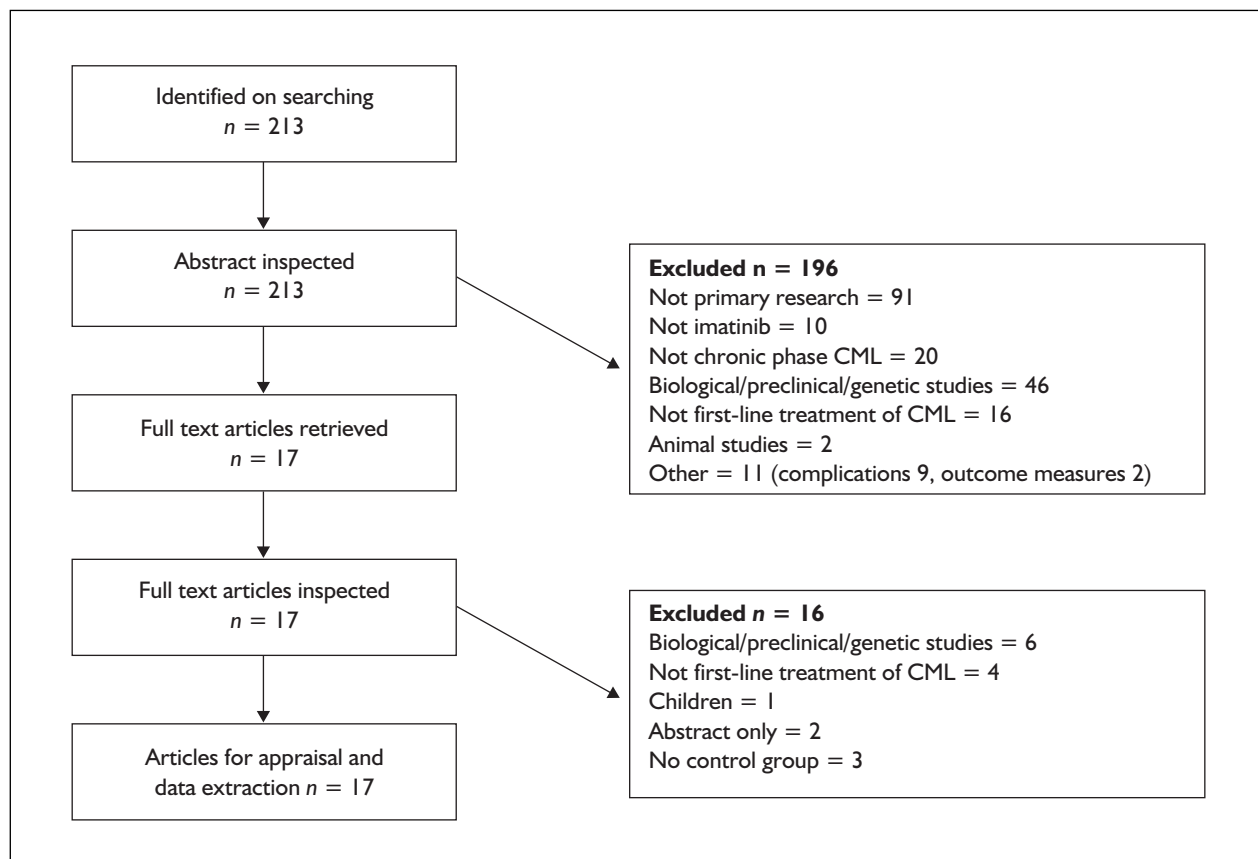


FIGURE 4 Flowchart showing the inclusion/selection process for imatinib

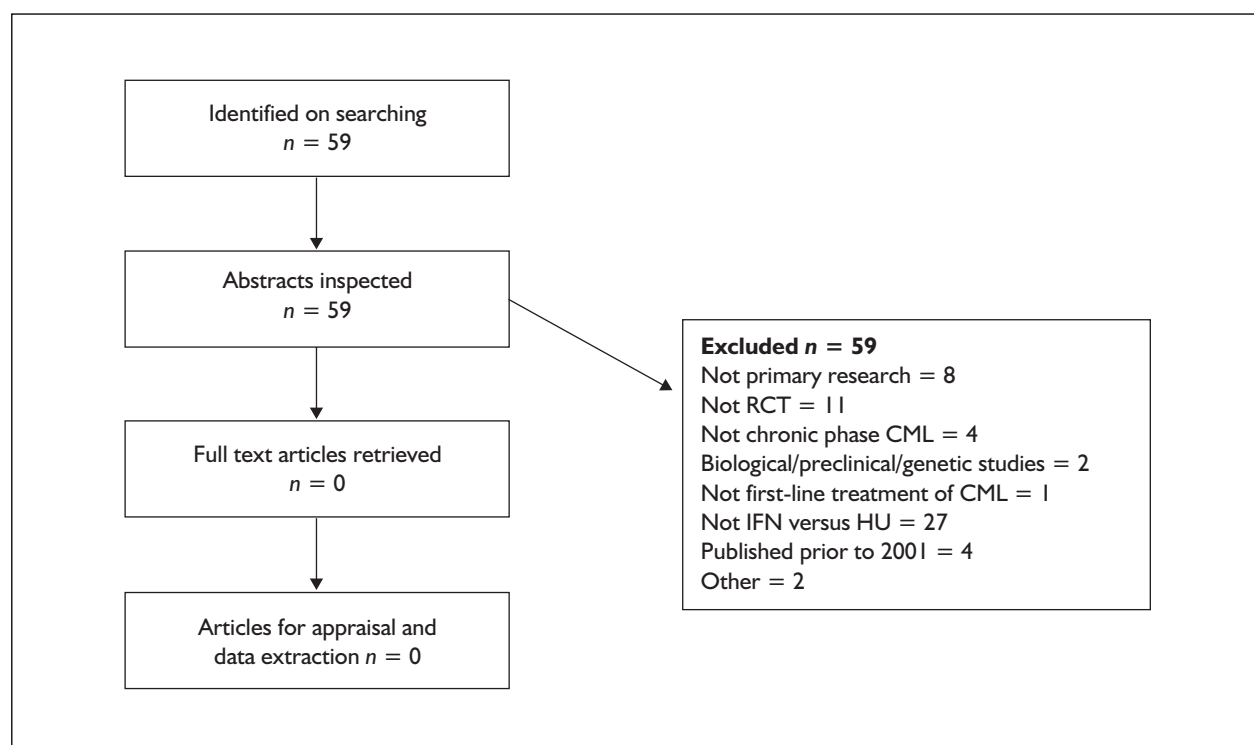


FIGURE 5 Flowchart showing the inclusion/selection process for IFN- α versus hydroxyurea (update search)

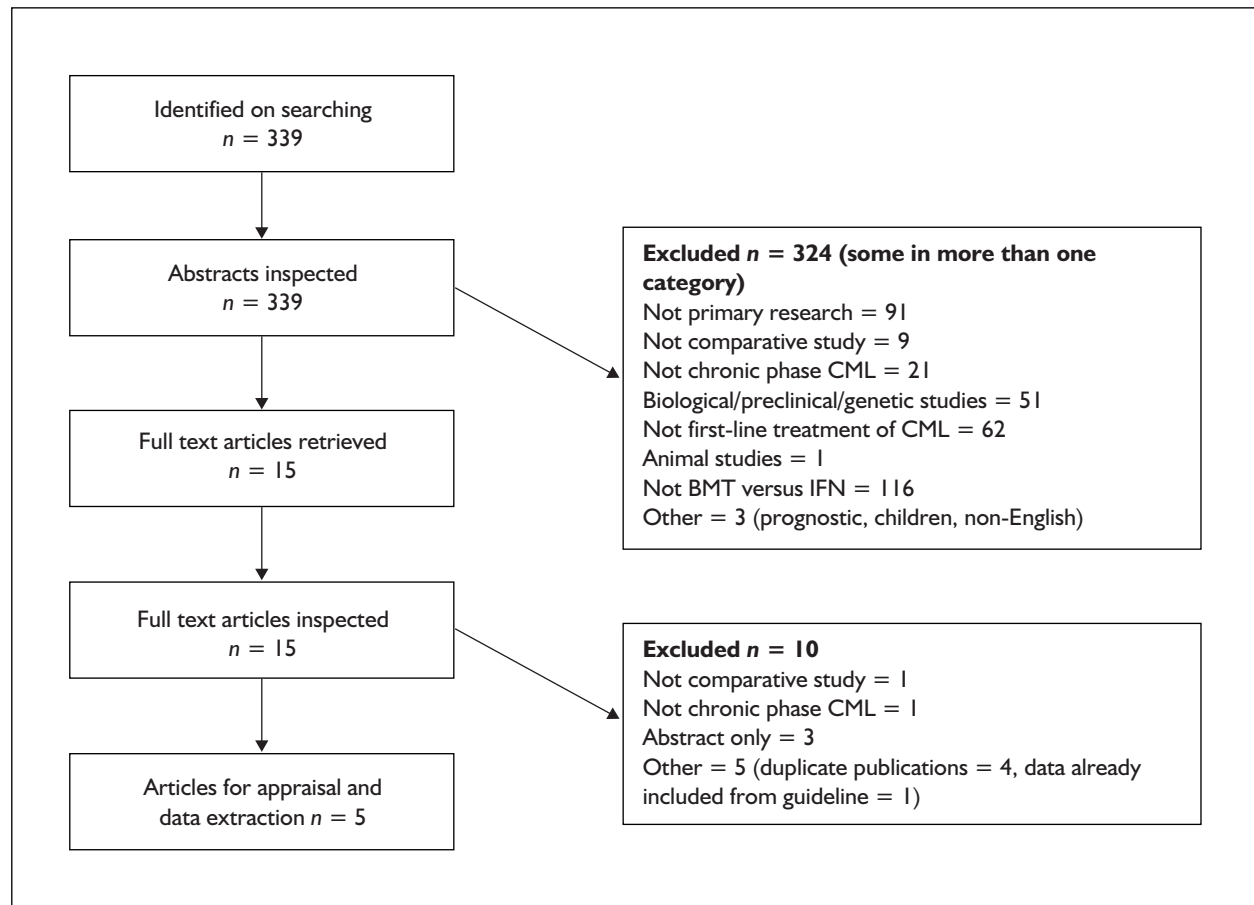


FIGURE 6 Flowchart showing the inclusion/selection process for IFN- α versus BMT

TABLE 5 Number and type of studies included

Intervention and comparison	Systematic reviews	RCTs	Non-randomised comparative studies
IFN- α vs imatinib	0	1	0
IFN- α vs hydroxyurea	0	4	– ^a
IFN- α vs BMT	0	0	5

^a Study design was excluded for this comparison.

Imatinib versus IFN- α plus Ara-C

Quality of study

The included study⁶³ is referred to as study 0106 and was performed by Novartis. It is also referred to as the International Randomised Study of Interferon + Ara-C vs STI571 in CML (IRIS). Subsequent to the literature search it has been published with updated data.⁶⁷ The study randomised a total of 1106 people to treatment with either imatinib or IFN- α plus Ara-C. The study enrolled people between June 2000 and February 2002. The median age of participants was 51 years and median length of follow-up was 13–14 months.

The quality of the included study (Novartis study 0106⁶³) is shown in *Table 6*. Novartis performed the day-to-day management of the trial, held the database and performed the statistical analysis. An external steering group monitored trial progress and quality control measures were implemented. There is the possibility of bias due to undisclosed data.

Internal validity

Sample size

The study randomised 553 people to receive imatinib and 553 to receive IFN- α plus Ara-C. A sample size calculation was performed before commencing the study. The original protocol sample size calculation was based on a difference in time to treatment failure (median of 4.8 years on imatinib versus 3.6 years on IFN- α plus Ara-C), which resulted in a total sample size of 351 patients per treatment arm with allowance for 17.5% dropout (total sample size 850).

An amendment was made to the protocol which changed the primary outcome measure to time to progression (with 5-year progression-free rate on the control arm expected to be 50%). The amended sample size calculation was performed: based on a hazard ratio of 0.75 for imatinib compared with IFN- α plus Ara-C, which translates into progression-free survival (PFS) of 50% in the

TABLE 6 Summary of the quality of the included study comparing imatinib with IFN- α

Quality criteria	
Proper randomisation?	?
Adequate concealment?	✓
Groups similar at baseline?	✓
Eligibility criteria stated?	✓
Outcome assessors blinded?	✗
Providers of care blinded?	✗
Patients blinded?	✗
Point estimates and measures of variability?	✓
Power calculation performed at study design?	✓
All patients accounted for?	✓
Analysis performed on ITT?	✓

✓, yes; ✗, no; ?, not reported.

IFN- α plus Ara-C arm and 60% in the imatinib arm, approximately 822 patients needed to be recruited with an allowance for a dropout of 10% per year (total of 1032 patients).

This was also considered to be sufficient power for the secondary outcome measure which was changed, in an amendment to the original protocol, to major CR. There was sufficient power to detect a 10% increase in major CR for imatinib compared with IFN- α plus Ara-C (assumed to be 41%).

Selection bias

Randomisation was performed at a central office. Staff members in each participating unit were required to call the number of an automated voice response system to request treatment assignment. The method used to generate the random sequences was not reported, and randomisation was stratified by country. No details are provided to indicate how many people were screened in each centre before randomisation, but on average between five and six people were recruited per centre. No postrandomisation exclusions are reported in the ITT analysis, although two people in the imatinib group and 20 in the IFN- α plus Ara-C group never started treatment.

TABLE 7 Reasons for discontinuation of treatment in study 0106

	Novartis study 0106 ⁶³	
	Imatinib (n = 553)	IFN- α + Ara-C (n = 553)
Adverse reactions	11 (2%)	31 (6%)
BMT	5 (0.9%)	7 (1%)
Refusal/voluntary withdrawal	10 (2%)	74 (13%)
Protocol violations	10 (2%)	15 (3%)
Loss of contact with patient	2 (0.4%)	6 (1%)
Therapeutic inefficiency/resistance	9 (2%)	29 (5%)
Administrative problems	0	6 (1%)
Death	4 (0.7%)	2 (0.4%)
Total	51 (9%)	170 (31%)

The imatinib and IFN- α plus Ara-C groups were essentially similar at baseline for age, gender, weight, Eastern Co-operative Oncology Group (ECOG) status, previous treatment with hydroxyurea and Sokal scores.

Performance bias

Performance bias refers to systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation. The study was open label. IFN- α was administered subcutaneously, whereas imatinib was taken orally. Concurrent treatments may have differed between treatment groups but are not detailed.

Detection bias

Detection bias refers to systematic differences between comparison groups in how outcomes are ascertained, diagnosed or verified.

It is unlikely that there were systematic differences in how the objective study outcomes were measured between the two treatment groups. Detailed assessment schedules were part of the trial protocol. Outcome assessors and providers of care and patients were not blinded. There is a possibility of detection bias for the subjective outcome measures such as quality of life and treatment intolerance.

Outcomes may have been influenced by a desire to cross over to the alternative treatment group (especially for the initial IFN- α plus Ara-C arm). Quality of life assessment and intolerance to the treatment were assessed at the time the patient crossed over. If patients thought that a poor result would assist them in crossing over then a bias may have been present. It is also possible that if healthcare professionals felt that it was in the best interest of the patient to cross over, their assessment of outcomes may have differed in

comparison to patients on the alternative treatment. Any bias of this nature is likely to have favoured imatinib.

Attrition bias

Attrition bias refers to systematic differences between comparison groups in withdrawals or exclusions of participants from the results of a study.

All people who were enrolled in the trial were accounted for. In the imatinib group 51/553 (9%) discontinued treatment, compared with 170/553 (31%) in the IFN- α plus Ara-C group. The reasons for treatment discontinuation are shown in *Table 7*. The main reason for the difference in discontinuation was withdrawal of consent in the IFN- α plus Ara-C group. Those who discontinued treatment were given a final study visit and evaluation. People discontinuing owing to adverse events were followed weekly for 4 weeks or until resolution of the adverse event. Survival of all patients who discontinued treatment is planned for 8 years.

There is likely to be a systematic difference between the people who discontinue in the two groups.

In addition, 7/553 (1%) people in the imatinib group crossed over treatment compared with 218/553 (39%) in the IFN- α plus Ara-C group. The reasons for crossing over to the other treatment arm are shown in *Table 8*. The main reason for the difference in cross-over rates was intolerance of treatment. Note that patient request to cross over was allowed by amendment 3 to the trial protocol. In addition, there were incentives for institutions to cross patients over to treatment with imatinib, as imatinib was funded by the pharmaceutical company, whereas IFN- α plus Ara-C was provided within healthcare budgets.

TABLE 8 Reasons for crossing over to the other treatment arm

	Novartis study 0106 ⁶³	
	Imatinib (n = 553)	IFN- α + Ara-C (n = 553)
Intolerance of treatment	4 (0.7%)	126 (23%)
No complete HR at 6 months ^a	0	41 (7%)
No major CR at 12 months ^b	0	1 (0.2%)
No major CR at 24 months	0	1 (0.2%)
Increase in WBC count	2 (0.4%)	25 (5%)
Loss of complete HR	0	20 (4%)
Loss of major CR	1 (0.2%)	4 (0.7%)
Total	7 (1%)	218 (39%)

^a Only before protocol amendment (November 2000).
^b Changed to 24 months in protocol amendment (January 2002).

The high discontinuation rate (31%) combined with the high cross-over rate (39%) in the IFN- α plus Ara-C group give a combined attrition rate of 70% for that group (median follow-up of 13 months). The study is therefore highly prone to attrition bias, as those who dropped out of the study may have differed from those who remained. Owing to the high rates of attrition and cross-over, it is important to perform analyses on an ITT basis. The study did perform ITT analyses in which all people randomised to IFN- α plus Ara-C were analysed in that group regardless of whether they had crossed over treatment. Any attrition bias is likely to favour the IFN- α plus Ara-C group. However, as the response to IFN- α plus Ara-C is slower than to imatinib, and 91% of cross-overs were within the first year, some responses after cross-over may still be attributable to IFN- α plus Ara-C.

Minor discrepancies were noted in the numbers reported: only seven patients are reported as crossing over from imatinib to IFN- α plus Ara-C, but 17 are reported as discontinuing second line treatment with IFN- α plus Ara-C (i.e. must have crossed over from imatinib).

In the original protocol, the primary end-point was time to progression and was defined as:

- **failure:** death due to any cause, progression to accelerated or blast phase, loss of major CR, loss of HR, increase in WBC count (as a reason for cross-over), discontinued owing for reasons other than progression or death
- **censored:** cross-over for reasons other than progression, or still on treatment without progression.

The primary end-point was changed during the study. Patients discontinuing treatment were censored, as opposed to failing. This is likely to favour the IFN- α plus Ara-C arm, but may be a form of informative censoring, that is, there may be a relationship between those censored and the outcome. This leads to further possibilities of bias.

Reporting bias

The study reported point estimates as well as measures of variability (confidence intervals for survival estimates). Several analyses were performed, including first-line treatment and per protocol analyses. These are not presented here; the ITT analysis is more conservative but less biased.

External validity

The study provided sufficient details to make an assessment of generalisability. Eligibility and exclusion criteria were described. Patient details such as age, gender and risk scores were provided. Patients were recruited from a number of different countries, predominantly the USA.

The patients in this study had generally less severe disease than those enrolled in the studies comparing IFN- α and hydroxyurea (see Appendix 7, Patient characteristics and treatment details). The results are likely to be generalisable to a less severe population than would be seen in clinical practice (Table 9).

Patient characteristics

Patient characteristics and treatment details are summarised in Table 10.

TABLE 9 Comparison of Sokal score low-risk groups (imatinib and IFN- α studies)

Study (treatment)	% Sokal low-risk group
Novartis study 0106 ⁶³ (imatinib)	50.4
Benelux (IFN- α) ⁵	29
Broustet (IFN- α) ⁶	29.2
Hehlmann (IFN- α) ⁷	27.1

TABLE 10 Patient characteristics and treatment details

Study characteristic	Imatinib	IFN- α + Ara-C	Total
Median haemoglobin level (g/dl) (range)	12.3 (4.3–21.9)	12.2 (4.2–16.8)	12.3 (4.2–21.9)
Median WBC ($10^9/l$) (range)	95 (4–537)	85 (3–1082)	90 (3–1028)
Splenomegaly (any)	23%	27%	25%
Hepatomegaly (any)	10%	8%	9%
Extramedullary involvement	27%	31%	29%
Median age (years) (minimum–maximum)	50 (18–70)	51 (18–70)	51 (18–70)
Gender ratio, M:F (% male)	342:211 (62)	310:243 (56)	652:454 (59)
Median time since diagnosis (months)	2.14	1.77	1.97
Sokal score	Low 53% Intermediate 29% High 19%	Low 48% Intermediate 30% High 22%	Low 50% Intermediate 29% High 21%
Previous treatment, anagrelide permitted	HU 88%	HU 85%	HU 87%
Concomitant drugs	HU, leucopheresis, allopurinol and anagrelide permitted	HU, leucopheresis, allopurinol and anagrelide permitted	HU, leucopheresis, allopurinol and anagrelide permitted
Median length of follow-up (months)	14	13	?

The type of IFN used was IFN- α_{sc} , with a target dose of 5 MU/m² per day.
HU, hydroxyurea; M:F, male to female.

TABLE 11 Main results from the imatinib versus IFN- α plus Ara-C trial

Treatment	Imatinib	IFN- α + Ara-C	p-Value
Total number of people progressing	24/553 (4.3%)	103/553 (18.6%)	<0.001 ^a
Overall survival (%)	542/553 (98.0)	533/553 (96.4)	ns
Complete HR (%)	523/553 (94.6)	423/553 (76.5)	<0.001
	(95% CI 92.3 to 96.3)	(95% CI 72.7 to 80.0)	
Partial HR (%)	NR	NR	
Major HR (%)	NR	NR	
Complete CR (%)	375/553 (67.8)	110/553 (19.9)	<0.001 ^a
Partial CR (%)	82/553 (14.8)	110/553 (19.9)	0.03 ^a
Major CR (%)	457/553 (82.6)	220/553 (39.8)	<0.001
	(95% CI 79.2 to 85.7%)	(95% CI 35.7 to 44)	
Withdrawal due to side-effects	11/553 (2.0)	31/553 (5.6)	0.002 ^a
Cross-over due to intolerance	4/553 (0.7)	126/553 (22.8)	<0.001 ^a

^a Calculated by the authors of this assessment from reported figures.
NR, not reported; ns, not significant.

Study results

The primary end-point was time to progression. Secondary end-points were survival and quality of life. *Table 11* reports the main results in the ITT analysis.

Figure 7 shows a Kaplan–Meier estimate of those people on imatinib compared with IFN- α plus Ara-C who did not die, progress to the accelerated or blast phase, lose a response or show an increased WBC count. A greater proportion of

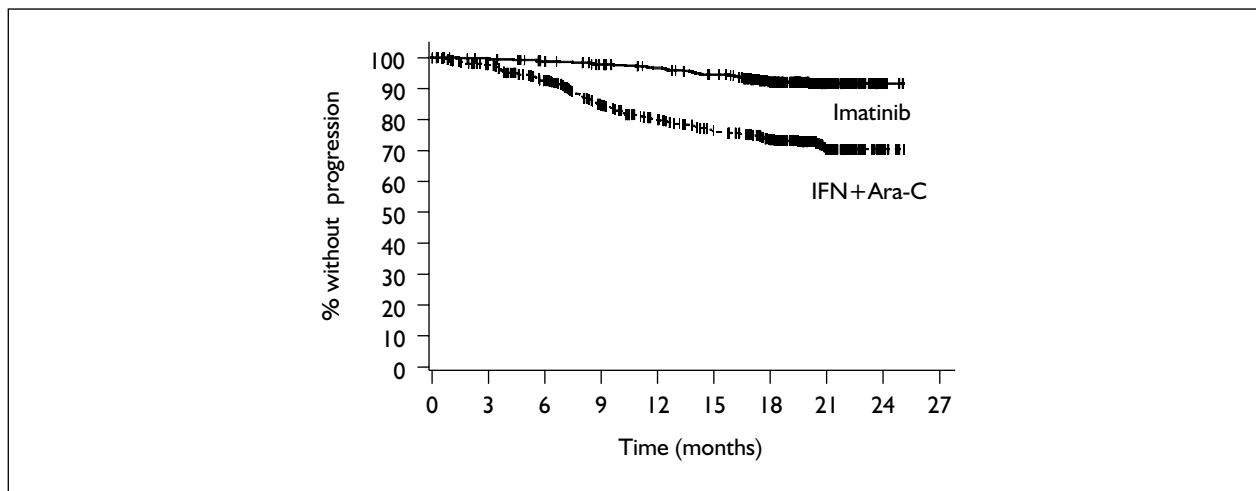


FIGURE 7 Time to progression for imatinib compared with IFN- α plus Ara-C. (Source: data derived from O'Brien S, University of Newcastle: personal communication.)

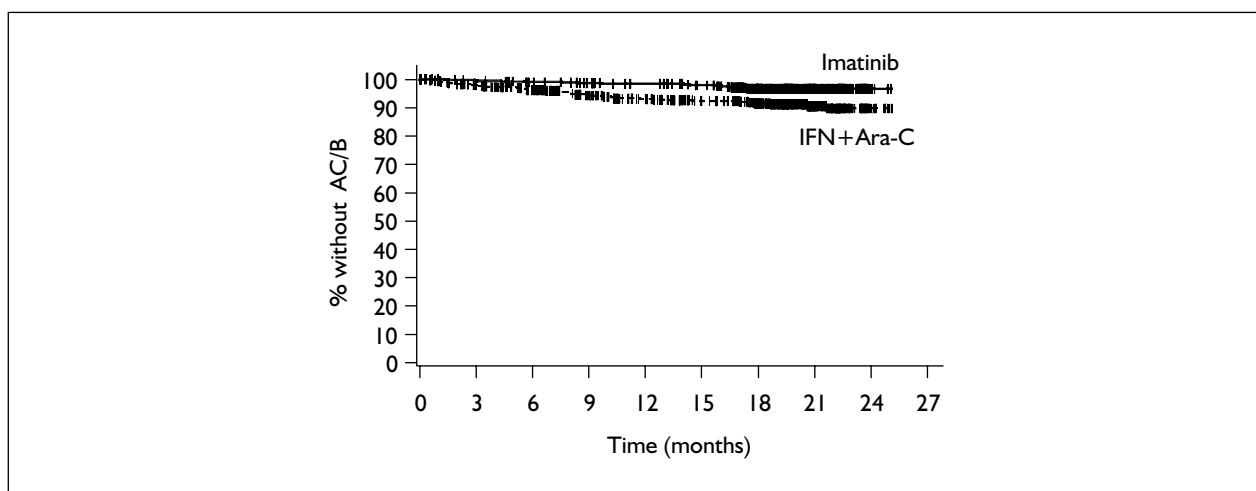


FIGURE 8 Proportion of patients not progressing to the accelerated or blast phase with imatinib compared with IFN- α plus Ara-C. (Source: data derived from O'Brien S, University of Newcastle: personal communication.)

patients treated with imatinib did not experience progression as defined above compared with those receiving IFN- α plus Ara-C ($p < 0.001$).

At the 12-month follow-up, the Kaplan–Meier estimated proportion of patients who had not progressed to the accelerated or blast phase was 98.5% with imatinib (based on eight events) and 93.1% with IFN- α plus Ara-C (based on 33 events) ($p < 0.001$) (Figure 8).

Quality of life

All patients included in the study were assessed for quality of life except for Danish participants and Flemish-speaking patients in Belgium. A total of 1067 people was included. Quality of life was assessed in included patients at baseline, monthly

for 6 months, then at the end of 9, 12, 18 and 24 months. Quality of life assessment also occurred when a patient crossed over to the other treatment. The following instruments were used to assess quality of life: Functional Assessment of Cancer Therapy–Biological Response Modifier (FACT-BRM), Global Rating of Change (GRC) scale and the European Quality of Life instrument (EQ-5D). The primary quality of life outcome was the Trial Outcome Index, which was derived from the FACT-BRM, using three of the latter's four domains: physical well-being, functional well-being and the treatment subscale, which assesses the impact of agents on physical and emotional/cognitive functioning. The FACT-BRM categories of social and emotional well-being were omitted from the Trial Outcome Index.

TABLE 12 Quality of life results for the Trial Outcome Index

Time of assessment	Imatinib (n = 533)	IFN- α + Ara-C (n = 534)	p-Value
Baseline	83.6 \pm 10.5	81.4 \pm 1.1	<0.068
Month 1	84.2 \pm 1.1	64.6 \pm 1.1	<0.0001
Month 2	85.4 \pm 1.0	63.6 \pm 1.0	<0.0001
Month 3	86.4 \pm 1.0	66.1 \pm 1.2	<0.0001
Month 4	86.9 \pm 1.1	67.6 \pm 1.2	<0.0001
Month 5	86.8 \pm 1.1	68.1 \pm 1.3	<0.0001
Month 6	86.6 \pm 1.2	68.6 \pm 1.4	<0.0001
Month 9	87.0 \pm 1.3	71.8 \pm 1.7	<0.0001
Month 12	87.2 \pm 0.9	78.0 \pm 1.5	<0.0001

Data are shown as mean \pm SE.

A brief assessment of the quality of life evaluation is presented in Appendix 5. Criteria were taken from a systematic review by Clark and colleagues.⁶⁸ Overall, the FACT-BRM appears to be reliable and valid, although only four of the six subscales were used in the Trial Outcome Index. Interpretation is hampered by differential completion rates in the two groups, 80% at 12 months in the imatinib group and 59% in the IFN- α plus Ara-C group. There was also a large number of withdrawals in the IFN- α plus Ara-C arm.

An additional concern is whether patients knew that their rating of quality of life may affect their ability to be able to cross over to the alternative treatment. There is, therefore, a possibility of responder bias, although there is no evidence as to whether or not this occurred. The analysis appears to impute missing values through a pattern mixture technique. Analysis of raw scores reveals a similar pattern to the adjusted scores, although absolute values are slightly higher.

Table 12 summarises the quality of life data from the Trial Outcome Index, analysed on an ITT basis.

The small non-significant difference at baseline favours imatinib. Better quality of life scores were found with imatinib than IFN- α plus Ara-C at each subsequent assessment point. Quality of life scores increased with time in both study groups. The difference between the two groups was greatest at month 2, and least at month 12. The increase in the IFN- α plus Ara-C group may be partly accounted for by cross-over to imatinib.

The GRC scale was used to validate (as a supplementary measure) the Trial Outcome Index on a subset of 200 people in the USA. Results are shown in Table 13. Note that not all patients completed each assessment.

From baseline to month 1 of treatment the IFN- α plus Ara-C patients mostly reported being the same or worse, whereas the imatinib patients mostly reported being the same or better. By month 5–6 equivalent numbers of people in each group reported feeling better; however, a proportion of those (32%) in the IFN- α plus Ara-C group had crossed over to imatinib by then.

Adverse effects

Adverse events were reported for the study population who received at least one dose of study medication (imatinib $n = 551$ and IFN- α plus Ara-C $n = 533$). First, the most frequently reported adverse events classified by organ system class are shown (Table 14). Only adverse events that affected more than 15% of either treatment group are included. Total percentages are presented along with the proportion of people experiencing grade 3 and 4 adverse events.

Both treatments were associated with high numbers of adverse events, with nearly all patients experiencing an event within the trial period. In general, IFN- α plus Ara-C was associated with more adverse events and with more serious adverse events. The most common adverse events associated with imatinib treatment were gastrointestinal, musculoskeletal and skin events. For IFN- α plus Ara-C the most common adverse events were general, gastrointestinal and musculoskeletal events.

Table 15 summarises adverse events in more detail, according to their preferred term. All adverse events are reported that affected more than 10% of either group. Total percentages are presented along with the numbers experiencing grade 3 and 4 events.

It can be seen that imatinib and IFN- α plus Ara-C have different side-effect profiles. Imatinib is

TABLE 13 GRC scale scores (ITT analysis)

Baseline to month 1	Imatinib	IFN- α + Ara-C
Number of patients	84	90
A lot better	15 (18)	4 (4)
Somewhat better	22 (26)	7 (8)
About the same	38 (45)	27 (30)
Somewhat worse	9 (11)	34 (38)
A lot worse	0	18 (20)
Month 2 to month 3		
Number of patients	94	100
A lot better	19 (20)	11 (11)
Somewhat better	23 (24)	11 (11)
About the same	48 (51)	49 (49)
Somewhat worse	4 (4)	25 (25)
A lot worse	0	4 (4)
Month 5 to month 6		
Number of patients	94	82
A lot better	11 (12)	14 (17)
Somewhat better	20 (21)	16 (20)
About the same	52 (55)	40 (49)
Somewhat worse	10 (11)	10 (12)
A lot worse	1 (1)	2 (2)

Data are shown as *n* (%).

TABLE 14 Most frequently reported adverse events by organ system (affecting more than 15% of people)

Organ system class	All grades		Grades 3/4	
	Imatinib (%)	IFN- α + Ara-C (%)	Imatinib (%)	IFN- α + Ara-C (%)
Eye disorders	30.1	21.2	1.3	2.4
Gastrointestinal disorders	73.3	82.6	6.0	14.8
General disorders	59.3	91.9	3.3	35.3
Infections and infestations	55.2	46.3	3.6	5.1
Investigations	24.7	34.1	4.4	6.6
Metabolic and nutritional disorders	18.0	45.2	1.6	3.8
Musculoskeletal disorders	71.0	74.9	6.5	17.8
Nervous system disorders	46.3	68.7	3.4	16.5
Psychiatric disorders	25.2	57.8	0.9	17.3
Respiratory/thoracic disorders	40.5	49.7	2.0	4.9
Skin and subcutaneous disorders	60.8	63.2	2.9	3.9
Vascular disorders	11.3	17.3	1.8	2.6
Any event	98.0	99.6	41.0	75.0

associated with more of the following kinds of adverse events than IFN- α plus Ara-C: muscle cramps, periorbital oedema, rash, nasopharyngitis, oedema peripheral, dyspepsia, pharyngolaryngeal pain, upper respiratory tract infection and weight increase. However, all the other adverse effects are more common with IFN- α plus Ara-C. Note that IFN- α alone has fewer adverse effects than the combination with Ara-C.

