Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia

Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Chronic myeloid leukaemia (CML) is a form of cancer affecting the blood, characterised by excessive proliferation of white blood cells in the bone marrow and circulating blood. The molecular hallmark is the presence of an acquired breakpoint cluster region (BCR)–Abelson oncogene (ABL) fusion gene in myeloid progenitors. In the UK, an estimated 560 new cases of CML are diagnosed each year.

Imatinib [originally STI571; Gleevec® (USA) or Glivec® (Europe/Australia/Latin America), Novartis] was the first tyrosine kinase inhibitor (TKI) to be used in the treatment for CML and has been widely used. Trials of imatinib are still ongoing, but current evidence suggests that patients whose disease responds to treatment with imatinib may remain symptom free for at least 10 years.

Current NHS treatment options for CML include imatinib and allogeneic haematopoietic stem cell transplantation. Resistance to imatinib is a well-documented clinical problem and may be primary (initial refractoriness to imatinib) or acquired (develops during treatment). Clinical studies suggest that approximately 20% of individuals may display primary resistance to imatinib and a further 20% may develop resistance during treatment.

Available treatment options for imatinib-resistant (ImR) or imatinib-intolerant (ImI) disease include high-dose imatinib (HDI) [800 mg every day (q.d.)], interferon-α (IFN) and hydroxycarbamide (Hydrea®, Bristol-Myers Squibb).

Dasatinib [Sprycel®, Brystol-Myers Squibb (BMS)] is an oral TKI with activity against a range of tyrosine kinases. Dasatinib is licensed for the treatment of adults with chronic phase (CP), accelerated phase (AP) or blast crisis (BC) CML with resistance or intolerance to prior therapy including imatinib. The drug received accelerated approval for this indication by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Nilotinib (Tasigna®, Novartis) is also a second-generation oral TKI. Nilotinib is licensed for the treatment of adults with CP and AP Philadelphia chromosome-positive CML, with resistance or intolerance to prior therapy including imatinib, and has been approved for this indication by the FDA and EMA.

Objectives

In chronic phase

- In those patients who have ImR disease, what is the clinical effectiveness and cost-effectiveness of treatment with dasatinib or treatment with nilotinib, using HDI as a comparator?
- In those patients who have ImI disease, what is the clinical effectiveness and cost-effectiveness of treatment with dasatinib or treatment with nilotinib, using IFN as a comparator?

In accelerated phase

- In those patients who have ImR disease, what is the clinical effectiveness and cost-effectiveness of treatment with dasatinib or treatment with nilotinib, using HDI as a comparator?
- In those patients with ImI disease, what is the clinical effectiveness and cost-effectiveness of treatment with dasatinib or treatment with nilotinib, using hydroxycarbamide as a comparator?

In blast crisis

- In those patients who have ImR disease, what is the clinical effectiveness and cost-effectiveness of treatment with dasatinib following initial cytoreductive treatment, using HDI as a comparator?

Methods

Clinical effectiveness systematic review

A literature search was conducted in a range of electronic databases (for example MEDLINE and EMBASE, etc.) up to January 2009 (and rerun in June 2009). Studies were included if they compared treatment with dasatinib or treatment with nilotinib with any relevant comparator treatment in participants with ImR or ImI CML. The use of data from Phase II and non-randomised studies was considered only where there was insufficient evidence from good-quality randomised controlled trials (RCTs). Data from included studies were extracted by one reviewer and checked independently by a second. Quality was assessed by one reviewer and judgements checked by a second. Where appropriate, meta-analysis was used to estimate summary measures of relevant outcomes. All selected articles were scanned for short- and long-term adverse effects of treatment.

Review of economic evaluations and manufacturer submissions

A literature search was conducted in a range of electronic databases (for example MEDLINE and EMBASE, etc.) up to January 2009 (and rerun in June 2009) to identify economic evaluations of dasatinib and nilotinib which met the inclusion criteria.

The cost-effectiveness analyses reported in manufacturer submissions to the National Institute for Health and Clinical Excellence (NICE) were critically appraised using widely accepted frameworks. For AP and BC, a more detailed critique and exploration of the manufacturer models was undertaken as we did not develop a de novo evaluation in those phases of CML because of lack of appropriate evidence.

