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

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## *Executive summary*

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# 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.

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- 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.

## Publication

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Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

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