Cost-efficacy of imatinib versus allogeneic bone marrow transplantation with a matched unrelated donor in the treatment of chronic myelogenous leukemia: a decision-analytic approach

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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 for the treatment of chronic myelogenous leukaemia (CML). An initial dosage of 400 mg/day, followed by doses of 600 or 800 mg/day, appears to have been considered.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with CML.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The clinical evidence and most resource use data came from studies published between 1996 and 2003. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A Markov model was constructed to simulate the disease-state transitions of a cohort of patients from diagnosis through the first 2 years of treatment. Cycles of 3 months were used. The analysis referred to a hypothetical 35-year-old man with Philadelphia chromosome-positive CML in the chronic phase.

In the BMT arm, patients transitioned through three health states, specifically, haematologic and cytogenetic remission, graft failure and death. Graft-versus-host disease (GVHD) was the most relevant complication considered with allogeneic BMT. Patients in the initial remission state could either remain in remission, relapse again into the chronic phase, or progress into the accelerated phase or blast crisis.

Six health states were considered in the imatinib arm. These were complete haematologic response with accompanying karyotypic response, complete haematologic response without karyotypic response, no response or partial response,
progression to the accelerated phase, progression to blast crisis, and death. Significant haematologic (neutropenia, thrombocytopenia) or non-haematologic (life-threatening oedema) side effects of imatinib were considered.

Outcomes assessed in the review
The outcomes assessed were the clinical inputs used to populate the decision model, such as transition probabilities across health states.

Study designs and other criteria for inclusion in the review
The authors stated that a systematic review of the published literature was undertaken to identify the primary estimates.

Sources searched to identify primary studies
MEDLINE (from 1966 to 2004) and International Pharmaceutical Abstracts were searched for relevant studies.

Criteria used to ensure the validity of primary studies
The validity of the primary studies was ensured by selecting studies with high internal validity, such as clinical trials and meta-analyses.

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

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

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The outcomes estimated from the review of the literature were not reported.

Measure of benefits used in the economic analysis
The summary benefit measure used was the 2-year survival rate. This was estimated using a modelling approach. No discounting appears to have been used.

Direct costs
The perspective adopted in the study was that of the third-party payer, thus only the direct medical costs were included in the analysis. The study focused on relevant laboratory tests, procedures, clinical follow-up, drugs, hospital stay, interventions, and the treatment of toxicities or adverse effects for each stage of the cohort. In particular, the resources associated with allogeneic BMT included initial diagnosis, identification and evaluation of the donor, marrow harvesting and treatment, pre-conditioning (including total body irradiation and high-dose cyclophosphamide), GVHD prevention, BMT, hospital costs associated with length of stay, and follow-up (routine physician visits, laboratory work, bone marrow biopsies, and outpatient drugs for the prevention of side effects). Resources associated with imatinib were
initial diagnosis, drug acquisition, and follow-up (e.g. routine physician visits, laboratory work, bone marrow biopsies, and the treatment of significant adverse events). The unit costs were not presented separately from the quantities of resources used. The costs were estimated from Physicians' Fee Reference and Physicians' Fee and Coding Guide using Current Procedural Terminology codes, while average wholesale prices were used to derive the drug costs. The daily rate of a conventional private room supplied with positive-pressure filtered air was determined by expert clinical opinion. The resource use data came mainly from published data, mainly clinical trials. The initial costs were considered one-time expenditures and were not discounted, while subsequent costs were discounted at an annual rate of 5%. The price year appears to have been 2004.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was carried out on all cost inputs, which were the parameters with the greatest uncertainty. The discount rate was also varied. The authors set the ranges used. A first-order Monte Carlo simulation (50,000 trials) was also performed to obtain point estimates, 95% confidence intervals (CIs) and a cost-effectiveness plane for cost-effectiveness ratios.

**Estimated benefits used in the economic analysis**
The survival rate was 0.91 with imatinib and 0.44 with BMT (difference 0.47).

**Cost results**
The 2-year costs were $78,000 with imatinib and $114,000 with BMT (cost-difference 36,000).

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the two treatment strategies. The average cost per survival was $86,000 with imatinib and $261,000 with BMT. The incremental analysis revealed that imatinib dominated BMT, which was both less effective and more expensive.

The Monte Carlo simulation showed that the 95% CIs for costs were $28,000 to $110,000 for imatinib and $80,000 to $170,000 for BMT. The point estimates for the average cost-effectiveness ratios were $81,000 (95% CI: 74,000 - 111,000) with imatinib and $142,000 (95% CI: 98,000 - 171,000) with BMT. The cost-effectiveness plane showed that imatinib was dominant in 84.69% of the cases, while BMT dominated in 0.76% of simulations.

The sensitivity analysis showed that the cost of imatinib (400 mg/day) provided the greatest variability in the model.

**Authors' conclusions**
Imatinib was often more effective and less expensive than bone marrow transplantation (BMT) with a matched unrelated donor (MUD) in the short-term treatment of newly diagnosed, Philadelphia chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase.
CRD COMMENTARY - Selection of comparators
The authors explained the choice of the comparators, which were appropriate for the study question. The exclusion of interferon-alpha as an alternative comparator was justified. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a review of the literature. The sources searched to identify the primary estimates were reported, but not details of the method and conduct of the review. Most of the evidence appears to have been derived from clinical trials and meta-analyses, which should ensure the robustness of the primary studies. However, no information on the clinical inputs used in the model was provided, as the results of the review were not reported. Uncertainty related to the clinical data was not investigated in the sensitivity analysis. This would appear to be a strong limitation of the study.

Validity of estimate of measure of benefit
The use of survival rate as the summary benefit measure was appropriate as this represented the main dimension of health for patients suffering from CML. The assessment of benefits was restricted to a 2-year interval, which might limit the possibility of making comparisons with the benefits of other health care interventions. The use of long-term data would have been interesting. The impact of the interventions on quality of life was not addressed.

Validity of estimate of costs
The categories of costs included in the analysis were consistent with the perspective adopted. The costs of adverse events, which are particularly relevant in the context of treatments for CML, were considered. A breakdown of the cost items was reported, but there was no information on the unit costs or quantities of resources used. This limits the possibility of replicating the cost analysis in other settings. The sources of the data were given. The price year was reported, which aids reflation exercises in other time periods. Statistical analyses of the costs were carried out in the probabilistic sensitivity analysis, and the key costs were varied in the univariate sensitivity analysis. Thus, the issue of uncertainty around the cost estimates was satisfactorily addressed.

Other issues
The authors stated that no direct comparisons of imatinib and BMT were found in the literature, thus the results of the current study could not be compared with those from other studies. However, it was noted that the survival results confirmed those observed in other studies. In terms of the generalisability of the study results to other settings, the authors stated that caution is required when extrapolating their findings, owing to the nature of the clinical and economic inputs and the perspective chosen for the analysis. The authors stated also that the model was limited to a 2-year horizon because of a lack of long-term evidence. Further, the model results might not be generalisable to all patients with CML. A justification for the choice of cycle length and health states was provided. In addition, the authors stated that the model structure was consistent with data published in several clinical trials.

Implications of the study
The study results support the use of imatinib for the treatment of patients with CML. Future research should investigate the impact of the interventions on health-related quality of life using long-term data.

Source of funding
None stated.

Bibliographic details