The Peninsula Technology Assessment Group cost–utility model

A decision-analytic model was developed to estimate the cost-effectiveness of dasatinib and nilotinib in CML-CP. The model closely resembles a Markov state-transition approach, using an 'area under the curve' method to determine state probabilities at each cycle of the model. The model has five health states: CP on treatment, CP no longer receiving treatment, AP, BC and death. The influence of a major cytogenetic response (MCyR) on overall survival (OS), which underpins the approach, was modelled using the hazard ratio for OS in responders versus non-responders derived from a meta-analysis of studies of imatinib [principally the landmark International Randomized Study of Interferon versus STI571 (IRIS)]. The modelled population was aged 56 years at the start of the analysis, which runs to a lifetime horizon (44 years) with a 2-month cycle. Future costs and benefits were discounted at 3.5% per annum.

Two separate models were implemented: one simulating a cohort of individuals who have shown or developed resistance to normal-dose imatinib (ImR) and one representing individuals who have been unable to continue imatinib treatment because of adverse events (AEs) [imatinib intolerant (ImI)].

One-way, multiway and probabilistic sensitivity analyses were performed to explore structural and parameter uncertainty.

Results

Number and quality of effectiveness studies

The systematic review included 15 studies. Three studies had a randomised controlled design; the remainder were observational. The majority of evidence – all three RCTs and 8 of 12 observational studies – related to dasatinib. Five of the identified studies investigated the effectiveness of nilotinib.

The three included RCTs all have substantial methodological flaws. The observational studies provide evidence that was difficult to assess, compare and generalise. None of the identified evidence allowed us to address any of our research questions directly. The absence of any meaningful data with which to assess the relative effectiveness of the interventions had limited our assessment of clinical effectiveness to a review of the absolute treatment effects reported in the literature.

Summary of benefits and risks

Dasatinib in chronic phase

A complete cytogenetic response (CCyR) was shown by about half of all study participants; around two-thirds of ImI individuals and 30–40% of ImR individuals achieved a CCyR. A MCyR was shown by about 60% of all study participants, with slightly more (75%) in the ImI population than in the ImR population (50%). Most of those patients who achieved a MCyR maintained it for at least 2 years. A complete haematological response (CHR) was achieved or maintained in around 90% of cases.

Three-quarters of study participants experienced progression-free survival (PFS) of 2 years or more. For OS, only around 10% of people were expected to die within 2 years of commencing treatment and more than four-fifths of the population should survive for at least 3 years.

Haematological AEs were common in all studies, with grade 3–4 neutropenia and thrombopenia each affecting around 50% ± 10% of individuals taking dasatinib, although rates may be lower (20–30%) at the currently recommended dosage of 100 mg q.d. Non-haematological AEs were also frequently reported, with the most common being diarrhoea, dyspnoea, fatigue, headache, nausea, pleural effusion and rash. Overall, grade 3–4 non-haematological AEs appeared to be fairly rare, with only dyspnoea and pleural effusion occurring in > 5% of any of the reported cohorts. Approximately 5–15% of study participants discontinued dasatinib therapy because of AEs, with the lowest withdrawal rate (4.8%) in the group receiving the currently recommended dosage of 100 mg q.d.

Dasatinib in accelerated phase

A CCyR was shown by about one-third of all study participants and a MCyR by approximately 35–45%, with no evidence of a difference in efficacy between ImR and ImI individuals. It appeared that 80–90% of those achieving a MCyR would maintain it for at least 1 year. A CHR

was achieved or maintained in around 50% of cases, again with no evidence of difference between ImR and ImI individuals.

Average PFS in AP was a little over 2 years. Average OS was a little over 2.5 years. Two-thirds to three-quarters of individuals appeared to survive for 2 years or more.

Haematological AEs were extremely common. The majority of participants experienced grade 3–4 neutropenia and thrombopenia; anaemia and leucopenia were almost as prevalent. The most commonly reported non-haematological AEs were diarrhoea, dyspnoea, fatigue, headache, nausea, pleural effusion and rash. The grade 3–4 toxicities reported at a frequency of > 10% were diarrhoea, febrile neutropenia and fluid retention. Up to 30% of study participants discontinued dasatinib therapy because of AEs.

