Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses

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Executive summary

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Executive summary

Background

Chronic myeloid leukaemia (CML) is one of the blood cancers in which there is an overproduction of one type of white blood cell (WBC), the granulocytes, by the bone marrow. The typical CML progression course has three phases: the chronic phase (CP), the accelerated phase (AP) and the blast crisis (BC) phase. An estimated 530 cases of CML are newly diagnosed in the UK each year. CML occurs in all age groups, with a mean age at diagnosis of 57 years.

With the advent of a new class of drugs for the treatment of CML, known as tyrosine kinase inhibitors (TKIs), with imatinib being the first, the natural history of the disease has been markedly changed. Current evidence suggests that patients whose disease responds favourably to treatment with imatinib may remain essentially symptom free for at least 10 years. UK guidelines recommend imatinib as a first-line treatment for CML in the CP.

Nilotinib and dasatinib were initially developed for the treatment of patients who are resistant or intolerant to imatinib, and were selected due to their potency and activity against mutated forms of BCR–ABL1 (oncogene fusion protein consisting of BCR and ABL). Nilotinib and dasatinib are now being considered as alternative treatments to imatinib as a first-line treatment.

Objectives

This technology assessment reviews the available evidence for the clinical effectiveness and cost-effectiveness of dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of Philadelphia chromosome-positive (Ph+) CML. The questions addressed are as follows.

In CP:

1. What is the clinical effectiveness of first-line treatment for newly diagnosed Ph+ CML with dasatinib or with nilotinib or with imatinib (standard dose), using each of the three treatments as comparators?
2. What is the cost-effectiveness of first-line treatment for newly diagnosed Ph+ CML with dasatinib or with nilotinib or with imatinib (standard dose), using each of the three treatments as comparators?

Methods

The assessment comprises a systematic review of clinical effectiveness and cost-effectiveness studies, a review and critique of manufacturer submissions and a de novo economic analysis.

Clinical effectiveness methods

Clinical effectiveness systematic review

For the assessment of effectiveness, a literature search was conducted in a range of electronic databases including MEDLINE, EMBASE and The Cochrane Library (2002 to May 2011).

Studies were included if they were of:

- randomised controlled trials or systematic reviews of randomised controlled trials
- adults with CML in chronic phase (CP-CML), naive to any treatment specifically directed against CML
- interventions – dasatinib, nilotinib or imatinib (standard dose)
- comparators – imatinib or nilotinib where the intervention is dasatinib; imatinib or dasatinib when the intervention is nilotinib; dasatinib or nilotinib when the intervention is standard-dose imatinib.

Surrogate outcomes systematic review

Owing to the lack of long-term follow-up in the identified trials, the potential impact of surrogate outcomes on survival or progression-free survival (PFS) is particularly important. We therefore conducted a review of the evidence for complete cytogenetic response (CCyR) and major molecular response (MMR) as markers for long-term outcomes such as survival.

Clinical effectiveness: results

Number and quality of clinical effectiveness studies

The searches identified 3228 titles and abstracts. Two clinical trials (dasatinib vs imatinib and nilotinib vs imatinib) were included. No direct comparisons of dasatinib and nilotinib were identified. Overall, the quality of both studies was considered good.

Summary of benefits and risks

Survival (event free, progression free and overall) was not significantly different for dasatinib or nilotinib compared with imatinib with the 24-month follow-up data available.

The rates of CCyR and MMR were higher for patients receiving dasatinib compared with imatinib for 12 months' follow-up (CCyR 83% vs 72%, $p < 0.001$; MMR 46% vs 28%, $p < 0.0001$). The significant difference remained for MMR at 18 months' follow-up (56% vs 37%, $p < 0.001$). The rates of CCyR and MMR were higher for patients receiving nilotinib compared with imatinib for 12 months' follow-up (CCyR 80% vs 65%, $p < 0.001$; MMR 44% vs 22%, $p < 0.0001$). For 24 months' follow-up, nilotinib continued to be significantly superior compared with imatinib (CCyR 87% vs 77%, $p < 0.001$; MMR 62% vs 37%, $p < 0.001$). Haematological events across all grades were lower for patients receiving nilotinib compared with imatinib.

With no head-to-head trials comparing dasatinib and nilotinib, an indirect comparison was carried out, which showed no difference between dasatinib and nilotinib for CCyR or MMR rates for 12 months' follow-up (CCyR odds ratio 1.09, 95% CI 0.61 to 1.92; MMR odds ratio 1.28, 95% CI 0.77 to 2.16).

