Cytarabine added to interferon improves the cost-effectiveness of initial therapy for patients with early chronic phase chronic myelogenous leukemia


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
Three technologies for the treatment of chronic myelogenous leukaemia (CML) were compared. The treatments were chemotherapy with hydroxyurea (default strategy), interferon (IFN)-alpha alone and IFN-alpha combined with cytarabine.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The population comprised newly diagnosed patients with CML. The inclusion criteria of the main study (Guilhot et al., see Other Publications of Related Interest) were CML patients under 70 years of age (median age 50 years) who had tested positive for the Philadelphia chromosome, were in the chronic phase of the disease, had been diagnosed within the last 6 months, and had previously been treated only with hydroxyurea. Patients with features of accelerated or blastic phases of CML were not eligible. Those with a history of depressive illness or another psychiatric disorder, or severe hepatic, renal or cardiovascular disorders were also not eligible.

Setting
The setting was tertiary care (a US oncology specialty institution). The economic study was carried out in Texas, USA.

Dates to which data relate
According to the main effectiveness study (Guilhot et al., see Other Publications of Related Interest), the effectiveness data were gathered from January 1991 to May 1996. The resource use data were derived from a prior model of IFN-alpha versus chemotherapy published in 1996 (Kattan et al., see Other Publications of Related Interest). The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a clinical study carried out by the French Chronic Myeloid Leukemia Study Group (FCMLG) and a decision analysis to estimate the long-term outcomes.

Study sample
The authors provided only brief details of the main study (Guilhot et al., see Other Publications of Related Interest). All reported details of this study are given here. The study randomly assigned previously untreated patients with CML to either chemotherapy with hydroxyurea and IFN-alpha alone, or the combination plus monthly courses of cytarabine.
The IFN-alpha arm comprised 361 patients, while the IFN-alpha plus cytarabine arm comprised 360 patients. No power calculations were reported.

**Study design**
The main study was a prospective randomised study. In the present study, the authors did not report whether the clinical study was conducted in single or multiple centres. The median follow-up was 43 months for all patients and 46 months for those living.

**Analysis of effectiveness**
The basis of the analysis was intention to treat. The health outcomes used to assess the patients were:

- complete haematologic remission at 6 months,
- cytogenetic responses at 12 months,
- toxicity rates,
- SCT, and
- survival rates.

The comparability of the patient groups was not reported.

**Effectiveness results**
On the IFN-alpha arm, 233 of 361 were in complete haematologic remission at 6 months. Toxicity necessitating discontinuation (i.e. grade 3 or higher) had occurred in 26 patients, one had undergone SCT, and 11 had progressive disease or had died. Nonresponding patients either reverted to chemotherapy or were administered cytarabine.

On the IFN-alpha/cytarabine arm, 262 of 360 (73%) patients were in complete haematologic remission at 6 months. IFN toxicity necessitating discontinuation had occurred in 28 patients, and cytarabine toxicity (any) was found in 54. Three patients had undergone SCT, and 5 patients had progressive disease or died. Nonresponders reverted to chemotherapy.

At 12 months, 92 of the original IFN-alpha patients had persistent major cytogenetic responses. Toxicity was discovered in 33 patients, and 26 had progressed or died.

For combined therapy, 203 patients had cytogenetic responses, a further 50 demonstrated toxicity, and 19 had progressed or died.

The 3-year survival rate was 85.7% in the IFN-alpha/cytarabine arm and 79.1% in the IFN-alpha arm.

**Clinical conclusions**
The authors did not report a clinical conclusion from this clinical study.

**Modelling**
A decision tree, modified from another decision model (Kattan et al., see Other Publications of Related Interest), was used to determine the initial allocation of patients into remission status and to characterise the initial 12 months of treatment. The model included the possibility of a single crossover to include or discontinue cytarabine or IFN-alpha at either 6 or 12 months. At any time in the first 12 months, either allogeneic or autologous marrow stem cell transplantation (SCT) could be performed. After 12 months, a Markov model was invoked to follow the natural history of the patient. Four health states were defined. These were chronic disease, progressive disease, toxicities and death.
The cycle of the model was 1 month. A lifetime horizon was used.

**Outcomes assessed in the review**
The outcomes assessed were the transition probabilities among the health states, and the state utilities. The transition probabilities included transition to progressive disease among patients who did not have cytogenetic response, with or without IFN-alpha, and of those treated with cytarabine and IFN-alpha.

**Study designs and other criteria for inclusion in the review**
The transition probabilities and the state utilities were derived from a cost-effectiveness analysis conducted by the authors (Kattan et al., see Other Publications of Related Interest). In the present study, the authors did not provide any details of the methods used in the previous cost-effectiveness analysis.