Dose changes, for whatever reason, occurred at different rates in each group, with 87% of the

IFN- α plus Ara-C group having their initial dose changed compared with 45% of the imatinib group. There were six deaths thought to be unrelated to CML in the imatinib arm and seven in the IFN- α plus Ara-C arm. In addition, several independent case reports have recently been published on the side-effects of imatinib for CML. A summary of these studies is presented in *Table 16*.

In total, 37 people were affected. Of these 37 reports of adverse events, 25 (68%) were for

TABLE 15 Adverse events according to preferred terms affecting at least 10% of people

Adverse events	All grades		Grades 3/4	
	Imatinib (%)	IFN- α + Ara-C (%)	Imatinib (%)	IFN- α + Ara-C (%)
Nausea	42.5	60.8	0.4	5.1
Muscle cramps	33.4	8.6	0.7	0.2
Fatigue	30.7	64.7	1.1	24.0
Diarrhoea	30.3	40.9	1.3	3.2
Headache	28.5	41.8	0.4	3.2
Arthralgia	26.3	38.3	2.2	6.8
Periorbital oedema	25.8	1.1	0.2	0
Myalgia	20.7	38.5	1.5	7.7
Rash	19.8	14.4	1.3	1.1
Nasopharyngitis	19.2	7.7	0	0.2
Oedema peripheral	15.8	3.9	0.2	0
Dyspepsia	15.1	9.0	0	0.8
Pain in limb	14.7	15.0	1.1	2.6
Vomiting	14.7	26.6	0.9	3.4
Back pain	14.5	18.6	0.9	2.4
Pharyngolaryngeal pain	14.2	11.4	0.2	0
Dizziness	13.2	23.1	0.5	3.4
Cough	12.5	21.6	0.2	0.6
Upper respiratory tract infection	12.5	7.9	0.2	0.4
Pyrexia	11.8	38.6	0.5	2.8
Weight increase	11.6	1.5	0.7	0.2
Insomnia	11.4	18.4	0	2.3
Abdominal pain	10.3	10.3	1.1	1.9
Abdominal pain upper	9.6	12.2	0.5	1.5
Depression	8.9	34.7	0.5	12.4
Bone pain	8.0	14.6	0.9	3.0
Constipation	7.6	13.9	0.7	0.2
Rigors	6.9	33.8	0	0.8
Anxiety	6.5	10.9	0.2	2.6
Dyspnoea	6.5	14.4	1.3	1.7
Pruritus	6.5	11.3	0.2	0.2
Influenza-like illness	6.4	18.4	0	1.1
Night sweats	6.4	15.0	0.2	0.4
Anorexia	4.7	31.3	0	2.4
Sweating increase	3.3	14.4	0	0.4
Alopecia	2.2	14.6	0	0.2
Weight decrease	2.2	16.9	0	1.1
Asthenia	1.6	10.9	0	1.9
Dry mouth	1.6	10.3	0	0.2
Mucosal inflammation	0.7	10.1	0	3.2

adverse events that were listed as some of the most commonly reported in *Table 16*. These reports confirm oedema and skin reactions as serious potential adverse events associated with imatinib.

Research in progress

The search strategy identified three studies that are currently in progress (*Table 17*). These will help to fill gaps in the current evidence base for imatinib and to resolve some of the current uncertainties. No trials comparing imatinib with BMT are yet in progress.

IFN- α versus hydroxyurea

Quality of studies

The four included studies were all RCTs. They each compared treatment with IFN- α versus hydroxyurea and enrolled between 58 and 326 people. The median age of participants ranged from 47 to 59 years and the longest period of follow-up was a median of 112 months.

The quality of the four included RCTs is detailed in Appendix 7. Overall, the studies were of reasonable

TABLE 16 Summary of literature on side-effects of imatinib

Study	Study design	Type of side-effect	Number of people reported with side-effect
Etienne <i>et al.</i> , 2002 ⁶⁹	Case series (n = 133)	Repigmentation of grey hair	9/133 (occurring after median of 5 months of treatment)
Drummond <i>et al.</i> , 2002 ⁷⁰	Case series (n = 82)	Rashes <i>Patient number</i> 1, eczematous eruptions, grade 2 2, eczematous eruptions, grade 2 3, eczematous eruptions, grade 2 4, eczematous eruptions, grade 2 5, eczematous eruptions, grade 2 6, eczematous rash on face and limbs then on rechallenge generalised exfoliate dermatitis 7, biopsy-proven small vessel skin vasculitis 8, erythema nodosum	8/82 (10%) <i>Patient number</i> 1, rash resolved, continued imatinib 2, rash resolved, continued imatinib 3, antihistamine treatment 4, steroid cream treatment 5, oral prednisolone (8 weeks) 6, discontinued imatinib 7, oral prednisolone (4 months) 8, oral prednisolone plus azathioprine, discontinued imatinib
Milojkovic <i>et al.</i> , 2002 ⁷¹	Case series (n = 41)	Grade I-IV dermatosis (including one case of severe dose-limiting erythroderma)	11/41
Ebnoether <i>et al.</i> , 2002 ⁷²	Case reports (n = 2, 61-year-old female and 68-year-old male)	Massive cerebral oedema	2
Barton <i>et al.</i> , 2002 ⁷³	Case report (51-year-old male)	Cardiac tamponade, oedema, weight gain, effusions and ascites	1
Vidal <i>et al.</i> , 2002 ⁷⁴	Case report (58-year-old male)	Imatinib-induced Stevens-Johnson syndrome (severe allergic reaction)	1
Lim and Muir, 2002 ^{75,76}	Case report	Erosive oral lichenoid reaction to imatinib	1
Esmaeli <i>et al.</i> , 2002 ⁷⁷	Case report (63-year-old male)	Severe periorbital oedema	1
Konstantopoulos <i>et al.</i> , 2002 ⁷⁸	Case report (42-year-old female)	Pityriasis rosea skin eruptions	1
Brouard and Saurat, 2001 ⁷⁹	Case report	Severe adverse cutaneous reaction (acute generalised exanthematous pustulosis)	1
Ohyashiki <i>et al.</i> , 2002 ⁸⁰	Case report (56-year-old female)	Focal necrosis resembling acute viral hepatitis	1

quality. The main potential sources of bias were lack of blinding and allocation concealment.

Study and patient characteristics

The four included studies were published between 1991 and 1998. They enrolled a total of 902 patients. Studies were conducted in France, Germany, Italy and Belgium/The Netherlands/Luxembourg (Benelux). Median length of follow-up was 51 months in the Benelux study (1998)⁵ and 112 months in the Italian study (1998).²¹ Length of follow-up was not stated in the Broustet trial (1991)⁶ and was 3 years after the last patient

was randomised in the study by Hehlmann and colleagues (1994).⁸¹ Patient characteristics and treatment details are presented in more detail in Appendix 7.

Compared with patients in the Novartis study 0106⁶³ (imatinib versus IFN- α plus Ara-C), the patients in these trials appear to have slightly more severe disease.

Study results

Median 1-year survival across the four studies was 96% (range 95–98%) for IFN- α and 96% (range

TABLE 17 Studies of imatinib in progress as at March 2003

Study/question	Lead investigator(s)	Organisation	Expected completion date	Study design	Patients	Methodology
Multicentre Phase I/II study to determine the safety, tolerability and efficacy of PEG IFN (PEG Intron) in combination with STI-571 (imatinib) in patients with chronic phase CML (PISCES)	S O'Brien	Royal Victoria Infirmary, Newcastle upon Tyne, UK	2003	Case series	Chronic phase CML, aged 2–18 years	Study will follow a dose escalation schedule to define the maximum tolerated dose of both PEG IFN and imatinib. Safety and survival will be collected for 2 years
Phase I pilot, open-labelled, single-centre multiple ascending dose study to evaluate the pharmacokinetics and safety of administration of STI-571 in patients with haematological malignancies undergoing allogeneic SCT	R Powles	The Royal Marsden NHS Trust, Surrey, UK	1 March 2001	Case series	Patients with haematological malignancies undergoing allogeneic SCT	Dose finding study
STI-571 Prospective International Randomized Trial (SPIRIT)	B Druker, F Guilhot, S O'Brien	Portland, Oregon, USA; Poitiers, France; Newcastle upon Tyne, UK (multicentre)	Not stated; study still awaiting funding in the UK	Phase III, multicentre, open-label, prospective randomized trial	Patients must be newly diagnosed with CML (<3 months) and have been treated with only hydroxyurea and/or anagrelide	Study compares imatinib alone at 400 vs 600 mg vs imatinib + Ara-C vs imatinib + IFN- α in patients with chronic phase CML

TABLE 18 Main results from IFN- α versus hydroxyurea trials

	Benelux, 1998 ⁵		Broustet et al., 1991 ⁶		Hehlmann et al., 1994 ⁸¹		Italian Cooperative, 1998 ²¹		Median (range) overall	
	IFN- α	HU	IFN- α	HU	IFN- α	HU/BU	IFN- α	HU	IFN- α	HU
Median survival	61 months	66 months	–	–	66 months	56.2 months	76 months (95% CI 69 to 86)	52 months (95% CI 43 to 66)	66	56.2
1-year survival (%)	98	97	–	–	95	96	96	96	96 (95–98)	96 (96–97)
Complete HR (%)	62	42	–	–	–	–	31	39	47 (31–62)	41 (39–42)
Partial HR (%)	–	–	67	88	–	–	52	51	60 (52–67)	70 (51–88)
Major HR (%)	–	–	–	–	0	0	83	90	42 (0–83)	45 (0–90)
Complete CR (%)	9	0	7	0	4	0	5	1	6 (4–9)	0 (0–1)
Partial CR (%)	7	2	46	31	2	1	2	1	5 (2–46)	2 (1–31)
Major CR (%)	16	2	53	31	6	1	7	2	12 (6–53)	2 (1–31)
Withdrawal due to side-effects	24	4	25	4	18	–	24	1	24 (18–25)	4 (1–4)

BU, busulfan; HU, hydroxyurea.

96–97%) for hydroxyurea (Table 18). The median percentage of patients having a complete HR was 47% (range 31–62%) for IFN- α and 41% (range 39–42%) for hydroxyurea. Median complete CR was 6% (range 4–9%) for IFN- α and 0 (range 0–1%) for hydroxyurea. The median percentage of people withdrawing owing to side-effects was 24% (range 18–25%) for IFN- α and 4% (1–4%) for hydroxyurea.

Results are discussed in more detail and survival curves are presented in Appendix 7.

Adverse effects

In general, more adverse effects were reported for IFN- α than for hydroxyurea treatment. The only adverse effects reported for hydroxyurea were fatigue/fever/pain/headache, renal including vasculitis, drug eruption and general intolerance. A wider variety of adverse effects was reported for IFN- α , with the most common including fatigue/fever/pain/headache, neurological, psychiatric, anorexia/nausea/diarrhoea and thyroid insufficiency (see Appendix 7).

Median withdrawal due to side-effects across the four studies was 24% (range 18–25%) for IFN- α and 4% (range 1–4%) for hydroxyurea. For IFN- α this is a slightly lower percentage than those who withdrew or crossed over for intolerance (29%) in Novartis study 0106.⁶³

IFN- α versus BMT

Quality of studies

The five included studies all compared BMT with IFN- α , although none was randomised. They enrolled between 89 and 840 people. The median age of participants ranged from 31 to 35 years in the BMT groups and from 41 to 54 in the IFN- α groups. The longest period of follow-up for the IFN- α groups was a median of 78 months (median length of follow-up not stated for the BMT groups).

The quality of the included studies is detailed in Appendix 8. Overall, the studies were of variable quality, with the main potential biases being lack of randomisation, groups dissimilar at baseline, lack of blinding and potential lack of study power.

TABLE 19 Main results from BMT versus IFN- α studies

	Gaziev et al., 2002 ¹⁰		Ohnishi et al., 2001 ¹²		Ohnishi et al., 2000 ¹¹		Italian Cooperative, 1999 ⁸²		Gale et al., 1998 ⁹	
	BMT	IFN- α	BMT	IFN- α	BMT	IFN- α	BMT	IFN- α	BMT	IFN- α
Median survival	Not reached	7 years			Related donor: not reached in 6 years; unrelated donor: approx. 4.4 years	Not reached in 6 years	Not reached in 10 years	HU/BU: 4.5 years; IFN- α : 6 years	Not reached in 8 years	Approx. 5.2 years (adjusted)
1-year survival rate (%)									84% (adjusted)	96% (adjusted)
5-year survival rate (%)			Predicted: related donors: 72%; unrelated donors: 67%	Predicted 79%	Predicted: related donor: 93.3%; unrelated donor: 21.9%	Approx. 61%	Approx. 65%	HU/BU: approx. 45%; IFN- α : approx. 58%		
10-year survival rate (%)	56% (95% CI 47 to 68%)	33% (95% CI 16 to 54%)					55% (95% CI 45 to 65%)	32% (95% CI 26 to 39%)		
Other survival rate (%)					Predicted 6-year 93.3%	Predicted 6-year 54.5%			7-year 58% (95% CI 50 to 65%)	7-year 32% (95% CI 22 to 41%)
Time at which group had survival advantage	After 4 years	Before 4 years					Versus chemotherapy after approx. 3 years; versus IFN- α after approx. 5 years	HU/BU: before 3 years; IFN- α : before 5 years	After 5.5 years	Before 2.5 years

TABLE 20 Adverse events reported with BMT

Complications	Italian Cooperative 1999 ⁸²	Ohnishi et al., 2000 ¹¹	Gaziev et al., 2002 ¹⁰
	BMT	BMT	BMT
Death due to transplant related complications	43/120 (36%)	–	47/105 (45%)
Death due to GVHD	–	Related donors: 1/15 (7%); Unrelated donors: 3/8 (38%)	–
Death due to thrombocytopenic purpura	–	Unrelated donors: 1/8 (13%)	–
Rejection or graft failure	–	–	0
GVHD ^a (grade II–IV)	–	–	38/100 (38%)
GVHD ^a (grade III–IV)	–	–	23/100 (23%)
Fungal infections	–	–	33/100 (33%)
<i>Candida</i> species infections	–	–	24/100 (24%)
Cytomegalovirus infection	–	–	13/100 (13%)
Relapse	15/120 (13%)	–	16/105 (15%)

^a GVHD is a complication of BMT where there is a reaction of donated bone marrow against a patient's own tissue. It can be fatal and is due to the donor's immune cells recognising the host cells as foreign.

Study and patient characteristics

The five included studies were published between 1998 and 2002. Two studies^{11,12} enrolled patients prospectively and concurrently. The other three studies appear to be retrospective comparisons of patients based on available databases.^{9,10,82} Two studies were conducted in Italy and two in Japan, and the final study was multicentre and international. Length of follow-up was not stated in the Italian Cooperative Study,⁸² and was only stated for the IFN- α group in the studies by Ohnishi (2000 and 2001)^{11,12} and Gaziev and colleagues.¹⁰ These three studies reported follow-up lengths for IFN- α of 54 months (range 30–76 months), 38 months (range 9–66 months) and 46.8 months (range 12–144 months), respectively. Gale and colleagues⁹ reported average follow-up of 51.6 months for the BMT group and 78 months for the IFN- α group.

Patient characteristics are summarised in Appendix 8. The median age in the IFN- α treatment arms ranged from 41 to 54, compared with 31 to 36 for the BMT treatment arms. In four of the five included studies, patients receiving drug therapy were newly diagnosed, whereas patients receiving BMT did so on average 9–29 months after registration in the trial. This is likely to bias against BMT in the survival analyses.

Treatment details are summarised in Appendix 8. The type of BMT varied between studies and included HLA-identical sibling donors, identical twins, HLA-identical relatives and HLA-matched unrelated donors.

Study results

Four out of the five studies showed a long-term survival advantage for BMT compared with IFN- α , but a short-term (0–4 years approximately) disadvantage (*Table 19*). Median survival had not yet been reached in four studies and was not reported in the other study.

Adverse effects

None of the included studies reported side-effects for the IFN- α treatment arms. Three of the five included studies reported complications arising from BMT (*Table 20*). Complications included GVHD (up to 38%), death due to complications (up to 45%) and infections (up to 33%).

Research in progress

The search strategy identified two studies comparing BMT and IFN- α that are currently in progress (see Appendix 8). It is reported that these trials have been halted because of poor recruitment subsequent to the advent of imatinib (Apperley J, Hammersmith Hospital, London: personal communication).

Indirect comparison of imatinib versus hydroxyurea

Imatinib was more effective than IFN- α plus Ara-C in terms of surrogate outcomes (HR and CR) and PFS. IFN- α was superior to hydroxyurea in terms of overall survival and CR (see Study results, p. 27). It is therefore likely that in a similar group of patients imatinib will be more effective than hydroxyurea for first-line treatment of patients with chronic phase CML.

TABLE 21 Comparison of main results for hydroxyurea and imatinib

	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1994 ⁸¹	Italian Cooperative, 1998 ²¹	Median from HU studies (range)	Imatinib (Novartis study 0106) ⁶³
	HU	HU	HU/BU	HU	HU	Imatinib
Median survival (months)	66	–	56.2	52	56.2	NA
% 1-year survival	97	–	96	96	96 (96–97)	98.0
% complete HR	42	–	–	39	41 (39–42)	94.6 (95% CI 92.3–96.3)
% partial HR	–	88	–	51	70 (51–88)	
% major HR	–	–	0	90	45 (0–90)	
% complete CR	0	0	0	1	0 (0–1)	67.8
% partial CR	2	31	1	1	2 (1–31)	14.8
% major CR	2	31	1	2	2 (1–31)	82.6 (95% CI 79.2–85.7)
% withdrawal due to side-effects	4	4	–	1	4 (1–4)	2.0

TABLE 22 Reported adverse events associated with hydroxyurea

Adverse effect	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1991 ⁸¹	Italian Cooperative, 1998 ²¹
	HU	HU	HU	HU
Fatigue, fever, pain, headache	2.1	–	0.5	–
Renal including vasculitis	1.1	–	–	–
Drug eruption	1.1	–	–	–
General intolerance	–	11.5	–	–

Table 21 shows that imatinib is associated with much higher rates of CR and HR than hydroxyurea. Survival with imatinib is slightly higher and withdrawal due to adverse events is similar compared with hydroxyurea. Such a comparison must be made with caution and assumes that patient groups are comparable, which may not be the case.

The reviewers are unable to comment on the relative efficacy in subgroups of higher risk patients, older patients or those with co-morbidity, owing to the lack of appropriate data for comparisons.

Hydroxyurea is generally considered to be well tolerated. Table 22 shows reported rates of adverse effects with hydroxyurea. This may be compared with 41% of patients taking imatinib suffering a grade 3 or 4 event at some time (Table 14), but only 2% discontinuing treatment because of adverse effects. It is, however, possible that the severity of events differs and that reporting for imatinib has been more vigilant.

Indirect comparison of imatinib versus BMT

When considering short-term follow-up, imatinib has better outcomes (PFS) than IFN- α plus Ara-C, whereas IFN- α has better survival than BMT. By inference it therefore seems that imatinib is likely to be associated with better survival than BMT in approximately the first 4 years. It is not possible to comment on the longer term relative survival of the two treatments because of the lack of longer term imatinib data.

It is reasonable to assume that treatment with imatinib (Tables 14–16) will be associated with fewer adverse events in the short term than BMT (Table 20). The spectrum of events is also likely to be very different. Once again, caution needs to be applied when making such comparisons, as populations may not be similar.

Chapter 5

Results of economic analyses

Results of systematic review of existing economic literature

Only one published abstract of an economic evaluation of imatinib was identified, along with three published economic evaluations of IFN- α , and two published evaluations of BMT. The abstract on imatinib is briefly described and assessed and economic studies of IFN- α and BMT in the treatment of CML are briefly evaluated. These IFN- α and BMT evaluations have been considered for comparative purposes, to assist judgements about the validity and robustness of the economic evaluations for imatinib.

The imatinib abstract outlines a Markov cost-utility analysis of imatinib compared with hydroxyurea in the chronic phase, and combination chemotherapy or palliative care in the accelerated and blast phases.

Two published studies present decision analyses and Markov models comparing the cost-effectiveness of IFN- α with hydroxyurea.⁸³ One study performed an economic analysis of IFN- α usage in CML using a Gompertz function to model survival.⁸⁴

One BMT evaluation is a study of the costs and cost-effectiveness of unrelated donor transplantation for chronic phase CML and the other is a Markov model decision analysis comparing early, delayed and no transplantation for people with chronic phase CML.

It should be noted that across the identified economic studies there is likely to be wide variation in health systems, which will affect costs and results. Results are presented as they are reported. Caution is necessary when applying results to another setting as they may not be transferable.

Markov models

A Markov model is a type of mathematical model containing a finite number of mutually exclusive and exhaustive health states, having periods of uniform length, and in which the probability of movement from one state to another depends on

the current state.⁸⁵ The transition probabilities are applied to each cycle of the model, the cycle being of fixed duration, and are the probability of moving from one state to another.

Markov models allow for the synthesis of data on costs, effects and health-related quality of life, of alternative clinical strategies through the calculation of life expectancy, quality-adjusted life expectancy and lifetime costs, by tracking a simulated hypothetical cohort through the model.⁵⁹

One of the main limitations of Markov models is the underlying assumption often referred to as 'zero memory'. Transition probabilities depend only on current health state and not on past health states.⁸⁶ Another limitation is the assumption that all people in a particular health state are identical. The assumptions are unlikely to be met in practice, but it is difficult to determine the impact of this on overall results.⁵⁹

Economic analysis of imatinib (abstract only)

*Warren and colleagues (2002)*⁸⁷

The aim of this evaluation was to summarise the clinical evidence and perform an economic evaluation of imatinib for the chronic, accelerated and blast phases of CML. A Markov model was developed and showed the progression of a cohort of CML patients receiving imatinib or the comparative treatments (hydroxyurea in the chronic phase and combination chemotherapy or palliative care in the accelerated and blast phases).

Clinical data on HR and CR and disease progression were obtained from three studies (references not provided). The abstract does not provide the utility values or describe how they were obtained.

The incremental cost-effectiveness of imatinib over hydroxyurea in chronic phase was £35,002 per QALY, that of imatinib compared with combination chemotherapy or palliative care in accelerated phase was £21,826 per QALY, and in the blast phase £43,467 per QALY. The year of costs was not stated but the abstract was presented in 2002.

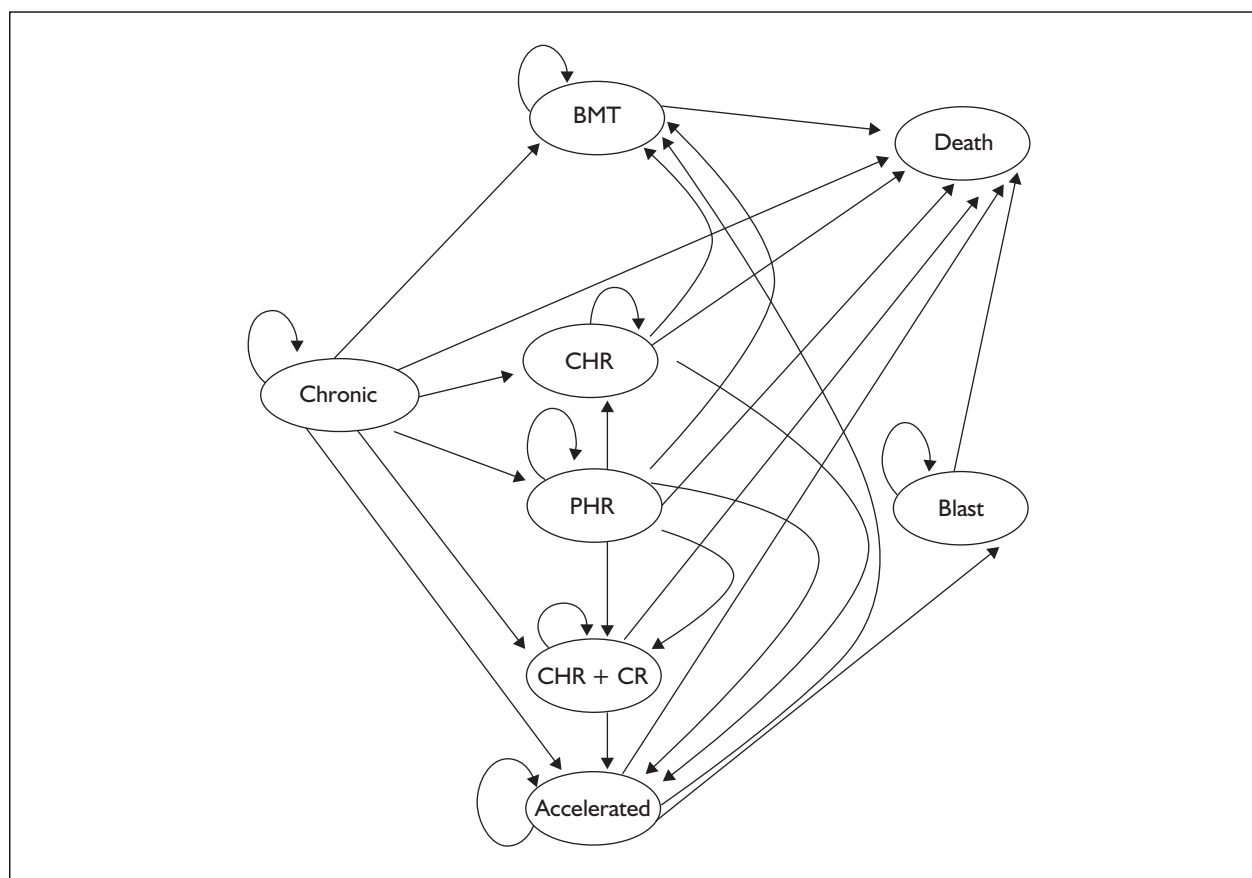


FIGURE 9 Influence diagram showing transitions between health states in the Markov model used by Kattan and colleagues⁸⁸

The abstract did not provide details of sensitivity analysis. The authors concluded, “there is strong evidence to suggest that Glivec is associated with high rates of response resulting in comparatively high long-term survival rates and an acceptable cost per QALY ratio”. Given the lack of long-term survival data this conclusion does not appear warranted.

Economic analysis of IFN- α Kattan and colleagues (1996)⁸⁸

The aim of this evaluation was to compare the cost-effectiveness of IFN- α and hydroxyurea as first-line therapy for patients with CML. A Markov model was developed containing eight health states [haematological response (HR) + cytogenetic response (CR), complete haematological response without cytogenetic response (CHR), partial haematological response (PHR), chronic phase, accelerated phase, blast phase, BMT and death]. In this model it is possible to progress to death from all other health states (Figure 9).

Clinical data on survival, HR and CR were obtained from studies by Hehlmann and colleagues,⁸¹ The Italian Cooperative Study Group

on CML,⁸⁹ Ozer and colleagues⁹⁰ and Kantarjian and colleagues.⁹¹ Utilities were assessed by a clinical panel, and were 0.9 for patients receiving IFN- α therapy, 1.0 for patients receiving HU therapy and 0.5 for patients in the blast or accelerated phase.

The incremental cost-effectiveness of IFN- α over hydroxyurea was US\$26,500 per life-year saved. When adjusted for quality of life the estimated cost-effectiveness ratio increased to US\$34,800 per QALY. Year of costs was not stated, but the paper was published in 1996.

The cost-effectiveness ratio of IFN- α was dependent on the age of the patient and the monthly cost of IFN- α , with the cost-effectiveness ratio being most favourable in younger patients. The authors concluded that compared with hydroxyurea, IFN- α is, in most clinical scenarios, a cost-effective initial therapy for patients with chronic phase CML who can tolerate the drug.

Liberato and colleagues (1997)⁸³

The purpose of this study was to evaluate the cost-effectiveness of IFN- α compared with conventional

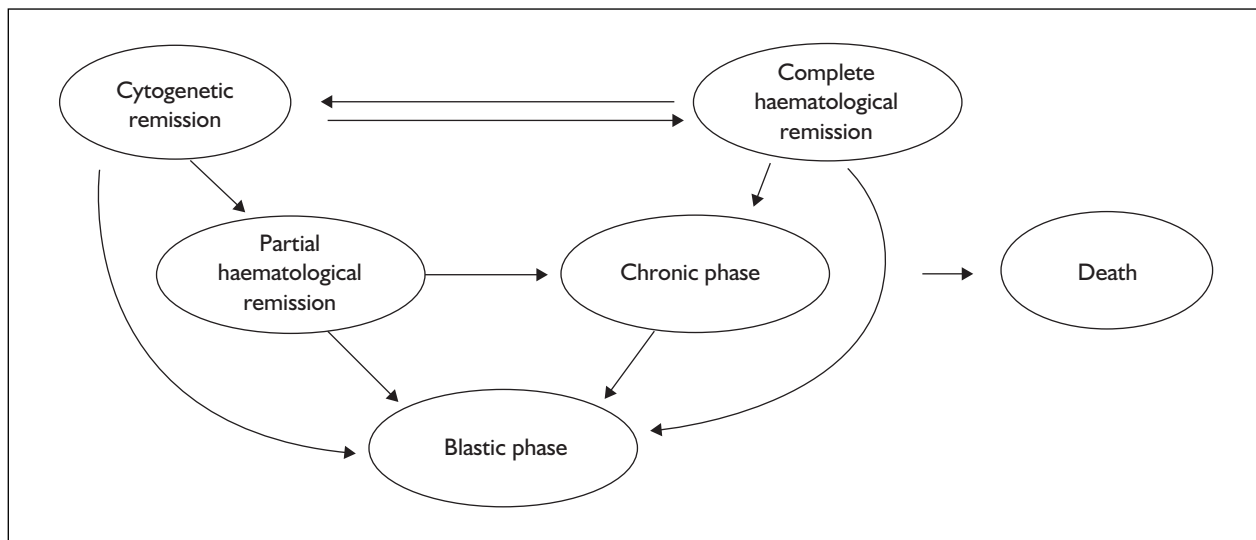


FIGURE 10 Influence diagram showing transitions between health states in the Markov model used by Liberato and colleagues⁸³

chemotherapy in patients with CML. A decision analysis was designed which incorporated a Markov model to estimate the cost-utility of IFN- α (Figure 10).

It is unclear from the study report whether patients can progress to death from all health states. Two scenarios were modelled:

1. prolonged treatment for patients who achieved a haematological response
2. prolonged treatment only for patients who achieved a cytological remission within 2 years.

Effectiveness data were taken from nine studies, including five RCTs. Interferon treatment increased quality-adjusted life expectancy by 15.5 months (scenario 1) and 12.5 months (scenario 2) relative to conventional chemotherapy. Utilities were estimated by ten physicians and were 0.875 for patients receiving IFN- α therapy, 0.98 for patients on hydroxyurea, 0.94 for patients receiving busulfan and 0.5 for patients in the blast phase. The study reports an ICER of US\$89,500 (scenario 1) and US\$63,500 (scenario 2) per QALY gained. The year in which these costs were based is not stated, but the paper was published in 1997.

The results were sensitive to the cost of IFN- α therapy and the probability of cytogenetic response. The authors conclude that IFN- α is substantially superior to conventional chemotherapy in terms of quality-adjusted survival, but at current doses the ICERs range from US\$50,000 to US\$100,000 per QALY gained.

Messori (1998)⁸⁴

The aim of this evaluation was to assess the cost-effectiveness of IFN- α treatment for CML. The total area under the survival curve for each drug was calculated, using a Gompertz function to extend the observed 1-year survival curve (the Gompertz function is frequently used to estimate survival curves.) No adjustment for the quality of life-years gained was included.

Four RCTs formed the basis of the effectiveness data. The ICER of IFN- α versus cytotoxic therapy ranged from US\$93,000 to US\$226,000 per discounted life-year gained (with the study published in 1998; no cost year is given).

Conclusions were sensitive to the dose of IFN- α used. When adding in a non-randomised trial with particularly favourable results for IFN- α , the cost-effectiveness ratio ranged from US\$56,022 for a dose of 10 MU per patient per week to \$204,680 for an IFN- α dose of 60 MU per patient per week.

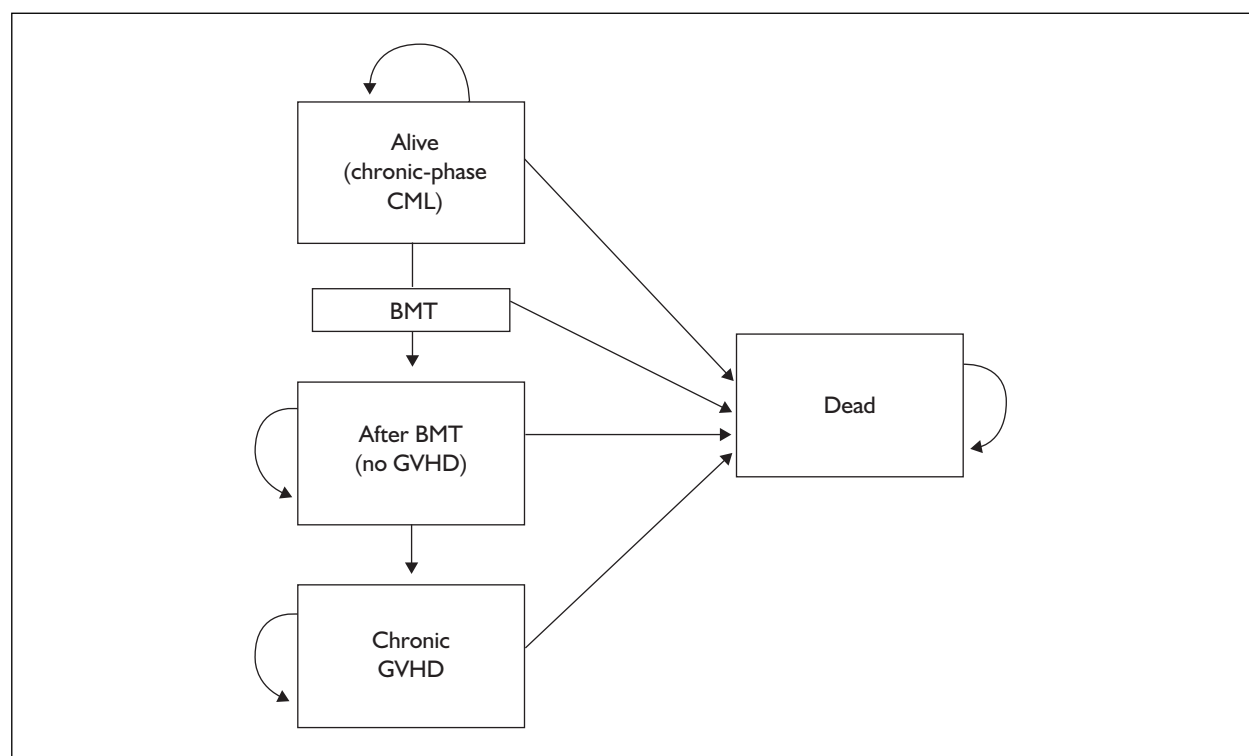
The authors of this evaluation conclude that long-term treatment with IFN- α without careful selection of patients may not be cost-effective.

