Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of imatinib mesylate (IM) as second-line treatment for patients with chronic myeloid leukaemia (CML) who had failed first-line interferon (IFN)-alpha therapy. IM was assumed to be administered at a dose of 400 mg/day on an outpatient basis.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with CML who had previously not responded to IFN-alpha therapy.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
Some effectiveness data were derived from studies published between 1995 and 2002. No dates for the resource use data were explicitly reported. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of studies and experts' opinions.

Modelling
A Markov model with monthly cycles and a lifetime horizon was used to simulate disease progression for a hypothetical cohort of 1,000 patients with CML for whom IFN-alpha had failed as first-line therapy. Patients in the chronic phase of CML could either stay in that phase or respond to therapy, having either a complete haematologic response accompanied by a major cytogenetic response (CytR), complete haematologic response (CHR) without major CytR, or partial haematologic response (PHR). The patients remained in their response state until disease progression. If disease progression occurred, the patients stopped receiving active treatment and moved into either the accelerated phase or blast-crisis phase, in which they received chemotherapy or palliative care. The patients could also die from causes unrelated to the disease. Details of the health states and the structure of the model were provided.
Outcomes assessed in the review
The outcomes estimated from the literature were the probabilities of responses to treatment, the probability of disease progression, and mortality rates.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. Most of the data came from clinical trials. In particular, response rates with IM were derived from a Phase II trial, while response rates with hydroxyurea came from two trials with IFN-alpha as the comparator. Transition probabilities for IM were based on a Phase II trial for the first 12 months and on an Italian trial for the following months. Expected survival was estimated from life tables. The statistical approach used to estimate progression data from clinical trials was reported (Weinbull survival curves).

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The use of clinical trials ensured the internal validity of the primary studies. However, no head-to-head comparisons between IM and hydroxyurea were found.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Seven primary studies provided clinical evidence.

Methods of combining primary studies
Each study represented a source of some clinical data. The studies were not combined.

Investigation of differences between primary studies
Not stated.

Results of the review
With hydroxyurea:
the probability of a major CytR was 0.0025 in months 1 - 8 and 0 after month 8;
the probability of CHR was 0.1345 in months 1 - 8 and 0 after month 8; and
the probability of PHR was 0.1345 in months 1 - 8 and 0.0011 after month 8.

With IM:
the probability of CytR was 0.0496,
the probability of CHR was 0.0236, and
the probability of PHR was 0.
In terms of disease progression, 70% of patients entered the accelerated phase and 30% progressed directly to blast crisis.

For patients receiving chemotherapy or palliative care in the accelerated phase, the monthly probability of progressing into blast crisis was 0.1091. The monthly probability of death in blast crisis was 0.1428.

**Methods used to derive estimates of effectiveness**
A panel of 6 UK consultant haematologists was contacted to derive quality of life (QoL) data associated with specific health states. The clinicians determined QoL using the self-reported description component of the EuroQol (EQ-5D) instrument. Average values of all estimates were used in the model. Other assumptions required in the decision model were also made.

**Estimates of effectiveness and key assumptions**
In the chronic phase, the utility was 0.90 and was the same for IM and hydroxyurea. In the accelerated phase, the utilities varied between 0.01 for patients undergoing chemotherapy and 0.34 for patients receiving palliative care in the home. For blast-crisis patients, the corresponding utilities were -0.09 (chemotherapy) and 0.04 (palliative care), respectively. The transition probabilities relating to response for subsequent years of treatment with IM were the same as in year 1 until year 10. After year 10, IM-treated patients did not experience cytogenetic or haematologic responses.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the quality-adjusted life-years (QALYs). These were estimated by combining survival data from the literature with QoL data derived by the panel of experts. Median survival rates were also reported. An annual discount rate of 1.5% was applied to the QALYs.