**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**
Not stated. The authors did not report any details of the methods used in the previous cost-effectiveness analysis.

**Methods of combining primary studies**
Not stated.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
Transition to progressive disease among patients who did not have cytogenetic response was 1.54%/month.

Transition to progressive disease among patients who did have cytogenetic response was 0.23%/month in the IFN-alpha alone arm and 0.08%/month in the IFN-alpha/cytarabine arm.

The utility values were 1.0 with chemotherapy, 0.9 with IFN, 1.0 with cytarabine, 0.5 with progressive disease, and 0 with toxicity.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions to derive the probability of transition from progressive disease to death.

**Estimates of effectiveness and key assumptions**
The authors assumed that once progression occurred all patients would have the same chance of death - 15%/month
once progression to accelerated or blast phase supervened.

**Measure of benefits used in the economic analysis**
The number of years of life saved and the quality-adjusted life-years (QALYs) gained were used as outcome measures. The state utilities were drawn from another study (Kattan et al., see Other Publications of Related Interest). The health benefits were discounted at a rate of 3% per year.

**Direct costs**
The cost data were drawn from a US oncology specialty institution. The costs included in the analysis were for drug treatment, autologous and allogeneic bone marrow transplant, progressive disease and other medical costs. Resource use and the costs were not reported separately. The estimation of costs was updated from the previous model (Kattan et al., see Other Publications of Related Interest). The price year was not stated. The costs were discounted at a rate of 3% per annum and their values reported. The authors reported the total discounted costs per patient.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors stated that all probabilities and utility values were subjected to a sensitivity analysis across their clinical ranges. However, not all of these ranges, nor the method of range selection, were reported.

The following sensitivity and scenario analyses were reported explicitly.

a) A quality adjustment of 50% (quality of life with IFN-alpha therapy was allowed to vary from 0.5 to 1.0).

b) The cost of IFN-alpha was varied from its baseline of $3,000/month. IFN-alpha is an expensive component in the treatment of CML and its average wholesale prices vary around the world.

c) The transition to progressive disease from cytogenetic responders was assumed constant, regardless of therapy.

d) The benefit of cytarabine was modelled as an additive to IFN-alpha alone, and no crossover of the patients was allowed.

e) SCT was ignored to determine the impact of this alternative on cost-effectiveness.

f) Although the starting age of the patient cohort was 50 years, the starting ages were varied from 30 to 80.

**Estimated benefits used in the economic analysis**
For a 50-year-old with newly diagnosed CML, the median estimated survival under the model for chemotherapy with hydroxyurea was 58 months, compared with 79 months on IFN-alpha and 100 months on cytarabine plus IFN-alpha.

The life expectancy was 3.89 years with hydroxyurea chemotherapy, 7.73 years with IFN-alpha alone, and 9.35 years with cytarabine plus IFN-alpha.
The number of QALYs for each treatment strategy was not reported.

**Cost results**
The total discounted costs were $10,400 for hydroxyurea chemotherapy, $79,400 for IFN-alpha alone, and $105,300 for cytarabine plus IFN-alpha.

**Synthesis of costs and benefits**
Compared with hydroxyurea alone, IFN-alpha generated 46 discounted months of additional life expectancy at an extra cost of $69,000, or $18,000/life-year saved.

Cytarabine plus IFN-alpha yielded 65 discounted months of additional life expectancy at a cost of $92,000, or $17,400/life-year saved, compared with hydroxyurea chemotherapy.

Compared with IFN-alpha alone, the marginal cost-effectiveness of adding cytarabine was $16,000/life-year saved, indicating that the addition of cytarabine dominated the IFN-alpha arm.

When quality adjustments were incorporated (IFN-alpha at 90% and progressive disease at 50%), compared with hydroxyurea chemotherapy alone, the marginal cost-effectiveness of IFN-alpha rose to $23,700/QALY gained, and that of cytarabine plus IFN-alpha to $21,450/QALY gained.

The marginal cost-effectiveness of combination therapy was $16,900/QALY gained versus IFN-alpha alone. This was consistent with the weak dominance of combination therapy over IFN-alpha alone.