Summary of surrogate outcomes review

There was evidence of an association between short-term cytogenetic response and molecular response, and longer-term survival in patients treated with imatinib for CP-CML. No evidence from dasatinib or nilotinib studies was identified. Patients who experience either a CCyR or MMR following 12 months' imatinib treatment have better long-term (5-year) overall survival (OS) (CCyR 97.4% vs 74.1%; MMR 96.6% vs 91.2%) and polymerase chain reaction (PCR) (CCyR 96.8% vs 75.2%; MMR 95.8% vs 89%) than patients who are non-responders at 12 months. However, these differences were not shown to be statistically significant.

Cost-effectiveness: methods

Cost-effectiveness systematic review

For the cost-effectiveness review, the inclusion and exclusion criteria were the same as for the clinical effectiveness review, except study design, for which full cost-effectiveness analyses, cost-utility analyses, cost–benefit analyses and cost-consequence analyses were included.

Peninsula Technology Assessment Group cost-effectiveness analysis: methods

Our cost-effectiveness modelling attempted to provide a range of scenario analyses to reflect the significant structural uncertainty and related different approaches to estimating OS. We used:

1. A cumulative survival approach, in which OS is the cumulative result of the time on first-, second- and (where relevant) third-line treatments, plus time in AP and BC phases.
2. A surrogate survival approach, in which OS is estimated from 12-month CCyR and MMR response rates from the two key trials [ENESTnd (Evaluating Nilotinib Efficacy and Safety in clinical Trials – Newly Diagnosed patients) and DASISION (Dasatinib vs Imatinib in Patients With Newly Diagnosed Chronic Phase CML)] combined with the relationship of these surrogate outcomes to longer-term survival. This was based on our systematic review of such relationships in trials and observational studies of imatinib.

Under the cumulative survival approach, time to treatment discontinuation was extrapolated using trial data for time on TKI treatment (first or second line) and the fitting of Weibull curves. Time on treatment with hydroxycarbamide was estimated first by estimating OS following hydroxycarbamide in CP-CML, and then calculating the constant transition probabilities between CP and AP, AP and BC, and BC and death, which would achieve the same OS (and given mean duration in AP and BC of 9.6 and 6 months, respectively).

Under the surrogate survival approach (which was used only in scenarios where TKIs were not used as second-line treatment), OS was predicted from the meta-analysis of either CCyR or MMR at 12 months, and the proportions of patients in the relevant two trials who achieved these responses. These extrapolations adjusted for non-CML-related mortality and made use of historical data from imatinib trials.

Cost-effectiveness: findings and results

Summary of economic evaluations

Our literature search did not identify any published full economic evaluations meeting the inclusion criteria.

Peninsula Technology Assessment Group cost-effectiveness modelling results

We present cost-effectiveness results for each of four main 'scenarios'. In scenario 1, we do not model second-line nilotinib or dasatinib. In scenario 2, again, we do not model second-line nilotinib but we use the simplified method, whereby the post-TKI per-patient costs and QALYs are set to be equal across treatment arms. We believe that this approach is appropriate owing to the substantial uncertainty in the type, and associated costs and quality of life, of post-TKI treatments. Scenario 3 is the same as scenario 1, but allowing for second-line nilotinib. First-line dasatinib is predicted to provide very poor value for money compared with first-line imatinib, regardless of the model structure (whether or not we allow for second-line treatment with

nilotinib and regardless of when parameters are varied within plausible ranges), with ICERs of between £256,000 and £450,000 per QALY.

Conversely, the findings for the cost-effectiveness of first-line nilotinib compared with first-line imatinib are more complex. Assuming that first-line imatinib is followed by second-line nilotinib (i.e. scenarios 3 and 4) on nearly all occasions, nilotinib is predicted to yield slightly fewer QALYs (–0.1 or –0.5) at lower cost than imatinib (between £18,500 and £22,000 lower). Under these scenarios, the small estimated QALY losses implied by using first-line nilotinib would yield NHS cost savings of either £192,000 per QALY or £46,000 per QALY. When we assume that first-line imatinib is not followed by second-line nilotinib (scenarios 1 and 2), first-line nilotinib often lies close to the £20,000 and £30,000 per QALY willingness-to-pay threshold (with base-case ICERs for these two scenarios of £20,000 or £25,000 per QALY, respectively).

