Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia
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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 (Gleevec), versus interferon-alpha plus low-dose cytarabine (INF+LDAC), as first-line treatment for patients with newly diagnosed chronic-phase chronic myeloid leukaemia (CML) who were not candidates for allogeneic stem cell transplantation.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with newly diagnosed chronic-phase CML who were not candidates for allogeneic stem cell transplantation.

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

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1995 and 2003. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A decision model was used to estimate the long-term costs and survival for imatinib in comparison with IFN+LDAC, but no explicit information on this model was provided.

Outcomes assessed in the review
The outcomes estimated from the literature were:
the proportion of patients with complete cytogenetic response (CCyR) at year 2;
the proportion of patients discontinuing first-line treatment at year 2;
the duration of second-line treatment with IFN+LDAC;
the number of months in accelerated phase;
the number of months in blast crisis;
the utility weight in chronic phase;
the utility weight in accelerated phase or blast crisis;
the number of inpatient days per month in chronic phase;
the number of specialist visits per month in chronic phase;
the number of generalist visits per month in chronic phase;
the number of nurse visits per month in chronic phase;
the number of inpatient days per month in accelerated phase and blast crisis;
the number of specialist visits per month in accelerated phase and blast crisis;
the number of generalist visits per month in accelerated phase and blast crisis;
the number of nurse visits per month in accelerated phase and blast crisis; and
the percentage of patients receiving treatment in advanced phases of CML.

Other outcomes were also derived from the literature, but their values were not reported. These outcomes were survival for the 2 years after the initiation of treatment and beyond this 2-year period, hazard ratios of the increased risk of death among patients with and without a CCyR, and the proportions of patients switching to second-line treatments.

**Study designs and other criteria for inclusion in the review**
It was unclear whether a systematic review of the literature had been undertaken to identify relevant studies. Most of the evidence came from a clinical trial, the International Randomized Interferon versus STI571 Study (IRIS), which was a multi-country trial with a median follow-up of 19 months. Other data came from other trials (e.g. the study carried out by the Italian Cooperative Study Group on CML), as well as from census statistics.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
Twelve primary studies provided the evidence.
Methods of combining primary studies
In general, each study provided a number of estimates that were not combined with other data. When multiple data were available, conservative estimates were selected.

Investigation of differences between primary studies
Not stated.

Results of the review
The proportion of patients with CCyR at year 2 was 0.738 with imatinib and 0.142 with IFN+LDAC.

The proportion of patients discontinuing first-line treatment at year 2 was 0.132 with imatinib and 0.225 with IFN+LDAC.

The median duration of second-line treatment with IFN+LDAC was 34 months.

The mean number of months in accelerated phase was 9.64.

The mean number of months in blast crisis was 13.12.

The mean utility weight in chronic phase was 0.854 with imatinib and 0.710 with IFN+LDAC.

The mean utility weight in accelerated phase or blast crisis was 0.595.

The mean number of inpatient days per month in chronic phase was 0.131 with imatinib and 0.245 with IFN+LDAC.

The mean number of specialist visits per month in chronic phase was 0.632 with imatinib and 1.054 with IFN+LDAC.

The mean number of generalist visits per month in chronic phase was 0.177 with imatinib and 0.231 with IFN+LDAC.

The mean number of nurse visits per month in chronic phase was 0.079 with imatinib and 0.465 with IFN+LDAC.

The mean number of inpatient days per month in accelerated phase and blast crisis was 0.738.

The mean number of specialist visits per month in accelerated phase and blast crisis was 1.048.

The mean number of generalist visits per month in accelerated phase and blast crisis was 0.167.

The mean number of nurse visits per month in accelerated phase and blast crisis was 0.309.

The percentage of patients receiving treatment in advanced phases of CML was 0.948.

Methods used to derive estimates of effectiveness
The authors made some assumptions because of the lack of reliable published data.

Estimates of effectiveness and key assumptions
Patients receiving imatinib as first-line treatment could switch to IFN+LDAC and then to hydroxyurea until disease progression, while patients receiving IFN+LDAC as first-line treatment could switch to hydroxyurea at the time of discontinuation. Patients who did not switch to second-line therapy were assumed to receive first-line therapy until disease progression. The utility values for patients receiving hydroxyurea were derived from patients receiving imatinib.

Measure of benefits used in the economic analysis
The summary benefit measures were the expected survival and number of quality-adjusted life-years (QALYs) over the patients' lifetime. The utility weights required to estimate the QALYs were obtained from the IRIS trial using the EuroQol-5D. Survival estimates were discounted at an annual rate of 3%.

**Direct costs**

Discounting was relevant since the lifetime costs were estimated, and an annual discount rate of 3% was applied. The unit costs were presented separately from the quantities of resources used for almost all cost items. The health services considered in the economic evaluation were medications (imatinib, IFN, cytarabine, hydroxyurea and chemotherapy), outpatient visits (specialist, nurse and generalist), and inpatient stay. The cost/resource boundary of the health care system was adopted. The costs were derived from average wholesale prices and Medicare reimbursement rates. The resource use data came from published sources and conservative assumptions. The price year was 2002.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were not included.

**Currency**

US dollars ($).