Table 23 summarises the results of the three cost-effectiveness studies comparing IFN- α with chemotherapy for CML.

There is a wide range of estimates for the cost-effectiveness of IFN- α for CML. There are several reasons for this variation. There are obvious differences in methodology, with the Liberato⁸³ and Kattan⁸⁸ studies using Markov models to

TABLE 23 Summary of cost-effectiveness studies comparing IFN- α and chemotherapy

Study	ICER
Kattan <i>et al.</i> , 1996 ⁸⁸	US\$34,800 per QALY gained
Liberato <i>et al.</i> , 1997 ⁸³	US\$89,500 and US\$63,500 per QALY gained
Messori <i>et al.</i> , 1998 ⁸⁴	US\$93,000 to US\$226,000 per life-year gained

**FIGURE 11** Influence diagram showing transitions between health states in Lee and colleagues⁹⁴

calculate cost per QALY, and the Messori study⁸⁴ using a Gompertz model without quality adjustment of life-years gained. Quality adjustment in the latter is likely to increase further the ICER.

The estimates from the Liberato study⁸³ are similar to the lower estimates of the Messori Study.⁸⁴ The combination of higher survival values and lower costs of IFN- α therapy account for the significantly lower ICERs in the Kattan study than in the studies by Liberato⁸³ and Messori.⁸⁴ Kattan and colleagues⁸⁸ also used slightly higher values of estimated survival gains from IFN- α than the other two studies.^{83,84} Kattan and colleagues⁸⁸ also used lower estimates of cost per patient of IFN- α therapy than the other two studies, as IFN- α therapy is more expensive in Italy than in the USA. Kattan and colleagues⁸⁸ did not include costs such as drug administration, laboratory processing and physician time, in contrast to the Messori study.⁸⁴

Economic analysis of BMT

Lee and colleagues (1997)⁹⁴

The aim of this evaluation was to compare early, delayed and no transplantation for patients with chronic phase CML. A Markov model was constructed that compared different strategies and considers age, quality of life, risk aversion and the competing risks for CML progression and transplant toxicity. The model contains five states (Figure 11).

The life expectancy of patients not receiving transplants was obtained from published studies by Ohnishi,⁹⁵ Allan,⁹⁶ The Italian Cooperative Study Group on CML,⁹⁷ Sokal,⁹⁸ Hehlmann,⁹⁹ Sonnenberg¹⁰⁰ and Hehlmann.⁷ Survival curves were extrapolated by using a function fitted to the clinical data. Outcomes for those who underwent unrelated BMT were obtained from two registries, and inputs for GVHD were obtained from a published study by McGlave and colleagues.¹⁰¹

Utilities were derived using the standard gamble method with 12 physicians and were 0.979 for life without chronic GVHD after transplantation and 0.9 for life with chronic GVHD after transplantation.

The results of the evaluation showed that for newly diagnosed patients with CML transplantation within the first year provides the greatest quality-adjusted expected survival, although this benefit decreases with increasing patient age. The authors give an example of a 35-year-old patient with an intermediate prognostic score. Transplantation within the first year results in 5.3 more discounted QALYs than no transplantation. Results were shown to be reasonably robust in sensitivity analysis.

Lee and colleagues (1998)¹⁰²

The aim of this study was to assess the costs and cost-effectiveness of unrelated donor BMT for chronic phase CML. This study builds on the Markov model described above⁹⁴ by incorporating extensive cost data. It specifically compares BMT within the first year after diagnosis and IFN- α or hydroxyurea.

Effectiveness and utilities were used as described above.⁹⁴ Cost data were obtained from retrospective analysis of two cohorts of patients undergoing BMT at separate hospitals, the Red Book (US national formulary) and hospital accounting systems. The following cost data were obtained for people undergoing BMT: donor identification, pretransplant testing, marrow collection, inpatient and outpatient care costs, and outpatient medication costs. The following costs were obtained for non-transplant management of CML: medication costs, outpatient visits, phlebotomy, blood tests, inpatient costs for induction chemotherapy and hospitalisation for blast crisis.

The ICER of transplantation within 1 year of diagnosis versus non-transplantation in the base case of a 35-year-old patient was US\$51,800 per QALY gained, with sensitivity analysis ratios ranging from US\$50,000 to US\$100,000. All costs were adjusted to 1996 US dollars.

Cost-effectiveness and cost utility of imatinib-independent economic model

Key model parameters

This section describes and tabulates the key inputs used as base-case estimates in the independent economic model. *Table 24* shows the costs that are

used in the model (see Chapter 3, 'Methods for economic analysis', p. 12, for a description of methods).

The numbers of outpatient visits, bone marrow tests, blood transfusions, radiology tests and inpatient visits were modelled in the probabilistic sensitivity analysis by assuming a standard deviation of one-third the number of visits/tests and randomly sampling from a normal distribution.

Table 25 shows the utilities associated with the various health states as used in the independent economic model (see Chapter 3, 'Methods for economic analysis', for a description of methods).

Tables 26 and *27* show the relative risks applied to the independent economic model for survival/progression, response and risk score (see Chapter 3 for a description of methods).

The risk score relative risks were calculated using the Italian Study Group's Sokal data.²¹

In addition, the following assumptions were included in the economic model (see Chapter 3 for a description of methods).

- Overall death rate was modelled from the mortality curve of the Italian trial.²¹ It was assumed that 60% of those in blast crisis were dead in 6 months.
- Complete CR is only possible from the chronic phases within the model.
- It is assumed that 30% of all progression from chronic phase is to accelerated phase and 70% to blast phase (based on data from Novartis study 0106, 2002⁶³).
- Transitions from chronic to CR are only permitted in the first 5 years of the model.
- The numbers of outpatient visits, bone marrow tests, radiology tests, inpatient visits and blood transfusions are the same for a given phase regardless of assigned treatment.
- Admissions to hospital in blast phase are assumed to be for 3 days.
- A CR is not possible for those treated with hydroxyurea.

Table 28 outlines the transitions between health states used in the independent economic model (see Chapter 3 for a description of methods and *Figures 2* and *3* for flowcharts).

Validation of curves

To validate the survival and progression data used in the model, model-derived data were plotted on

TABLE 24 Description of costs and amount per month used in the economic model

Drug/test	Health state	Dose/number per cycle	Cost per month	Source
Imatinib	Chronic and CR	400 mg/day	£1580.72	BNF 44, dose from Novartis study 0106, 2002 ⁶³
Imatinib	Accelerated and loss of CR	600 mg/day	£2371.08	BNF 44
IFN- α	Chronic and CR	5 MU/day	£1109.90	BNF 44, dose from Novartis study 0106, 2002 ⁶³
IFN- α	Accelerated and loss of CR	5 MU/day	£1109.90	BNF 44
Hydroxyurea	Chronic and accelerated	2 g/day	£14.56	BNF 44, dose from Novartis study 0106, 2002 ⁶³
Mercaptopurine	Blast	150 mg/day	£67.05	BNF 44
Outpatient visit	Chronic Accelerated Blast	1 (SD 0.33) 3 (SD 1) 6 (SD 2)	£114.00 (half initial and half follow-up visits)	Clinical estimate, cost from SUHT database 2001/02
Bone marrow test	Chronic Accelerated Blast	0.5 (SD 0.17) 0.5 (SD 0.17) 1 (SD 0.33)	£271.00	Clinical estimate, cost from SUHT database 2002/03
Blood transfusion	Chronic Accelerated Blast	0.25 (SD 0.08) 0 9 (SD 3)	£3243 (composed of 20 units of full blood, 10 units of platelets and 2 hours of nursing time grade D/E)	Clinical estimate, cost from Novartis, study 0106, 2002 ⁶³
Radiology test	Chronic Accelerated Blast	0 0 9 (SD 3)	£54 (one X-ray and one CT scan)	Clinical estimate, cost from SUHT database 2002/03
Inpatient visit	Chronic Accelerated Blast	0 0 3 (SD 1)	£209 per day (each stay is 3 days)	Clinical estimate, cost from SUHT database 2001/02

SD, standard deviation used to sample randomly from a normal distribution for probabilistic sensitivity analysis.

TABLE 25 Utility values associated with health states used in the independent economic model

Health states	Utility values (SD)	Source	Distribution used in probabilistic sensitivity analysis
Chronic phase: imatinib treatment	0.8539 (0.1925)	Novartis study 0106, 2002 ⁶³	Beta
Chronic phase: imatinib treatment after loss of CR	0.8539 (0.1925)	Novartis study 0106, 2002 ⁶³	Beta
Chronic phase: IFN- α treatment	0.7104 (0.2658)	Novartis study 0106, 2002 ⁶³	Beta
Chronic phase: IFN- α treatment after loss of CR	0.7104 (0.2658)	Novartis study 0106, 2002 ⁶³	Beta
Chronic phase: hydroxyurea treatment	0.9 (0.2 ^a)	Kattan <i>et al.</i> , 1996 ⁸⁸	Beta
CR: imatinib treatment	0.8539 (0.1925)	Novartis study 0106, 2002 ⁶³	Beta
CR: IFN- α treatment	0.7104 (0.2658)	Novartis study 0106, 2002 ⁶³	Beta
Accelerated phase: imatinib treatment	0.729 (0.204)	Novartis study 0106, 2002 ⁶³	Beta
Accelerated phase: IFN- α treatment	0.729 (0.204)	Novartis study 0106, 2002 ⁶³	Beta
Accelerated phase: hydroxyurea treatment	0.729 (0.204)	Novartis study 0106, 2002 ⁶³	Beta
Blast phase: mercaptopurine	0.524 (0.424)	Novartis study 0106, 2002 ⁶³	Beta

^a Estimated.

TABLE 26 Relative risks of imatinib and hydroxyurea compared with IFN- α used in the economic model for survival, progression and response

Relative risk	IFN- α ^a	Imatinib (SE)	Source of imatinib estimate	Hydroxyurea (SE)	Source of hydroxyurea estimate	Distribution used in probabilistic sensitivity analysis
Progression	1	0.8347 (0.103)	Modelled from 18-month data from Novartis study 0106, ⁶³ using an exponential distribution	1.26 (0.103)	Benelux, 1998 ⁵	Log-normal
Mortality	1	0.5872 (0.25)	Modelled from 18-month data from Novartis study 0106, ⁶³ using a Weibull distribution	1.19 (0.106)	Benelux, 1998 ⁵	Log-normal
CR	1	3.41 (0.130)	Based on 12-month data from Novartis study 0106, 2002 ⁶³	0	NA	Log-normal

^a Hydroxyurea and imatinib are modelled relative to IFN- α ; therefore, the RRs for IFN- α are equal to 1.

TABLE 27 Relative risks for all treatments according to risk score

Risk score	All treatments	Source of estimate	Distribution used in probabilistic sensitivity analysis
Low versus intermediate	1.197	Hazard ratio calculated from the Italian Sokal study ²⁸	Log-normal
Low versus high	1.280	Hazard ratio calculated from the Italian Sokal study ²⁸	Log-normal

the same graph as original data. Comparisons showed similar curves for progression and survival (Figure 12),²¹ as well as time to loss of CR.²⁵ A more detailed description and figures are presented in Appendix 9.

Results of economic model

Discounted and undiscounted cost-utility estimates (ICERs) are shown in Tables 29 and 30, respectively.

Subgroup cost-utility analysis was also performed and Tables 31 and 32 show the cost per QALY of IFN- α and hydroxyurea compared with imatinib for low-risk and high-risk patients (see Table 27 for values used).

In all scenarios presented in this section imatinib is more costly than IFN- α and hydroxyurea, but also produces more QALYs. The ICER of imatinib compared with IFN- α ranged from £26,180 to £31,761. IFN- α does not appear to be cost-effective compared to hydroxyurea and is

associated with more cost and similar QALYs. This is because the adverse effects have a marked impact on the utility valuation of IFN- α plus Ara-C. For intermediate- and high-risk patients, IFN- α is dominated by hydroxyurea (fewer QALYs and more expensive).

Sensitivity analysis

A probabilistic analysis was undertaken to explore the effects of uncertainty in model parameters on outputs. Results are presented in Table 33, showing the average results obtained from 1000 simulations (for a description of methods see Chapter 3).

The results of each of the simulations are plotted on a cost-effectiveness plane in Figure 13. Costs and QALYs are presented for each of the three treatments (each treatment is represented by a different marker).

The probabilistic analysis also generates a cost-effectiveness acceptability curve. This is a way of relating uncertainty in cost-effectiveness to the

TABLE 28 Transition values and sources used in the independent economic model

Transition	Value	Source
First-line treatment		
Chronic to accelerated	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Chronic to blast	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Chronic to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Accelerated to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Blast to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
CR to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Chronic to CR	Median time to response 18 months (probability 0.0085 per cycle)	Italian Cooperative Study Group, 1998 ²¹
Accelerated to blast	Median time in accelerated phase 18 months (probability 0.109 per cycle)	Kantarjian <i>et al.</i> , 1995 ⁹¹
CR to chronic2 ^a	Time to loss of response curve (cycle dependent)	Bonifazi <i>et al.</i> , 2001 ²⁵
Second-line treatment with IFN-α for those who failed imatinib		
Chronic2 to dead	Survival curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Chronic2 to accelerated	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Chronic2 to blast	% progression curve (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Second-line treatment with imatinib for those who failed IFN-α		
Chronic2 to dead	Survival curve (cycle dependent)	Kantarjian <i>et al.</i> , 2002 ⁶² (for first 5 cycles) Italian Cooperative Study Group, 1998 ²¹ (for cycles 6 onwards)
Chronic2 to accelerated	% progression curve (cycle dependent)	
Chronic2 to blast	% progression curve (cycle dependent)	Kantarjian <i>et al.</i> , 2002 ⁶² (for first 5 cycles) Italian Cooperative Study Group, 1998 ²¹ (for cycles 6 onwards)
Chronic2 to CR	Time to response curve (cycle dependent for first 5 cycles)	Kantarjian <i>et al.</i> , 2002 ⁶² (for first 5 cycles, then the rate from cycle 5 for cycles 6–20, then no response)

^a Chronic2 is a state for those who lost their CR but have not progressed.

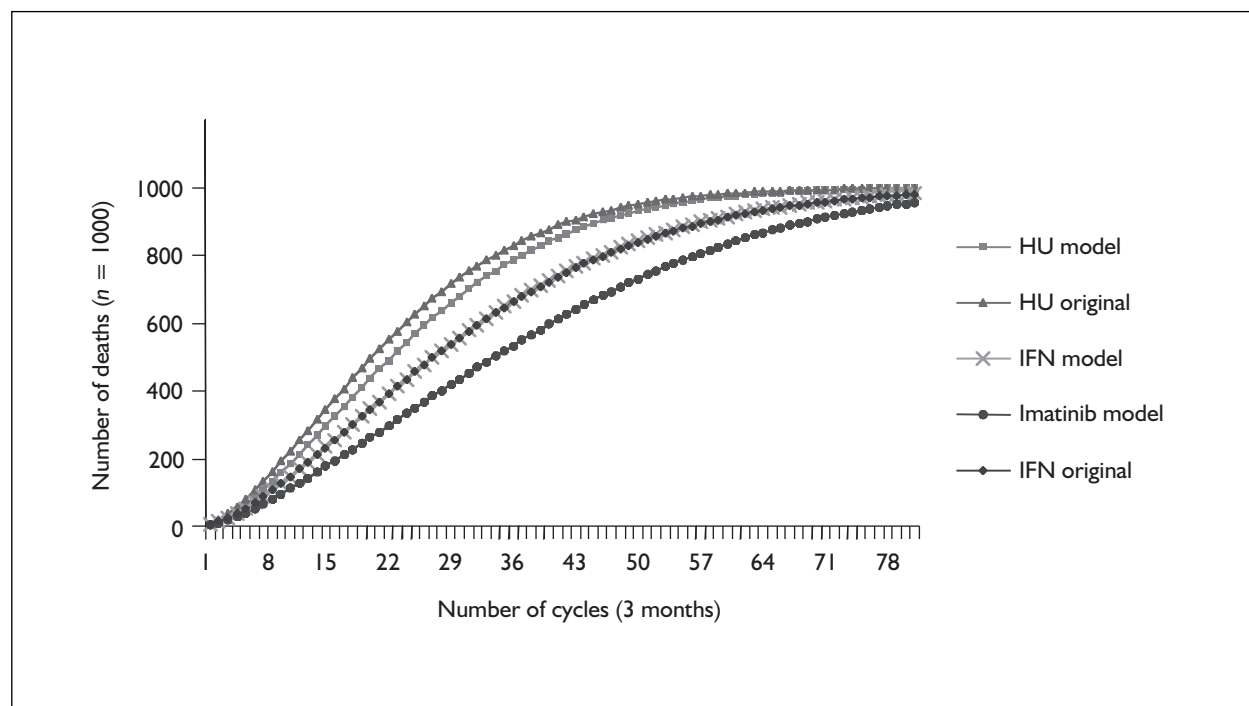


FIGURE 12 Model output data compared with original data from the Italian Cooperative Study²¹

TABLE 29 Discounted cost per QALY of IFN- α and hydroxyurea compared with imatinib

	Cost per person (£)	QALYs per person
Drug		
HU	38,322	4.99
Imatinib	215,684	7.03
IFN- α	163,581	5.04
ICERs		
Imatinib versus HU	86,934	per QALY
IFN- α versus HU	2,505,364	per QALY
Imatinib versus IFN- α	26,180	per QALY

TABLE 30 Undiscounted cost per QALY of IFN- α and hydroxyurea compared to imatinib

	Cost per person (£)	QALYs per person
Drug		
HU	46,591	5.01
Imatinib	235,403	7.25
IFN- α	167,052	5.10
ICERs		
Imatinib versus HU	84,100	per QALY
IFN- α versus HU	1,293,948	per QALY
Imatinib versus IFN- α	31,761	per QALY

TABLE 31 Discounted cost per QALY of IFN- α and hydroxyurea compared with imatinib for intermediate-risk patients

	Cost per person (£)	QALYs per person
Drug		
HU	31,105	4.52
Imatinib	188,525	6.30
IFN- α	135,158	4.50
ICERs		
Imatinib versus HU	88,459	per QALY
IFN- α versus HU	-4,507,569	per QALY
Imatinib versus IFN- α	29,605	per QALY

TABLE 32 Discounted cost per QALY of IFN- α and hydroxyurea compared with imatinib for high-risk patients

	Cost per person (£)	QALYs per person
Drug		
HU	28,777	4.35
Imatinib	179,417	6.04
IFN- α	125,982	4.31
ICERs		
Imatinib versus HU	89,045	per QALY
IFN- α versus HU	-2,120,182	per QALY
Imatinib versus IFN- α	30,753	per QALY

decision-maker's maximum willingness to pay for an additional QALY gained (Figures 14 and 15). The probability that a treatment is cost-effective at a particular maximum willingness to pay value is plotted. The points are joined to form a curve.

The ICER of two therapies is represented by the value at which the appropriate two lines cross. Imatinib and IFN- α cross at around £27,000, and imatinib and hydroxyurea at about £86,000. It may be considered that hydroxyurea is a less

TABLE 33 Discounted cost per QALY of IFN- α and hydroxyurea compared with imatinib from probabilistic analysis

	Cost per person (£)	QALYs per person
Drug		
HU	37,950	4.98
Imatinib	215,927	7.03
IFN- α	162,591	5.06
ICERs:		
Imatinib versus HU	86,901	per QALY
IFN- α versus HU	620,474	per QALY
Imatinib versus IFN- α	27,059	per QALY

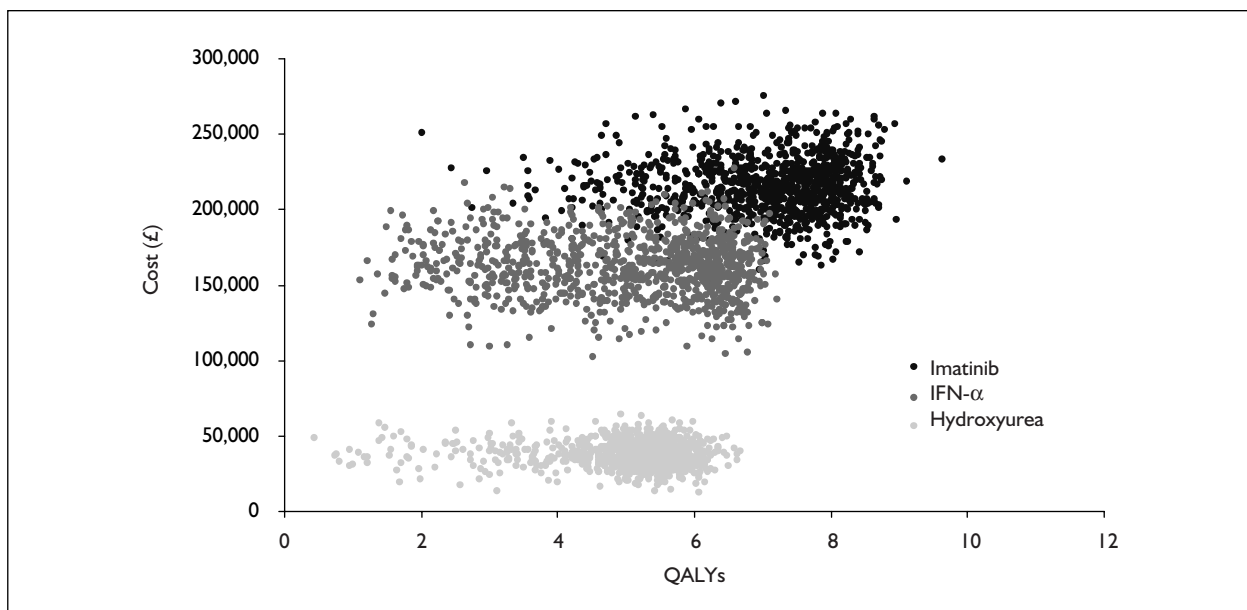


FIGURE 13 Cost-effectiveness plane for the independent probabilistic economic analysis

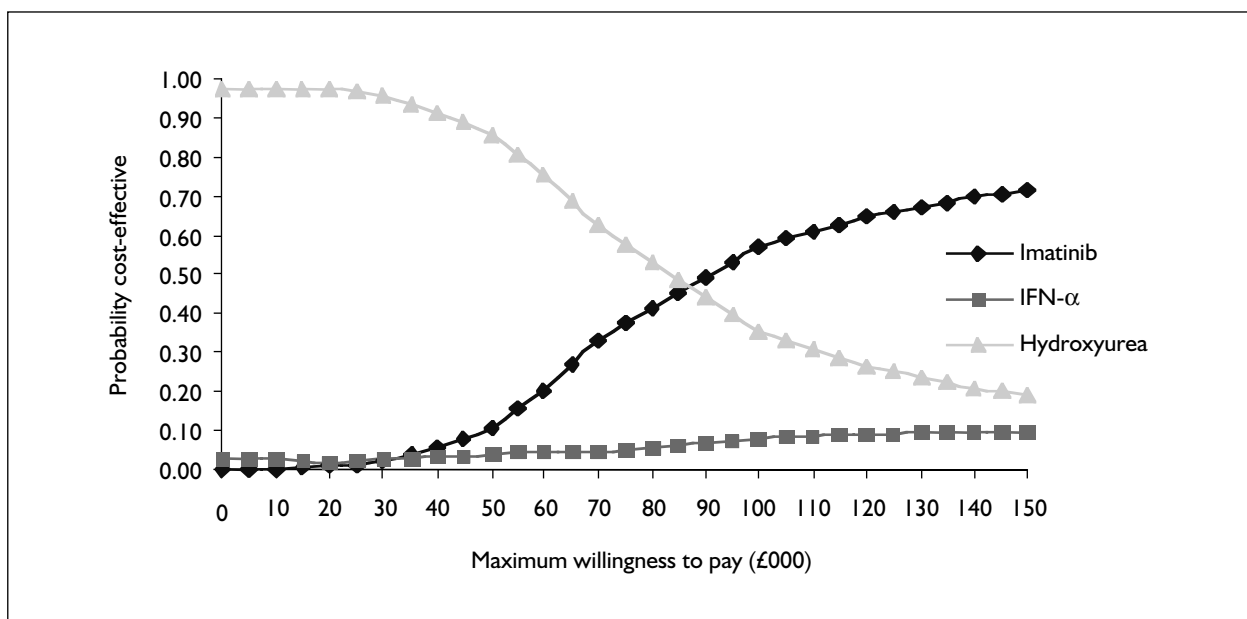


FIGURE 14 Cost-effectiveness acceptability curve for IFN- α , imatinib and hydroxyurea

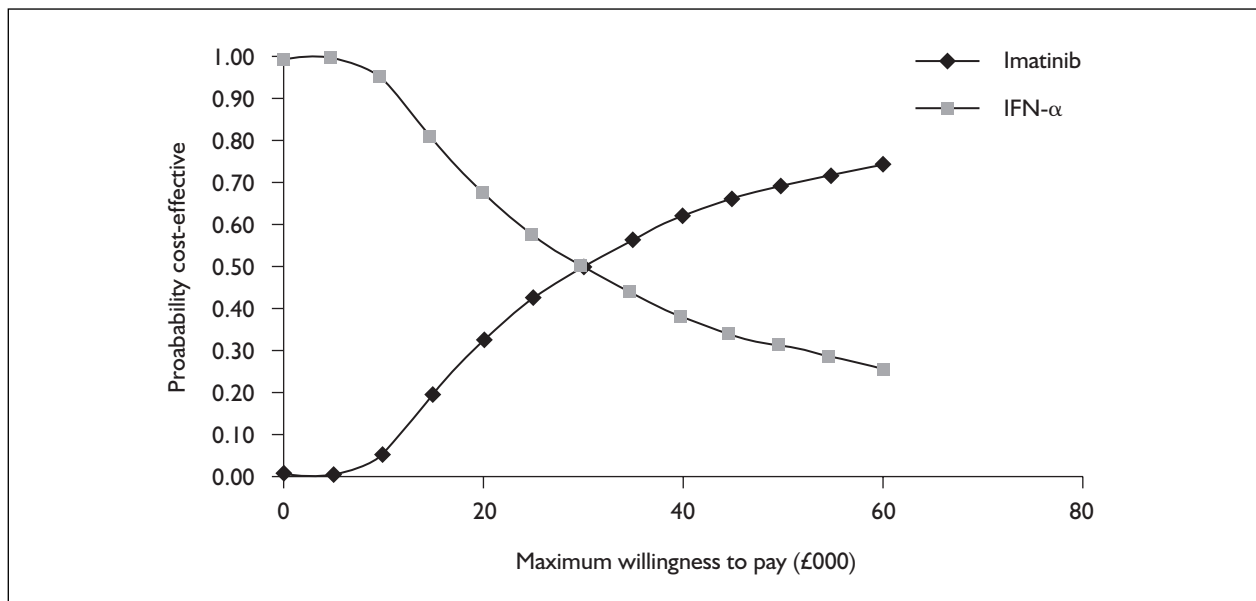


FIGURE 15 Cost-effectiveness acceptability curve for IFN- α and imatinib

appropriate comparator than IFN- α for treatment in chronic phase CML as hydroxyurea is less effective than IFN- α . It is used in those patients who cannot tolerate IFN- α treatment, or occasionally as first-line treatment for other reasons such as frailty.

It can be seen that with three comparisons, hydroxyurea has the greatest probability of being cost-effective up to a value of £95,000. If, however, only imatinib and IFN- α are considered, imatinib becomes more cost-effective above £31,000.

In addition, one-way sensitivity analyses were performed to determine the parameters to which results were most sensitive. A full description of the assumptions varied, the values used and justifications made is presented in *Table 34* (methods are described in *Chapter 3*).

The estimate of cost-utility for imatinib compared with IFN- α is most sensitive to the dose of IFN- α , the type of second-line treatment, chronic phase utilities and the relative risk of CR.

In general, the estimates were insensitive to the changes made. Sensitivity analysis results are shown for general assumptions, costs, utilities and relative risks of progression and survival in Appendix 10. A summary of the sensitivity analyses resulting in ICERs above £30,000 and below £20,000 is shown in *Figures 16* and *17*, respectively.

The comparisons between imatinib and hydroxyurea were moderately sensitive to changes

in the relative risk (survival and progression) of hydroxyurea compared with IFN- α . If this relative risk is increased to 1.5, the ICER for imatinib/hydroxyurea drops to £67,075. The model is not sensitive to the utility of hydroxyurea and imatinib in the chronic phase, with minimal change in the ICER (to £78,196). The comparison between IFN- α and hydroxyurea is very sensitive to the assumptions about relative risk of survival and progression. The ICER drops to £190,303 when the relative risk is increased to 1.5. Given the uncertainty around this value, it would be unwise to draw any firm conclusions about the ICER for IFN- α and hydroxyurea.

The range of ICERs when considering all one-way sensitivity analyses for imatinib compared with IFN- α was £13,555 to £51,870 (see Appendix 10). There were no reasonable assumptions under which dominance shifted to IFN- α . The maximum estimate was obtained when assuming that the dose of imatinib would be increased to 600 mg in the chronic and accelerated phases and 800 mg in the blast phase. The minimum estimate was obtained when substituting survival and progression curves from the Benelux study.⁵

The ICER for imatinib compared with IFN- α falls within the range considered by many decision-makers as cost-effective. This is due to a combination of markedly better utility values in the chronic phase and improved survival. If IFN- α is assigned equivalent utility values to imatinib, then the ICER is £42,556. If the survival, progression and CR of imatinib are identical to

TABLE 34 Sensitivity analysis values and sources

Assumptions	Value	Source
General		
Benelux survival curves	Survival curve (cycle dependent)	Benelux, 1998 ⁵
Benelux progression curves	Survival curve (cycle dependent)	Benelux, 1998 ⁵
Benelux survival and progression curves	Survival curve (cycle dependent)	Benelux, 1998 ⁵
Second-line hydroxyurea for all treatments		Arbitrary
Imatinib arm: second-line treatment with imatinib 600 mg (chronic phase) and 800 mg (accelerated phase)	Cost £2372/month and £3161/month	Arbitrary
Imatinib arm: second-line treatment with imatinib 400 mg and IFN- α 3 MU	Cost £1581/month and £395/month	O'Dwyer <i>et al.</i> , 2002 ³⁷
Imatinib: second-line treatment with imatinib 600 mg and IFN- α 5 MU	Cost £2372/month and £666	O'Dwyer <i>et al.</i> , 2002 ³⁷
Pegylated IFN- α instead of standard IFN- α	Cost £1104/month	Trabacchi <i>et al.</i> , 2002 ³⁹ and O'Brien <i>et al.</i> , 2002 ³⁸
Progression to blast and accelerated phases	30% and 60% of total progression	Clinician estimate from Novartis study 0106, 2002 ⁶³
IFN- α chronic2: transitions same as first-line IFN- α	Progression and survival curves (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Imatinib chronic2: transitions same as first-line IFN- α	Progression and survival curves (cycle dependent)	Italian Cooperative Study Group, 1998 ²¹
Transitions from chronic to CR permitted	Only in first 3 years of model	Arbitrary
Transitions from chronic to CR permitted	Only in first 10 years of model	Arbitrary
Chronic to CR: median time to response	6 months	Arbitrary
Chronic to CR: median time to response	12 months	Arbitrary
Chronic to CR: median time to response	24 months	Arbitrary
Costs and QALYs discounted	6%	Arbitrary
Costs and QALYs discounted	0%	Arbitrary
Costs		
Imatinib dose	600 mg chronic, 800 mg accelerated	Arbitrary
IFN- α dose	3 MU	Arbitrary
IFN- α dose	7 MU	Arbitrary
Outpatient visits:		
chronic	2, 0.5	Double and half clinician estimate
accelerated	6, 1.5	
blast	12, 3	
Bone marrow tests:		
chronic	1, 0.25	Double and half clinician estimate
accelerated	1, 0.25	
blast	2, 0.5	
Transfusion:		
chronic	0.5, 0.125	Double and half clinician estimate
accelerated	0.25	
blast	18, 4.5	
Transfusion (imatinib only): accelerated	3, 6, 9	Arbitrary
Radiology:		
chronic	0.5	Double and half clinician estimate
accelerated	0.5	
blast	24, 6	
Inpatient visits:		
chronic	0.5	Double and half clinician estimate
accelerated	0.5	
blast	6, 1.5	

continued

TABLE 34 Sensitivity analysis values and sources (cont'd)

Assumptions	Value	Source
Utilities		
Kattan estimates	Chronic IFN- α 0.9 Chronic hydroxyurea 1.0 Accelerated 0.5 Blast 0.5	Kattan et al., 1996 ⁸⁸
Novartis clinician estimates	Chronic imatinib 0.91 CR imatinib 0.91 Accelerated 0.01 Blast -0.09 Hydroxyurea 0.90 IFN- α 0.832	Novartis study 0106, 2002 ⁶³
Novartis study 0106	Accelerated 0.5952 Blast 0.5952 Hydroxyurea 0.8445	Novartis study 0106, 2002 ⁶³
Relative risks for survival and progression		
Imatinib:	progression mortality CR	0.6, 0.7, 0.9, 1.0 0.4, 0.5, 0.7, 0.8, 0.9, 1.0 1, 1.5, 2, 2.5, 3, 4, 4.5
IFN- α :	progression mortality CR	0.8, 0.9, 1.1, 1.2 0.8, 0.9, 1.1, 1.2 0.8, 0.9, 1.1, 1.2
Hydroxyurea:	progression mortality CR	1, 1.5, 2, 2.5 1, 1.5, 2, 2.5 0.25, 0.5, 1

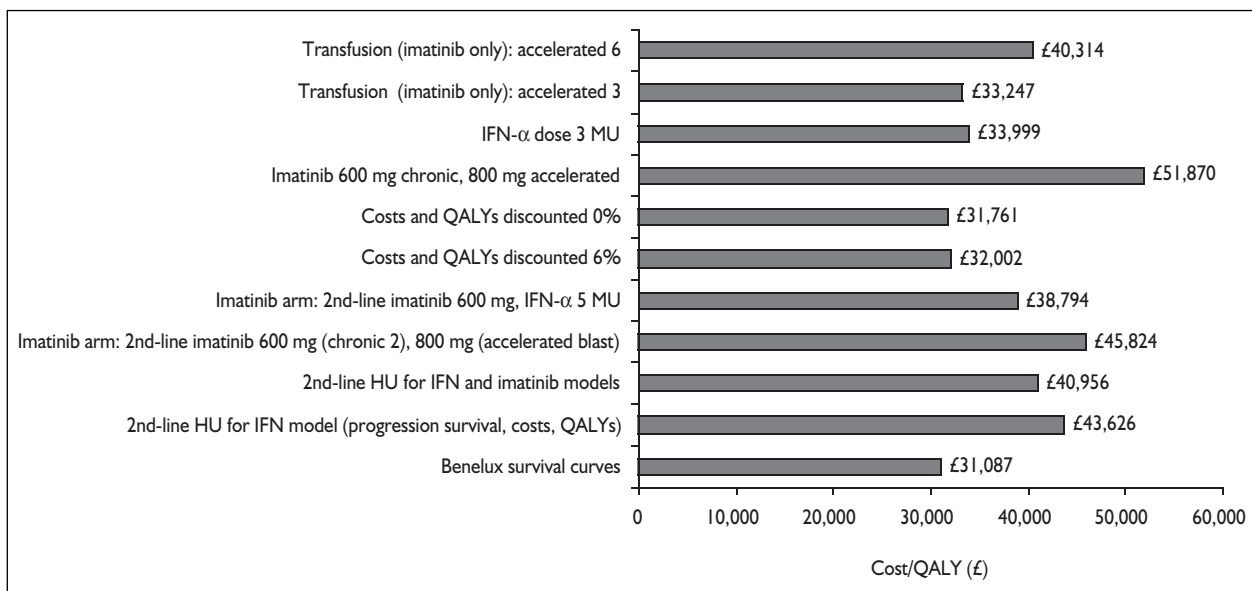


FIGURE 16 Summary of sensitivity analyses (imatinib versus IFN- α) resulting in ICERs above £30,000

IFN- α , the ICER is £48,463. If the utility values for IFN- α are 0.75 or lower then the ICER remains under £30,000.

