Infusion of a high number of CD34+ cells provides a rapid hematopoietic recovery and cost savings in autologous peripheral blood stem cell 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 impact of the infusion of different doses of CD34+ cells on haematopoietic recovery was studied in patients with advanced malignancy who received autologous peripheral blood stem cell transplantation (ABSCT). The different doses of CD34+ cells infused were <2.5 x 10^6/kg, >/=2.5 to 5 x 10^6/kg, and >/=5 x 10^6/kg.

Type of intervention
Other: Supplementary treatment and rehabilitation.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with advanced malignancy, who received ABSCT following high-dose chemotherapy or total body irradiation. The authors reported no further inclusion or exclusion criteria.

Setting
A setting was not explicitly stated, but it appears to have been secondary care. The economic study was carried out in Japan.

Dates to which data relate
The dates to which the effectiveness evidence, resources and prices related were not reported.

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

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

Study sample
Power calculations were not used to determine the sample size. A total of 69 consecutively enrolled patients, aged from 18 to 67 years, with advanced malignancy and who received ABSCT following high-dose chemotherapy or total body irradiation, were included. However, it was not reported if any patients refused to participate or were excluded from the study for any reason. The sample included 43 men and 26 women with a median age of 50 years. Patients suffered from a variety of advanced malignancies, such as acute myelogenous leukaemia, acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, multiple myeloma, Hodgkin's disease, myelodysplastic syndrome, small cell lung cancer, invasive
thymoma, and rhabdomyosarcoma. The patients were divided into three groups according to the number of infused CD34+ cells. It was unclear how the number of cells administered was determined.

Group A comprised 23 patients who received $<2.5 \times 10^6$/kg CD34+ cells.

Group B comprised 25 patients who received $\geq 2.5$ to $5 \times 10^6$/kg CD34+ cells.

Group C comprised 21 patients who received $\geq 5 \times 10^6$/kg CD34+ cells.

**Study design**

The study was a single-centred, non-randomised trial. The duration of follow-up was not explicitly stated, nor was any loss to follow-up reported.

**Analysis of effectiveness**

The analysis of effectiveness appears to have been conducted on an intention to treat basis, although the authors did not explicitly state this. The threshold targets were reported to be $0.5 \times 10^9$/L neutrophils and $50 \times 10^9$/L platelets. The primary health outcomes used in the analysis were:

- the median period to reach $>0.5 \times 10^9$/L neutrophils;
- the median period to reach $>50 \times 10^9$/L platelets;
- the median number of febrile days; and
- the median days when parenteral antibiotics were given in each group.

The authors did not draw any comparisons between the characteristics of the groups at baseline. They also did not make any adjustments for confounding factors.

**Effectiveness results**

No patients died from the complications of ABSCT, and all patients reached the threshold of $>0.5 \times 10^9$/L neutrophils.

The median period to reach $>0.5 \times 10^9$/L neutrophils was 11 days (range: 9 - 29) in group A and 11 days (range: 8 - 15) in group B, and significantly shorter (9 days, range: 8 - 17) in group C, ($p<0.01$).

The median period to reach $50 \times 10^9$/L platelets was 18 days (range: 11 - 229) in group A and 17 days (range: 13 - 76) in group B, and significantly shorter (14 days, range: 10 - 24) in group C, ($p<0.05$).

In 6 patients in group A the platelet count did not reach $50 \times 10^9$/L, although it did reach $20 \times 10^9$/L. All other patients reached the desired threshold.

The median days when parenteral antibiotics were given were 7 (range: 0 - 30) in group A, 10.5 (range: 4 - 30) in group B, and 8.5(range: 0 - 23) in group C. There was no significant difference between any two of the three groups.

Eleven patients (47.8%) received RC-MAP (packed red blood concentrate) in group A, as did 11 patients (44%) in group B and 7 patients (33.3%) in group C. There was no significant difference between any two of the three groups.

All patients received packed platelet concentrate (PC) transfusions after ABSCT. The median units of transfused PC were 40 in groups A and B, and 25 in group C. The patients in group C received significantly fewer PC transfusions than patients in groups A and B, ($p<0.05$).

Overall, 19 patients (27.5%) had no febrile episodes and 30 patients (43.5%) had 1 to 3 days of fever (temperature $\geq$...
38 degrees C). Seventeen patients (73.9%) in group A, 18 patients (72%) in group B, and 14 patients (66.7%) in group C had no febrile episodes or less than 3 days of fever. The medians for febrile days were 1 in groups A and C, and 2 in group B.

Clinical conclusions
The authors concluded that the infusion of $\geq 5 \times 10^6$/kg CD34+ cells in ABSCT induces a more rapid platelet recovery. It decreases the transfusions of PC required and shortens the period to haematopoietic recovery.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary measure of benefit was produced. In effect, the study was a cost-consequences analysis.

