GM-CSF versus G-CSF: engraftment characteristics, resource utilization, and cost following autologous PBSC transplantation


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 GM-CSF (sargramostim; Immunex, Seattle) administered subcutaneously following autologous peripheral blood stem cell (PBSC) transplantation. A dose of 250 microg/m2, beginning day 6 after stem cell infusion, was administered until the absolute neutrophil count (ANC) reached 1500/mm3 for 3 consecutive days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who underwent PBSC transplantation.

Setting
The setting was the bone marrow transplant unit of a hospital. The economic study was carried out in Florida, USA.

Dates to which data relate
The effectiveness and resource use data appear to have been collected between February 1997 and October 1999 (taking into account that there appears to have been an error in the reporting of the period to which the historical controls related). The price year was not explicitly stated, but it may have been 2000.

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

Link between effectiveness and cost data
The costing was carried out on the same sample of patients as that used for the effectiveness analysis. The costing was performed prospectively for the intervention group, and possibly retrospectively for the control group.

Study sample
No power calculations to assure a certain power were performed in the planning phase of the study. Patients referred for autologous PBSC transplantation between December 1998 and October 1999, to the hospital where the study was carried out, were considered for inclusion. Patients were excluded if they were receiving CD34+ stem cell doses of at least 6 x 10^6 cells/kg. The historical controls were matched according to similar disease type, stem cell dose, disease stage and conditioning regimen. Further minor criteria, used as required, were the number of cycles of prior
chemotherapy, number of different chemotherapy regimens, prior radiation treatment and dose, and prior alkylator therapy. In total, 44 patients were included in the effectiveness analysis, 22 received GM-CSF after autologous PBSC transplantation and 22 received G-CSF. The authors did not any report evidence that the study sample was representative of the study population.

**Study design**
This was a prospective observational study with matched historical controls, which was performed at a single centre. The patients appear to have been followed up for study purposes until the ANC reached 1,500/mm^3^ for 3 consecutive days, although the actual duration of follow-up was not reported. Eight patients (12 doses) in the GM-CSF group and three (four doses) in the G-CSF group had to discontinue treatment before they achieved an ANC of at least 1,500/mm^3^ for 3 consecutive days.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes used for the intervention and control groups were:

- the median time to reach an ANC of at least 100/mm^3^;
- the median time to reach an ANC of at least 500/mm^3^;
- the median time to reach an ANC of at least 1,000/mm^3^;
- the median time to reach a platelet engraftment of at least 20,000/mm^3^;
- the median number of platelet transfusions and red blood cell transfusions;
- the median time with a temperature of at least 38 degrees C, or at least 38.5 degrees C;
- the duration of neutropenic fever; and
- the number of days that patients received intravenous antibiotics.

The intervention and control groups were shown to be similar according to the matching criteria used in the study, age and gender. The authors stated that the supportive care received did not differ significantly between the groups.

**Effectiveness results**
The patients in the GM-CSF group experienced a temperature of at least 38 degrees C for longer (median 6 days, range: 1 - 9) than G-CSF patients (median 3 days, range: 0 - 14), (p=0.05).

The difference in the median time that GM-CSF patients experienced febrile neutropenia (3 days, range: 0 - 7) in comparison with G-CSF patients (2 days, range: 0 - 7) almost achieved statistical significance, (p=0.07).

The other primary outcomes were not significantly different when the intervention and control groups were compared.

**Clinical conclusions**
There were no significant differences in the time to neutrophil recovery between the two groups (GM-CSF and G-CSF). However, more patients in the GM-CSF group had their treatment discontinued and experienced a longer time with a temperature of at least 38 degrees C.

**Measure of benefits used in the economic analysis**
No summary measure of benefit was used in the economic analysis, as the authors considered that there were no
significant differences in the effectiveness results between the growth factors GM-CSF and G-CSF. The economic analysis was therefore based on the differences in costs only.

**Direct costs**
The resource quantities were reported, but not the unit costs used to value them. The perspective adopted appears to have been that of the hospital. The costs included in the economic analysis were those related to the growth factors, antibiotics, chest X-rays and blood cultures ordered. Not all of the costs relevant to the perspective adopted were reported. The costs of transfusion, nursing and other supportive care were excluded due to the difficulties involved in their measurement, as acknowledged by the authors. The direct costs were obtained from the average wholesale prices used in the hospital where the study was carried out. Therefore, the costs were estimated from actual data. The price year may have been 2000. No discounting appears to have been performed since the costs were incurred in less than 2 years. The costs reported were the average costs per patient.