The cost of adverse effects has not been modelled. This is likely to favour IFN- α in the analysis as

adverse effects are more common and severe with IFN- α , and hence would incur additional costs for no additional benefit. The utility values used were derived from patients, which is not strictly appropriate for a societal analysis. However, sensitivity analysis using clinician-derived

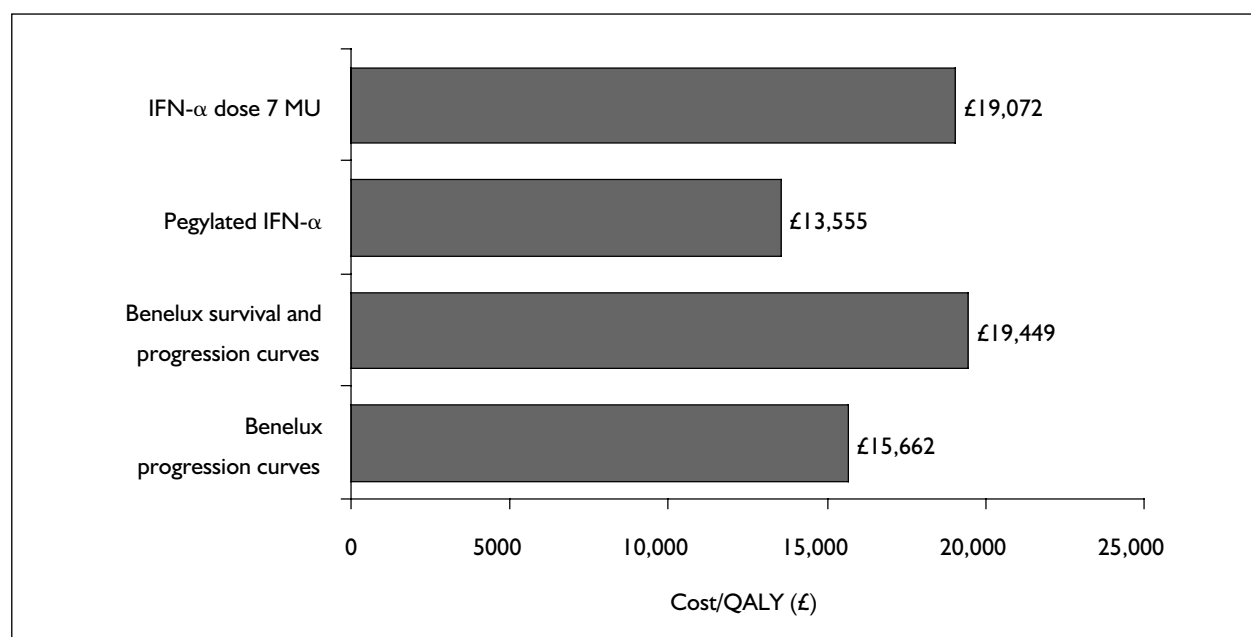


FIGURE 17 Summary of sensitivity analyses (imatinib versus IFN- α) resulting in ICERs below £20,000

estimates (no public estimates were available) does not materially alter the conclusions.

Appendix 12 provides details of further sensitivity analyses carried out at the request of the NICE appraisal committee following completion of the initial modelling study reported here. This re-estimated the relative effectiveness of imatinib based on treatment completers to limit the potentially biasing effect (against imatinib) of cross-overs in the IRIS trial. Based on the combination of most or least favourable assumptions regarding relative risk using 18- and 21-month progression data, the ICERs for imatinib compared with IFN were £17,445 to £29,901 and compared with hydroxyurea were £54,613 to £95,451.

Novartis economic model and comparisons with the independent model

Novartis economic model

The purpose of this economic evaluation was to compare the cost-effectiveness of imatinib with IFN- α plus Ara-C for the treatment of newly diagnosed patients with CML in whom BMT was not considered a therapeutic option. The model used a Markov structure containing the following health states: chronic phase, complete HR, partial HR and complete CR, accelerated phase and blast

crisis death. In this model it is only possible to die from CML from the blast state. From other states, deaths from non-CML causes are permitted.

The model crosses patients from imatinib to IFN- α plus Ara-C and vice versa when they progress or lose a response. Third-line treatment for all patients is hydroxyurea. The model runs for 30 years.

The cost-effectiveness analysis is based on data from Novartis study 0106.⁶³ Two different methods were used to estimate survival:

- **CR method:** modelling the relationship between CR and survival based on the IFN- α literature and then applying this to the response rates seen in study 0106. After 2 years, survival is based on whether patients had a CR (during the first 2 years), independently of treatment (data taken from study by Bonifazi²⁵)
- **PFS method:** the imatinib group uses PFS data from the Novartis study 0106⁶³ for the first 12 months, and then assumes the PFS of IFN- α plus Ara-C for subsequent years (Italian Cooperative Study Group, 1998²¹).

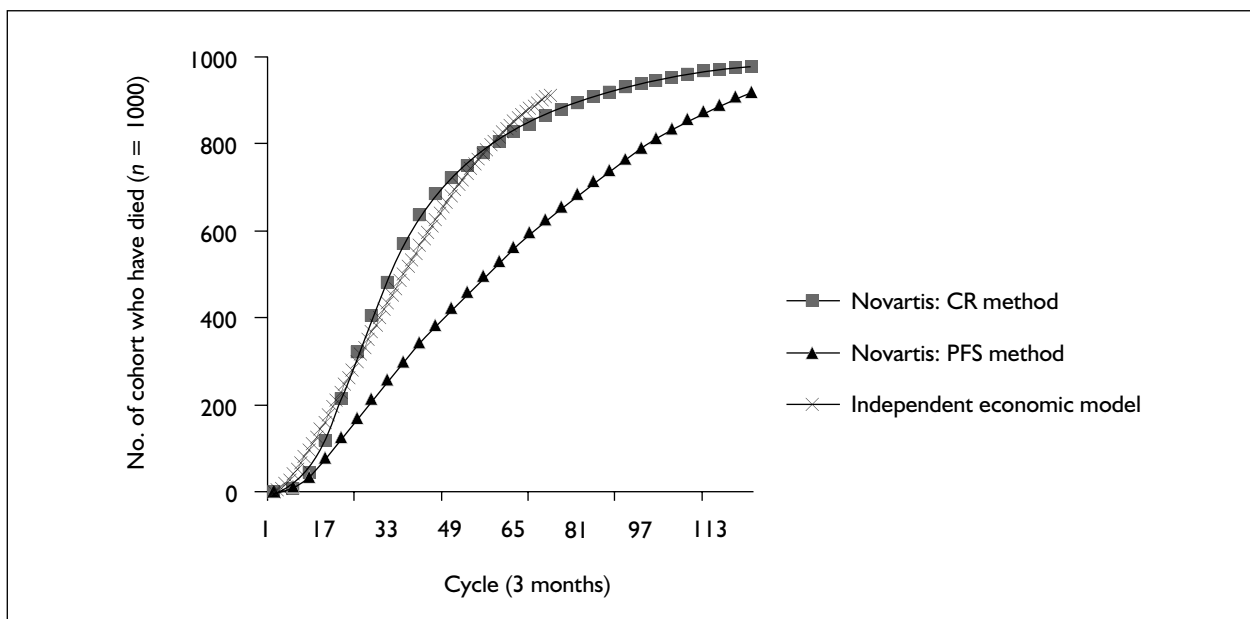
Unit costs were drawn from NHS sources. The following costs were included: drug treatment, palliative care (in hospital and at home), outpatient visits, bone marrow tests, blood transfusions, radiology tests and nurse visits. Costs were discounted at 6%. Quality of life data (EQ-5D) were obtained from trial 0106 and

TABLE 35 Summary of results from the industry economic model

	IFN- α plus Ara-C	Imatinib (survival modelled using method 1)	Imatinib (survival modelled using method 2)
Total cost (discounted)	5,987,634	14,950,238	11,739,633
Total QALYs (discounted)	466	941	680
Incremental cost	–	8,962,604	5,751,999
Incremental QALYs	–	475	214
ICER	–	18,865	26,850

TABLE 36 Comparison of ICERs between the independent economic model and two Novartis models⁶³

	Independent economic model	Novartis, 2002 (based on CR approach) ⁶³	Novartis, 2002 (based on PFS approach) ⁶³
ICER imatinib versus IFN- α	£26,180	£18,865	£26,850

**FIGURE 18** Survival from the independent model compared with two Novartis models

provide utility estimates. QALYs were discounted at 1.5%.

A summary of results is presented in *Table 35*.

Sensitivity analysis varied the dose of IFN- α , the cost of hospitalisation, the cost and QALY discount rates. The model was most sensitive to the cost of IFN- α and the discount rate.

Quality assessment of the Novartis model

Comments on the quality of the industry model, using combined criteria from the Drummond⁶¹

and Sculpher¹⁰³ economic checklists are detailed in Appendix 11.

Detailed comparisons between the Novartis model and independent economic model

Table 36 summarises the ICERs produced by the Novartis models compared with the independent economic model.

Figure 18 shows survival in the Novartis model compared with the independent economic model. The figure shows how many people have died at each time-point, starting with a cohort of 1000

TABLE 37 Results for the independent model when assuming IFN- α survival rates for the imatinib cohort after 12 months

	Cost per person (£)	QALYs per person
Drug		
HU	38,317	4.99
Imatinib	204,680	6.11
IFN- α	163,564	5.04
ICERs		
Imatinib versus HU	148,383	per QALY
IFN- α versus HU	2,468,015	per QALY
Imatinib versus IFN- α	38,411	per QALY

TABLE 38 Results if independent model utilities are changed to be the same as the Novartis model

	Cost per person (£)	QALYs per person
Drug		
HU	38,322	4.70
Imatinib	215,684	7.01
IFN- α	163,581	5.01
ICERs		
Imatinib versus HU	76,709	per QALY
IFN- α versus HU	394,237	per QALY
Imatinib versus IFN- α	26,124	per QALY

people. It can be seen that the Novartis CR approach and the independent model are reasonably similar, with the independent model giving a higher death rate in the first couple of years and after approximately 12 years. The Novartis PFS approach gives a lower death rate than the other two techniques.

At the end of 20 years, a higher proportion of the Novartis cohort (7%) remains in CR, compared with the independent model (2%). Somewhat perversely, it appears that prolonged survival is associated with a higher ICER, presumably because costs continue to accrue at a greater rate than benefits.

The independent model results in an ICER for imatinib and IFN- α that is similar to the Novartis PFS approach (despite survival being more similar to the CR approach). One of the main differences between the three models is the modelling of survival and progression. The Novartis models assume IFN- α plus Ara-C survival rates for imatinib after 12 months. The independent economic model applies a continuing relative risk of benefit (for the length of the chronic phase) for imatinib. There are no long-term empirical data to support or refute either technique. By changing the independent economic model so that it too assumes IFN- α survival rates after 12 months, the

resulting ICER moves up to £38,411 for imatinib versus IFN- α (Table 37).

The independent model assumes longer survival in accelerated phase than the Novartis model, which postulates a median of 6 months. The independent model runs for a total of 20 years, compared with 30 years for the Novartis models. Reducing the Novartis model to 20 years would lead to an increase in the ICERs to approximately £29,000 (PFS method) and £20,000 (CR method).

The Novartis models assume 31 days of inpatient care if a patient received palliative care. The independent economic model assumes 9 days of inpatient stay per cycle in the blast phase. By changing the independent model to assume 12 days of inpatient care per cycle (3 months) in the accelerated and blast phases, the ICER for imatinib versus IFN- α decreases to £24,396.

The Novartis models assume that once a patient experiences disease progression they receive no further active treatment, only palliation. However, this incurs considerable costs.

The Novartis and independent economic model use the same utility values for chronic phase imatinib, chronic phase IFN- α plus Ara-C, and CR for imatinib and IFN- α plus Ara-C. The Novartis

TABLE 39 Results if the Novartis clinician estimates for utility are used in the independent economic model

	Cost (£ per person/year)	QALYs (per person/year)
Drug		
HU	38,322	4.41
Imatinib	215,684	7.01
IFN- α	163,581	5.09
ICERs		
Imatinib versus HU	68,313	per QALY
IFN- α versus HU	184,022	per QALY
Imatinib versus IFN- α	27,199	per QALY

model uses 0.8445 for chronic phase hydroxyurea, whereas the independent model uses 0.9; the Novartis model uses 0.5952 for both accelerated and blast phases, whereas the independent model uses 0.729 for accelerated and 0.524 for blast. If the independent model is adjusted to have the same utilities as the Novartis model then the ICERs shown in *Table 38* result. The changes make little difference to the ICER comparing imatinib and IFN- α , but more difference to the ICER for IFN- α compared with hydroxyurea.

The Novartis model also provides clinician estimates of utility. Using these figures in the independent economic model results in the data shown in *Table 39*. The resulting ICER for imatinib versus IFN- α is slightly higher, but the most

marked difference is that the ICER for IFN- α compared with hydroxyurea is considerably lower.

The independent model assumes that 30% of people progress from the chronic phase to the accelerated phase, whereas the Novartis model postulates that 70% progress. The ICER in the independent model changes to £22,178 if the Novartis figure is used.

In conclusion, the main differences between the Novartis model and the independent economic model in the resulting ICER for imatinib versus IFN- α are the modelling of survival for imatinib after 12 months, and the progression from the chronic phase to the accelerated and blast phase.

Chapter 6

Implications for other parties

Improvements in quality of life are reported for those with CML taking imatinib, compared with IFN- α plus Ara-C. In some cases, anecdotal evidence suggests that people with CML are able to return to work after switching from treatment with IFN to imatinib. The financial impact for patients and their families of treatment with imatinib is possibly lower than for those taking IFN- α . There may be productivity impacts on those of working age, both directly to the patient involved and indirectly through the impact on their family and carers.

For retired people, the impact of CML on family and carers may be reduced, although there is no empirical evidence on this issue.

The impact of imatinib on primary care services is uncertain. Remission rates associated with imatinib will possibly lead to lower monitoring costs and costs of attendance. There are unlikely to be major impacts on NHS staffing levels.

Currently, approximately 10% of all patients with CML are enrolled in trials of imatinib sponsored by the pharmaceutical company that funds their treatment.

Children and the elderly have generally been excluded from pharmaceutical trials (although new trials in children are planned or underway). Imatinib is not currently licensed in the UK for children.

Chapter 7

Factors relevant to the NHS

Clinical and consumer interest in imatinib is such that uptake of imatinib is likely to be rapid. Imatinib has been given orphan drug status by EMEA and the FDA. NICE recommended imatinib for second-line treatment after failed IFN- α in September 2002. In December 2002 imatinib was licensed by EMEA for first-line use in the management of CML.

The reviewers have not attempted to collect and synthesise evidence regarding patients' views, experiences and wishes. Such good quality evidence (if available) would be useful to help inform imatinib policy decisions.

Costs to the NHS, other than direct drug costs, are difficult to predict. It is not known whether imatinib will result in fewer outpatient and inpatient visits while patients are undergoing therapy. It is possible that expensive PCR monitoring will become routine and bone marrow tests, radiology and blood transfusions may all increase in frequency. It is also likely that imatinib will be offered to people who would not be offered IFN- α because of the potential for adverse effects.

The total cost impact on NHS budgets, in addition to the above, will depend on the number of people eligible for first-line treatment with imatinib, the uptake of first-line treatment with imatinib, the cost of imatinib and cost savings from avoided IFN- α therapy.

Assuming an annual incidence in England and Wales of 531, a 10% BMT rate, 90% uptake and a dose of 400 mg, the annual costs of treating all

remaining patients with imatinib, IFN- α or hydroxyurea are shown in *Table 40*, and range from approximately £1,000,000 for hydroxyurea to £10,000,000 per year for imatinib. Calculations are based on the independent economic model.

Table 41 estimates current drug costs for the NHS and provides an estimated impact on the NHS of introducing imatinib (while accounting for the savings as a result of less IFN- α and hydroxyurea use).

Two scenarios are presented. Both scenarios assume that the current cost consists of 45% of new cases of CML being offered IFN- α , 45% hydroxyurea and 10% BMT. Scenario 1 gives the cost of imatinib less the current spend, assuming that 5% remain treated with IFN- α and 65% are treated with imatinib, 10% have BMT and 20% are treated with hydroxyurea. Scenario 2 gives the cost of imatinib less the current spend, assuming that 5% remain treated with IFN- α and 75% are treated with imatinib, 10% have BMT and 10% are treated with hydroxyurea.

The estimated current spend on treatment with IFN- α and hydroxyurea alone is approximately £20,000,000. The estimated impact of scenario 1 less the current spend is around £16,000,000 and the estimated impact of scenario 2 less the current spend is approximately £20,000,000 for the first 5 years of treatment. *Table 42* shows the net impact (cumulative) on the NHS over the next 5 years. Costs will be between £4 and 6 million in the first year, rising to between £16 and 20 million by year 5.

TABLE 40 Estimated cost of treatment with imatinib, IFN- α or hydroxyurea

	Assume all drug treatment with imatinib	Assume all drug treatment with IFN- α	Assume all drug treatment with hydroxyurea
% of CML population treated with drugs:	90%	90%	90%
Year 1	10,378,869	6,422,191	1,670,511
Year 2	10,073,609	7,127,177	2,122,093
Year 3	8,871,058	6,625,447	1,966,709
Year 4	7,251,156	5,498,471	1,551,262
Year 5	5,410,930	4,043,731	1,052,829
Total	41,985,621	29,717,017	8,363,404

TABLE 41 Estimated total impact on the NHS

	Current spend (45% IFN-α, 45% HU)	Scenario 1 (65% imatinib, 5% IFN-α, 20% HU)		Scenario 2 (75% imatinib, 5% IFN-α, 10% HU)	
% of CML population treated with drugs	90%	90%		90%	
	Total (£000)	Total (£000)	Incremental costs (scenario 1 – current spend)	Total (£000)	Incremental costs (scenario 2 – current spend)
Year 1	4552	9251	4699	10340	5788
Year 2	5202	9160	3958	10154	4952
Year 3	4833	8113	3280	8976	4143
Year 4	3965	6623	2657	7335	3370
Year 5	2866	4912	2054	5457	2590
Total	21420	38061	16641	42264	20844

TABLE 42 Net impact on the NHS over 5 years

Net cost (£000)		
	Scenario 1	Scenario 2
Year 1	4699	5788
Year 2	8657	10740
Year 3	11938	14883
Year 4	14595	18253
Year 5	16641	20844

The estimated net impact is difficult to capture because of uncertainty regarding long-term survival with imatinib. The total prevalence of CML may rise and many of these patients will be on long-term imatinib therapy. No attempt was

made to calculate the net impact on the NHS after 5 years, but it is likely to be greater than the 5-year estimates assuming that prolongation of survival does occur.

Chapter 8

Discussion

Early results of imatinib for first-line therapy are promising, although only 18-month follow-up data are currently available. Imatinib is associated with higher cytogenetic response rates, a longer median time to progression and fewer side-effects. No comparisons of imatinib with hydroxyurea or BMT were found. Assuming that complete CR is causally associated with prolonged survival (which may or may not be justified), it is likely that imatinib will be associated with better outcomes than hydroxyurea and, at least in the short term, better outcomes than BMT (for approximately the first 4 years).

Limitations of included studies

Only one RCT of imatinib compared with IFN- α plus Ara-C as first-line therapy is available to date, provided by Novartis.⁶³ Not all aspects of the trial have been made available for independent scrutiny. RCTs are associated with fewer threats to internal validity when well conducted. They are potentially the best tool for answering questions of effectiveness. The current clinical question is, however, difficult to study in a rigorous RCT, because of ethical issues and patient preferences. In the Novartis study 0106,⁶³ as a result of the popularity and perceived effectiveness of imatinib by patients and clinicians, there were high cross-over rates to that treatment arm, and higher loss to follow-up in the IFN- α plus Ara-C treatment arm. The trial was open label with no blinding, which introduces possibilities for performance and measurement bias. The study should be applicable to the UK setting, although as entry criteria were rigorous, a low-risk group of patients was included. Many patients who will be seen in the clinical setting were not recruited.

Owing to the lack of long-term data beyond 18 months, this assessment relies on surrogate outcomes that may not directly relate to survival.

Results of systematic reviews

Imatinib was associated with higher rates of CR than IFN- α plus Ara-C and lower rates of progression to the accelerated or blast phase at 12

months. Overall survival was not statistically significantly different between the two groups. Withdrawal due to side-effects was slightly higher for IFN- α plus Ara-C than for imatinib and cross-over due to intolerance was much higher in the IFN- α plus Ara-C group. Quality of life was better in the imatinib group than in the IFN- α plus Ara-C group when assessed at 1, 3 and 6 months using the FACT-BRM instrument.

IFN- α is more effective than hydroxyurea in prolonging survival. Median survival across the four IFN- α versus hydroxyurea studies was greater for IFN- α . However, IFN- α also has greater side-effects and much higher withdrawal rates.

Four out of the five studies comparing BMT and IFN- α showed a long-term survival advantage for BMT compared with IFN- α , but a short-term (0–4 years approximately) disadvantage. In the BMT group death due to transplant-related complications ranged from 36 to 45% (median 38%).

Cost-effectiveness results

The independent economic model gave estimates for the ICER of imatinib compared with IFN- α of £26,180 per QALY (ranging from £13,555 to £51,870), whereas the Novartis models gave estimates of £18,865 to £26,850 per QALY. Using less conservative estimates of the relative effectiveness of imatinib, based on treatment completers, the present authors' estimates of the ICER compared to IFN- α were between £17,445 and £29,901 per QALY. Even under these more favourable assumptions the ICER for imatinib compared with hydroxyurea remained relatively high, in the range £54,613 to £95,451 per QALY.

BMT could not be modelled in the time available, and such an analysis would have relied heavily on speculative data. Hence, the authors are not able to comment on the potential cost-effectiveness of imatinib compared with BMT, and suggest that this is an area where research is urgently required.

There are several different possible pathways for management of CML. This review has modelled imatinib (first line), IFN- α (second line) and

mercaptopurine (blast phase) compared with IFN- α (first line) and imatinib (second line and blast phase). These are only two possibilities for what may occur in clinical practice. Possible alternative options include the use of combination therapy and dose reductions or escalations. To complicate matters further, BMT may be available for certain patients and optimal timing of this option is not clear. A recent paper by Goldman and colleagues¹⁰⁴ suggests that with the advent of imatinib there are now two possible approaches to managing newly diagnosed CML patients for whom a suitable donor is available. First, all such patients could be offered an initial trial with imatinib, with responders continuing indefinitely and non-responders proceeding to transplant. Alternatively, it may be possible to define a category of low-risk patients who could be recommended initial transplants.¹⁰⁴

This analysis describes an interesting position. IFN- α is at present considered standard therapy for people in whom BMT is not an option. However, the analysis suggests that IFN- α itself is not a cost-effective option compared with hydroxyurea, owing to a combination of higher costs, a moderate increase in longevity and a considerable decrease in quality of life in many people. Strictly speaking, IFN- α should be ruled out of this analysis by extended dominance, and the ICER of relevance is that of imatinib/hydroxyurea. However, hydroxyurea as a comparator treatment may not be considered to be a realistic alternative to combine with imatinib to achieve extended dominance.

The complexity of possible management pathways and the incorporation of BMT have not been completely captured within the independent economic model. There is a need for consensus development work to identify a more limited range of treatment options to model and, possibly, a need to produce cost-effective guidelines.

Assumptions, limitations and uncertainties of this review

The scope of this assessment was limited to first-line treatments for adults with CML. It included only English language studies, which may not be representative of the entire literature available. However, several studies conducted in non-English-speaking countries were included.

Because of the lack of comparative evidence for imatinib, BMT and hydroxyurea, indirect

comparisons based on the common comparator IFN- α have been presented. Such indirect comparisons are problematic because of the likely difference in populations and should be interpreted with much caution. However, they do provide some indication of the expected difference in outcomes between the treatments.

It is currently not known whether treatment with imatinib will need to be continued indefinitely. It is thought possible that IFN- α can be stopped in some cases after several years of treatment. Pegylated interferon has recently been used for the treatment of CML and it is unknown how this treatment option will compare directly with imatinib or whether it will be beneficial in combination therapy.

One of the uncertainties with this assessment is around long-term outcomes with imatinib. Currently, 18-month data are available, whereas for IFN- α 10-year trial follow-up data have been published. Although CR is generally agreed to correlate with survival for IFN- α , the assumption of a similar relationship for imatinib is speculative, and will partly depend on the degree of resistance to imatinib that emerges over time. Disease progression on imatinib and a failure to maintain response in the blast phase are, at least partly, due to an inability to maintain BCR-ABL kinase activity, indicating resistance. The mechanisms of resistance for imatinib are not clear. It is unknown whether combination therapy (such as imatinib plus IFN- α , or imatinib plus Ara-C) will help to overcome disease resistance, and research on this is still in the early stages. However, it is encouraging that 3-year follow-up data on imatinib as second-line treatment for failed IFN- α show that survival with imatinib remains above 90% at 3 years.⁶²

The independent economic model assumes that once a patient fails imatinib by losing their CR a further CR is not possible. Although studies have demonstrated that responses are still possible with second-line treatment, a simpler approach to the modelling was taken. It is likely that the impact would be negligible owing to the small number of the cohort affected.

The results of this assessment are likely to be generalisable to many of those in the UK with CML. The results may be less applicable to high-risk patients, the elderly, those eligible for BMT or children. CML is rare in children, but trials of imatinib are either planned or underway and effectiveness in this group will be an important future investigation.

Need for further research

Long-term follow-up data from the first- and second-line imatinib trials are critical to determine the effect on survival, duration of response and development of resistance.

Research is also needed into specific subgroups such as high-risk patients, the elderly, children or those eligible for BMT. Long-term comparisons of imatinib (possibly non-randomised owing to ethical and other considerations) with BMT performed in the early stages of CML are important to identify whether and when a survival advantage shifts from imatinib to BMT.

Imatinib is likely to be used in combination with other therapies, and detailed research is necessary to determine optimal treatment pathways.

More detailed economic studies are also required to aid appraisal of imatinib compared with BMT, and in high-risk patients, and to help provide cost-effective guidelines.

Further investigation of the effect of CML and imatinib on quality of life is important, especially in terms of eliciting societal values.

Chapter 9

Conclusions

Imatinib appears to be more effective than IFN- α in terms of CR and PFS, with fewer side-effects. Assuming that complete CR is causally associated with prolonged survival, it is likely that imatinib will be associated with better outcomes than hydroxyurea and, at least in the short term, better outcomes than BMT (for approximately the first 4 years).

The ICER of imatinib compared with IFN- α was £26,180 per QALY gained and was relatively robust when subjected to a number of sensitivity analyses. This figure is similar to industry estimates of between £18,000 and £26,000 per QALY.

However, there is uncertainty concerning longer term outcomes, resistance and duration of response. The place of imatinib in the management of CML, alongside BMT and in combination with other chemotherapeutic agents, remains to be established in detail. Further research and long-term follow-up of existing studies are needed.



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Kim Dalziel undertook the protocol design, inclusion process, data extraction, quality assessment, report writing and economic analysis. Ali Round was involved in the protocol design, inclusion process, report writing and economic

analysis, and Ken Stein in the protocol design and report writing. Ruth Garside carried out data extraction and report writing (background), and read and commented on the report. Alison Price carried out the literature searches.

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Appendix I

Prognostic scores

The Sokal score

Score = $\text{Exp}[0.0116 (\text{age}-43.4)$
 $+ 0.0345 (\text{spleen size} - 7.51)$
 $+ 0.188 ([\text{platelets}/700]^2 - 0.563)$
 $+ 0.0887 (\text{blasts} - 2.1)]$

Low risk	< 0.8
Intermediate risk	= 0.8–1.2
High risk	> 1.2

New prognostic score (interferon score)²⁴

New score = $0.6666 \times \text{age}$ (0 when age < 50, otherwise 1)
 $+ 0.042 \times \text{spleen size}$ (cm below costal margin)
 $+ 0.0584 \times \text{blasts}$ (%)
 $+ 0.0413 \times \text{eosinophils}$ (%)
 $+ 0.2039 \times \text{basophils}$ (0 when basophils < 3%; otherwise 1)
 $+ 1.0956 \times \text{platelet count}$ (1 when platelets < 1500, otherwise 1) $\times 1000$

Low risk	≤ 780
Intermediate risk	= 780–1480
High risk	> 1480

Appendix 2

Resistance to imatinib

There are several possible mechanisms for resistance to imatinib.

Cell intrinsic mechanisms (cellular level)

These are changes within the cell that reduce the sensitivity of BCR-ABL to imatinib. There is experimental evidence to support the existence of these changes:⁵² cells from patients collected at various stages in the CML disease process showed a ten-fold reduction in sensitivity to imatinib *in vitro*. Various mechanisms could account for this.

- **Gene amplification:** this has been demonstrated in several patients who have relapsed following treatment with imatinib. The drug may select for proliferation of clones with multiple copies of BCR-ABL in some patients.⁵² Demonstrated amplification of the BCR-ABL target gene has also been noted in resistant clones of cultured cells.⁵⁴ The degree of amplification was proportional to the final selection concentration of imatinib. It has also been observed that a withdrawal of imatinib from resistant cell cultures caused the BCR-ABL level to drop.⁵⁴
- **Point mutations** within the kinase domain of BCR-ABL confer resistance to imatinib. This has been demonstrated empirically,⁵² and again, selection pressure conferred by the drug may play a part.
- **Overexpression of the multidrug resistance gene** increases levels of P-glycoprotein, a cell membrane protein that pumps drugs out of the cell and lowers net intracellular drug concentration. This has been reported *in vitro*.¹⁰⁵
- **Secondary genetic changes** could provide signals that replace BCR-ABL as the determinant of cell proliferation^{52,53} These could be compensating mutations in other genes or other chromosomal changes (e.g. loss of tyrosine phosphatase activity, loss of apoptosis genes, or gain of function mutations in viability genes).¹⁰⁶ This has not yet been demonstrated empirically as a mechanism of resistance to imatinib.
- **Cellular drug metabolism or efflux.**

- **Recovery of protein tyrosine phosphorylation** may be accomplished in a compensatory fashion by a mechanism not involving BCR-ABL.⁵⁴ Activation of an alternative tyrosine kinase may be a possible explanation for imatinib resistance.¹⁰⁵ Cells may develop methods to increase degradation or metabolism of the drug or increased efflux may be present.¹⁰⁶

Cell extrinsic mechanisms (organismal level)

Imatinib is 95% bound in plasma.

- **Functional sequestration of the drug:** Preclinical studies in mice have demonstrated that α_1 -acid glycoprotein can bind imatinib in serum and inhibit activity against BCR-ABL.¹⁰⁷ Co-administration of other drugs can reduce this.
- **Functional inactivation of the drug** through enzyme modification: this is a theoretical possibility, but has not been demonstrated.

