Randomized placebo-controlled trial of granulocyte-macrophage colony-stimulating factor in patients with chemotherapy-related febrile neutropenia


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
Using granulocyte-macrophage colony-stimulating factor (GM-CSF), in addition to standard inpatient antibiotic therapy, in patients with chemotherapy-related febrile neutropenia.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Adult patients with chemotherapy-related febrile neutropenia (<0.5 x 10^9)

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

Dates to which data relate
The effectiveness and resource use data were collected from 1991 to 1994. Price data referred to 1992.

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

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size: a total of 70 patients per study group was required based on an anticipated difference in hospitalisation of 2 days with the assumed 11 days for the control group, alpha = 0.05, and beta = 0.25. Initially, 153 adult patients with severe neutropenia and fever were included in the study. The number of patients assigned randomly to the GM-CSF group and the placebo group were 74 and 79 respectively. In the GM-CSF and the placebo groups, 9 and 10 patients, respectively, were excluded from the study. Overall, 134 patients were analysed. Of these, 65 with a median age of 49 (range: 19 - 73) years received GM-CSF and 69 with a median age of 48 (range: 16 - 70) years received placebo.
Study design
This study was a multicentre clinical trial (six hospitals and the Cancer Institute). The follow-up period was 14 days. The loss to follow up was 5 patients in the GM-CSF group and 6 patients in the placebo group. Patients were stratified according to solid or hematologic tumours and hospital attended.

Analysis of effectiveness
The analysis of the clinical study was based on both intention to treat and treatment completers only (per-protocol analysis). The main primary outcome was hospitalisation time with GM-CSF or placebo, (which leads to the period of resolution of neutropenia (>1.0x10^9/L) and fever (temperature < 37.5 degrees C)) in conjunction with quality of life (six dimensions: mobility, emotional reactions, energy, social isolation, pain, sleep). The instruments used to valuate the quality of life score in both treatment groups were the Karnofsky performance index (generic instrument), the Nottingham Health profile (generic instrument), the Rotterdam Symptom Checklist (cancer-specific instrument) and the EuroQoL (valuation instrument, patient and population scores). The mortality rates were also reported. The groups were shown to be comparable in terms of age, sex, tumour type, and neutrophil count. The effects of confounding variables were assessed by analysing the risk of hospitalisation in a Cox proportional regression model (adjusted risk reductions were calculated).

Effectiveness results
In the GM-CSF group, according to an intention-to treat analysis, the number of days of hospitalisation was 6 (range: 3 - 14) as opposed to 7 (range: 3 - 14) days in the placebo group, (p=0.27). At day 4, the GM-CSF group had a median neutrophil count of 2.5 x 10^9/L (range: 0 - 25) versus 1.3 x10^9/L (range: 0 - 9) in the placebo group, (p<0.001). No significant differences were observed in time to resolution of fever (days): 3 days (range: 1 - 14) for both GM-CSF and placebo arms. The scores for the Karnofsky performance index were greater for the GM-CSF than for the placebo group (74 versus 63), (p=0.034). Patients in the placebo group showed less complaints than patients receiving GM-CSF treatment. The GM-CSF arm had a more pronounced health-related quality of life dimension than the placebo group in terms of mobility, emotional, and energy problems. No significant differences were noticed in the EuroQoL scores taking into account patient values. The patient value was better for the placebo arm than for the GM-CSF group (66 versus 54) as was the population score (57 versus 55). The Rotterdam Symptom Checklist demonstrated that patients in the placebo group experienced fewer problems concerning appetite and energy than patients in the GM-CSF group, (p<0.01). No differences were shown in terms of tiredness, dry mouth or sweating. The adjusted risk reduction for the number of days of hospitalisation was 29%, (p=0.12). The mortality was 1 patient in the GM-CSF group versus 2 patients in the control group (NS).

Clinical conclusions
In three previous studies, a significant advantage was observed for GM-CSF or G-CSF treatment. In the present study, only a trend toward an advantage for GM-CSF application was seen. The difference might be ascribed to differences in patient categories and treatment protocols.

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.

Direct costs
Costs were not discounted due to the short follow-up period. Quantities were not reported separately from the costs. The cost items were reported separately. The cost analysis covered the costs of hospital, consultations, laboratory services, diagnostic (including imaging) procedures, antibiotics, and GM-CSF. Hospital costs included the costs of manpower (doctors, nurses, etc), materials (medical devices, supportive patient care, etc), and overhead. The perspective adopted in the cost analysis was not explicitly specified. The resource use data were gathered from all registry forms and from daily data forms. The sources of cost data were different national and local organisations. The price data referred to 1992.
Statistical analysis of costs
The Mann-Whitney test was used to compare the groups in terms of costs.

Indirect Costs
Not considered.

Currency
US dollars ($). The approximate exchange rate used was $1 = 1.8 Dutch guilders.

Sensitivity analysis
Not carried out.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
The GM-CSF group had a median total cost of $4,140 (range: $1,710 - $14,650) versus $3,590 (range: $1,680 - $10,990) in the placebo group, (p<0.05).

Synthesis of costs and benefits
Costs and benefits were not combined.

Authors' conclusions
The application of GM-CSF in febrile neutropenia did not result in a significant shortening of the hospitalisation period, nor of the time to resolution of fever, despite a faster recovery of neutrophils for the whole group of patients.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparator is clear.

Validity of estimate of measure of effectiveness
The effectiveness results are likely to be internally valid given the use of a randomised design.

Validity of estimate of measure of benefit
In view of the lack of a summary benefit measure, the study may be regarded as a cost-consequences analysis.

Validity of estimate of costs
Quantities were not systematically reported separately from the prices. Adequate details of methods of cost estimation were given.

Other issues
The issue of generalisability to other settings or countries was not addressed, although adequate comparisons were made with other studies in the literature. A combination of costs and benefits would have aided the objective assessment of the effects of the intervention.

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