Dasatinib in blast crisis

A CCyR was shown by about one-third of study participants and a MCyR by around 45%, although considerable variability in rates was found. Where reported, the achievement of a MCyR in myeloid blast crisis (MBC) was less common than in lymphoid blast crisis (LBC). A CHR was achieved or maintained in around one-third of cases.

Most study participants achieved ⩾ 3–6 months' PFS and only one-quarter to one-third of individuals experienced OS of > 2 years.

A substantial majority experienced multiple cytopenias at grade 3–4 severity. The most frequently reported non-haematological AEs were diarrhoea, dyspnoea, fatigue, nausea, peripheral oedema, pleural effusion, pyrexia, rash and vomiting. Grade 3–4 pleural effusion occurred in > 10% of participants in MBC. Gastrointestinal haemorrhage and febrile neutropenia were also reported at frequencies > 10%. The studies suggest that serious AEs may be less common in participants in LBC. The reported frequency of study participants who discontinued dasatinib therapy as a result of AEs varied between 0% and 15%.

Nilotinib in chronic phase

A CCyR was shown by about one-third of all study participants and a MCyR in a little under half, with little difference between the ImI and ImR subgroups. Around 85% who showed a MCyR maintained it for at least 18 months. A CHR was achieved in around 80% of cases and ImI individuals may have a higher likelihood of CHR.

The majority of individuals receiving nilotinib in CML-CP experienced > 3 years' PFS; a little under two-thirds had PFS of ⩾ 2 years. For OS, only around 10% had died following 2 years of treatment.

Haematological AEs were common. Grade 3–4 neutropenia and thrombopenia each affected around 30% in the published study. The most common non-haematological AEs were constipation, diarrhoea, fatigue, headache, nausea/vomiting, pruritus and rash, with between one-tenth and one-quarter of participants experiencing such events. Overall, grade 3–4 AEs appear rare, with only rash exceeding a 3% incidence in any of the identified evidence. A total of 15% of study participants discontinued nilotinib therapy because of AEs.

Nilotinib in accelerated phase

A CCyR was shown by about one-sixth of all study participants and a MCyR by about 30%, with no difference between the ImR and ImI populations. The evidence on a CHR was very heterogeneous. On average, a CHR was achieved in around half of all cases.

Average PFS was a little under 1.5 years. Around two-thirds of individuals could expect an OS of ≥ 2 years.

Haematological AEs were common. Grade 3–4 neutropenia and thrombopenia each affected approximately 20–35% in the published study. The most frequently reported non-haematological AEs were alopecia, constipation, diarrhoea, fatigue, headache, muscle spasms, myalgia, nausea/vomiting, pruritus, pyrexia and rash, with between 10% and 20% of participants experiencing such events. Grade 3–4 non-haematological AEs were very rare, with only rash exceeding a 1% incidence in any of the identified evidence. Approximately 10% of study participants discontinued nilotinib therapy because of AEs.

Summary of costs

According to the March 2009 edition of the *British National Formulary* (BNF) the cost of treatment with dasatinib (100 mg q.d.) was £86.85 per day and the cost of treatment with nilotinib (400 mg b.i.d.) was £86.89 per day.

Summary of cost-effectiveness

We were unable to locate any fully published economic evaluations of any of the interventions.

Although there were methodological similarities in the economic evaluations carried out by the Peninsula Technology Assessment Group (PenTAG) and the manufacturers in CP, in all cases the cost-effectiveness estimates from our economic evaluation were less favourable than those presented in the manufacturer submissions.

In AP and BC, we provide a review, critique and exploration of the economic evaluations provided in the manufacturer submissions.

However, our models were reliant on an array of major assumptions and were subject to a number of limitations. The most critical of these was that the models were necessarily parameterised on the basis of a heterogeneous collection of observational data, in which the outcome measures on which we rely have been defined and measured in different ways, at different times and in different populations.