Pharmacological resistance at organismal level

This has been documented not as a lack of initial response but as a resistance following treatment with imatinib. In a study of mice resistant to imatinib, the recovered tumour cells retain the same sensitivity to imatinib as the parental cells. The mice, however, had a raised plasma acid glycoprotein level. Acid glycoprotein levels may impact on the bioavailability of imatinib, especially in later stages of disease.⁵⁴

It is likely that no single mechanism explains all resistance to imatinib, although some are more commonly seen than others. It is also possible that cellular and organismic types of resistance are complementary rather than mutually exclusive.¹⁰⁸ Mechanisms of resistance to imatinib may also be multifactorial.¹⁰⁶

Appendix 3

Search strategies

STI 571 (imatinib mesylate and CML)

Updated search from 31 August 2001 to October 2002

Databases and years searched	Date searched and search files	No. of hits (download file)
MEDLINE 31 August 2001 to 3 October 2002 (Update codes)	Date searched: 14 October 2002 Reran sti571 (saved strategy on Webspirs sti-cml-med) (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS)) and (((gleevec or glivec or imatinib or sti 571 or sti-571 or sti571) or (stl 571 or stl-571 or stl571 or stl571 or stl-571 or stl 571) or ((gleevec or glivec or imatinib or sti 571 or sti-571 or sti571) or (stl 571 or stl-571 or stl571 or stl571 or stl-571 or stl 571))) and (UD=20010831-20021003) and (LA=ENGLISH)) and (('Leukemia-Myeloid-Chronic' / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml) or (('Leukemia-Myeloid-Chronic' / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml))) and (UD=20010831-20021003) and (LA=ENGLISH)))	178 of which 9 controlled clinical trials
Pubmed (last 90 days)	Date searched: 8 October 2002 gleevec OR glivec OR imatinib OR sti 571 OR sti-571 OR sti571 OR stl 571 OR stl-571 OR stl571 OR stl571 OR stl-571 OR stl 571	64
EMBASE July 2001 to September 2002	sti_emb Run on 8 October 2002 (((imatinib or glivec or gleevec) and (English in la)) or ((sti 571 or sti-571 or sti571 or stl 571 or stl-571 or stl571 or stl571 or stl-571 or stl571) and (English in la))) and (((chronic near myel* near (leukemia or leukaemia)) or cml) and (English in la)) or ('chronic-myeloid-leukemia' / all subheadings)) and (('clinical-trial' / all subheadings) or ('phase-3-clinical-trial' / all subheadings) or ('phase-1-clinical-trial' / all subheadings) or ('phase-2-clinical-trial' / all subheadings) or ('phase-4-clinical-trial' / all subheadings))	81
January 2001 to September 2002	Saved strategy: sti-cost-emb (cost* or economic*) and (gleevec or glivec or imatinib or sti 571 or sti-571 or sti571 or stl 571 or stl-571 or stl571 or stl571 or stl-571 or stl 571) Retrieved 28	15
Science Citation Index 2002 English-only titles	Title=sti 571 or sti571 or stl571 or stl 571 or imatinib or gleevec or glivec or stl571 or stl 571;	297 (18 downloaded)
Web of Science Proceedings 2002	Title=sti 571 or sti571 or stl571 or stl 571 or imatinib or gleevec or glivec or stl571 or stl 571	8
Cochrane Library, Issue 3, 2002	sti 571 or sti571 or stl571 or stl 571 or imatinib or gleevec or glivec or stl571 or stl 571	0

continued

Databases and years searched	Date searched and search files	No. of hits (download file)
National Research Register, Issue 3, 2002	Saved strategy sti571_cml sti 571 or sti571 or stl571 or stl 571 or imatinib or gleevec or glivec or stl571 or stl 571 (most in combination with pegIFN)	18
American Society of Clinical Oncology Annual Meeting Abstracts, 2002	Sti571 or glivec or imatinib http://www.asco.org/asco/ascoMainConstructor/1,1003,_12-002095,00,00.asp Includes Druker RCT first phase study of Imatinib v iFN http://www.asco.org/asco/ascoMainConstructor/1,1003,_12-002326-00_29-00A-00_18-002002-00_19-001,00.asp	30+
BIOSIS	Date searched: 15 October 2002 al: sti571 or al: sti 571 or al: sti-571 or al: stl 571 or stl571 or	155 found
Limited to 2002 publication year and meeting abstracts	stl-571 or al: imatinib or glivec or gleevec and al: cml or chronic myeloid leuke*ria	42 downloaded
Total references in STI571_Update database after download and deduplication		214

Web links

FDA website: FDA Oncology Tools Study – Details for imatinib mesylate for initial therapy of chronic myelogenous leukaemia; see:

- <http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=239>
- <http://www.cptech.org/ip/health/gleevec/> Information on imatinib
- The Pharmaceutical Journal. <http://www.pharmj.com/Editorial/20020525/news/imatinib.html>

Hydroxyurea and IFN- α and CML

Updated search from June 2001 to October 2002

Databases and years searched	Date searched and search files	No. of hits (download file)
MEDLINE August 2001 to October 2002	Date searched: 14 October 2002 Saved as hydroxy_update_med (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS)) and (((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((hydroxyurea and (UD=20010831-20021003) and (LA=ENGLISH)) or ((‘Hydroxyurea-’ / all subheadings in MIME,MJME) and (UD=20010831-20021003) and (LA=ENGLISH))))	7
Pubmed (last 90 days)	hydroxyurea and chronic myeloid leukemia	3
EMBASE July 2001 to September 2002	Date searched: 15 October 2002 Saved as cml_hydroxy_emb ((explode ‘clinical-trial’ / all subheadings) and (((hydroxyurea) or (‘hydroxyurea-’ / all subheadings)) and ((cml or chronic myeloid leuk*emia) or (‘chronic-myeloid-leukemia’ / all subheadings))) and (LA=ENGLISH)	26

continued

Databases and years searched	Date searched and search files	No. of hits (download file)
ISI Science Citation Index 2001–2002	Date searched: 16 October 2002 hydroxyurea and (cml or chronic myeloid leuk*emia)	15
Cochrane Library, Issue 3, 2002	Date searched: 16 October 2002 Saved as cml_hyd Limited to 2001-2002 and included new updates	4
National Research Register, Issue 3, 2002	Date searched: 16 October 2002 Saved as cml_hydroxy (overlap with bmt & IFN)	31
BIOSIS 2001–2002	((al: (hydroxyurea)) and al: (interferon*)) and al: (chronic myeloid leukemia)	5
Total references in database after deduplication		60

BMT and IFN- α and CML

New search 14 October 2002, all years

Databases and years searched	Date searched and search files	No. of hits (download file)
MEDLINE 1966 to October 2002	Date searched: 14 October 2002 Strategy saved on Webspurs – IFN_BMT_med (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS)) and (((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((interferon*) or (explode ‘Interferon-alpha’ / all subheadings in MIME,MJME)) and ((‘Bone-Marrow-Transplantation’ in MIME,MJME) or (bone near marrow near transplant*) or (bmt)))	77
Pubmed (last 30 days)	Date searched: 14 October 2001 (((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((interferon*) or (explode ‘Interferon-alpha’ / all subheadings in MIME,MJME)) and ((‘Bone-Marrow-Transplantation’ in MIME,MJME) or (bone near marrow near transplant*) or (bmt)))	31
EMBASE 1980 to September 2002	Date searched: 15 October 2002 ((‘clinical-trial’ / all subheadings) or (‘phase-3-clinical-trial’ / all subheadings) or (‘phase-1-clinical-trial’ / all subheadings) or (‘phase-2-clinical-trial’ / all subheadings) or (‘phase-4-clinical-trial’ / all subheadings)) and (((bone marrow transplant*) or (bmt) or (‘bone-marrow-transplantation’ / all subheadings) and ((interferon*) or (‘alpha-interferon’ / all subheadings))) and (((chronic near myel* near (leukemia or leukaemia)) or cml) and (English in la) or (‘chronic-myeloid-leukemia’ / all subheadings)))	129
ISI Science Citation Index All years 1981–2002	Date searched 16 October 2002 interferon* and (bmt or bone marrow transplant*) Title only	87

continued

Databases and years searched	Date searched and search files	No. of hits (download file)
Cochrane Library, Issue 3, 2002	Date searched 16 October 2002 Saved as cml_bmt	12
National Research Register, Issue 3, 2002	Date searched 16 October 2002 Saved as cml_bmt_ifn	42
BIOSIS, All years, meeting abstracts	al: bone marrow transplant* and al: interferon* and al: chronic myeloid leukemia	39
Total records in Reference Manager database		349

Appendix 4

Excluded studies

Imatinib

The following studies, which were included in the previous NICE assessment report, were excluded for this report

- Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, *et al.* Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002;**346**:645–52. (Not first-line treatment of CML.)
- Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, *et al.* Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* 2002;**99**:3530–9. (Not first-line treatment of CML.)
- Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti PC, Guilhot F, *et al.* Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002;**99**:1928–37. (Not first-line treatment of CML.)

The following were excluded from the update search at full text stage

- Barbany G, Hoglund M, Simonsson B. Complete molecular remission in chronic myelogenous leukemia after imatinib therapy. *N Engl J Med* 2002;**347**:539–40. (Not first-line treatment of CML.)
- Feng L, Drummond M, Cervantes F, Holyoake T, Kaeda JS. Molecular remission following treatment with STI571 for chronic myeloid leukaemia: a report from the UK571 study group. British Society for Haematology 2002; 42nd Annual Scientific Meeting, Brighton, UK, 15–18 April 2002. *Br J Haematol* **117**(Suppl 1):4–Science. (Preclinical/biological/genetic studies.)
- Fruehauf S, Toplay J, Schad M, Ho AD, Zeller WJ. Rationale for combination therapy of chronic myelogenous leukemia with imatinib and irradiation or alkylating agents: implications for pretransplant conditioning. International Society for Experimental

- Hematology Annual Meeting 2002; Abstract No. 224. (Preclinical/biological/genetic studies.)
- Huntly JP, Guilhot F, Byrne J, Hennig E, Muller C, Niederwieser D, *et al.* Treatment with Imatinib appears to improve the poor prognosis associated with derivative chromosome 9 deletions in patients with CML. European Hematology Association (EHA) Annual Meeting 2002; Abstract No. 0978. (Not first-line treatment of CML.)
- Jones GR, Johnson FL, Rosamilia M, Druker BJ. Activity and Safety of Gleevec (STI-571), an abl tyrosine kinase inhibitor in children with Philadelphia chromosome-positive leukemias. American Society for Hematology Conference 2001; Abstract No. 2475. (Children.)
- Jorgensen H. Will drug combinations effectively eradicate quiescent leukaemic stem cells in chronic myeloid leukaemia (CML)? 31st Annual Meeting of the International Society for Experimental Hematology, Montreal, Quebec, Canada, 5–9 July 2002. *Exp Hematol* **73**. (Preclinical/ biological/genetic studies.)
- Kantarjian H, Cortes J, O'Brien S, Giles FJ, Thomas D, Faderl S, *et al.* High rates of early major and complete cytogenetic responses with imatinib mesylate therapy given at 400 mg or 800 mg orally daily in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (PH+CML-CP). American Society of Clinical Oncology Scientific Meeting 2002; Abstract No. 1043. (Abstract only.)
- Kantarjian HM, Cortes J, O'Brien S, Giles F, Thomas D, Garcia-Manero G, *et al.* Imatinib mesylate (STI571) therapy of Philadelphia chromosome-positive chronic myeloid leukemia in early chronic phase (PH+CML Early CP). American Society for Hematology Conference 2001; Abstract No. 577. (Abstract only.)
- Korycka A, Robak T. The comparison of influence of STI571 used alone or in combination either with 2-chlorodeoxyadenosine or fludarabine on the normal and chronic myelogenous leukemia progenitor cells in vitro. European Hematology Association (EHA) Annual Meeting 2002. (Preclinical/biological/genetic studies.)
- Marin D, Markt S, Bua M, Armstrong L, Goldman JM, Apperley JF, *et al.* The use of imatinib (STI571) in chronic myeloid leukemia:

some practical considerations. *Haematologica* 2002;**87**:979–88. (Not first-line treatment of CML.)

- O'Brien SG, Vallance SE, Craddock CM. Pegintron and STI571 Combination Evaluation Study (PISCES) in chronic phase chronic myeloid leukaemia. British Society for Haematology 2002; 42nd Annual Scientific Meeting, Brighton, UK, 15–18 April 2002. *Br J Haematol* **117**(Suppl 1):3–4. (No control group.)
- O'Dwyer ME, Mauro MJ, Aust S, Kuyf J, Paquette R, Sawyers C, *et al.* Ongoing evaluation of the combination of Imatinib mesylate (Glivec™) with low dose interferon-alpha for the treatment of chronic phase CML. European Hematology Association (EHA) Annual Meeting 2002. (No control group.)
- Schad M, Toplay J, Zeller W, Fruehauf S. Imatinib in combination with 17-allylamino-17-dexethoxy-geldanamycin (17-AAG) for treatment of chronic myelogenous leukemia. European Hematology Association (EHA) Annual Meeting 2002; Abstract No. 1005. (Preclinical/biological/genetic studies.)
- Topaly J, Schad M. Imatinib in combination with 17-allylamino-17-demethoxy-geldanamycin (17-AAG) for treatment of chronic myelogenous leukemia. 31st Annual Meeting of the International Society for Experimental Hematology, Montreal, Quebec, Canada, 5–9 July 2002. *Exp Hematol* **72**. (Preclinical/biological/genetic studies.)
- Trabacchi E, Bassi S, Saglio G, Rege-Cambrin G, Bonifazi F, De Vivo A, *et al.* Pegylated recombinant interferon alpha2b (Pegintron) associated with imatinib mesylate (Glivec) in Ph chronic myeloid leukaemic (CML) in early chronic phase: a phase II study of the ICSG on CML. European Hematology Association (EHA) Annual Meeting 2002. (No control group.)
- Vasilica M. The use of Glivec in chronic myeloid leukemia: report of 10 cases in a single institution. 31st Annual Meeting of the International Society for Experimental Hematology, Montreal, Quebec, Canada, 5–9 July 2002. *Exp Hematol* **96**. (Not first-line treatment of CML.)

IFN- α versus hydroxyurea

The following studies, which were included in the previous NICE assessment report, were excluded for this report

- Shepherd PC, Richards SM, Allan NC. Progress with interferon in CML – results of the MRC

UK CML III study. *Bone Marrow Transplant* 1996;**17** Suppl 3:S15–18. (More than 25% of HU group received an alternative treatment.)

- Ohnishi K, Tomonaga M, Kamada N, Onozawa K, Kuramoto A, Dohy H, *et al.* A long term follow-up of a randomized trial comparing interferon-alpha with busulfan for chronic myelogenous leukemia. *Leuk Res* 1998;**22**:779–86. (More than 25% of HU group received an alternative treatment.)

No articles were excluded from the update search at full text stage as none was identified as being relevant.

IFN- α versus BMT

The following were excluded from the search at full text stage

- Baccarani M. A prospective study of alpha-interferon and autologous bone marrow transplantation in chronic myeloid leukemia. *Br J Haematol* 1996;**93**:264. (Not comparative study; case series.)
- Gale RP, Park RE, Dubois RW, Herzig GP, Hocking WG, Horowitz MM, *et al.* Delphi-panel analysis of appropriateness of high-dose therapy and bone marrow transplants in chronic myelogenous leukemia in chronic phase. *Leuk Res* 1999;**23**:817–26. (Patients not in chronic phase CML.)
- Guilhot F, Sobocinski K, Guilhot J, Zhang M, Giralt S, Harousseau JL, *et al.* Comparison of HLA-identical sibling bone marrow transplants (BMT) versus interferon plus cytarabine (IFN/Ara-C) for chronic myelogenous leukemia (CML) in chronic phase (CP). *Blood* 2000;**96**:2343. (Abstract only.)
- Hehlmann R, Berger U, Hochhaus A, Reiter A, Pffirmann M, Hasford J, *et al.* Genetic randomization of allogeneic BMT vs drug treatment in chronic myelogenous leukemia: the German CML study III. 42nd Annual Meeting of the American Society of Hematology, San Francisco, California, USA, 1–5 December 2000. *Blood* **96**(11 Part 1):141a. (Abstract only.)
- Hehlmann R, Berger U, Hochhaus A, Reiter A, Pffirmann M, Hasford J, *et al.* Randomized comparison of allogeneic BMT and IFN-based therapy in chronic myeloid leukemia (CML). Annual Meeting of the German and Austrian Society for Hematology and Oncology, Graz, Austria, 21–2 October 2000. *Onkologie* **23**(Sonderheft 7):89. (Abstract only.)

- Ohnishi K, Ino T, Kishimoto Y, Usui N, Shimazaki C, Ohtake S, *et al.* Multicenter prospective study of interferon-alpha versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia: an interim analysis of the Kouseisho leukemia study group. *Blood* 2001;**98**:1468. (Duplicate publication.)
- Ohnishi K. Multicenter prospective study of interferon-alpha versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia: an interim analysis of the Kouseisho Leukemia Study Group. 43rd Annual Meeting of the American Society of Hematology, Part 1, Orlando, Florida, USA, 7–11 December 2001. *Blood* **98**(11 Part 1):348a. (Duplicate publication.)
- Silver RT, Woolf SH, Hehlmann R, Appelbaum FR, Anderson J, Bennett C, *et al.* An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. *Blood* 1999;**94**:1517–36. (Guideline, studies included separately.)
- Tura S. Monitoring the effect of allogeneic bone marrow transplantation (BMT) and of alpha-interferon (IFN) in chronic myeloid leukemia. A national prospective study in Italy. *Blood* 1996;**88**:2717. (Duplicate publication.)
- Tura S, Russo D, Fanin R, Zuffa E, Patriarca F, Fiacchini M, *et al.* Prognostic factors in chronic myeloid-leukemia – relationship with interferon and bone-marrow transplantation. *Leuk Lymphoma* 1993;**11**:67–71. (Duplicate publication.)

Appendix 5

Quality assessment of quality of life measurement in the imatinib versus interferon-alpha plus cytosine arabinoside trial

Criteria are taken from a systematic review by Clark and colleagues.⁶⁸

Quality criteria	Comments
QoL definition	Not explicit, although the trial states that side-effects can have a debilitating effect on QoL
Reasons for selecting the instrument	FACT-BRM: used in clinical trials, contains general domains as well as treatment specific modules and has been validated. The version used here was IFN defined, which may bias in favour of imatinib GRC scale: assist with interpretation of QoL scores EQ-5D: to obtain utility measures for use in the economic analysis
Domains	FACT-BRM: physical well-being, functional well-being, social well-being, emotional well-being and the impact of biological response modifiers on physical and emotional/cognitive functioning GCR scale: measures how patients rated their change in QoL since their previous visit on a five-point scale from very much better to very much worse (completed for six questions each relating to a FACT-BRM domain)
Single composite score	FACT-BRM: the 27 items make up subscales that match each domain. The score is adjusted for incomplete data using a pattern-mixture technique
Separate global rating	Yes
Supplemental patient comments	No additional patient comments were incorporated
Distinguishes overall QoL from health-related QoL	Uncertain
Rating of importance	The analysis was performed using standard techniques for the FACT-BRM; there is no indication that important items were identified and ranked according to personal value in this study
Relevance of items to patients	There is no demonstration in this study, or reference to previous studies, that the included items were relevant to patients in this study
Relevance of items from clinical experience	The treatment specific subscales (impact of biological response modifiers on physical and emotional/cognitive functioning) were thought to be the most likely to be affected by drug therapy
Reliability in current or previous studies	The study report states that the FACT-BRM is a "fully validated instrument"
Criterion or construct validity in current or previous studies	The analysis involved recalculation of "rasch" scores which provided supplemental evidence of the validity of the FACT-BRM. It does not appear that the instrument was compared with a gold standard measure (criterion validity)

continued

Quality criteria	Comments
Responsiveness	There was evidence of statistically significant changes when changes in treatment occurred. GRC scale score used to calibrate the FACT-BRM measure in a subset of patients from the USA
Interpretability	A change of 5 points on the FACT-BRM was said to be clinically significant according to a report on clinically relevant differences. The FACT-BRM scores were calibrated using the GRC scores obtained from the same population. There is also the possibility of informative censoring, because patients are censored for progression and loss of response, which are related to prognosis
Acceptability	The response rate for the QoL measurement was moderate, with 80% of the imatinib group and 59% of the IFN- α + Ara-C group being assessed at 12 months
Feasibility	Uncertain
Standardisation	There are published manuals that provide instructions regarding the analysis of FACT-BRM data
QoL, quality of life.	

Appendix 6

Data extraction tables

Imatinib

Reference and design	Intervention	Patients	Outcome measures
Bolton and Gathmann, 2002 ⁸	<i>Intervention:</i> imatinib <i>Comparison:</i> IFN- α + Ara-C	<i>Total number:</i> 1106 <i>Intervention:</i> 553 <i>Comparison:</i> 553	<i>Outcome measures used:</i> PFS, QoL, CR, HR, overall survival, adverse events
<i>Date of recruitment:</i> June 2000 to January 2002 ⁸	<i>Previous treatment:</i> HU and/or anagrelide	<i>Disease point:</i> chronic Ph+	<i>Length of follow-up:</i> median 14 months for imatinib group and 13 months for IFN- α + Ara-C group
<i>Country:</i> multi-centre (16 countries)	<i>Intervention dose, timing and route:</i> 400 mg/day oral	<i>Time since diagnosis:</i> within 6 months of diagnosis	
<i>Study design:</i> RCT	<i>Comparison dose, timing and route:</i> target dose of 5 MU/m ² per day IFN- α with maximum dose of 40 mg per day for 10 days per month of Ara-C	<i>Inclusion criteria:</i> age 18–70 years, enrolled within 6 months of diagnosis, previously untreated, Ph+ CML, no evidence of extramedullary involvement (except spleen/ liver)	
	<i>Rules for dose escalation:</i> imatinib: increased to maximum of 400 mg twice per day for patients who failed to achieve complete HR in 3 months or minor CR in 12 months or for patients who lose a major CR; IFN- α + Ara-C: dose escalated to maximum of 5 MU and 40 mg/day if tolerated	<i>Exclusion criteria:</i> patients in whom BMT is indicated and available, ECOG status \geq 3, uncontrolled medical problems, HIV, undergone major surgery in previous 4 weeks, pregnant, breast-feeding, history of another malignancy within past 5 years, non-compliant/potentially unreliable patients.	
	<i>Concurrent treatments:</i> HU, leucopheresis, allopurinol and anagrelide permitted	<i>Participant characteristics:</i> Imatinib: median age 50 years, M:F ratio 342:211, Sokal score low 53%, int 29%, high 19% IFN- α + Ara-C: median age 51 years, M:F ratio 310:243, Sokal score low 48%, int 30%, high 22%	
Results			
Outcome	Imatinib	IFN + Ara-C	p-value
Rate of complete HR	94.6%	76.5%	< 0.001
Rate of major CR	82.63%	39.8%	< 0.001
Rate of complete CR	67.8%	19.9%	< 0.001
Survival without progression (12 months)	97.2%	90.3%	< 0.001
Survival without accelerated or blast phase (12 months)	98.5%	93.1%	< 0.001
Overall survival rate	98.9%	97.9%	ns
218/553 (39%) of the IFN- α + Ara-C group crossed over to the other treatment, compared with 7/553 (1%) of the imatinib group			
51/553 (9%) of the imatinib group discontinued treatment, compared with 170/553 (31%) of the IFN- α + Ara-C group. Reasons for discontinuing included adverse events, unsatisfactory therapeutic effect, no longer required study drug (BMT), protocol violation, patient withdrew consent, loss to follow-up, administrative problems and death			
<i>continued</i>			

Methodological comments

Proper randomisation? Uncertain, performed by a central independent party, stratified by country, but method not specified
Allocation concealment? Yes
Groups similar at baseline? Yes for age, gender, weight, ECOG status, previous treatment with HU, Sokal scores
Eligibility criteria stated? Yes
Outcome assessors blinded? No
Providers of care blinded? No
Patients blinded? No
Point estimate and measure of variability reported? Yes
Power calculation performed at study design? Yes
All patients accounted for? Yes
Analysis performed on ITT basis? Yes

int, intermediate; Ph+, Philadelphia-positive.

IFN- α versus hydroxyurea

Reference and design	Intervention	Patients	Outcome measures
Benelux, 1998 ⁵ Date of recruitment: 1987 Country: Belgium, The Netherlands and Luxembourg Study design: RCT	Intervention: IFN- α_{2b} Comparison: HU Previous treatment: HU Intervention dose, timing and route: 3 MU 5 days/week s.c. Comparison dose, timing and route: not stated, oral Rules for dose escalation: HU adjusted to keep WBC $5-15 \times 10^9/l$ Concurrent treatment: HU	Total number: 195 Intervention: 100 Comparison: 95 Disease point: chronic Time since diagnosis: newly diagnosed Inclusion criteria: newly diagnosed, untreated, aged > 18 years, adequate hepatic and renal function Exclusion criteria: abnormalities other than Ph+, not Ph+/BCR-ABL Participant characteristics: IFN- α : median age 55.7 (range 20-83) years, M:F ratio 58:42, Sokal score low 29%, int 43%, high 28% HU: median age 56.4 (27-84) years, M:F ratio 53:42, Sokal score low 30%, int 33%, high 37%	Outcome measures used: HR, CR survival, WBC Length of follow-up: median 51 months, for living patients 66 months
Results			
1-year survival was 98% for the IFN- α group and 97% for the HU group. Complete HR was 62% for the IFN- α group and 38% for the HU group. Complete CR was 9% for the IFN- α group and 0% for the HU group. Partial CR was 7% and major CR was 16% in the IFN- α group, compared with 2% partial CR and 2% major CR in the HU group			
In the IFN- α group 24% of patients withdrew because of adverse effects, compared with 4% in the HU group			
Methodological comments			
Proper randomisation? Uncertain Allocation concealment? Uncertain Groups similar at baseline? Yes Eligibility criteria stated? Yes Outcome assessors blinded? No Providers of care blinded? No Patients blinded? No Point estimate and measure of variability reported? Yes Power calculation performed at study design? Yes All patients accounted for? Yes Analysis performed on ITT basis? Yes			
s.c., subcutaneous.			

Reference and design	Intervention	Patients	Outcome measures
Broustet et al., 1991 ⁶ Date of recruitment: 1990 Country: France Study design: RCT	Intervention: IFN- α_{2b} Comparison: HU Previous treatment: leucopheresis Intervention dose, timing and route: 4 MU daily s.c. Comparison dose, timing and route: not stated, oral Rules for dose escalation: HU according to WBC, IFN- α dose reduced if adverse effects Concurrent treatments: not stated	Total number: 58 Intervention: 24 Comparison: 26 Disease point: chronic Time since diagnosis: less than 3 months Inclusion criteria: Ph+ CML, no previous treatment (except leucopheresis), less than 3 months after diagnosis, aged > 18 years Exclusion criteria: karyotypic abnormalities other than Ph+, patients who may benefit from an allograft Participant characteristics: IFN- α : median age 55.6 \pm 10.6 years, M:F ratio 15:9, Sokal score low 29.2%, int 50%, high 20.8% HU: median age 58.6 \pm 7.1 years, M:F ratio 16:10, Sokal score low 26.9%, int 46.2%, high 26.9%	Outcome measures used: HR, CR, adverse effects Length of follow-up: not stated
Results			
A partial HR was achieved by 67% of the IFN- α group and by 88% of the HU group. A complete CR was achieved by 7% of the IFN- α group and by none of the HU group. A partial CR was achieved by 46% and a major CR by 53% of the IFN- α group, compared with 31% partial CR and 31% major CR in the HU group			
25% of patients in the IFN- α group withdrew because of side-effects, compared with 4% of the HU group			
Methodological comments			
Proper randomisation? Yes, centralised randomisation list, equilibrated every four patients			
Allocation concealment? Uncertain			
Groups similar at baseline? Yes			
Eligibility criteria stated? Yes			
Outcome assessors blinded? No			
Providers of care blinded? No			
Patients blinded? No			
Point estimate and measure of variability reported? No			
Power calculation performed at study design? No, uncertain that study had sufficient power			
All patients accounted for? Yes			
Analysis performed on ITT basis? No			

Reference and design	Intervention	Patients	Outcome measures
<p>Hehlmann <i>et al.</i>, 1994⁸¹</p> <p>Date of recruitment: 1983</p> <p>Country: Germany</p> <p>Study design: RCT</p>	<p>Intervention: IFN-α_{2a} or IFN-α_{2b}</p> <p>Comparison: HU</p> <p>Previous treatment: none</p> <p>Intervention dose, timing and route: 5 MU daily s.c.</p> <p>Comparison dose, timing and route: HU 40 mg/kg daily oral</p> <p>Rules for dose escalation: rules for dose change/stop</p> <p>Concurrent treatments: not stated</p>	<p>Total number: 327</p> <p>Intervention: 133</p> <p>Comparison: 194</p> <p>Disease point: chronic</p> <p>Time since diagnosis: newly diagnosed</p> <p>Inclusion criteria: newly diagnosed, not pretreated, chronic phase. Also six of: unexplained fatigue, weight loss > 10% in 6 months, fever of > 38.5°C on 5 consecutive days, organomegaly related symptoms, leucocytes > $50 \times 10^9/l$ and or thrombocytosis > $1 \times 10^{12}/l$</p> <p>Exclusion criteria: lack of consent, living overseas, psychiatric problems, language barriers assessed as too difficult to keep to protocol</p> <p>Participant characteristics: IFN-α: median age 47.4 (range 18–85) years M:F ratio 88:45, Sokal score low 27.1%, int 35.3%, high 37.6% HU: median age 46.9 (15–84) years, M:F ratio 98:96, Sokal score low 29.4%, int 33.5%, high 37.1%</p>	<p>Outcome measures used: HR, CR survival, adverse effects</p> <p>Length of follow-up: not clear, “3 years after last patient randomised”</p>
<p>Results</p> <p>1-year survival was 96% in the IFN-α group and 96% for HU. Complete HR was 31% for IFN-α and 39% for HU. Partial HR was 52% for IFN-α and 51% for HU. Major HR was 83% for IFN-α and 90% for HU. Complete CR was 5% for IFN-α and 1% for HU. Partial CR was 2% for IFN-α and 1% for HU. Major CR was 7% for IFN-α and 2% for HU.</p> <p>24% of the IFN-α group and 1% of the HU group withdrew because of side-effects.</p>			
<p>Methodological comments</p> <p>Proper randomisation? Yes, using Efron lists, stratified for hospitals, randomised centrally by telephone</p> <p>Allocation concealment? Uncertain</p> <p>Groups similar at baseline? Yes</p> <p>Eligibility criteria stated? Yes</p> <p>Outcome assessors blinded? No</p> <p>Providers of care blinded? No</p> <p>Patients blinded? No</p> <p>Point estimate and measure of variability reported? Yes</p> <p>Power calculation performed at study design? Yes</p> <p>All patients accounted for? Yes</p> <p>Analysis performed on ITT basis? Yes</p>			

Reference and design	Intervention	Patients	Outcome measures
Italian Cooperative, 1998 ²¹	<i>Intervention:</i> IFN- α <i>Comparison:</i> HU/BU	<i>Total number:</i> 322 <i>Intervention:</i> 218 <i>Comparison:</i> HU/BU 104	<i>Outcome measures used:</i> CR survival, adverse effects
<i>Date of recruitment:</i> 1986	<i>Previous treatment:</i> none	<i>Disease point:</i> chronic	<i>Length of follow-up:</i> living patients
<i>Country:</i> Italy	<i>Intervention dose, timing and route:</i> 9 MU daily s.c.	<i>Time since diagnosis:</i> not stated	95–129 months, median 112 months
<i>Study design:</i> RCT	<i>Comparison dose, timing and route:</i> HU/BU not stated, oral	<i>Inclusion criteria:</i> Ph+ CML in first chronic phase, minimal pretreatment (< 100 mg BU or < 50 g HU) or none	
	<i>Rules for dose escalation:</i> not stated	<i>Exclusion criteria:</i> > 70 years, accelerated or blast phase, any associated disorder that could influence treatment or its toxicity	
	<i>Concurrent treatments:</i> HU, BU	<i>Participant characteristics:</i> IFN- α : age not stated, M:F ratio not stated, Sokal score not stated HU/BU: age not stated, M:F ratio not stated, Sokal score not stated	
Results			
1-year survival rates were 95% for the IFN- α group and 96% for the HU/BU group. Neither group reported any patients with major HR. 4% of the IFN- α group experienced complete CR compared with none of the HU/BU group. There was 2% partial CR and 6% major CR in the IFN- α group, compared with 1% partial CR and 1% major CR in the HU/BU group			
18% of the IFN- α group withdrew because of side-effects.			
Methodological comments			
<i>Proper randomisation?</i> Uncertain, allocation 2 IFN- α :1 HU/BU			
<i>Allocation concealment?</i> Uncertain			
<i>Groups similar at baseline?</i> No			
<i>Eligibility criteria stated?</i> Yes			
<i>Outcome assessors blinded?</i> No			
<i>Providers of care blinded?</i> No			
<i>Patients blinded?</i> No			
<i>Point estimate and measure of variability reported?</i> Yes			
<i>Power calculation performed at study design?</i> Not stated			
<i>All patients accounted for?</i> Yes			
<i>Analysis performed on ITT basis?</i> Yes			

INF- α versus BMT

Reference and design	Intervention	Patients	Outcome measures
Gale <i>et al.</i> , 1998 ⁹ Date of recruitment: patients diagnosed between 1983 and 1991 Country: international, multicentre Study design: non-randomised comparative study	Intervention: non-T-cell depleted, HLA-identical sibling BMT Comparison: HU or IFN- α Previous treatment: IFN- α with or without HU ($n = 131$), or HU ($n = 417$) BMT preconditioning: IFN- α with or without HU IFN- α /HU dose, timing and route: IFN- α 5 MU daily s.c. HU 40 mg/kg daily oral Rules for dose escalation: Rules for dose change/stop Concurrent treatments: post-transplant methotrexate and cyclosporine for GVHD prophylaxis	Total number: 744 Intervention: 548 Comparison: 196 Disease point: chronic Time since diagnosis: median time from diagnosis to transplant 10.1 (range 2–84) months Inclusion criteria: ≥ 15 and ≤ 55 years of age Exclusion criteria: patients with $> 10\%$ circulating blasts at diagnosis (IFN- α /HU group only) Participant characteristics: BMT: median age 35 (range 15–54) years, M:F ratio 331:217, Sokal score low 41%, int 37%, high 22% IFN- α /HU: median age 41 (range 15–55) years, M:F ratio 119:77, Sokal score low 37%, int 42%, high 21%	Outcome measure used: survival Length of follow-up: BMT: median 51.6 months; IFN- α : median 78 months

Results

Adjusted probability of survival after diagnosis (adjusted for time to transplant, age, gender, spleen size and year of diagnosis):

	RR of death	
	BMT group	IFN/HU group
Year of diagnosis 1988 or later	0.58 ($p = 0.003$)	ns
Spleen size ≥ 10 cm	ns	2.11 ($p < 0.001$)
Female	0.65 ($p = 0.02$)	0.63 ($p = 0.03$)
Age > 35 years	1.14 ($p = 0.04$)	ns

The 7-year probability of survival was 58% in the BMT group (95% CI 50 to 65%) compared with 32% in the IFN- α /HU group (95% CI 22 to 44%).