The results of the sensitivity analyses were as follows.

a) Even at a quality adjustment of 50% (quality of life with IFN-alpha therapy was allowed to vary from 0.5 to 1.0), the cost-effectiveness of both IFN-alpha based strategies was acceptable. Over the entire range, cytarabine plus IFN-alpha was preferable to IFN-alpha alone.

b) In varying the cost of IFN-alpha, the relative order of the treatments did not change, although the cost per QALY depended linearly on the cost of IFN-alpha.

c) When the slower rate of disease progression in those patients who achieve cytogenetic remission with the combined therapy compared with IFN-alpha alone was ignored, the cost-effectiveness of the combined therapy versus IFN-alpha alone rose from $16,900/QALY gained to $19,800/QALY gained.

d) When the benefit of cytarabine was modelled as an additive to IFN-alpha alone and no crossover of the patients was allowed, with other conditions as their baseline values, the benefit of cytarabine was 6.1 quality-adjusted months at a discounted cost of $3,700 ($7,200/QALY). The benefit of cytarabine would have to drop to less than one month for the cost-effectiveness to exceed the recognised benchmark of $50,000/QALY gained.

e) When the possibility of an allogeneic or autologous SCT was eliminated, the cost-effectiveness of additive cytarabine over IFN-alpha alone rose to $19,100/QALY gained. The other relationships maintained their relative distance.

f) As the starting age of the cohort was varied from 30 to 80 years, the marginal cost-effectiveness of additive cytarabine over IFN-alpha alone ranged from $18,000/QALY gained at age 30 to $31,000/QALY gained at age 80.

**Authors' conclusions**
For all plausible ranges of the efficacy of interferon (IFN)-alpha and cytarabine, the combination therapies were cost-effective with respect to chemotherapy alone. Further, the increment in costs with cytarabine added to IFN-alpha was more than offset by the extra increment in quality-adjusted life expectancy. These results were sustained through a wide variety of sensitivity analyses.
CRD COMMENTARY - Selection of comparators
A justification was given for the comparators used. A background of randomised trials comparing IFN-alpha versus conventional chemotherapy has shown that IFN-alpha prolongs survival in patients with CML. Other studies of combinations of IFN-alpha with cytotoxic agents such as cytarabine have reported an increase in response rates, prolonged survival and a reduction in IFN-alpha-related toxicities. You should consider whether the comparators reflect widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
The main data to populate the model were provided by a clinical study carried out by the FCMLG (Guilhot et al., see Other Publications of Related Interest). This group conducted a prospective randomised trial, which was appropriate for the study question. The authors also used data from a prior model selectively to estimate transition probabilities and state utilities (Kattan et al., see Other Publications of Related Interest). However, only brief details of these two studies were provided, so the internal validity of the current study cannot be assessed without looking at the original studies in further detail. A systematic review of the literature was not undertaken to identify all relevant research and minimise biases. Uncertainty around all outcomes was evaluated in the model using a sensitivity analysis. The values used in the sensitivity analysis were not justified by reference to the literature.

Validity of estimate of measure of benefit
The authors used years of life saved and QALYs gained as the measures of health benefits. The estimation of quality adjustment factors was taken from the literature, and no further detail was provided. The estimation of benefits was modelled through a decision tree to determine the initial allocation of patients into remission status, and through a Markov model to follow the natural history of the patients. This model was appropriate to estimate the long-term benefits.

Validity of estimate of costs
The perspective of the analysis was not explicitly stated, but was consistent with that of a health care provider. As few details of the cost analysis were provided in the present study, it was unclear whether all the categories of cost relevant to the perspective adopted were included. For example, it was unclear whether the cost of adverse events following treatment with IFN-alpha alone or IFN-alpha/cytarabine were included in the "other medical costs" category. If the costs associated with the treatment of complications due to IFN therapy and cytotoxic agent were not included in the analysis, the cost-effectiveness of these therapies might have been overestimated.

The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The cost data were taken from a US oncology specialty institution and from a published study, and were updated. No sensitivity analysis was specifically conducted on resource use. A sensitivity analysis was performed by varying the cost of IFN-alpha or by ignoring SCT, and this enhances the interpretation of the results. The price year was not reported, which will hamper any possible future inflation exercises. Discounting was appropriately undertaken, as the costs were incurred over a patient(s) lifetime, although the authors did not report the undiscounted results or alternative discount rates, which could help evaluate the influence of future costs and benefits in the results.

Other issues
The authors compared their results with those from a comparative cost-effectiveness analysis of primary IFN therapy which was based on European studies. The latter study yielded much higher costs per life-year gained than the main study that formed the basis for this research. However, the doses, costs and duration of IFN therapy were higher in the study cited. Regardless, this analysis showed that the addition of cytarabine is the principal driver of reduced costs per life-year in CML. The issue of the generalisability to other settings was not directly addressed, although it was partially explored through sensitivity analyses. The authors appear to have presented their results selectively. The authors’ conclusions reflected the scope of the analysis. The only "limitation" stated by the authors was the need for better, patient-derived quality assessments of life on IFN-alpha therapy.
Implications of the study
The authors stated that the results of this study support the use of IFN-alpha and a low dose of cytarabine as the best standard of care.

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