**Statistical analysis of costs**
The means and standard deviations for the resource use considered in the economic analysis were reported. Statistical analyses of the resources used were performed, according to intervention and control group. However, no statistical analyses of the costs were reported.

**Indirect Costs**
No indirect costs were reported.

**Currency**
US dollars ($).

**Sensitivity analysis**
A threshold analysis was performed to assess the price of GM-CSF at which both strategies (GM-CSF and G-CSF) became equivalent in terms of the average costs per patient. In addition, the authors estimated the average costs per patient by applying the actual discounted acquisition prices derived from local institutional discounts. The area of uncertainty investigated was, therefore, variability in the cost data.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The average cost per patient (based upon a hypothetical 70-kg/1.73-m2 patient) was $3,417 for a GM-CSF patient versus $2,713 for a G-CSF patient.

The results of the threshold analysis showed that GM-CSF became cost-equivalent to G-CSF when its price was $94 per 250 microg. Moreover, when local institutional discounts on growth factors were considered, GM-CSF presented a slightly lower cost per patient ($1,924) in comparison with G-CSF ($2,029 per patient).

**Synthesis of costs and benefits**
The estimated benefits and costs were not combined.

**Authors’ conclusions**
The time to neutrophil recovery was similar when either GM-CSF or G-CSF were used after peripheral blood stem cell
(PBSC) transplantation. Considering the current discounts on the price of the growth factors received by the institution, GM-CSF was slightly more cost-effective.

**CRD COMMENTARY - Selection of comparators**

A justification was given for the comparator chosen. G-CSF after PBSC transplantation was the current practice in the authors’ setting before the introduction of GM-CSF. You should decide whether this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**

The analysis used a prospective observational study with historical controls, which may have been appropriate given the available data at the time of starting the study. An effort was made to keep both groups comparable in terms of predetermined criteria. However, this design is subject to bias. For example, the authors stated that the groups were not studied concurrently and were not treated by the same physicians, which may lead to differences in practice patterns over time. Therefore, a randomised controlled trial would have been more appropriate to minimise bias and uncontrolled effects due to confounding factors. The authors did not provide evidence that the study sample was representative of the study population. The fairly small sample size may have been a factor in the lack of significance when comparing the primary outcomes between both patient groups. Further, it should be noted that GS-CSF patients were receiving higher doses than G-CSF patients, which may also have influenced the final effectiveness results. These factors introduce uncertainty into the reliability of the effectiveness conclusions.

**Validity of estimate of measure of benefit**

No summary measure of benefit was used in the economic analysis since the authors found no significant differences in the effectiveness results. The economic analysis was therefore based on a cost-minimisation approach.

**Validity of estimate of costs**

The perspective adopted was not reported, but it was very limited since only some hospital costs were considered in the economic analysis. Moreover, not all of the costs relevant to this perspective were included. The costs of transfusion, nursing and other supportive care were excluded due to the difficulties in their measurement, as acknowledged by the authors. The resources use included in the analysis was reported separately, although the unit costs were not given. It was unclear whether all the costs were reported for the year 2000. No statistical analyses of the costs were performed, only of resources used. The sensitivity analyses focused only on the costs associated with the growth factors. Therefore, there is uncertainty surrounding the overall cost results.

**Other issues**

The authors compared their results with those from another study (Jansen et al., see Other Publications of Related Interest). The differences found may have been due to either differences in the administered doses or in the time of growth factor administration after stem cell transplantation. The issue of the generalisability of the results to other settings was not addressed. The study enrolled patients who underwent PBSC transplantation and this was reflected in the authors’ conclusions.

**Implications of the study**

The authors highlighted the need for a prospective randomised trial to optimally compare engraftment, side effects profiles, and the costs between these two growth factors. Although they suggested that GM-CSF is slightly more cost-effective than G-CSF after PBSC transplantation, this result was due to the discounts received by the hospital on the price of growth factors. Such a conclusion would not be valid if price discounts were not applied. Moreover, the fact that more GM-CSF patients discontinued treatment than G-CSF patients may be worthy of consideration before drawing conclusions from this study.
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