There was a statistically significant survival advantage for HU/IFN- α in the first 2.5 years after diagnosis, and a significant advantage for people undergoing BMT after 5.5 years (survival was similar in years 2.5–5.5). When considering only the 331 people who received a transplant within 1 year of diagnosis, there was a survival advantage for IFN- α /HU in the first 1.8 years and for BMT after 4.8 years. Survival in the BMT group did not differ according to Sokal risk group. For the IFN- α /HU group low-risk patients had significantly longer survival than intermediate- or high-risk patients

Methodological comments

Proper randomisation? No

Allocation concealment? NA

Groups similar at baseline? No, time to intervention was different but adjusted for using left-truncated Cox regression model. There were also differences in baseline patient characteristics (age, gender, spleen size, blasts and year of diagnosis), which were adjusted using covariates in the Cox model and by stratifying analysis by Sokal score

Eligibility criteria stated? Yes

Outcome assessors blinded? No, but outcome is objective

Providers of care blinded? Not possible

Patients blinded? No

Point estimate and measure of variability reported? Yes

Power calculation performed at study design? No

All patients accounted for? Yes

Analysis performed on ITT basis? NA

Reference and design	Intervention	Patients	Outcome measures
<p>Gaziev <i>et al.</i>, 2002¹⁰</p> <p>Date of recruitment: April 1981 to February 2000</p> <p>Country: Italy</p> <p>Study design: non-randomised comparative study</p>	<p>Intervention: BMT (HLA-identical sibling donors, identical twin or HLA phenotypically matched)</p> <p>Comparison: chemotherapy or IFN-α</p> <p>Previous treatment: not stated</p> <p>BMT preconditioning: either cyclophosphamide plus single-dose total body irradiation at 10 Gy or busulfan plus cyclophosphamide</p> <p>Comparison dose, timing and route: patients received different doses</p> <p>Rules for dose escalation: not stated</p> <p>Concurrent treatments: prophylactic antibiotics, acyclovir, amphotericin B and trimethoprim/sulfamethoxazole</p>	<p>Total number: 175</p> <p>Intervention: 105 (HLA-identical sibling donors 102, identical twins 2, HLA-identical relative donor 1)</p> <p>Comparison: 70</p> <p>Disease point: at start of trial 88 (84%) people were in chronic phase and 17 (16%) advanced phase</p> <p>Time since diagnosis: BMT: < 12 months 52%, 12–36 months 34%, > 36 months 14%. Year of diagnosis before 1990 63% for BMT and 67% for non-BMT</p> <p>Inclusion criterion: patients with CML</p> <p>Exclusion criteria: none stated</p> <p>Participant characteristics: Chronic phase BMT: median age 31 (range 10–53) years, M:F ratio 38:50, Sokal score low 59%, int 32%, high 9% Non-BMT: median age 43 (range 14–55) years, M:F ratio 45:25, Sokal score low 68%, int 29%, high 3%</p>	<p>Outcome measures used: survival, toxicity, relapse, GVHD</p> <p>Length of follow-up: median for IFN-α 46.8 (range 12–144) months</p>
<p>Results</p> <p>4/88 patients in the BMT group died before 21 days. Of the BMT patients 38/105 (36%) developed GVHD grade 2–4 and 23/105 (22%) grade 3–4. 70/105 (67%) BMT patients developed Gram-negative or -positive infections; 33% fungal infections with 24% <i>Candida</i> species</p> <p>Overall, 51/105 (49%) patients died, 26/105 (25%) within 100 days of transplant. Relapse for those having a BMT occurred in 12/88 (14%) chronic phase and 4/17 (24%) advanced phase patients. The estimated 10-year survival in patients receiving BMT in chronic phase was 56% (range 47–68%) and was significantly higher than chemotherapy at 10% (range 7–24%) and IFN-α at 33% (range 16% to 54%). Median survival for IFN-α was 7 years and for chemotherapy was 5 years (still not reached for BMT).</p>			
<p>Methodological comments</p> <p>Proper randomisation? No</p> <p>Allocation concealment? NA</p> <p>Groups similar at baseline? The BMT and non-BMT groups were matched for clinical and haematological features including Sokal score (but excluding age and gender). Groups were not similar for age and gender, with the BMT group being younger with more females</p> <p>Eligibility criteria stated? No</p> <p>Outcome assessors blinded? Not stated, although some outcomes were objective</p> <p>Providers of care blinded? Not possible</p> <p>Patients blinded? Not possible</p> <p>Point estimate and measure of variability reported? Yes</p> <p>Power calculation performed at study design? No</p> <p>All patients accounted for? Yes</p> <p>Analysis performed on ITT basis? Yes stated, although not strictly followed</p>			

Reference and design	Intervention	Patients	Outcome measures
<p>Italian Cooperative, 1999⁸⁰</p> <p><i>Date of recruitment:</i> January 1984 to December 1991</p> <p><i>Country:</i> Italy</p> <p><i>Study design:</i> cohort study</p>	<p><i>Intervention:</i> autologous BMT (twin, HLA-identical sibling with or without T-cell depletion, related donor partially HLA matched, or unrelated donor HLA matched)</p> <p><i>Comparison:</i> conventional chemotherapy or IFN-α</p> <p><i>Previous treatment:</i> BMT patients were initially treated with HU or IFN-α. Comparison groups were previously untreated</p> <p><i>BMT preconditioning:</i> total body irradiation and cyclophosphamide \pm BU, GVHD prophylaxis</p> <p><i>Comparison dose, timing and route:</i> IFN-α 9 MU/day, HU dose not predetermined</p> <p><i>Rules for dose escalation:</i> IFN-α escalated when patients progress</p> <p><i>Concurrent treatments:</i> cyclosporine and/or methotrexate (also given before treatment)</p>	<p><i>Total number:</i> 840</p> <p><i>Intervention:</i> 181/840 (22%) went on to have a BMT (HLA-identical sibling donor 153, identical twins 1, HLA-matched relative donor 9, HLA-matched unrelated donor 18)</p> <p><i>Comparison:</i> 659/840 (78%) did not go on to have a BMT</p> <p><i>Disease point:</i> all chronic phase when registered</p> <p><i>Time since diagnosis:</i> mean time from registration for BMT was 15.1 months (\pm 10.4)</p> <p><i>Inclusion criterion:</i> Ph+ CML</p> <p><i>Exclusion criteria:</i> patients > 56 years, patients previously treated for CML</p> <p><i>Participant characteristics:</i></p> <p><i>BMT:</i> median age 32 years, M:F ratio 71:49, Sokal score low 49%, int 29%, high 22%</p> <p><i>IFN-α:</i> median age 41.5 years, M:F ratio 190:132, Sokal score low 50%, int 27%, high 23%</p> <p><i>Chemotherapy:</i> median age 42 years, M:F ratio 192:145, Sokal score low 45%, int 32%, high 19%</p>	<p><i>Outcome measures used:</i> HR, CR, survival, leukaemia-free survival and relapse</p> <p><i>Length of follow-up:</i> Until June 1997</p>
<p>Results</p> <p>In the chemotherapy group 62% had a complete HR and in the IFN-α group 60%. Overall CR was 4% for chemotherapy and 35% for IFN-α.</p> <p>Based on 120 who underwent standard allogenic BMT: for allogenic BMT patients 43/120 (36%) died and 15/120 (13%) relapsed. At 10 years the overall survival rate was 55% (95% CI 45 to 65%) for BMT compared with 32% (95% CI 26 to 39%) for IFN-α and 18% (95% CI 14 to 22%) for chemotherapy. Median survival was not yet reached in BMT group and was 72 months in IFN-α group and 54 months in the chemotherapy group</p>			
<p>Methodological comments</p> <p><i>Proper randomisation?</i> No</p> <p><i>Allocation concealment?</i> NA</p> <p><i>Groups similar at baseline?</i> No, those undergoing BMT were significantly younger; groups had similar risk scores and blood profiles</p> <p><i>Eligibility criteria stated?</i> Yes</p> <p><i>Outcome assessors blinded?</i> Not stated, although some outcomes are objective</p> <p><i>Providers of care blinded?</i> Not possible</p> <p><i>Patients blinded?</i> Not possible</p> <p><i>Point estimate and measure of variability reported?</i> Yes</p> <p><i>Power calculation performed at study design?</i> No</p> <p><i>All patients accounted for?</i> No, the 61 patients who underwent non-standard allogenic BMT were excluded</p> <p><i>Analysis performed on ITT basis?</i> Not stated</p>			

Reference and design	Intervention	Patients	Outcome measures
<p>Ohnishi <i>et al.</i>, 2000¹¹</p> <p>Date of recruitment: May 1991 to December 1994</p> <p>Country: Japan</p> <p>Study design: prospective non-randomised comparative study</p>	<p>Intervention: BMT (HLA-matched sibling or donor)</p> <p>Comparison: IFN-α + chemotherapy</p> <p>Previous treatment: until BMT patients were given chemotherapy with or without IFN-α</p> <p>BMT preconditioning: HU and/or BU</p> <p>Comparison dose, timing and route: IFN-α dose adjusted between 3 and 9 MU/day</p> <p>Rules for dose escalation: dose adjusted to maintain WBC counts</p> <p>Concurrent treatments: not stated</p>	<p>Total number: 90 (1 non-evaluable)</p> <p>Intervention: 23 (HLA-identical relative donor 15, HLA-matched unrelated donor 8)</p> <p>Comparison: 66</p> <p>Disease point: chronic phase (unrelated donor group had 88% in chronic phase and 12% in blast phase at time of transplant)</p> <p>Time since diagnosis: time from onset to treatment IFN-α group < 6 months 61%, BMT group 23%. Median duration from registration to transplantation in BMT group 9 (range 2–27) months in family donor BMT and 29 (range 23–57) months in unrelated donor BMT.</p> <p>Inclusion criteria: newly diagnosed patients with CML, Ph+, chronic phase, score 0–2 on ECOG performance status, age 20–70 years</p> <p>Exclusion criteria: serious disorders in heart, lung, kidney or liver; serious infectious and psychiatric disorders, other neoplasms, hypersensitivity reaction against IFN-α and accelerated and blast patients. Patients > 45 years were not eligible for BMT and were given IFN-α</p> <p>Participant characteristics: IFN-α: mean age 50 years, M:F ratio 25:41, performance status (ECOG) 0 = 51%, 1 = 5%, 2 = 4% BMT: mean age 33 years, M:F ratio 9:14, performance status (ECOG) 0 = 17%, 1 = 2%, 2 = 0%</p>	<p>Outcome measures used: HR, CR, duration of chronic phase and survival</p> <p>Length of follow-up: median follow-up of 54 (range 30–76) months in the IFN-α group</p>
<p>Results</p> <p>In the IFN-α group 47/66 (71%) had a complete HR and in the BMT group (17/23) 74%. In the IFN-α group a complete CR was noted in 5/66 (8%). In the IFN-α group the predicted 6-year overall survival rate was 54.5%. In the BMT group the predicted 6-year survival was 93.3% for HLA-identical family donors (one death from GVHD) and the predicted 5.5-year survival was 21.9% for unrelated donors (three deaths from GVHD). When survival was assessed post-transplantation the predicted 5-year survival for family donor BMT was 93.3% and the predicted 3-year survival for unrelated donor BMT was 29.2%</p> <p>The outcome of family donor BMT was excellent compared with patients who achieved a CR. However, the outcome of unrelated donor BMT was inferior to that of patients with CR</p>			
<p>Methodological comments</p> <p>Proper randomisation? No</p> <p>Allocation concealment? NA</p> <p>Groups similar at baseline? No, patients were younger in the BMT group owing to the exclusion of patients older than 45 years</p> <p>Eligibility criteria stated? Yes</p> <p>Outcome assessors blinded? No, some outcomes are objective</p> <p>Providers of care blinded? Not possible</p> <p>Patients blinded? Not possible</p> <p>Point estimate and measure of variability reported? No</p> <p>Power calculation performed at study design? No</p> <p>All patients accounted for? Yes</p> <p>Analysis performed on ITT basis? Yes</p>			

Reference and design	Intervention	Patients	Outcome measures
<p>Ohnishi et al., 2001¹²</p> <p>Date of recruitment: February 1995 to November 1999</p> <p>Country: Japan (multicentre)</p> <p>Study design: prospective non-randomised comparative study</p>	<p>Intervention: BMT (HLA-identical relative or HLA-matched unrelated donor)</p> <p>Comparison: IFN-α</p> <p>Previous treatment: Until BMT, patients were given chemotherapy with or without IFN-α</p> <p>BMT preconditioning: HU and/or IFN-α</p> <p>Comparison dose, timing and route: IFN-α dose adjusted between 3 and 10 MU/day</p> <p>Rules for dose escalation: dose adjusted to maintain WBC counts</p> <p>Concurrent treatments: HU for the IFN-α group</p>	<p>Total number: 254 evaluable (279 recruited)</p> <p>Intervention: related BMT 50, unrelated BMT 29</p> <p>Comparison: 175</p> <p>Disease point: chronic phase (for unrelated donors 90% were in chronic phase, 7% accelerated and 3% blast at time of transplant)</p> <p>Time since diagnosis: median time from registration to transplant 9 (range 3–43) months for related donor group and 19 (range 7–45) months for unrelated donor group</p> <p>Inclusion criteria: newly diagnosed patients with CML, Ph+, chronic phase, score 0–2 on ECOG performance status, age ≥ 15 years</p> <p>Exclusion criteria: serious disorders in heart, lung, kidney or liver, serious infectious and psychiatric disorders, other neoplasms, hypersensitivity reaction against IFN-α and accelerated and blast patients. Patients > 50 years were not eligible for BMT and were given IFN-α</p> <p>Participant characteristics:</p> <p>IFN-α: median age 54 (range 19–79) years, M:F ratio 110:65, Sokal score 1.01 ± 0.84</p> <p>BMT (related donor): median age 36 (range 19–53) years, M:F ratio 33:17, Sokal score 0.76 ± 0.27</p> <p>BMT (unrelated donor): median age 31 (range 17–48) years, M:F ratio 16:13, Sokal score 0.80 ± 0.40</p>	<p>Outcome measures used: HR, CR, duration of chronic phase and survival</p> <p>Length of follow-up: median IFN-α group 38 (range 9–66) months</p>
<p>Results</p> <p>In the IFN-α group 148/175 (89%) had a complete HR compared with 53/79 (78%) in the BMT group. In the IFN-α group a major CR was noted in 62/175 (38%) of patients. In the BMT related donors group 2/50 (5%) had a complete CR, as did 1/29 (4%) in the unrelated donors group</p> <p>For the IFN-α group predicted 5-year survival was 79%. For the related donors BMT group predicted 5-year survival was 72% and for the unrelated donors BMT group was 67%. When survival was assessed post-transplant the predicted 4-year survival rate was 76% for the related donors BMT group and the predicted 3.5-year overall survival rate was 68% for the unrelated donors BMT group.</p>			
<p>Methodological comments</p> <p>Proper randomisation? No</p> <p>Allocation concealment? NA</p> <p>Groups similar at baseline? No, the BMT groups were significantly younger than the IFN-α group, the WBC count was significantly lower in the IFN-α group than for BMT, and the Sokal score was significantly higher in the IFN-α group than BMT</p> <p>Eligibility criteria stated? Yes</p> <p>Outcome assessors blinded? No, some outcomes are objective</p> <p>Providers of care blinded? Not possible</p> <p>Patients blinded? Not possible</p> <p>Point estimate and measure of variability reported? No</p> <p>Power calculation performed at study design? No</p> <p>All patients accounted for? Yes</p> <p>Analysis performed on ITT basis? Yes</p>			

Appendix 7

Interferon-alpha compared with hydroxyurea: quality assessment and effectiveness

Summary of the quality of included studies comparing IFN- α hydroxyurea

Quality criteria	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1994 ⁸¹	Italian Cooperative, 1998 ²¹
Proper randomisation?	?	✓	✓	?
Allocation concealed?	?	?	?	?
Groups similar at baseline?	✓	✓	✓	×
Eligibility criteria stated?	✓	✓	✓	✓
Outcome assessors blinded?	×	×	×	×
Providers of care blinded?	×	×	×	×
Patients blinded?	×	×	×	×
Point estimates and measures of variability?	✓	×	✓	✓
Power calculation performed at study design?	✓	×	✓	?
All patients accounted for?	✓	✓	✓	✓
Analysis performed on ITT?	✓	×	✓	✓

?, not stated/uncertain; ✓, yes; × = no.

Internal validity

Sample size

The Benelux study¹⁹⁹⁸⁵ randomised 100 people to receive IFN- α and 95 to the control group. Hehlmann and colleagues⁸¹ randomised 133 people to IFN- α , 194 to hydroxyurea and 186 to BU. Broustet and colleagues⁶ randomised 30 people to IFN- α and 28 to hydroxyurea and the Italian Cooperative Study Group²¹ randomised 218 people to IFN- α and 104 to conventional chemotherapy.

The Benelux⁵ and Hehlmann⁸¹ studies performed power calculations before the start of the studies to ensure adequate sample sizes. The Benelux study⁵ had power (at least 83 patients in each arm) to detect a 20% improvement from 50% to 70% for a 3-year median freedom from progression period ($\alpha = 0.05$, one-sided, power $\beta = 0.8$). Hehlmann and colleagues⁸¹ calculated that they needed 518 patients (130 IFN- α , 194 hydroxyurea and 194 busulfan) to detect a ratio of at least 1.42 in the median survival time in favour of IFN- α ($\alpha = 0.05$, two sided, $\beta = 0.20$).

The Italian Cooperative Study Group²¹ detected a statistically significant difference in median survival between the study groups. There is

therefore no possibility of a type 2 error owing to inadequate sample size.

The Broustet study⁶ did not test statistical significance and did not have sufficient power to detect a statistically significant difference between the two study groups. Using major CR as the main outcome and assuming a 53% response for IFN- α and a 31% response for HU, at least 39 people would be required per group to have a 50% chance of declaring their observed difference as significant ($\alpha = 0.05$, two-sided).

Selection bias

Two studies described the methods of randomisation^{6,81} and the other two studies failed to provide details of randomisation.^{5,21} Broustet and colleagues⁶ reported that randomisation of patients to IFN- α or hydroxyurea was performed by one centre according to a centralised randomisation list, calibrated every four patients. Hehlmann and colleagues⁸¹ state that randomisation lists were computed according to Elfron and stratified for participating hospitals. Suitable patients were randomised by telephone from a central location.

None of the included studies described concealment of group allocation.

The study groups were similar at baseline in three of the included studies.^{5,6,81} The IFN- α and hydroxyurea groups were similar at baseline for age, gender and Sokal score in the Benelux⁵ and Broustet⁶ studies. The IFN- α and hydroxyurea groups were similar for age and Sokal score in the Hehlmann study.⁸¹ The Italian Cooperative Study Group on CML²¹ failed to provide baseline demographic data for the study groups.

The Italian study²¹ is prone to bias owing to possible inadequate randomisation and possible incomparability of the two study groups.

Performance bias

In the comparison groups for all four studies treatment was administered orally, whereas in the intervention group treatment was administered subcutaneously. Few details of concurrent treatments are provided, so it is uncertain whether concurrent treatments varied between intervention and comparison groups.

Rules for dose escalation varied between IFN- α and hydroxyurea groups. The dose of hydroxyurea was usually adjusted to maintain the WBC count at a particular level. However, in comparison, IFN- α doses were usually adjusted systematically according to response and adverse effects.

Detection bias

None of the studies reported blinding outcome assessors, providers of care or patients. Each of the studies used an objective outcome measure.

Attrition bias

All four studies accounted for all of the people who were enrolled.^{5,6,21,81} Only the Broustet study⁶ lost contact with patients ($n = 2$). Three studies stated that they performed analysis on an ITT basis.^{5,21,81}

Patients with CML most frequently discontinue treatment because of adverse effects, disease progression, protocol violations, BMT or personal choice (see the table below).

Informative censoring may also be present. This occurs because of a relationship between reasons for censoring (loss to follow-up, protocol violations, BMT or disease progression) and prognosis.

Reporting bias

Three studies reported confidence intervals for survival estimates.^{5,21,81}

External validity

The studies all provided sufficient details to make an assessment of generalisability. All studies described eligibility criteria and exclusion criteria.^{5,6,21,81} Patient characteristics such as age, gender and risk scores were provided by three of the studies.^{5,6,81}

Patients in the IFN- α versus hydroxyurea studies had more severe disease than patients in the imatinib trial discussed previously (see *Table 10*). Patients presenting in clinical practice may, however, still have more serious disease than those enrolled in these trials, which may effect generalisability.

Reasons for discontinuation of treatment: IFN- α versus hydroxyurea

	Benelux, 1998 ⁵		Broustet et al., 1991 ⁶		Hehlmann et al., 1994 ⁸¹		Italian Cooperative, 1998 ²¹	
	IFN- α ($n = 85$)	HU ($n = 83$)	IFN- α ($n = 30$)	HU ($n = 28$)	IFN- α ($n = 133$)	HU ($n = 194$)	IFN- α ($n = 218$)	HU ($n = 104$)
Acceleration or blast crisis	37	52	1	2	–	–	–	–
Adverse reactions	24	4	6	1	24	1	39	–
Intercurrent other diseases	6	6	–	1	–	–	–	–
BMT	16	7	–	–	20	26	–	–
Refusal/voluntary withdrawal	1	10	3	1	10	11	–	–
Protocol violations	1	4	1	–	–	15	–	–
Treatment too recent	–	–	1	–	–	–	–	–
Loss of contact with patient	–	–	–	2	–	–	–	–
Therapeutic inefficiency/resistance	–	–	4	–	55	128	–	–
Disease evolved to acute phase	–	–	–	3	–	–	–	–
Second neoplasia	–	–	–	–	2	1	–	–
Total	85	83	16	10	111	182	114	37

Patient characteristics and treatment details from IFN- α studies

Study characteristic	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1994 ⁸¹	Italian Cooperative, 1998 ²¹
Median haemoglobin level reported (g/dl) (minimum–maximum)	11.8 (6.1–15.9)	Not stated	IFN- α 11.8 (4.2–15.4) HU 11.9 (6.1–16.3)	Not stated
Splenomegaly	IFN- α 61% HU 65%	Not stated	IFN- α 68.3% HU 72.6%	Not stated
Hepatomegaly	Not stated	Not stated	IFN- α 47.9% HU 46.3%	Not stated
Extramedullary involvement	Not stated	Not stated	IFN- α 9.2% HU 3.7%	Not stated
Median age (years) (minimum–maximum or \pm SD)	IFN- α 55.7 (20–88) HU 56.4 (27–84)	IFN- α 55.6 (\pm 10.6) HU 58.6 (\pm 7.1)	IFN- α 47.4 (18–85) HU 46.9 (15–84)	Not stated
Gender ratio M:F (% male)	IFN- α 58:42 (58) HU 53:42 (56)	IFN- α 15:9 (63) HU 16:10 (62)	IFN- α 88:45 (66) HU 98:96 (51)	Not stated
Time since diagnosis	Newly diagnosed	< 3 months	Newly diagnosed	Not stated
Sokal score	IFN- α : Low 29% Int 43% High 28% HU: Low 30% Int 33% High 37%	IFN- α : Low 29.2% Int 50% High 20.8% HU: Low 26.9% Int 46.2% High 26.9%	IFN- α : Low 27.1% Int 35.3% High 37.6% HU: Low 29.4% Int 33.5% High 37.1%	Not stated
Previous treatment	None	Leucopheresis	None	None
Interferon drug type	IFN- α_{2b}	IFN- α_{2b}	IFN- α_{2a} or α_{2b}	IFN- α
IFN- α dose	3 MU 5 days/week s.c.	4 MU daily s.c.	5 MU daily s.c.	9 MU daily s.c.
Concomitant drugs	HU	Not stated	Not stated	HU, BU
Median length of follow-up	51 months	Not stated	Not stated	112 months

Outcome assessment was not performed independently or blinded, although outcomes were objective.

Results and survival curves for IFN- α compared with hydroxyurea

The Benelux trial⁵ followed patients for a maximum of 7 years. *Figure 19* shows overall survival for the IFN- α and hydroxyurea (control) groups. At 3 years approximately 70% had

survived in the control group, compared with almost 80% in the IFN- α group. At 5 years survival was approximately 55% in both groups and at 7 years survival was approximately 32% in the IFN- α group and 36% in the control group. Overall the two survival curves were not statistically significantly different ($p = 0.84$).

Figure 20 shows time until disease progression for the IFN- α and hydroxyurea groups in the Benelux study. At 3-year follow-up approximately 40% in the IFN- α group had experienced disease progression, compared with approximately 42% in

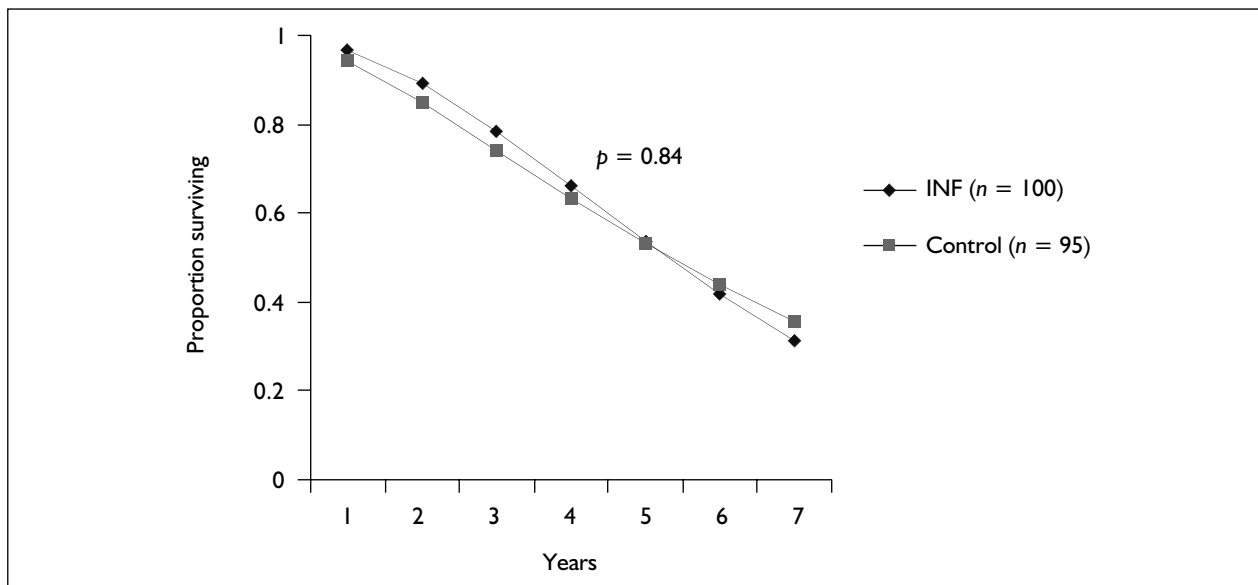


FIGURE 19 Overall survival, derived from data presented in the Benelux study⁵

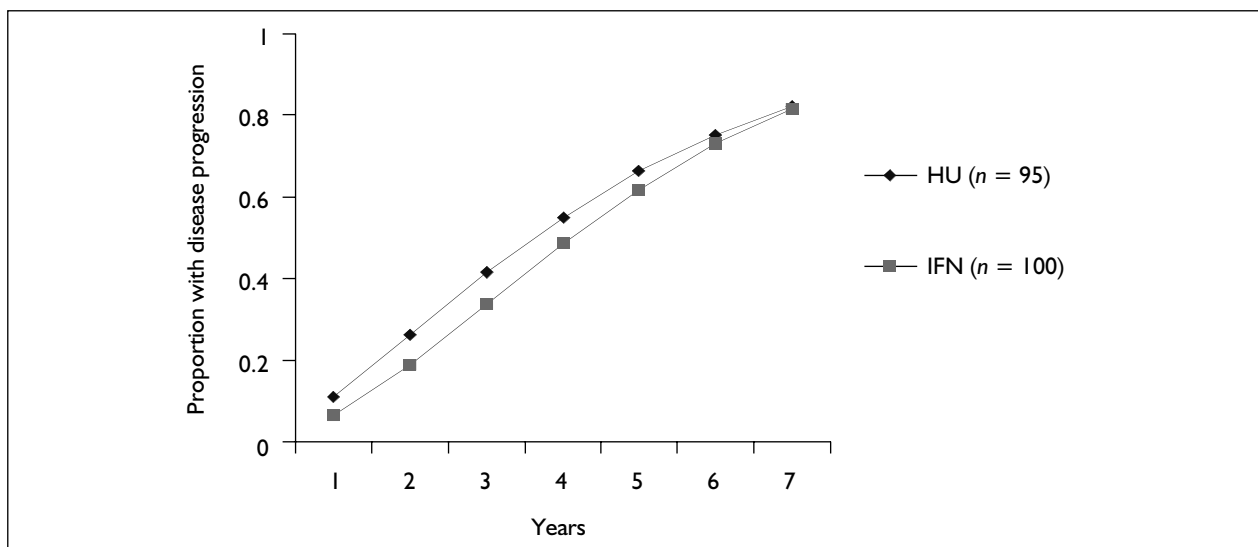


FIGURE 20 Time to disease progression, derived from data presented in the Benelux study⁵

the control group. Follow-up at 5 years showed that approximately 59% in the IFN- α group had progressed, compared with approximately 65% in the control group. At 7-year follow-up approximately 85% of the IFN- α group had experienced disease progression, compared with 80% in the control group. Overall, the curves for time until disease progression were not statistically significantly different.

The study by Broustet and colleagues⁶ does not provide survival curves or time to disease progression curves.

Hehlmann and colleagues⁷ present 10-year survival curves of IFN- α compared with hydroxyurea for treatment of CML (Figure 21). Average 3-year survival for both groups was 70%. At 5-year follow-up approximately 58% of the IFN- α group was alive compared with approximately 45% of the hydroxyurea group. At 7-year follow-up the IFN- α group experienced approximately 28% survival and at 9-year follow-up the hydroxyurea group experienced approximately 4% survival (the difference in length of follow-up is explained by recruitment of IFN- α patients starting 2.9 years after recruitment of hydroxyurea patients).

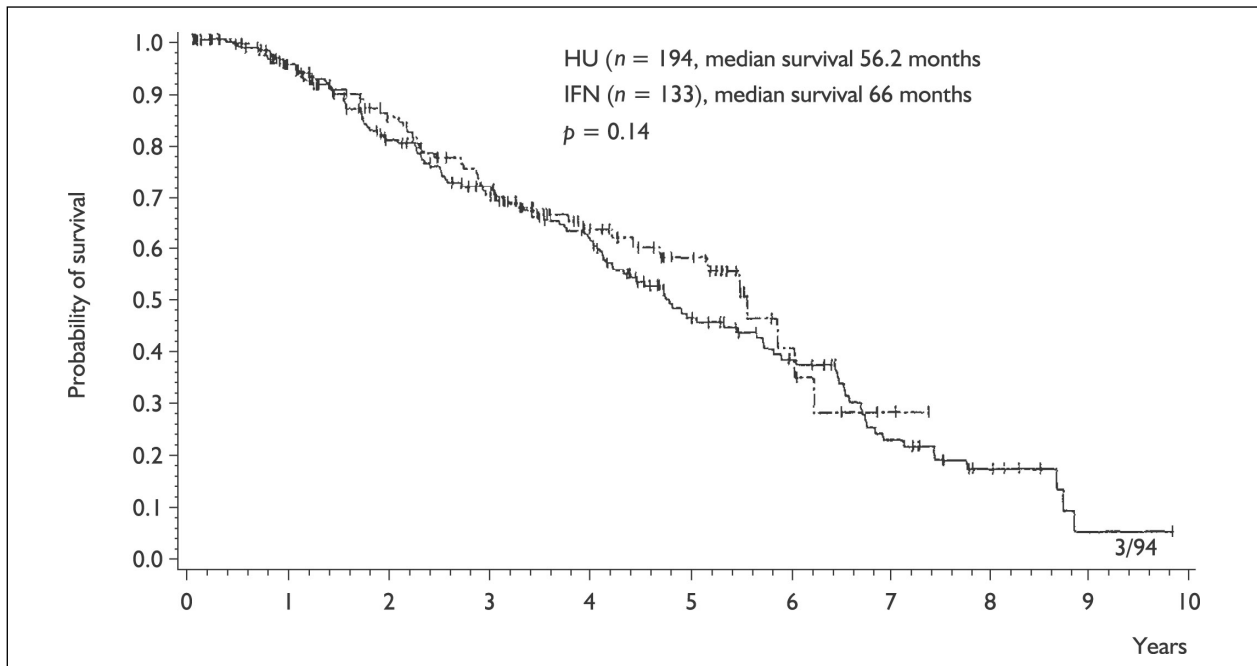


FIGURE 21 Overall survival. From Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, et al. Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood* 1994;84:4064–77. Copyright American Society of Hematology, used with permission.