**Direct costs**
The analysis of the costs was carried out from the perspective of the UK NHS. The health service costs considered were drugs, outpatient visits, bone marrow tests, blood transfusions, radiology tests, nurse home visits, general practitioner home visits, palliative care and conventional chemotherapy. The unit costs were presented separately from the quantities of resources used. The estimation of resource use was mainly based on authors' assumptions. The costs came from typical NHS sources, including the British National Formulary, NHS reference costs, and the Personal Social Services Research Unit. Discounting was relevant, given that a lifetime horizon was adopted in the model, and an annual rate of 6% was applied. The price year was 2001.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not relevant to the perspective adopted in the study and were not included.

**Currency**
UK pounds sterling (£).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the robustness of the cost-utility ratios to variations in the model inputs. For example, the cost of palliative care and IM, discount rate, switch of nonresponders to hydroxyurea, utility values, and the cost of adverse events. The authors appear to have set the alternative values used.
Estimated benefits used in the economic analysis
The median survival rate was 56 months with hydroxyurea and 77 months with IM.

The QALYs were 3.49 with hydroxyurea and 5.95 with IM (difference 2.46).

Cost results
The costs per patient were 15,566 with hydroxyurea and 110,103 with IM (difference 94,536).

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and QALYs of the alternative treatments.

The incremental cost per QALY gained with IM over hydroxyurea was 38,468.

The univariate sensitivity analysis showed that the cost-utility ranged from 14,195 with a substantial reduction in the price of IM, to 62,745 when using an annual discount rate of 6% for both the costs and QALYs.

The results of the analysis were robust to variations in other costs, utility values, and assumptions about the discontinuation of IM treatment.

Authors’ conclusions
Imatinib mesylate (IM), as second-line treatment for chronic myelogenous leukaemia (CML), led to considerable health benefits in comparison with hydroxyurea, at a cost of 38,468 per quality-adjusted life-year (QALY) gained from the perspective of the UK National Health Service (NHS).

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear and appropriate. Hydroxyurea represented the recommended second-line treatment for patients with CML, while IM was the new medication. The treatment doses were reported for both hydroxyurea and IM. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from a review of published studies and experts' opinions. A systematic review of the literature, to identify primary studies, does not appear to have been performed. Therefore, such studies might have been identified selectively. The evidence on treatment efficacy came from clinical trials, which usually have a high internal validity. However, since information on the design and other characteristics of the primary studies was not provided, it was difficult to assess the robustness of most clinical estimates. The authors acknowledged that data on treatment response were estimated from different sources, but this was due to the lack of Phase III head-to-head clinical studies. Data on mortality were derived from life tables, which represent a typical source of information for all-cause mortality. Data on QoL were estimated from a panel of experts, and average values were calculated. Extensive sensitivity analyses on utility values and other model inputs were performed to test the robustness of the model results to variations in the clinical inputs.

Validity of estimate of measure of benefit
The benefit measure used in the analysis was appropriate since QALYs capture the impact of the interventions on survival and QoL, which are the most relevant dimensions of care for patients with CML. QALYs are comparable with the benefits of other health care interventions. Discounting was applied, in accordance with UK guidelines in use at the time of the study, and the impact of alternative discount rates was assessed in the sensitivity analysis. Information on the source of the utility weights and the approach used to calculate QALYs was provided.
Validity of estimate of costs
The perspective adopted in the study was explicitly stated, and the cost categories included in the analysis were consistent with that perspective. The unit costs were presented separately from the quantities of resources used for many items, which enhances the possibility of replicating the cost analysis in other settings. The source of the data was reported for all items. No statistical analyses of the costs were performed, although some key cost estimates were varied in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods. Discounting was appropriately conducted and alternative discount rates were investigated in the sensitivity analysis.

Other issues
The authors stated that no published studies had evaluated the cost-effectiveness of second-line treatments in the chronic phase of CML. Therefore, comparisons with the findings from other studies were not made. The issue of the generalisability of the study results to other settings was not addressed, although several sensitivity analyses on key estimates were performed. The study referred to patients with CML in whom first-line IFN-alpha therapy has failed, and this was reflected in the authors' conclusions.

Implications of the study
The study results suggested that IM may be a cost-effective second-line treatment for patients with CML. The authors suggested that the model could be updated as soon as long-term data from ongoing trials become available.

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Other publications of related interest


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