Chronic phase in imatinib-resistant disease

In the PenTAG economic analysis, both the deterministic and probabilistic results suggest that it was unlikely that dasatinib would be considered to provide acceptable value for money.

In our base-case deterministic analysis, our model predicted that dasatinib would typically be taken for far longer than the other technologies under review, thus incurring much higher drug acquisition costs. However, this additional expenditure was not counterbalanced by an equivalent effectiveness gain. Dasatinib was therefore estimated to have a high cost–utility ratio, approximately £91,000 for every additional quality-adjusted life-year (QALY) gained.

The analysis of uncertainty identified the duration of treatment as the most important single assumption. When treatment duration for dasatinib was assumed to be the same as for nilotinib (i.e. considerably reduced), dasatinib dominated HDI. Results were also sensitive to the assumption of a MCyR rate for dasatinib, even though when all individuals were assumed to achieve a response, the incremental cost-effectiveness ratio (ICER) did not reach conventional levels of willingness to pay (WTP).

In contrast, nilotinib was estimated to dominate HDI in people with ImR disease. This finding was again sensitive to treatment duration (i.e. cost). When this was assumed to be the same as for dasatinib, the ICER exceeded £100,000, demonstrating the critical importance of the duration and cost of technology used, given the similar estimated OS durations between comparators. For nilotinib, a substantial and longer time was spent after progression in CP but before the onset of AP (i.e. without incurring costs of nilotinib treatment), the converse being true for dasatinib.

Chronic phase in imatinib-intolerant disease

Our analysis predicted that the costs of dasatinib and nilotinib would exceed those for IFN, and that substantial incremental QALY gains would be achieved, these being greater for dasatinib than nilotinib (2.2 QALYs vs 1.2 QALYs). However, these benefits were not sufficiently large to outweigh the difference in costs, and the ICERs for both drugs versus IFN were higher than conventional levels of WTP. Incremental analysis of the three options suggested that nilotinib would be extendedly dominated (i.e. a combination of dasatinib and IFN would achieve greater gains for the same cost) and the ICER for dasatinib high at £82,600 per QALY. This finding was robust to extensive one-way sensitivity analyses and the use of alternative data to underpin the surrogate role of a MCyR on OS. Probabilistic sensitivity analysis suggested a probability that IFN would be the preferred treatment at a WTP of £30,000 per QALY of 100%.

Accelerated phase

Our assessment was based on the manufacturer submissions to NICE.

Dasatinib

In the BMS evaluation, compared with HDI, treatment with dasatinib increased OS by 1.88 years and increased total costs by £57,000, giving an ICER of £35,319. Compared with nilotinib, dasatinib increased OS by 0.93 years and increased total costs by £30,000, giving an ICER of £36,778.

The probabilistic sensitivity analysis predicted a probability of 63.4% that dasatinib was cost-effective compared with HDI (at a WTP of £30,000 per QALY). Compared with nilotinib, the corresponding figure was 30%.

We have several major concerns with these analyses. The data on HDI were inappropriate, originating from a study of standard-dose imatinib in an imatinib-naive population, although no estimate in the correct population existed. Also, all interventions were assumed to be taken at the recommended dose despite evidence that this was not the case and the model predicted much shorter OS than was seen in the studies, calling the validity of the approach into question. Using alternative values for the dose intensity of treatments and the BNF price of dasatinib alone gave ICERs which were in excess of £40,000.

Nilotinib

In ImR patients, compared with HDI, the Novartis economic analysis predicted a base-case cost per QALY of £18,541. In ImI patients, compared with hydroxycarbamide, the Novartis economic analysis predicted a base-case cost per QALY of £79,914.

We have several major concerns with this analysis: the clinical effectiveness data used to populate the model for both HDI and hydroxycarbamide were seriously flawed; interventions were assumed to be taken at the recommended dose with no consideration of reported dose intensities; disease progression within AP was assumed to lead directly to BC and progression-free survival data were subject to a high degree of extrapolation.

Exploration of the model and revision of errors in calculating the effectiveness of HDI (albeit using inappropriate data) suggest that nilotinib may be less effective and cheaper, such that over £100,000 might be saved in association with each QALY forgone by using nilotinib instead of HDI.