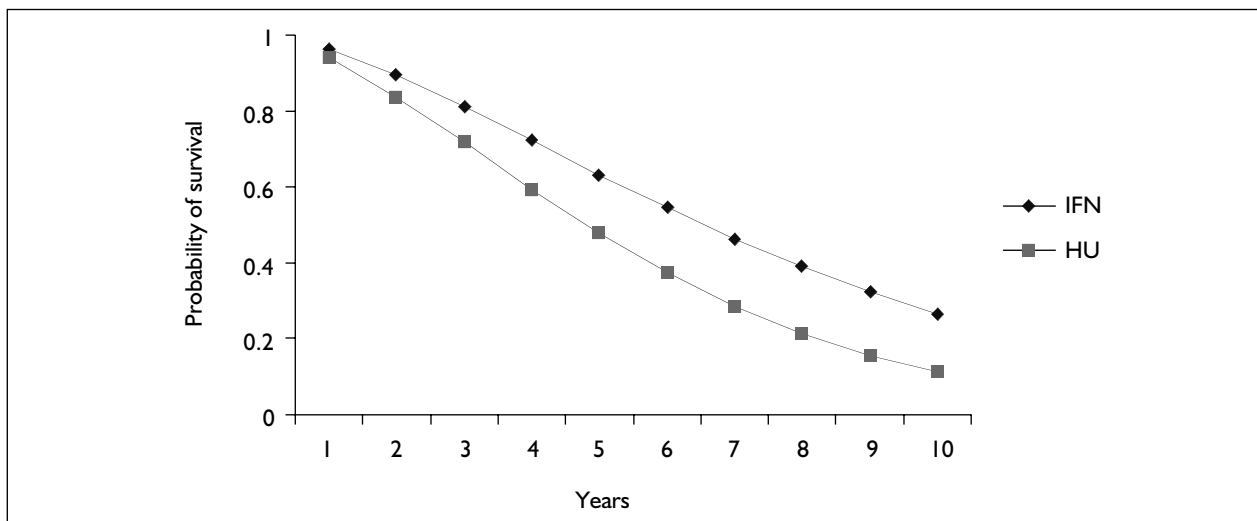


FIGURE 22 Overall survival, derived from data The Italian Cooperative Study Group on CML study²¹

The Italian Cooperative Study Group on CML²¹ followed patients for a maximum of 10 years and compared IFN- α with conventional chemotherapy.

Figure 22 illustrates overall survival. At 3-year follow-up 74% of the IFN- α group were still alive, compared with 71% of the chemotherapy group. At 5-year follow-up 54% of the IFN- α group had survived, compared with 43% of the chemotherapy group. At 10-year follow-up 8% of the IFN- α group were still alive, compared with 5% of the chemotherapy group.

Figure 23 illustrates the proportion of people progressing over 10 years in the Italian Cooperative Study Group on CML study.²¹ At 3-year follow-up approximately 22% of the IFN- α group had experienced disease progression, compared with approximately 35% in the chemotherapy group. At 5-year follow-up approximately 43% of the IFN- α group and 60% of the chemotherapy group had progressed. Disease progression was approximately 70% in the IFN- α group and 85% in the chemotherapy group at 10-year follow-up.

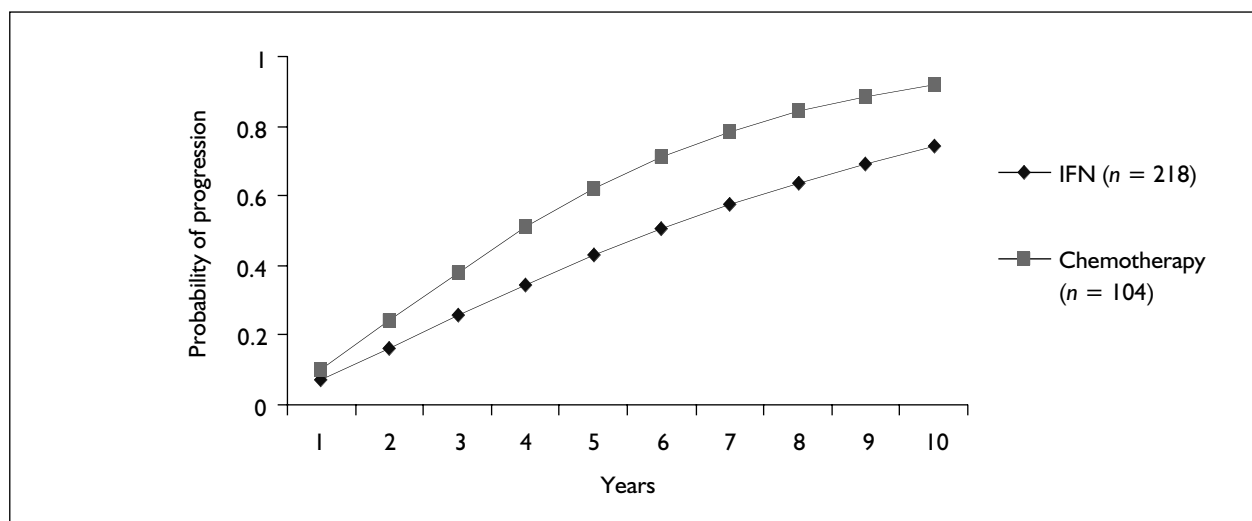


FIGURE 23 Disease progression, derived from data presented in The Italian Cooperative Study Group on CML²¹

Adverse effects of IFN- α and hydroxyurea reported in the included studies

Adverse effect	IFN- α				HU			
	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1994 ⁸¹	Italian Cooperative, 1998 ²¹	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1994 ⁸¹	Italian Cooperative, 1998 ²¹
Fatigue, fever, pain, headache	7%	4.2%	–	11.5%	2.1%	–	0.5%	–
Anorexia, nausea, diarrhoea	–	–	–	6.4%	–	–	–	–
Neurological, central	–	8.3%	–	2.8%	–	–	–	–
Neurological, peripheral	–	–	–	2.3%	–	–	–	–
Haematological	–	–	–	2.8%	–	–	–	–
Skin, itching, alopecia	3%	4.2%	–	3.2%	–	–	–	–
Liver	–	–	–	0.9%	–	–	–	–
Allergic reaction	–	–	–	0.9%	–	–	–	–
Neuropsychiatric	6%	4.2%	–	–	–	–	–	–
Renal, including vasculitis	4%	–	–	–	1.1%	–	–	–
Other	4%	–	–	–	–	–	–	–
Drug eruption	–	–	–	–	1.1%	–	–	–

continued

Adverse effect	IFN- α				HU			
	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1994 ⁸¹	Italian Cooperative, 1998 ²¹	Benelux, 1998 ⁵	Broustet et al., 1991 ⁶	Hehlmann et al., 1994 ⁸¹	Italian Cooperative, 1998 ²¹
General intolerance	–	–	–	–	–	11.5%	–	–
Hepatitis	–	8.3%	–	–	–	–	–	–
Thyroid insufficiency	–	8.3%	–	–	–	–	–	–
Inflammatory anaemia	–	4.2%	–	–	–	–	–	–
Flu/neurological/ psychiatric/ dermatological	–	–	18%	–	–	–	–	–

Appendix 8

Interferon-alpha compared with bone marrow transplantation: quality assessment and effectiveness

Summary of the quality of included studies comparing BMT with IFN- α

Quality criteria	Gaziev et al., 2002 ¹⁰	Ohnishi et al., 2001 ¹²	Ohnishi et al., 2000 ¹¹	Italian Cooperative, 1999 ⁸²	Gale et al., 1998 ⁹
Adequate randomisation?	×	×	×	×	×
Allocation concealed?	NA	NA	NA	NA	NA
Groups similar at baseline?	×	×	×	×	×
Eligibility criteria stated?	×	✓	✓	✓	✓
Outcome assessors blinded?	×	×	×	×	×
Providers of care blinded?	NP	NP	NP	NP	NP
Patients blinded?	NP	NP	NP	NP	NP
Point estimates and measures of variability?	✓	×	×	✓	✓
Power calculation performed at study design?	×	×	×	×	×
All patients accounted for?	✓	✓	✓	✓	✓
Analysis performed on ITT?	✓	✓	✓	?	NA

?, not stated/uncertain; ✓, yes; ×, no; NP, not possible; NA, not applicable.

Internal validity

Sample size

The sample sizes varied from 66 to 659 in the IFN- α treatment groups and from 23 to 518 in the BMT treatment groups (see the table below). None of the studies performed power calculations before the start of their studies. It is possible that some studies did not have sufficient power to detect a difference between the study groups.

Selection bias

None of the studies randomised people to study groups and it is questionable whether randomisation between these two possible treatments would be ethical. The studies by Ohnishi and colleagues^{11,12}

enrolled people prospectively, and both study groups were enrolled at the same time. The other studies^{9,10,82} appear to be retrospective comparisons of series of patients in available databases. Some of the series used for comparison originally enrolled patients consecutively.

None of the studies concealed treatment allocation; however, it is unlikely that allocation concealment would be possible with the current comparison between BMT and drug therapy.

None of the studies had similar baseline characteristics for the two groups. This is due to the different management of patients according to

Numbers of included patients in each study arm and breakdown of types of BMT

	IFN- α	HLA-identical sibling donor	Identical twins	HLA identical relative donor	Unrelated donor	Total BMT
Gaziev et al., 2002 ¹⁰	70	102	2	1	0	105
Ohnishi et al., 2001 ¹²	175	0	0	50	29	79
Ohnishi et al., 2000 ¹¹	66	23	0	0	0	23
Italian Cooperative, 1999 ⁸²	659	153	1	9	18	181
Gale et al., 1998 ⁹	196	518	0	0	0	518

age. Older patients are not generally considered suitable for BMT, so in all studies the BMT group was significantly younger than the IFN- α group. Although this is understandable in clinical practice it leaves the studies prone to selection bias and difficulty in interpreting results and comparing therapies.

Performance bias

There are systematic differences in how patients undergoing IFN- α therapy and BMT are treated, apart from the actual intervention. BMT requires intensive preconditioning with chemotherapy, an inpatient stay and different concurrent therapies, compared with IFN- α treatment alone.

These systematic differences in care other than the intervention under investigation may affect the outcomes of the study and lead to performance bias.

Detection bias

None of the studies reported blinding outcome assessors. Outcomes such as death, cytogenetic response and haematological response are, however, objective so that blinding of outcome measurement becomes less important. In circumstances such as this where one treatment (BMT) is very invasive and a major procedure and the other is a drug therapy (IFN- α), it is not possible to blind providers of care or patients themselves to treatment allocation.

Attrition bias

All of the included studies accounted for all patients, although one study excluded 61 of the patients enrolled who underwent non-standard BMT from the analysis.⁸²

Three studies stated that they performed analysis on an ITT basis,¹⁰⁻¹² one did not report any loss to follow-up⁹ and the other study did not comment.⁸²

None of the included studies reported the specific reasons, or the numbers associated with each reason for patients dropping out. The only information available is the number who died based on the survival curves (see pp. 105-6).

Reporting bias

Three studies report point estimates as well as measures of variability (confidence intervals for survival estimates).^{9,10,82}

External validity

The included studies provided information on which to make assessments regarding generalisability. Four studies provided details of exclusion criteria.^{9,11,12,82} All studies described the included patients with details of age, gender and risk score.

Outcome assessment was not performed independently or blinded, although outcomes were objective.

Patient characteristics of included studies comparing BMT and IFN- α

Study characteristic	Gaziev et al., 2002 ¹⁰		Ohnishi et al., 2001 ¹²		Ohnishi et al., 2000 ¹¹		Italian Cooperative, 1999 ⁸²		Gale et al., 1998 ⁹	
	BMT	IFN- α	BMT	IFN- α	BMT	IFN- α	BMT	IFN- α	BMT	IFN- α
CML phase	Chronic 84% Accelerated 10% Blast crisis 6%		Related donor: chronic 100%; unrelated donor: chronic 90%, accelerated 7%, blast 3%	Chronic	Related donor: chronic 100%; unrelated donor: chronic 88%, blast 12%	Chronic	120 people in standard allo-BMT group were all in chronic phase	Unable to ascertain	Chronic	Chronic
Median haemoglobin level reported (g/dl)	–	–	–	–	–	–	11.7 \pm 1.9	IFN- α : 11.9 \pm 2; chemo: 12.1 \pm 2.0	12 (2–17)	12 (4–16)
Median spleen size (cm)	5 (0–16)	5 (0–18)	\geq 10 cm: Related donor: 19%; unrelated donor: 25%	\geq 10 cm 10%	–	–	7.4 \pm 6.9	IFN- α : 6.4 \pm 6.5; chemo: 6.5 \pm 6.5	3 (0–26)	5 (0–30)
Median age (years)	31 (10–53)	43 (14–55)	Related donor: 36 (19–53); unrelated donor: 31 (17–48)	54 (19–79)	33	50	32	IFN- α : 41.5; chemo: 42	35 (15–54)	41 (15–55)
Gender ratio M:F (% male)	38:50 (43)	45:25 (64)	Related donor: 33:17 (66); unrelated donor: 16:13 (55)	110:65 (63)	9:14 (23)	25:41 (38)	71:49 (59)	IFN- α : 190:132 (59); chemo: 192:145 (57)	331:217 (60)	119:77 (61)
Time since diagnosis (months)	–	–	Related donor: 9 (3–43); unrelated donor: 19 (7–45)	Newly diagnosed	Related donor: 9 (2–27); unrelated donor: 29 (23–57)	Newly diagnosed	15.1 \pm 10.4	Previously untreated	10.1 (2–84)	Newly diagnosed
Sokal score	Low 59%, int 32%, high 9%	Low 68%, int 29%, high 3%	Mean: related donor: 0.76 \pm 0.27; unrelated donor: 0.80 \pm 0.40	Mean: 1.01 \pm 0.84	–	–	Low 49%, int 29%, high 22%	IFN- α : low 50%, int 27%, high 23%; chemo: low 45%, int 32%, high 19%	Low 41%, int 37%, high 22%	Low 37%, int 42%, high 21%

Treatment details of included studies comparing BMT and IFN- α

Four of the five included studies stated that people received chemotherapy and/or IFN- α before receiving a BMT. Three of the five included studies stated the concurrent treatments that people undergoing BMT received. The dose of IFN- α therapy was stated by three studies and ranged from 3 to 9 MU/day. The other two studies stated that doses varied mainly to maintain a certain WBC count.

Results for IFN- α compared with hydroxyurea and survival curves

The overall survival curve for IFN- α compared with BMT from the Gaziev study¹⁰ is shown in *Figure 24*. People receiving IFN- α have better survival during the first 4 years compared with

BMT. After 4 years the survival advantage switches to BMT and the difference increases as time progresses.

Ohnishi and colleagues in their later study¹² report the probability of survival associated with related donor BMT (R-BMT), unrelated donor BMT (U-BMT) and IFN- α over 5 years (*Figure 25*). There is no statistically significant survival difference between the three groups.

Ohnishi and colleagues¹¹ present curves for treatment with IFN- α and sibling donor or unrelated donor BMT with follow-up to a maximum of 6 years (*Figure 26*). When comparing treatments in this study, IFN- α does not have an initial survival advantage. Sibling donor BMT is associated with higher survival than unrelated donor BMT and treatment with IFN- α . Unrelated donor BMT has a survival advantage over IFN- α until the curves cross at approximately 4.3 years.

	Gaziev et al., 2002 ¹⁰	Ohnishi et al., 2001 ¹²	Ohnishi et al., 2000 ¹¹	Italian Cooperative, 1999 ⁸²	Gale et al., 1998 ⁹
Previous treatment for BMT group	BU	Chemotherapy with or without IFN- α	Chemotherapy with or without IFN- α	IFN- α or HU	IFN- α \pm HU
Type of drug treatment	IFN- α	IFN- α	IFN- α_{2b}	IFN- α	IFN
IFN- α dose	Varying	Adjusted to maintain WBC	3–9 MU/day	9 MU/day	5 MU/day
Type of BMT	HLA-identical sibling 102, identical twin 2, HLA-identical relative 1	HLA-identical relative 50, HLA-matched unrelated 29	HLA-identical relative 15, HLA-matched unrelated 8	HLA-identical sibling 153, identical twin 1, partially HLA matched relative 9, HLA matched unrelated donor 18	HLA-identical sibling donor
Concurrent treatments for BMT	Prophylactic antibiotics, acyclovir, amphotericin B and trimethoprim/sulfamethoxazole	Not stated	Not stated	Cyclosporine and/or methotrexate	Post-transplant methotrexate, cyclosporine
Median length of follow-up, IFN- α group (months)	46.8 (12–144)	38 (9–66)	54 (30–76)	Not stated	78
Median length of follow-up, BMT group (months)	Not stated	Not stated	Not stated	Not stated	51.6

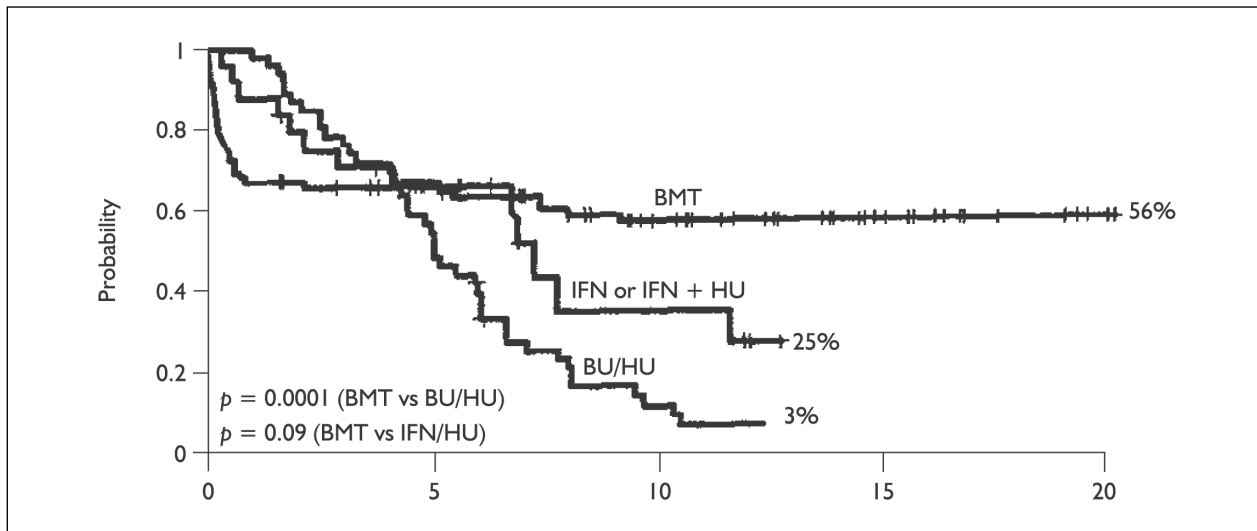


FIGURE 24 Overall survival, Gaziev and colleagues, 2002¹⁰

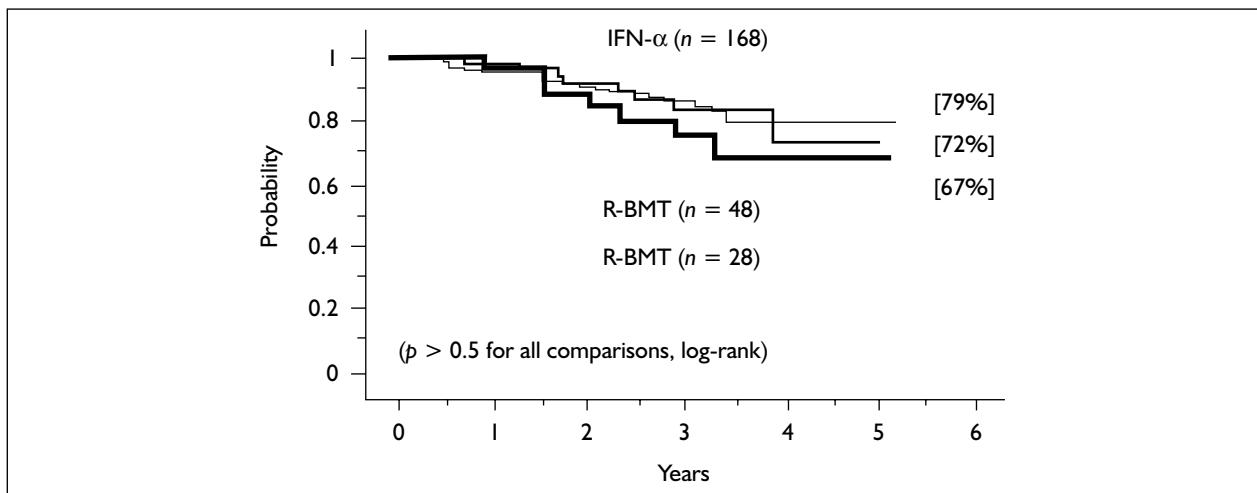


FIGURE 25 Overall probability of survival, Ohnishi and colleagues, 2001.¹² (Reproduced with permission.)

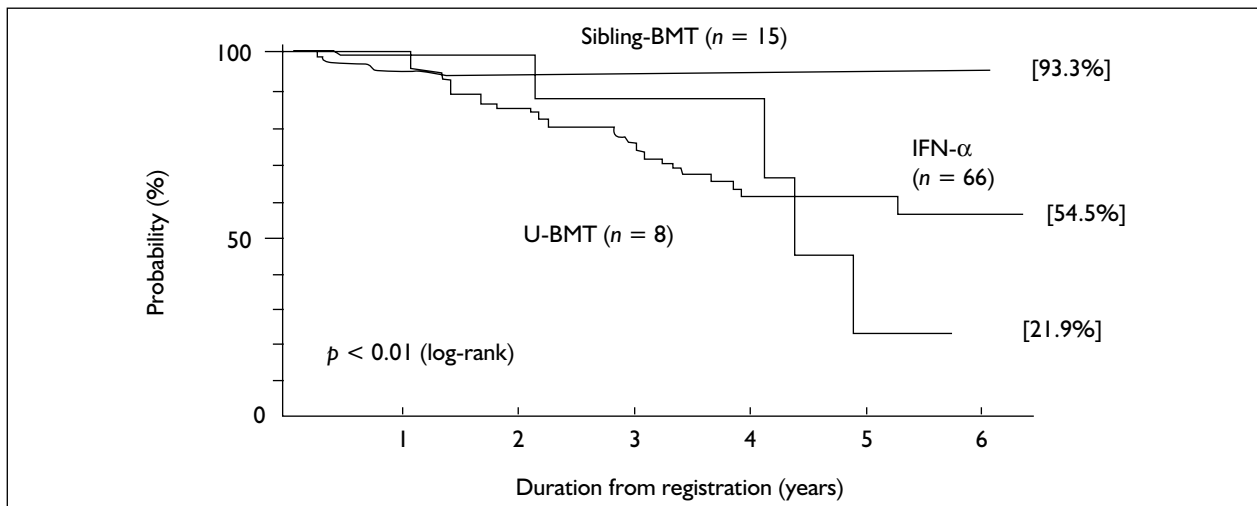


FIGURE 26 Probability of survival for those treated with IFN- α or BMT, Ohnishi and colleagues, 2000.¹¹ (Reproduced with permission.)

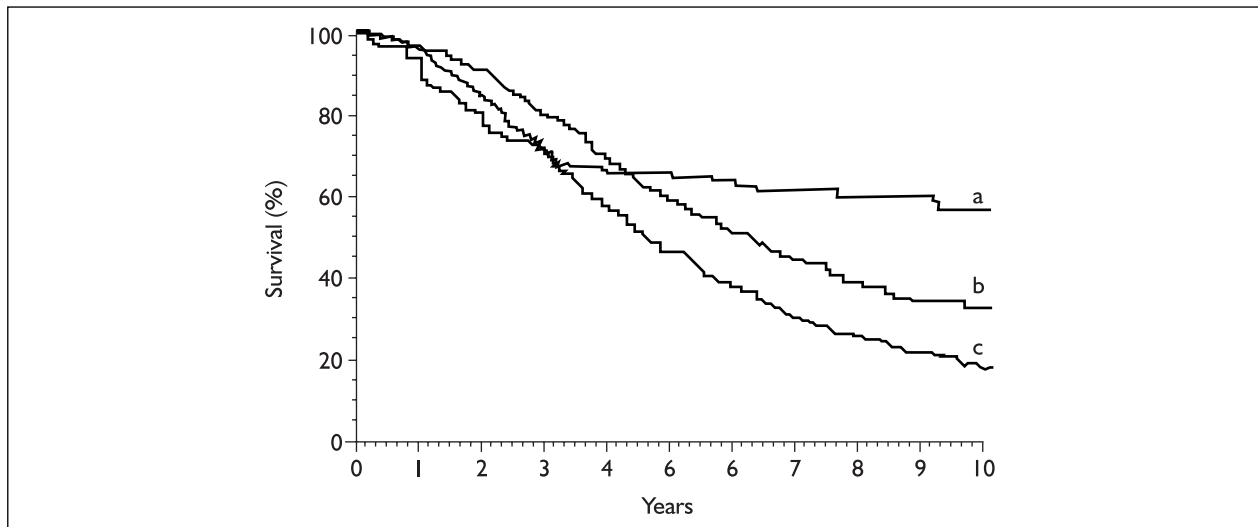


FIGURE 27 Overall survival for (a) BMT compared with (b) IFN- α and (c) chemotherapy (hydroxyurea, busulfan) derived from data presented in the Italian Cooperative Study Group on CML, 1999⁸²

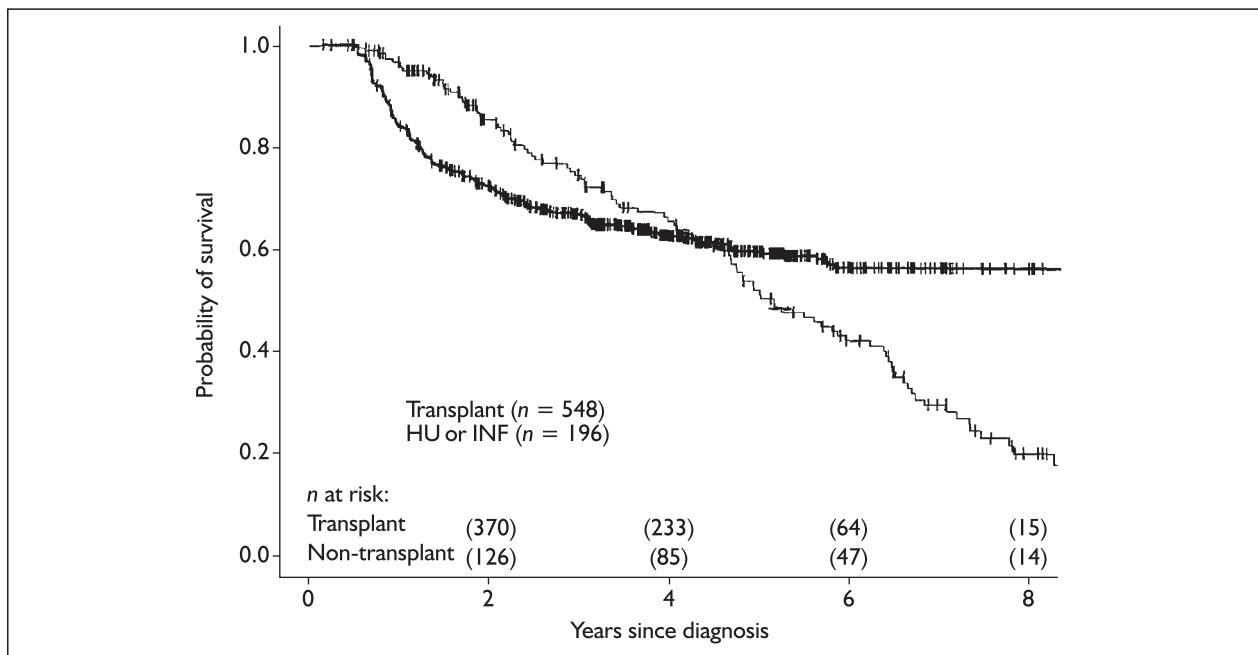


FIGURE 28 Overall survival, derived from data presented by Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H, et al. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. *Blood* 1998;**91**:1810–19. Copyright American Society of Hematology, used with permission.

The Italian Cooperative Study Group on CML⁸² presents an overall survival curve with a maximum of 10 years of follow-up data comparing BMT, IFN- α therapy and conventional chemotherapy (hydroxyurea/busulfan) (Figure 27). Both drug therapies have a survival advantage over BMT in the initial few years after treatment. BMT is associated with better survival than conventional chemotherapy after approximately 3 years and better survival than IFN- α after 4.5 years.

Gale and colleagues⁹ compared people receiving HLA-identical sibling donor BMTs with drug treatment (hydroxyurea or IFN- α) for a maximum period of 8 years (Figure 28). There is a survival advantage for those receiving drug therapy until 4.5 years.

Complications of BMT reported in the included studies

	Italian Cooperative, 1999 ⁸⁰	Ohnishi et al., 2000 ¹¹	Gaziev et al., 2002 ¹⁰
Complications	BMT	BMT	BMT
Death due to transplant-related complications	43/120 (36%)	–	47/105 (45%)
Death due to GVHD	–	Related donors: 1/15 (7%); unrelated donors: 3/8 (38%)	–
Death due to thrombocytopenic purpura	–	Unrelated donors: 1/8 (13%)	–
Rejection or graft failure	–	–	0
GVHD (grade II–IV)	–	–	38/100 (38%)
GVHD (grade III–IV)	–	–	23/100 (23%)
Fungal infections	–	–	33/100 (33%)
Candida species infections	–	–	24/100 (24%)
Cytomegalovirus infection	–	–	13/100 (13%)
Relapse	15/120 (13%)	–	16/105 (15%)

The authors and organisations listed are all those registered as participating in the trial. It is reported that both these trials have been halted because of poor recruitment following the advent of imatinib (Apperley J, Hammersmith Hospital, London: personal communication, 2003).

Studies of BMT and IFN- α studies currently in progress

Study/question	Principal investigator(s)	Organisation	Expected completion date	Study design	Patients	Methodology
An MRC/ECOG prospective randomised study to compare IFN- α n1 (Wellferon) vs 'IdAC' chemotherapy and autografting followed by Wellferon in patients with newly diagnosed chronic phase CML (CML 2000) (CML IV)	J Goldman, S O'Brien, J Rowe, M Tallman	Hammersmith Hospital, London, UK; Victoria Royal Infirmary, Newcastle upon Tyne, UK; Rush Presbyterian–St Luke's Medical Center, Chicago, USA; NWU, Chicago, USA (multicentre)	Closed	RCT	Newly diagnosed chronic phase CML	Multicentre prospective RCT
CML 2000 (CML Iva): an MRC prospective, randomised study to compare IFN- α \pm Ara-C against autografting followed by IFN- α \pm Ara-C in patients with newly diagnosed chronic phase CML	S O'Brien, A Carella, J Reiffers, J Apperley, J Goldman	Victoria Royal Infirmary, Newcastle upon Tyne, UK; Ospedale San Martino, Genova, Italy; Hôpital du Haut Leveque, Pessac Bordeaux, France; Hammersmith Hospital, London, UK; Hammersmith Hospital, London, UK (multicentre)	Closed	RCT	Chronic phase CML	Prospective multicentre randomised study

Appendix 9

Validation of survival progression and response curves from the model with published literature

Figure 29 shows the data used in the economic model for progression which was derived from the Italian Cooperative Study Group²¹ using a Weibull distribution. These data are similar to those produced in the original study as seen in *Figure 22* in Appendix 7.

Figure 30 shows overall survival data used in the economic model. There were derived from the Italian Cooperative Study Group on CML using a Weibull distribution. These data are similar to those shown in the original Italian study report (*Figure 23*, in Appendix 7).