**Sensitivity analysis**

Univariate sensitivity analyses were performed to examine the robustness of the base-case results to variations in some estimates. The variations investigated included:

- applying utility and resource use estimates from patients receiving IFN (instead of imatinib) as proxies for patients receiving hydroxyurea;
- instituting a policy whereby patients could receive first-line therapy with imatinib or IFN+LDAC beyond the first 2 years only if they had achieved a CCyR;
- increasing or decreasing the cost of study medications by 25%;
- assuming that all patients receiving IFN received the recommended target dose (5 MU/m² per day);
- using median (instead of mean) survival estimates of 6 months for time spent in the accelerated phase and blast crisis; and
- increasing the hazard rate of death by 50% for patients receiving first-line imatinib.

Alternative sources of values, which were generally derived from the literature, were also used for some inputs. A probabilistic simulation approach was used to assess the costs and benefits of the treatment strategies in a cohort of 1,000 patients. Mean values and 95% confidence intervals (CIs) were generated for the incremental cost-effectiveness ratios (ICERs).

**Estimated benefits used in the economic analysis**

The estimated, discounted life-years were 11.42 (undiscounted 15.30) with imatinib and 7.48 (undiscounted 9.07) with IFN+LDAC.

The estimated, discounted QALYs were 9.06 (undiscounted 12.11) with imatinib and 5.17 (undiscounted 6.26) with
IFN+LDAC.

Cost results
The discounted lifetime costs were $320,100 (undiscounted $424,600) with imatinib and $152,000 (undiscounted $182,800) with IFN+LDAC.

Synthesis of costs and benefits
ICERs and cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies under evaluation.

The incremental cost per life-year saved with imatinib over IFN+LDAC was $43,100 (95% CI: 37,600 - 51,100). The corresponding undiscounted figure was $39,100 (95% CI: 34,700 - 45,400).

The incremental cost per QALY gained was $43,300 (95% CI: 38,300 - 49,100). The corresponding undiscounted figure was $41,500 (95% CI: 37,300 - 46,400).

The bootstrap analysis showed a low variability in the ICERs. In 75% of simulations the incremental cost per QALY was lower than $45,000, while in 98% of simulations it was lower than $50,000.

The sensitivity analysis showed that the base-case ICERs were mostly affected by changes in values regarding discontinuing first-line therapy and changes in the dose or price of imatinib or IFN+LDAC.

When it was assumed that the first-line treatment would be discontinued if patients did not achieve a CCyR within 2 years, the incremental cost per life-year saved was $53,900 and the cost per QALY was $60,500.

Decreasing the cost of imatinib by 25% resulted in ICERs of $26,000 per life-year saved and $26,100 per QALY. Increasing the cost of imatinib by 25% resulted in ICERs of $60,900 per life-year saved and $61,100 per QALY.

When the cost of IFN was increased by 25%, the ICERs were $36,700 per life-year saved and $36,600 per QALY.

When the cost of IFN was decreased by 25%, the resulting ICERs were $48,900 per life-year saved and $49,200 per QALY.

With the use of the target dose of approximately 9.5 MU per day of IFN, the ICERs would have been much lower ($20,400 per life-year saved and $20,500 per QALY).

Changes in other variables, or the use of alternative values, did not lead to substantial changes in the base-case results.

Authors' conclusions
The incremental cost per quality-adjusted life-year (QALY) of imatinib versus interferon-alpha plus low-dose cytarabine (IFN+LDAC), for the treatment of patients with chronic myeloid leukaemia (CML), was within the widely accepted threshold of $50,000 per QALY for the cost-effectiveness of new health technologies.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the comparators, which were appropriate and based on a published trial. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came mainly from published studies, but it was not stated whether a systematic review of the literature had been undertaken to identify primary studies. Most of the evidence came from a multi-country clinical trial which had a high internal validity. The other sources of data appear to have been identified selectively. The issue
of comparability of the sources used was not addressed, and it was unclear whether the primary estimates were combined using a narrative approach. Some assumptions were also made. The impact of changes in model inputs was extensively investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of QALYs as a summary benefit measure was appropriate as it incorporated the impact of the interventions on survival and quality of life. The utility values were derived from a sample of patients. QALYs are comparable with the benefits of other health care interventions. Discounting was applied, as US guidelines recommend.

Validity of estimate of costs
The authors reported explicitly the perspective adopted in the study. As such, it appears that all the relevant categories of costs have been included in the analysis. The costs and the quantities were generally provided separately, which enhances the possibility of replicating the study results. The source of the data was reported for almost all items. Discounting was relevant because of the lifetime horizon of the study. Some categories of costs were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other settings.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies, probably because this study appears to have been the first study investigating the long-term outcomes associated with imatinib. The issue of the generalisability of the study results to other settings was not explicitly addressed. However, extensive sensitivity analyses were performed, which enhances the external validity of the analysis. Details on the distributions used for the probabilistic sensitivity analysis were also provided. The authors noted that the robustness of the results of the analysis relied on the validity of the primary estimates used in the study. It was also highlighted that their study was the first one to use utility weights derived directly from patients undergoing treatment. Finally, the analysis focused on the use of imatinib as first-line therapy and not as a second-line option, which could be investigated in future studies.

Implications of the study
The study results supported the use of imatinib as first-line treatment for patients with newly diagnosed chronic-phase CML who were not candidates for allogeneic stem cell transplantation. The authors point out that, as additional strategies emerge and long-term data become available, it will be important to evaluate the cost-effectiveness of add-on therapies and to update the evaluations of existing therapies.

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