Blast crisis

Our assessment was based on the manufacturer submissions to NICE.

In the evaluation of dasatinib submitted by BMS to NICE, compared with HDI, treatment with dasatinib was predicted to yield 0.45 QALYs and to cost £11,000 less, i.e. dasatinib was economically dominant.

Again, we had several major concerns with the analysis, particularly on the use of inappropriate clinical effectiveness data for HDI (as before) and the assumption that all treatments were used at recommended doses. When elements of the BMS's model were adjusted (dose intensity and dasatinib price), dasatinib remained dominant over HDI.

Discussion

The paucity of comparative clinical evidence in which treatment with dasatinib or nilotinib has been compared with any other treatment in individuals with ImR or ImI CML impacts on the assessment of both the cost-effectiveness and clinical effectiveness of the interventions. The uncertainties that necessarily and irrevocably exist in the data combine to give an evidence base that does not fully inform the decision problems faced by policy-makers, is difficult to interpret and which provides little opportunity for valid synthesis.

For all disease phases, the assessment contains absolute rather than relative clinical effectiveness estimates because of the observational nature of the included data and differences in the definitions of eligibility criteria, baseline characteristics and outcomes (including progression and the methods and timing of reporting outcomes). We were unable to identify any appropriate data with which to inform the clinical effectiveness of relevant comparator treatments in AP and BC, and have thus only produced a model in CP.

Our CP cost-effectiveness model should be viewed as an exploratory analysis of uncertainty in the available evidence, rather than a robust evaluation of cost–utility.

Strengths of the analyses

The strengths of this assessment include the comprehensive, explicit and systematic literature searches used to locate evidence both for the review of clinical effectiveness and to inform the economic modelling study; the use of the information that is most certain in the evidence base [cytogenetic response (CyR) rates] to predict long-term outcomes; and the extensive exploration of uncertainty.

Conclusions

Chronic phase chronic myeloid leukaemia

Effectiveness data were limited, but dasatinib and nilotinib appeared efficacious in terms of obtaining CyRs and haematological responses in both ImR and ImI populations. The extent to which greater frequency and/or degrees of response may impact on long-term outcomes was more difficult to conclude given the limited nature of the evidence base. In particular, only one

study had compared either agent (dasatinib) with HDI. The findings of this open-label study, that higher proportions of patients experience positive responses to dasatinib than HDI, were importantly confounded by substantial crossover at an early point in the follow-up.

In terms of cost-effectiveness, it was extremely difficult to reach any conclusions regarding either agent in the ImR population. All three models (Novartis, PenTAG and BMS) were seriously flawed in one way or another, again as a consequence of the paucity of data appropriate to construct robust decision-analytic models with currently available data.

The economic picture was similar for people who were intolerant of imatinib, for whom even fewer data exist, and this comparison was made more difficult in structural terms by the lack of clarity about what constitutes the appropriate comparator in current practice.

The findings of clinical effectiveness studies suggest, perhaps unsurprisingly, that better responses are shown in people for whom second-line therapy is indicated as a consequence of imatinib intolerance than in those who are resistant to first-line imatinib. However, reflecting the uncertainty about duration of therapy in particular, this ranking seems reversed in our economic analyses.

Accelerated and blast crisis chronic myeloid leukaemia

The economic evaluations carried out by the manufacturers of nilotinib and dasatinib were seriously undermined by the absence of evidence on HDI in these populations. In response to this, both models assumed that the clinical effectiveness of imatinib therapy could be adduced from evidence obtained in an imatinib-naive population using normal-dose imatinib. In addition to this factor, problems existed in all evaluations with respect to cost estimates and only in the BC analysis of dasatinib (in which the new TKI dominated) do findings appear robust to changes in parameter assumptions.

Suggested future research questions and priorities

There are several RCTs of the interventions under way. It is perhaps surprising given the oral nature of the interventions, and thus the relative ease of blinding of a study, that these are all open studies. We feel that a three-way, double-blind RCT of dasatinib, nilotinib and HDI would be the most useful addition to the scant existing evidence base.

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