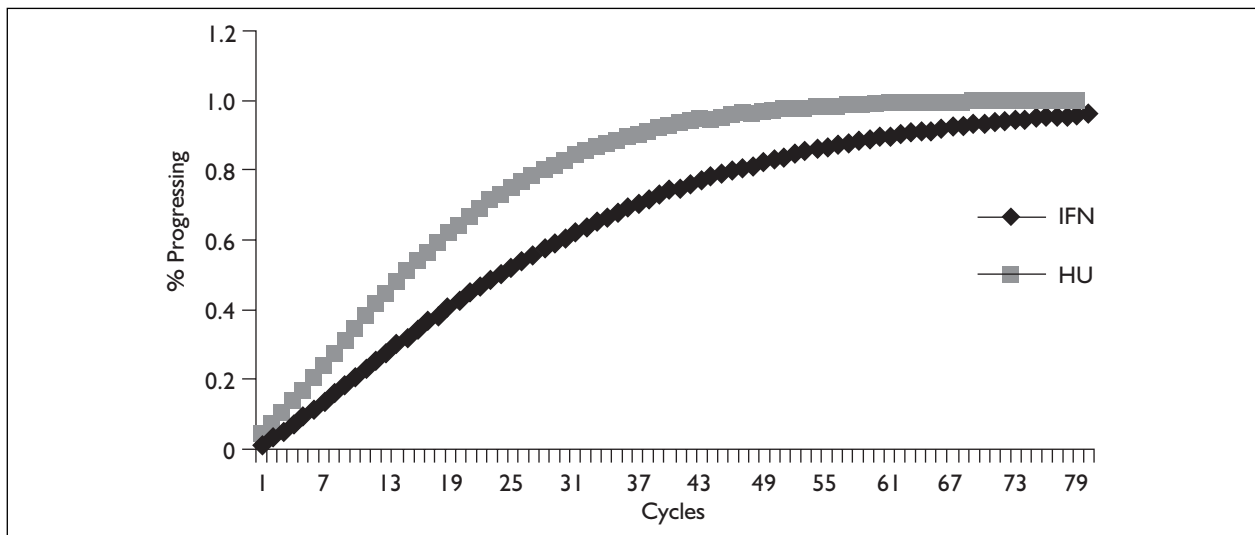


FIGURE 29 Data for progression used in the economic model, derived from the Italian study²¹ using a Weibull distribution

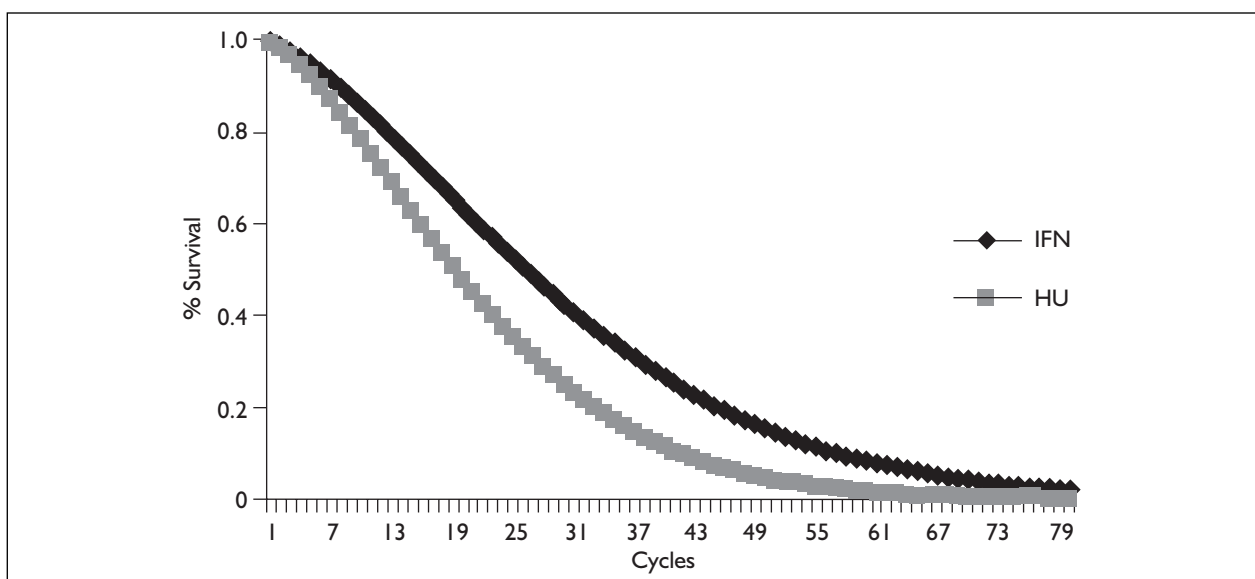


FIGURE 30 Data for survival used in the economic model, derived from the Italian study²¹ using a Weibull distribution

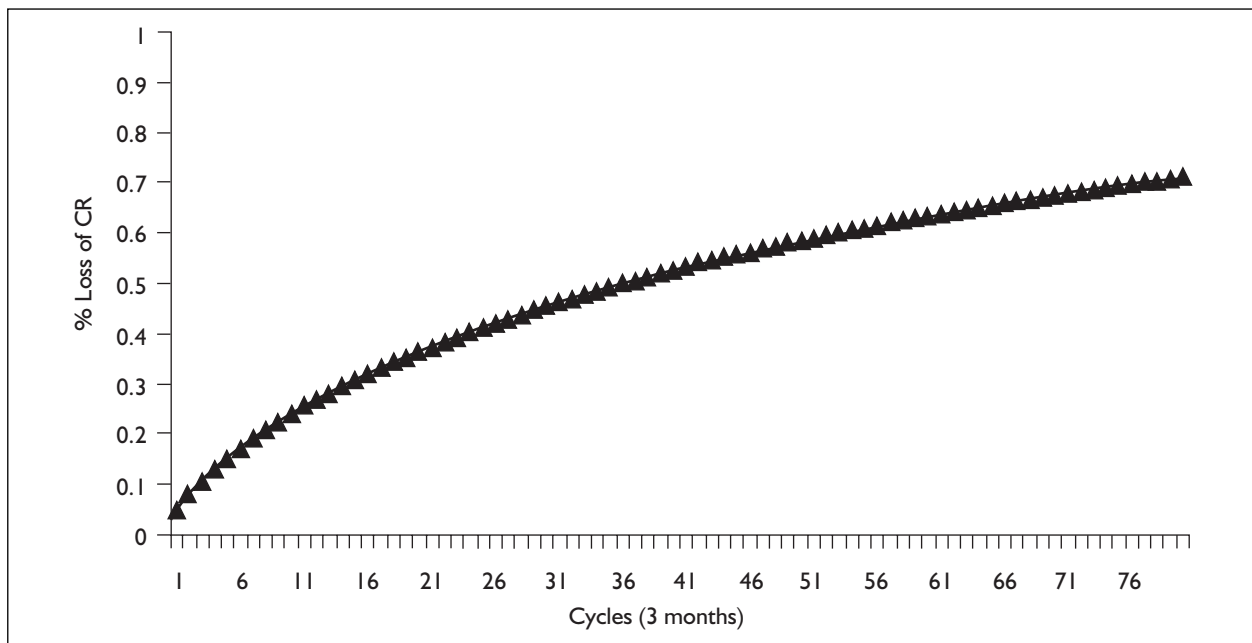


FIGURE 31 Percentage loss of response curve from the Bonifazi study,²⁵ fitted using a Weibull distribution

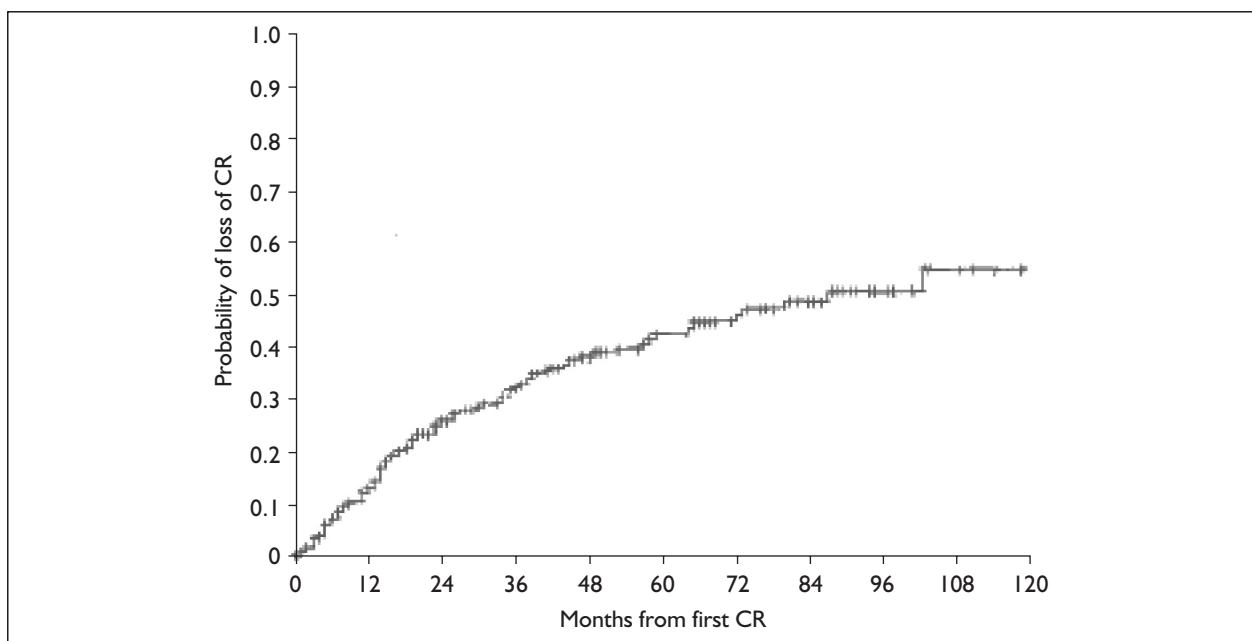


FIGURE 32 Percentage loss of response curve, from Bonifazi F, De Vivo A, Rosti G, Guilhot F, Guilhot J, Trabacchi E, et al. *Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders*. *Blood* 2001;**98**:3074–81. Copyright American Society of Hematology, used with permission.

The data for loss of CR were obtained from the study by Bonifazi and colleagues²⁵ by fitting a Weibull distribution and are shown in *Figure 31*.

The loss of response rate is similar to the original response curve from the Bonifazi study²⁵ (*Figure 32*).

Appendix 10

Sensitivity analysis for the independent economic model

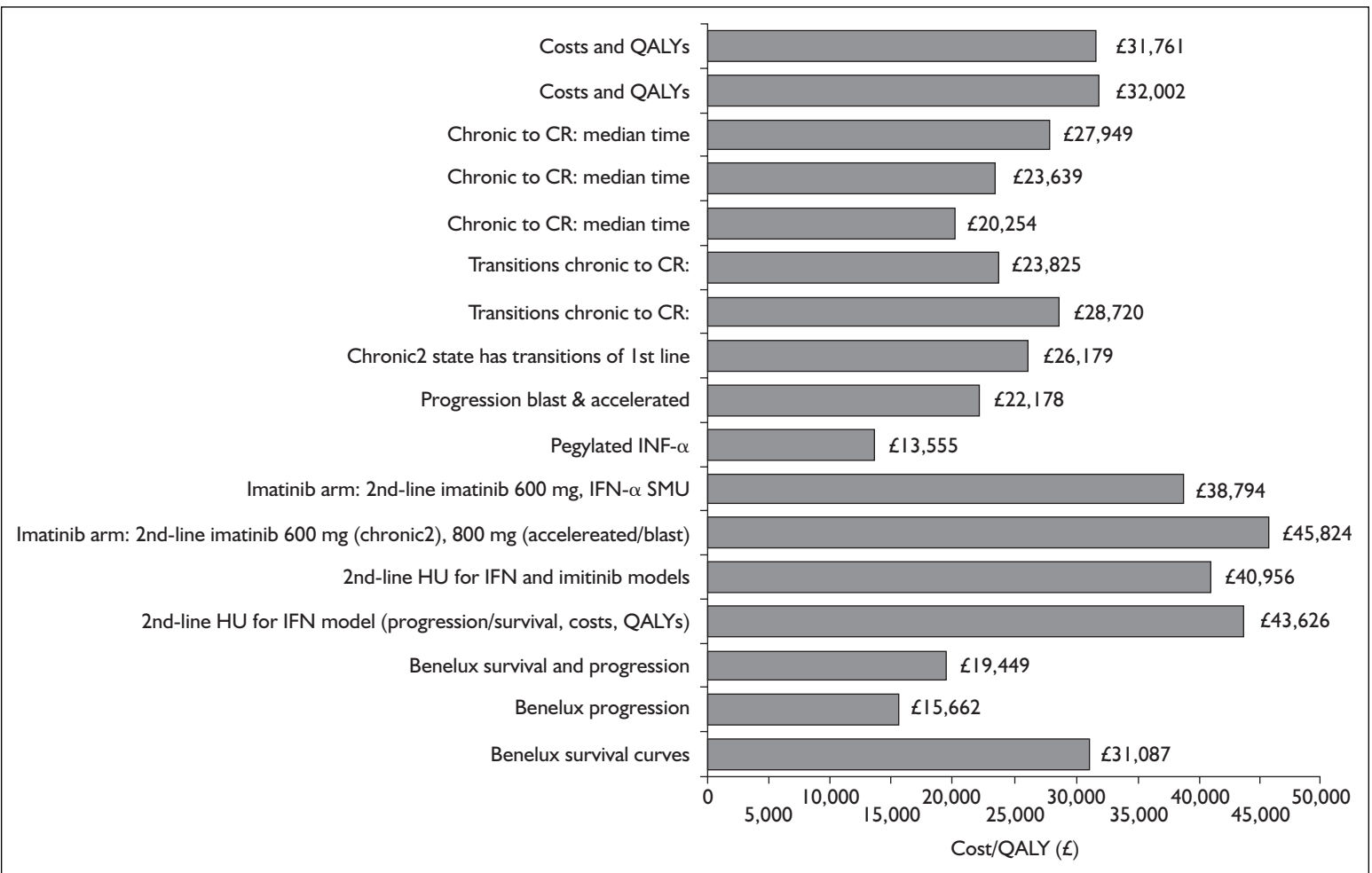


FIGURE 33 Sensitivity analysis of general model assumptions imatinib versus IFN-α



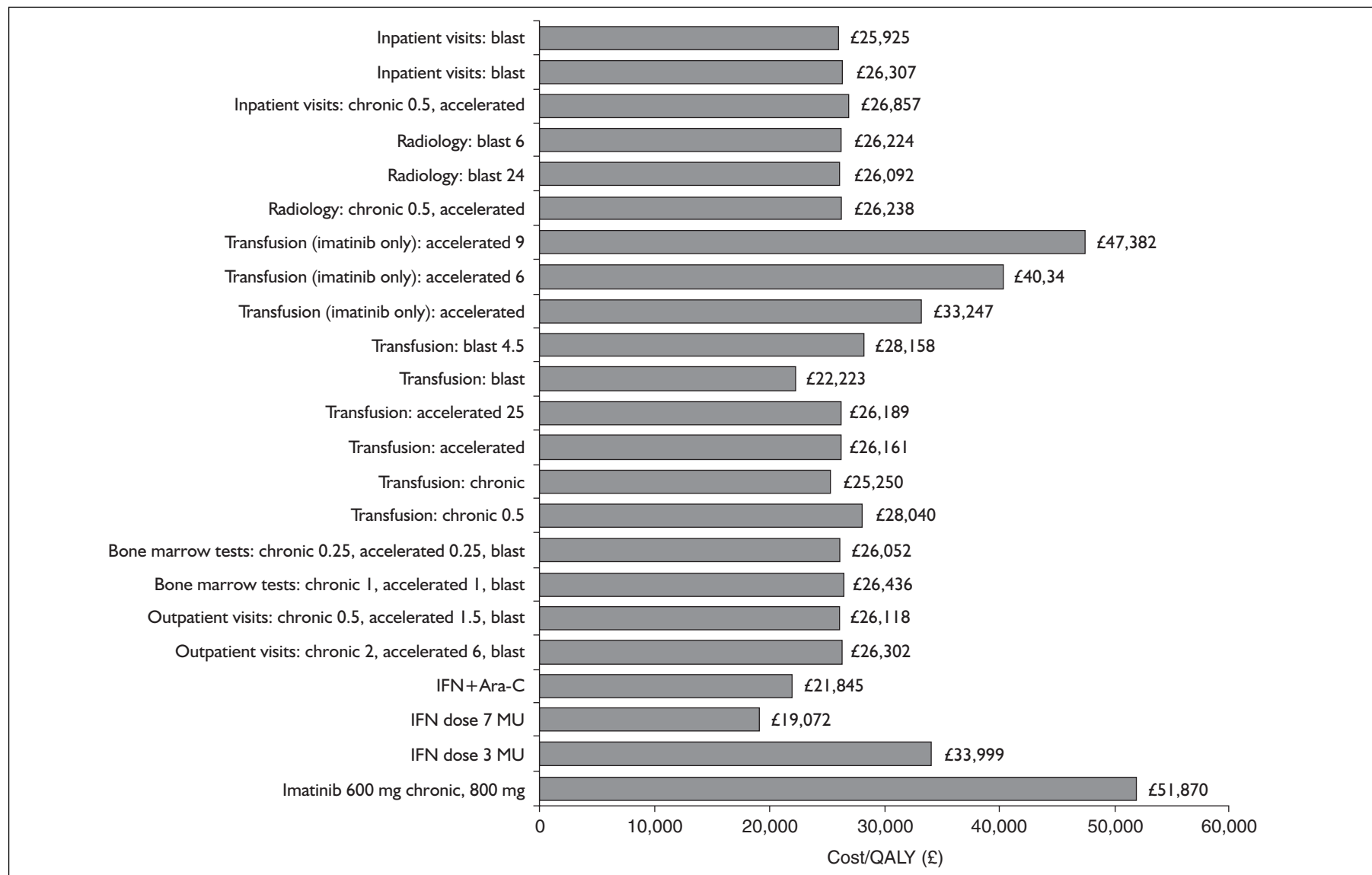


FIGURE 34 Sensitivity analysis of cost assumptions: imatinib versus IFN- α

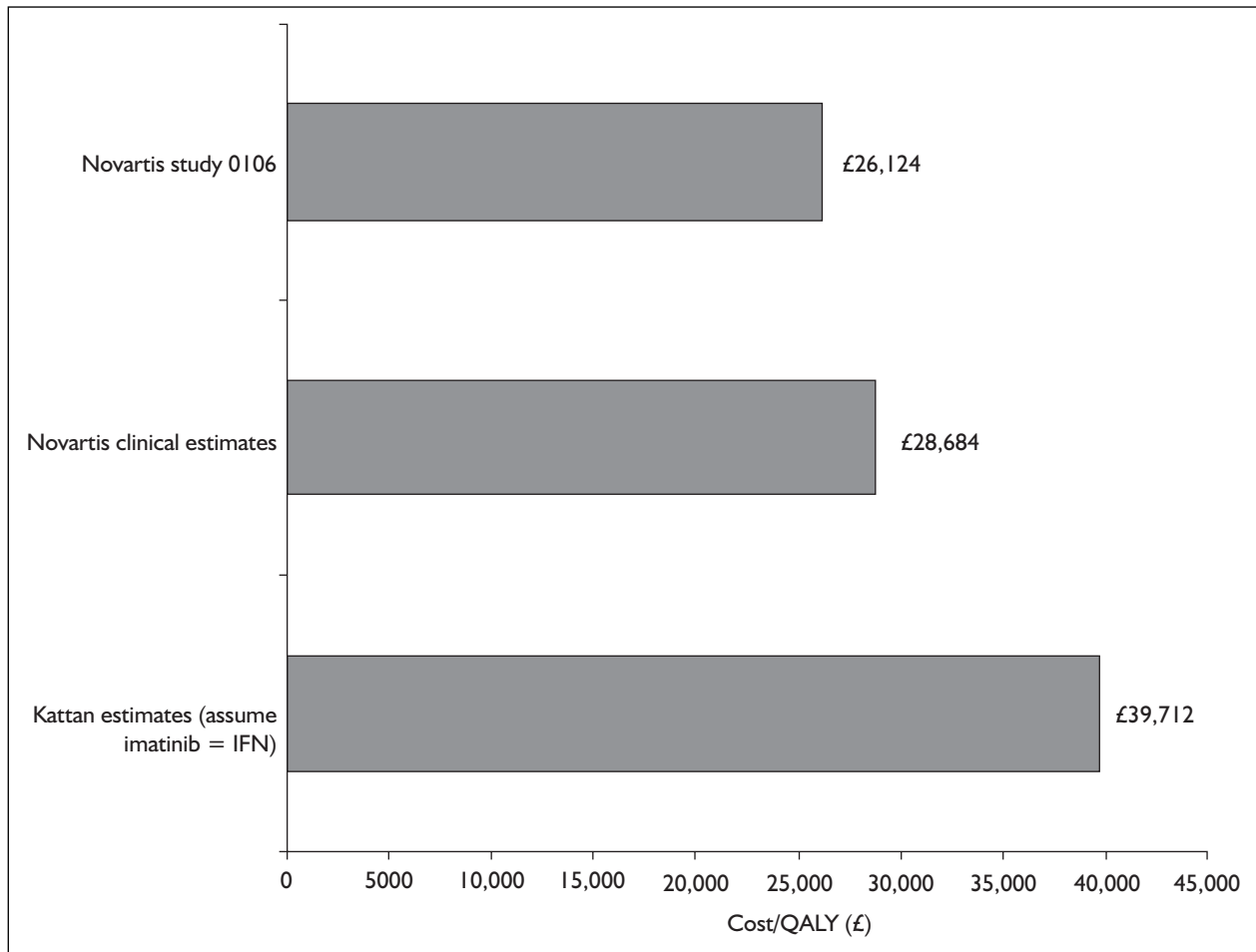


FIGURE 35 Sensitivity analysis of utilities: imatinib versus IFN- α

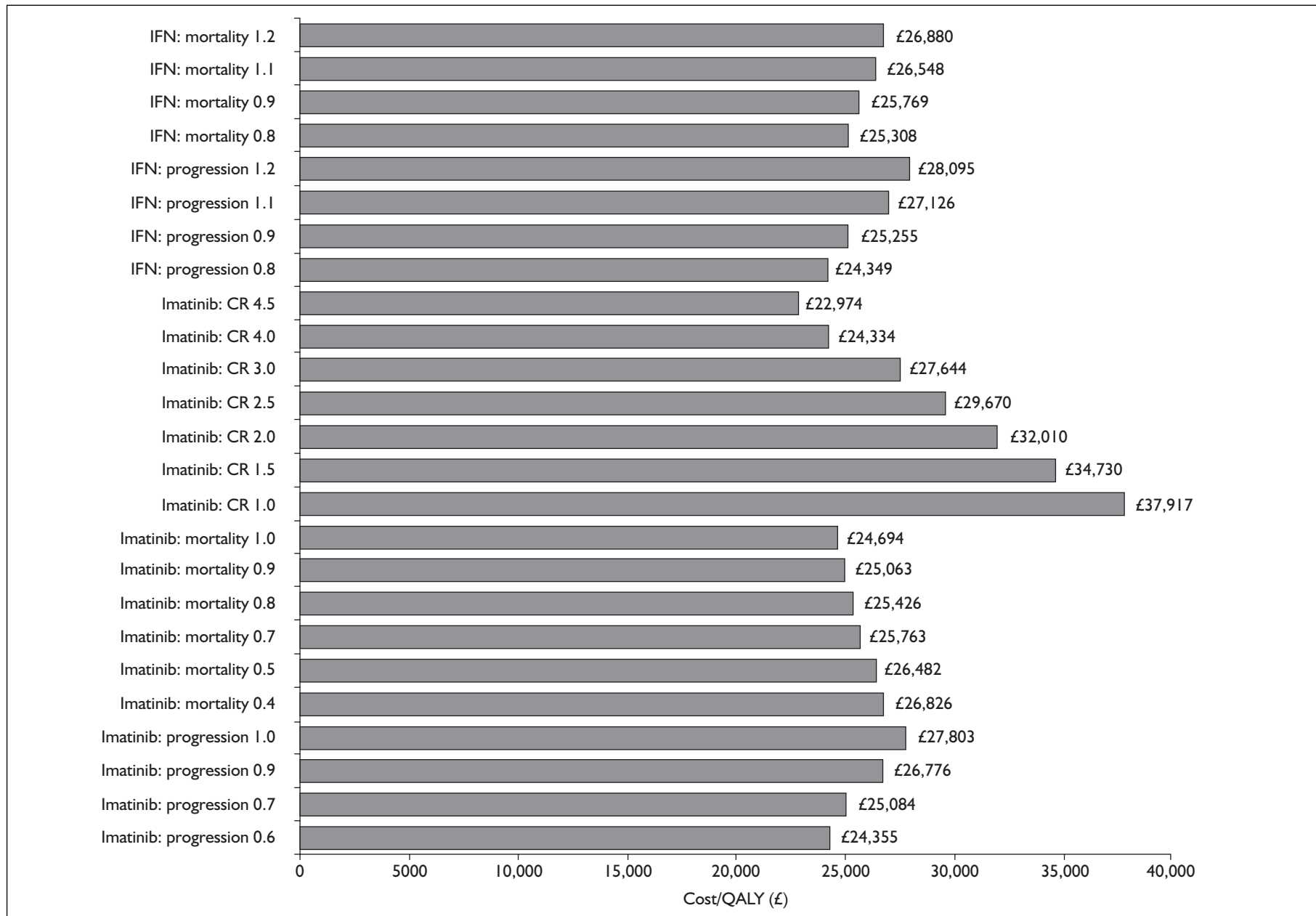


FIGURE 36 Sensitivity analysis of relative risks for progression and survival imatinib versus IFN- α

Appendix I I

Quality assessment of industry economic evaluation

Structure

Is there a clear statement of the decision problem, the context and the perspective?

The model aims to compare the cost-effectiveness of imatinib with IFN- α plus Ara-C for the treatment of newly diagnosed patients with CML in whom BMT was not considered a therapeutic option. The structure of the model is consistent with the stated disease problem. The perspective is the NHS, which is appropriate

Is a theory of the underlying disease detailed?

Details of CML and available treatments are presented. The model is consistent with the theory of disease

Are the underlying assumptions involved in the model clearly specified? Are they justified? Are the implications of relaxing these assumptions described?

Assumptions

Once patients fail treatment with imatinib they receive IFN- α plus Ara-C (justified)
 Once patients fail treatment with IFN- α plus Ara-C they receive imatinib (justified)
 Survival rates after 2 years are based solely on complete CR prior to 2 years (lack of long-term data makes this hard to verify)
 Conditional on complete CR status at 2 years, the survival distributions of imatinib and IFN- α are identical (there are no long-term data available to verify this)
 PFS for imatinib patients is the same as for IFN- α patients after 12 months (lack of data makes this difficult to verify, although this is likely to bias against imatinib)
 The rate of progression to accelerated and blast phases is the same from chronic, complete HR, partial HR and complete CR states (unlikely to be true; progression slower from complete CR state, biased against imatinib as produces more complete CR)
 There is a constant rate of HR, CR and loss of response applied over the model (these rates are more likely to be time dependent)
 Patients may only progress to death from causes other than CML, except from blast phase (this is likely to underestimate the death rate as some patients will die from CML causes from the other states)
 Movement from first-line treatment to second-line treatment is assumed to be a constant rate, based on data from the first 12 months (the rate of progression is unlikely to be constant and will probably increase with time)
 PFS on IFN- α second line is assumed to be an average of that for imatinib and hydroxyurea (no data to support or refute this)
 The median duration of palliative care in accelerated phase is 6 months (median survival in accelerated phase; this is probably an underestimate, not explored in sensitivity analysis)
 The median duration of palliative care in blast phase is 4.5 months
 The cost of adverse events is not considered. (likely to be a conservative estimate as more adverse effects reported with IFN in 0106 trial)

The implications of relaxing some of these assumptions are explored in sensitivity analyses

Disease states

Is the chosen model type appropriate for the time dimension of the disease process?

A Markov model is appropriate for a chronic condition such as CML

Is a justification of the choice of states within the model provided? If so, does this accord with the theory of disease process?

A detailed justification is not provided, although the states do accord with the theory of disease process. Surrogate outcomes are modelled and their relationship with survival is discussed in more detail in Chapter 2, Outcome measures (p. 8)

continued

<i>Is any empirical evidence provided on the suitability of the states (e.g. sensitivity to change in the underlying disease)?</i>	No
<i>Have any important disease states been omitted from the model?</i>	No, but all the complexity of the disease process may not have been fully captured
Options	
<i>Is there a clear statement of the options being evaluated?</i>	Yes, the model compares the following: imatinib (first line), IFN- α + Ara-C (second line), hydroxyurea (third line) with IFN- α + Ara-C (first line), imatinib (second line), hydroxyurea (third line)
<i>Do these appear to cover the range of logical and feasible options?</i>	There are additional options that are being used or considered in clinical practice, particularly for second-line treatment after imatinib fails. Some possible treatments include: increased dose of imatinib, combination therapy of imatinib + IFN- α and pegylated IFN- α . It would have been useful if some of these options had been modelled in sensitivity analyses, although there is a lack of currently available data on these various options. BMT is another whole area of options for a patient with CML. BMT has been excluded from the model, although the complexity of this justifies the omission
Time horizon	
<i>Is the time horizon of the analysis stated?</i>	The model runs for a total of 40 years. This is long enough to enable stable cost and effect differences between the treatment groups
<i>If so, is this justified in terms of the underlying disease and the effect of interventions?</i>	The model length may be longer than required as it is unlikely that CML patients would survive this long
Cycle length (if relevant)	
<i>If relevant, is the cycle length used in the model stated?</i>	Yes, cycles were 1 month
<i>Is justification offered on the choice of cycle length? If so, does the justification relate to the disease process?</i>	No detailed justification is provided, although a cycle length of 1 month is appropriate for the disease process
Data identification	
<i>Are the sources of parameter values in the model clearly stated?</i>	Yes
<i>Is reasonable empirical justification, from earlier iterations of the model, offered that these data are optimal?</i>	A formal value of information analysis was not undertaken to determine optimal data to incorporate
<i>For the first iteration of the model, has satisfactory justification been offered that data are based on a search of all the low-cost data sources (e.g. MEDLINE, DARE, Cochrane Library)?</i>	There is no indication that a formal search was conducted of all low-cost data sources. It is stated that the data used in this model are the "optimal available data", as the only direct comparative data between imatinib and IFN- α . An independent search did not identify further studies. However, other data are used to populate the model
<i>Are ranges specified for parameters?</i>	Some ranges are provided in the industry submission, although they do not seem to be incorporated in the economic model, certainly not in the form of stochastic analysis
<i>Is there evidence to suggest selective use of data?</i>	The model emphasises outcomes other than survival, and models survival based on CR and PFS. However, there are no long-term data available for survival

continued

<i>If some parameter estimates are based on elicitation of expert opinion, have the methods used for this purpose been adequately described (e.g. inclusion criteria, sample size, elicitation methods)?</i>	The following parameter estimate was based on expert opinion: “% of patients receiving IFN- α 2nd-line treatment who do not progress”. The methods used to obtain the estimate were not described
<i>Are the claims made about the model results tempered by the limitations of the data?</i>	The discussion clearly states that there are significant challenges associated with the lack of long-term efficacy data
Data incorporation <i>For each parameter value, is there clear and reasonable justification of how data have been incorporated into the model?</i>	Yes, the model is detailed and it is clear how data have been incorporated within the model
<i>Has a stochastic analysis been undertaken?</i>	No, uncertainty was explored by the use of one-way sensitivity analyses
<i>If so, do the distributions in parameter values reflect second order uncertainty?</i>	NA
<i>Have appropriate distributions been selected for each parameter?</i>	NA
<i>Have interval rates been translated into transition probabilities using the appropriate formula?</i>	Yes, a separate sheet titled “calc of trans probs” is provided and contains appropriately translated transition probabilities
<i>If appropriate, has a half cycle correction been applied to adjust time-related estimate in the model?</i>	It is not clear whether a half cycle correction has been applied to the model, although it is not likely to have a significant impact on overall estimates
Internal consistency <i>Is there a statement about the tests of internal consistency that were undertaken?</i>	The model provides estimates of cost–utility using two different methods of calculating PFS. The resulting ICERs were £18,865 and £26,850. These two methods are reasonably similar
External consistency <i>Are any relevant studies and/or models identified by the analyst for purpose of comparison?</i>	A search of the literature revealed no relevant published cost-effectiveness studies of imatinib and interferon for first-line treatment of CML. This is reasonable
<i>Have any comparisons of the outputs of the model with independent external sources been reported?</i>	The model reports that the 18-month figure for PFS presented at the American Society of Hematology was 96.7%, compared with 93% and 94% modelled estimates using the two different methods. Once again, this indicates that the economic model is making conservative estimates
<i>If so, are the conclusions justified? Have discrepancies been investigated and explained?</i>	Conclusions appear reasonable and estimates are likely to be conservative

Appendix 12

Further analysis carried out following the NICE appraisal committee meeting

Following the first meeting of the NICE appraisal committee, the authors were asked to review the impact of altering some of the assumptions in the economic model, particularly in relation to the use of effectiveness data based on ITT analysis.

ITT analysis theoretically provides the least biased estimate of the effect of imatinib in that analysis is carried out based on all patients randomised and in the groups to which they were randomised. ITT analysis therefore retains the control for unknown biases, which is the principle advantage of RCTs. In conditions where there is loss to follow-up or cross-over between groups, ITT analysis may be more conservative than analysis based on people for whom results are known or based on the actual treatment given (per protocol analyses).

In the IRIS trial, given the proportion of people who crossed over to imatinib, the ITT estimate of the relative effectiveness of imatinib is likely to be lower than that based on the actual drug taken. Hence, and at the request of the NICE appraisal committee, the relative benefit of imatinib with IFN was re-estimated, and the model was rerun using the new assumption. Further one-way sensitivity analyses were also performed, using the new assumptions.

New relative risks were estimated from the published report of the IRIS trial.⁶⁷ For CR, 18-month data were used from the Kaplan–Meier estimate of complete response. For progression to accelerated/blast phase, the relative hazard (as an estimate of the relative risk) was derived from the Kaplan–Meier estimates at 18 and 21 months. A Weibull distribution was fitted to the survival curves from the figures given in the report and a relative hazard calculated in Stata™. The 21-month figures are less reliable because of smaller numbers of events; therefore, the 18-month relative hazard estimates are used in the baseline case and the 21-month figures are shown separately.

The new relative risks applied in the model are shown in the following table, together with the range used in sensitivity analyses (SA) and the ICERs generated by the model.

Two other changes to the assumptions used in the model were also undertaken at the request of the NICE appraisal committee:

- The assumption that people who fail on imatinib will be treated with IFN is altered (second-line treatment with IFN), and an assumption is made that they will receive hydroxyurea instead.

Data used	RR of CR (range considered in SA)	RR of progression to accelerated/blast phase (range considered in sensitivity analysis)	ICER: imatinib vs IFN	ICER: imatinib vs hydroxyurea
18-month CR figures, 18-month progression	5.26 (2.5–7.5)	0.65 (0.40–0.85)	£20,755	£67,309
18-month CR figures, 21-month progression	5.26	0.47	£20,301	£59,174
Most favourable assumptions of RR from SA	7.5	0.4	£17,445	£54,613
Least favourable assumptions of RR from SA	2.5	0.85	£29,901	£95,451

- It is assumed that the utilities of people taking imatinib are equal to those of people taking hydroxyurea, both set at 0.85 (in the existing model, people taking hydroxyurea have a utility of 0.9; however, there are no empirical data to justify this).

Altering these assumptions, together with the changes made above, results in the following ICERs.

	ICER: imatinib vs IFN	ICER: imatinib vs hydroxyurea
Replace IFN as second line with hydroxyurea	£17,872	£64,481
Equal utilities for hydroxyurea and Imatinib	£17,872	£62,011
Both of the above	£17,872	£59,405



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