Imatinib for chronic myeloid leukaemia

The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review

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Executive summary

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Executive summary

Background

Chronic myeloid leukaemia (CML) is a rare blood cancer with an incidence of 1.0 per 100,000 in men and 0.8 per 100,000 in women. In CML, an excessive number of leukaemic white blood cells are produced that suppress the production of normal white blood cells. In 95% of cases of CML, patients have a specific chromosomal abnormality, the Philadelphia chromosome. This is a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9. The consequent molecular abnormality is a fusion protein, BCR-ABL, which is a tyrosine kinase.

CML is not currently curable with conventional chemotherapy or immunotherapy. Patients diagnosed in the chronic phase may expect a median survival of 3–5 years. Bone marrow transplant offers a cure but is only available to a minority of people.

Current drug treatments include interferon-alpha (IFN-α) and hydroxyurea. Imatinib mesylate is a new, rationally designed competitive inhibitor of the BCR-ABL protein tyrosine kinase.

Objectives

To systematically review the efficacy and cost-effectiveness of imatinib for the treatment of CML in the chronic, accelerated and blast phases, and compare it to existing drug regimes.

Methods

Nineteen electronic databases were searched from inception to August 2001.

Randomised controlled trials (RCTs), cohort studies and case series of existing first- and second-line drug treatments were included, subject to a minimum of 20 participants, as well as economic analyses and quality of life studies. Novartis provided pre-publication reports of three Phase II studies as commercial in confidence material (this status was later lifted). Main outcomes are survival at 1 year, haematological response (HR), cytogenetic response (CR) and adverse effects.

The report represents a narrative summary – no formal statistical synthesis of results was undertaken.

Results

Included studies

Three Phase II studies of imatinib, one in each phase of CML, were included. Eleven RCTs, ten in chronic phase CML and one in the accelerated/blast phase, were included, none of which included imatinib. In addition, 40 case series studies, 27 in the chronic phase and 13 in the accelerated and blast phases, were included. No published economic analyses of imatinib were found. No published studies reviewing quality of life with imatinib were found.

Study quality

The imatinib studies had not been peer reviewed at the time this report was written. There were important differences in patient characteristics, treatment and doses between trials. The RCTs were of moderate quality. The case series studies were often small and of widely varying quality. Comparisons between case series are particularly susceptible to confounding and should be interpreted with great caution.

Evidence of clinical effectiveness

The RCTs compared various IFN-α, hydroxyurea, busulphan and chemotherapy regimens. In the chronic phase, imatinib shows similar 1-year survival to other treatments, but higher complete HR and CR rates. No information on survival beyond 1 year was available.

In the accelerated phase, survival with imatinib appears to be longer than reports for other drugs, but this relies on comparisons of case series. In the blast phase, imatinib appears to show limited longer survival compared to other reports in the literature and complete CR and HR rates for imatinib are within the range of other studies. However, the characteristics of the patients enrolled in these other studies are not well described. There are few studies published and study populations are small. Absence of control groups limits the reliability of the analysis.

Cost-effectiveness

Novartis has funded an unpublished economic analysis of imatinib. The industry submission concludes that imatinib is a cost-effective treatment for CML in the chronic phase after IFN-α failure, in the accelerated phase and in blast crisis.

An extensive evaluation of the model's assumptions was carried out, and additional sensitivity analyses were undertaken. The cost per quality-adjusted life-year (QALY) estimates generated by the industry models may be underestimates. The model is sensitive to the (cumulative) assumptions made and when changed to reflect what we consider to be more realistic values, incremental cost-effectiveness ratios were: for the chronic phase, £45,592–£301,446; for the accelerated phase, £35,633–£56,052; and for the blast phase, £52,354–£64,724.

The cost per QALY of imatinib is high in all phases, but with a large potential range in the chronic phase. This reflects great sensitivity to long-term survival assumptions.

Conclusions

Based on the limited evidence available, imatinib appears to offer an alternative treatment for CML in the accelerated and blast phases.

As yet there is not enough information about imatinib in the chronic phase to draw firm conclusions. Cost–utility estimates for imatinib are particularly sensitive to assumptions about long-term survival, and may be extremely high.

Recommendations for further research

More research into imatinib for CML is needed. Key areas include:

- the efficacy of imatinib in chronic phase CML in the long term;
- RCTs to establish the effectiveness of imatinib in all phases of CML compared to IFN-α, hydroxyurea and other chemotherapy;
- further elucidation of the relationship between response rates (HR and CR) and long-term survival with different treatments in all phases of CML.

Publication

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