Direct costs
The perspective of the study was not reported, which makes it difficult to determine whether all the relevant cost categories were considered. The sources of the resource use and cost data were not reported, although the resource quantities might have been estimated using actual data derived from the study sample. The costs included in the analysis comprised only the additional costs for transfusion (units of RC-MAP and units of PC) and the additional costs of parenteral antibiotics after ABSCT. As all patients received prophylactic oral antibiotics (ofloxacin) and antifungal therapy (amphotericin B), the costs of these drugs were omitted from the analysis. The costs of recombinant human granulocyte colony stimulating factor (rh G-CSF) after ABSCT and hospitalisation were also excluded from the analysis. No dates were reported for any of the data used. Discounting was not relevant as the costs were incurred during a short time.

Statistical analysis of costs
The authors used an unpaired t-test to evaluate the costs of transfusion and antibiotics. A p-value of less than 0.05 was considered statistically significant.

Indirect Costs
No indirect costs were included.

Currency
Japanese yen (Y).

Sensitivity analysis
A sensitivity analysis was not carried out.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total costs for transfusion of blood products and parenteral antibiotics were Y778,500 (+/- 194,200) in group A, Y524,700 (+/- 82,100) in group B, and Y314,800 (+/- 38,700) in group C. The costs were significantly lower in group C than in group A and B, (p<0.05). The total costs of RC-MAP, PC and antibiotics were reported separately for each of the three groups.
Synthesis of costs and benefits
The costs and benefits were not combined since the study was, in effect, a cost-consequences analysis.

Authors' conclusions
The infusion of \( \geq 5 \times 10^6/\text{kg} \) CD34+ cells in autologous peripheral blood stem cell transplantation (ABSCT) resulted in significant cost-savings in terms of the administration of blood products and parenteral antibiotics. It also shortened the period to haematopoietic recovery.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was based on the results of published studies and several reports. The published studies indicated that the infusion of at least 2.0 or 2.5 \( \times 10^6/\text{kg} \) CD34+ cells ensures a threshold effect for a rapid haematopoietic recovery. The results of several reports have demonstrated that the infusion of higher CD34+ cell numbers reduces the cost of ABSCT. It was unclear which dose of CD34+ cells infused represented standard practice in the authors' setting. You should consider whether this is a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The study was based on a non-randomised trial. The authors did not report or discuss the characteristics of the three groups. It is therefore difficult to comment on possible confounding factors, such as the different age of the patients in the three groups and possible co-morbidities. The study sample was representative of the study population, as it comprised patients with different advanced malignancies who received ABSCT following high-dose chemotherapy or total body irradiation. The authors used the log-rank test to evaluate the haematopoietic recovery and an unpaired t-test to evaluate the units of transfused blood products, the duration of febrile days and parenteral antibiotics. Kaplan-Meier techniques were used to estimate the probability of achieving 0.5 \( \times 10^9/\text{L} \) neutrophils and 50 \( \times 10^9/\text{L} \) platelets in each group.

Validity of estimate of measure of benefit
There was no summary measure of benefit. The study was, in effect, a cost-consequences analysis.

Validity of estimate of costs
The authors did not explicitly state the perspective adopted, which makes it very difficult to judge whether all the relevant costs were included. The sources of the costs and quantities were not reported, nor were the dates to which they related or the price year. In addition, it was unclear whether charges were used to proxy prices. The costs that were common in all groups were omitted from the analysis, as were the costs of rh G-CSF after ABCST and hospitalisation. The authors limited their analysis by including only the additional costs for transfusion of units of RC-MAP and units of PC and parenteral antibiotics. The author used an unpaired t-test to evaluate the cost of transfusion and antibiotics, but they did not carry out any sensitivity analyses on the quantities of resources used or on the costs. This may limit the interpretation of the study findings. Overall, the cost details were very poorly reported.

Other issues
The authors compared their results with published studies, which demonstrated that their findings were consistent with what is already available in the literature. The authors did not include hospitalisation costs in their analysis, but they showed that the duration of stay in the sterile unit during neutropenia of \( < 1 \times 10^9/\text{L} \) after ABCST was shorter in group C (infusion of \( \geq 5.0 \times 10^6/\text{kg} \) CD34+ cells), owing to the rapid recovery in this group.

The authors did not discuss the generalisability of the results to other settings and did not conduct any sensitivity analyses. Given that the cost estimates and efficacy data appear to have been based on Japanese estimates and evidence, the results of the study may not be generalisable outside Japan. The study involved patients with advanced malignancy who received ABSCT following high-dose chemotherapy or total body irradiation, with different doses of CD34+ cells, and this was reflected in the authors' results and discussion, which were both well presented. The authors acknowledged
some of their study limitations and suggested that a larger sample size would be required to address them adequately.

**Implications of the study**
The implications are that an infusion of $\geq 5.0 \times 10^6$/kg CD34+ cells in ABSCT induces the period to haematopoietic recovery and reduces the cost of additional supportive therapy, enabling ABSCT to be performed safely and cost-effectively. The authors did not make any recommendations for policy or practice. They suggested that a large-scale study should be undertaken in Japan to investigate the effect of myeloablative chemotherapy or radiation therapy on haematopoietic recovery.

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