Discussion

Strengths and limitations of the systematic reviews

The systematic reviews were conducted by an independent research team using the latest evidence and to a prespecified protocol. The main limitations of the review of clinical effectiveness were a lack of long-term evidence on dasatinib and nilotinib used first line, the lack of evidence for the use of surrogate outcomes with dasatinib and nilotinib, and no head-to-head trials of dasatinib compared with nilotinib. The main limitation of the review of economic studies was a lack of any studies reporting the cost-effectiveness of dasatinib and nilotinib.

Strengths and limitations of the Peninsula Technology Assessment Group economic model

Strengths

- We have developed a model that is capable of using either a surrogates-based estimation of OS, a cumulative treatment duration approach, or a combination of both.
- It is based on the best available research evidence.
- Where research evidence is lacking, we have checked key assumptions and parameter inputs with relevant clinical and other experts, or surveys of clinicians where available.
- Good calibration of model survival outputs against IRIS (International Randomised Study of Interferon versus STI571) data (imatinib-arm only).

Limitations

Given that CML is a chronic condition, and that the main two randomised controlled trials (RCTs) provide very immature data on PCR, treatment duration and OS, the cost-effectiveness estimates of dasatinib and nilotinib are highly uncertain. The main limitations are therefore:

- Immaturity of empirical trial data relative to life expectancy, forcing either reliance on surrogate relationships or cumulative survival/treatment duration assumptions.
- Overall great uncertainty about the very heterogeneous treatment and care pathways that patients with CML may follow. There are very many potential care and disease state paths that might be followed, depending on how different people respond to treatment, their age, disease severity, availability of matched donors [for stem cell transplantation (SCT)], mutations that predict responsiveness to second-generation TKIs. This includes not modelling complex treatment sequences in advanced disease (e.g. second and third CPs, and SCT following disease progression), and not modelling possible cessation of TKIs in those who experience a deep and durable initial response.
- Uncertainty over which treatment sequences of alternative TKIs are seen as clinically feasible.

- Uncertainty in evidence regarding treatments post TKI failure in CP: proportion getting SCT, hydroxycarbamide as proxy for what in reality would be a range of treatments that might be offered.
- Also, uncertainty in survival and treatment costs following either SCT or hydroxycarbamide.
- Very limited sources of evidence for utility weights, and none available for post TKI failure in CP. Also, no valid and reliable studies were available to reflect possible HRQoL decrement of being on TKIs but not responding to them.
- For the surrogate survival method, we consider only the proportion of patients with or without a response at 12 months. We do not consider the depth, speed of achieving and duration of the MMR or CCyR. We also assume that, for a given response rate, OS is independent of treatment arm.

Conclusions

From the two trials available, both the second-generation TKIs dasatinib and nilotinib have a statistically significant advantage compared with the first-generation TKI imatinib 400 mg, as measured by surrogate outcomes. However, there are insufficient data to assess longer-term patient-relevant outcomes (e.g. PFS, OS, HRQoL). All three drugs were well tolerated with discontinuation due to adverse events < 10%.

With no head-to-head data available, an indirect comparison analysis showed no difference between dasatinib and nilotinib for the primary outcomes of CCyR or MMR for 12 months' or 24 months' follow-up.

Based entirely on imatinib treatment, there is observational association evidence supporting the use of CCyR and MMR at 12 months as surrogates for OS and PFS in patients with CP-CML.

Taking into account the treatment pathways for patients with CML, i.e. assuming the use of second-line nilotinib, first-line nilotinib appears to be more cost-effective compared with first-line imatinib for most scenarios. Dasatinib was not cost-effective compared with imatinib and nilotinib.

Suggested research priorities

- Given the immature stage of trials assessing dasatinib or nilotinib compared with imatinib, longer-term follow-up trial data are required. As well as the prespecified clinical outcomes (such as CCyR, MMR and survival), these should report both treatment duration and dose intensity information for those treated.
- With no current head-to-head data for dasatinib and nilotinib, a RCT assessing the two therapies directly would be valuable.
- More research-based data for assessing the predictive usefulness of surrogate outcomes (such as MMR and CCyR) within the CML population, especially for dasatinib and nilotinib.
- Better and more UK-specific data on the incidence and cost of SCTs in patients with chronic CML.
- Data on HRQoL for people in all stages of CML, and when on different treatments is lacking [ideally using the European Quality of Life-5 Dimensions (EQ-5D) or Short Form questionnaire-36 items (SF-36) generic HRQoL measures].

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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