Economic analysis of a randomised placebo-controlled phase III study of granulocyte macrophage colony stimulating factor in adult patients (> 55 to 70 years of age) with acute 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
Yeast-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) in adult patients (aged 55 to 70 years of age) with de novo acute myelogenous leukemia (AML) at a dose of 250 microg/m2, i.v. over 4 hours daily until the absolute Neutrophil count reached 1,500 cells/microL for 3 consecutive days or for a maximum of 42 days.

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Adult patients (aged over 55 and not exceeding 70 years of age) with de novo AML undergoing induction therapy.

Setting
Hospital. The economic study was carried out in the USA.

Dates to which data relate
Effectiveness and resource use data corresponded to patients who entered the study between September 1990 and November 1992. The price year was 1997.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Costing was retrospectively performed on a sub-sample of that used for the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size (the study sample was selected to identify a 7- to 9-day reduction in the median duration of neutropenia with a power greater than 80%). The study sample consisted of 124 patients randomly assigned to receive the GM-CSF and placebo (n=62 in each group). A total of 7 patients (2 from the GM-CSF group and 5 from the placebo group) were excluded from the study for the following reasons: prior chemotherapy, 1 patient; no follow up, 2; wrong diagnosis, 4. The remaining 117 patients had a median age of 64 years.
Study design
The study was a double-blind randomised controlled trial, carried out in 7 centres. The patients with complete response had a median follow-up of 13.1 months. A total of 18 randomised patients (8 in the intervention group and 10 in the placebo group) did not receive the study medication due to lack of response or early death. In the case of day-10 examination of bone marrow revealing aplastic without leukemia, randomised patients received blinded placebo or GM-CSF from day 11.

Analysis of effectiveness
The principle used in the analysis of effectiveness was reported to have been intention to treat. The clinical outcome measures were complete remission rate, median time for neutrophil recovery to 500/microL and to 1000/microL, survival (using the Kaplan-Meier method), the therapy-related mortality, grade 4-5 infections, grade 3-5 infections, the rate of grade 3-5 infections for the one-cycle and two-cycle patients, and adverse events. The study groups were reported to be comparable in terms of age, ECOG (the Eastern Cooperative Oncology Group) performance status, percentage of bone marrow blasts, circulating white blood cell count, circulating platelet, and FAB (French-American-British) classification. Logistic or proportional hazard regression was used to adjust for patient features known to be associated with outcome in acute leukemia trials.

Effectiveness results
The effectiveness results were as follows:

The GM-CSF group had a complete remission rate of 60% versus 44% in the placebo group (p=0.08).

The GM-CSF group had a median time for neutrophil recovery to 500/microL of 13 days versus 17 days in the control group (p=0.001, and p=0.013 when adjusted for covariates) and a median time for neutrophil recovery to 1000/microL of 14 versus 21 days (p=0.001 and p=0.001 when adjusted).

The corresponding values in terms of survival were 10.6 months in the GM-CSF group versus 4.8 months in the placebo group (p=0.048; p=0.021 when adjusted).

The therapy-related mortality was 6% in the GM-CSF group versus 15% in the placebo group (p=0.18).

The respective figures in terms of grade 4-5 infections were 9.6% in the GM-CSF group versus 36.2% in the placebo group (p=0.002), and 52% in the GM-CSF group versus 70% in the control group in terms of grade 3-5 infections, (p=0.07).

The rate of grade 3-5 infections for the one-cycle patients was 46% in the GM-CSF group versus 50% in the placebo group, while the respective values for the two-cycle patients were 42% in the GM-CSF group and 66% in the placebo group.

It was reported that the two study groups experienced similar types of adverse events except in terms of the rates of liver abnormalities (11.5% in the intervention group versus 42.6% in the control group, p=0.0006), neurologic changes (9.6% in the intervention group versus 26.3% in the control group, p=0.01), and haemorrhage (0% in the intervention group versus 8.5% in the control group, p=0.05).

Clinical conclusions
In summary, this double-blind study demonstrates that GM-CSF is safe and efficacious in adult patients (aged 55 to 70 years of age) with de novo AML undergoing induction therapy. Its main value appears to be in reducing the duration of neutropenia and therapy-related mortality and morbidity.

Modelling
A decision analytic model was used to estimate the resource use and costs associated with the alternative strategies adopted in the study.
Measure of benefits used in the economic analysis
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported. The economic analysis was performed based on the conservative assumption of equal efficacy for the two alternatives involved.

Direct costs
Costs were not discounted since the cost analysis covered the period of hospitalisation through discharge up to two cycles of induction chemotherapy. The days of hospitalisation were reported separately from the costs. Cost items were reported separately. The cost analysis covered the costs of hospital room, laboratory, pharmacy, blood products, diagnostic radiology, supplies, respiratory services, and EKG. The perspective adopted in the cost analysis was that of the third party payer. The charge data for 24 patients from the 7 study centres were the source of cost data. Department-specific cost-to-charge ratios were used to convert charges into costs. The date of the price data was 1997. The cost analysis did not cover the costs due to additional resources used prior to day 11 of induction therapy or after discharge.

Statistical analysis of costs
The Wilcoxon rank-sum test was used to compare the individual cost components in terms of median costs for infected and non-infected patients.

Indirect Costs
Not considered.

Currency
US dollars ($).

Sensitivity analysis
A series of one-way sensitivity analyses were performed on the price of GM-CSF, daily costs of patients experiencing severe infection, and probability of infection.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
The total inpatient costs for one-cycle patients were $38,617 in the GM-CSF group versus $37,037 in the placebo group. The respective values for the two-cycle patients were $37,467 in the GM-CSF group and $59,902 in the placebo group. The corresponding overall costs were $38,412 in the GM-CSF group versus $40,722 in the placebo group.

Synthesis of costs and benefits
Costs and benefits were not combined since, based on the assumption of equal efficacy for the two alternatives involved, the use of GM-CSF was associated with an overall cost saving of $2,310. The sensitivity analysis established the relative robustness of the results to changes in the main parameters of the model.

Authors' conclusions
In this clinical trial, GM-CSF use during induction chemotherapy for patients aged 55 to 70 years was associated with fewer days with neutropenia, a decrease in treatment-related toxicity and infectious toxicity, improvements in median survival rates, and $2,310 savings in costs of supportive care.
CRD COMMENTARY - Selection of comparators

The reason for the choice of the comparator is clear.

Validity of estimate of measure of benefit

The effectiveness results are likely to be internally valid given the double-blind randomised design of the study and the fact that power calculations were used to determine the sample size.

Validity of estimate of costs

Quantities of resource use were not fully reported, although adequate details of methods of cost estimation were given. The internal validity of the cost results should be assessed in light of the small sub-sample of patients used (n=24) and the retrospective nature of the study. The cost results may not be generalisable to other settings, as the authors acknowledge. Although the randomised control trial findings showed the beneficial effect of GM-CSF, the economic analysis was based on the conservative assumption of equal effectiveness and was, therefore, conducted as a cost-minimisation analysis. Costs to patients and others in society were not included and only a third party payer perspective was considered.

Other issues

The authors’ conclusions would appear to be justified. Sensitivity analyses were used to address the uncertainties in the data. The cost and effectiveness results may not be generalisable to other settings, populations, or countries, as acknowledged by the authors. Appropriate comparisons were made with other studies.

Implications of the study

This analysis can serve as a template for cooperative group cost analyses. Co-operation on study methodologies may allow for results that are relevant to both clinicians and policy makers.

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