Effect of cell determinant (CD)34(+) cell dose on the cost and consequences of peripheral blood stem cell transplantation for non-Hodgkin's lymphoma patients in front-line therapy

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
Cell determinant (CD) 34+ cell doses up to 5*10^6 per kg (5E6/kg) were compared with doses of higher than 5E6/kg for peripheral blood stem cell transplantation in front-line therapy.

Type of intervention
Pre-treatment assessment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with high- or intermediate-grade NHL, who were receiving intensive high-dose chemotherapy and peripheral blood stem cell transplantation (PBSCT). All patients had tumour burden, or at least one adverse prognostic factor defined by the International Prognostic Index.

Setting
The setting was tertiary care. The economic study was carried out in France.

Dates to which data relate
The effectiveness and resource use data referred to the period between December 1994 and December 1998. The base-case analysis used 1999 French prices.

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

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

Study sample
The study sample comprised 63 patients (out of 77 initially enrolled) who received high-dose chemotherapy and PBSCT as a front-line therapy. The patients were aged 19 to 60 years (mean: 43.4 years). Thirty-six were men and 27 were women. Thirty patients received CD34+ doses of less than or equal to 5E6/kg. Their mean age was 44.1 (+/-9.4) years and 50% were men. Thirty-three patients received doses higher than 5E6/kg. Their mean age was 42.7 (+/-12.7) years and 64% were men. The study was retrospective and no power calculations were performed.
Study design
This was a retrospective study that used the PBSCT arm of phase III of the multi-centre GOELAMS 072 trial. The study was carried out in 15 centres in France. The median duration of follow-up after PBSC transplantation was 16 months.

Analysis of effectiveness
The outcomes were analysed on the basis of treatment completers only. The primary health outcomes analysed were overall survival, event-free survival and the length of aplasia. The latter was defined as the number of days with a neutrophil count of less than 0.5E9/L, a leucocyte count of less than 1E9/L, and a platelet count of less than 20E9/L. Platelet engraftment was defined as a count of at least 20E9/L that was sustained without transfusion for 7 or more days.

All patients received 5 microg/kg/day granulocyte macrophage-colony stimulating factor (GM-CSF). This was administered subcutaneously from the day after the end of chemotherapy until completion of leucapheresis. Leucapheresis was provided when the neutrophil count was greater than 1E9/L and the platelet count was greater than 80E9/L. The initial criterion for adequacy of PBSC collections required at least 2E8/kg mononuclear cells and 2E4/kg colony-forming unit-granulocyte macrophage. The CD34+ cell count was used to judge the CD34+ harvest content in the study. The patients were treated with BEAM 400 (carmustine 300 mg/m2 day 1, etoposide 400 mg/m2 days 2 to 5, cytarabine 400 mg/m2 days 2 to 5, melphalan 140 mg/m2 day 6) followed by PBSCT on day 8.

During the post-transplant period, 5 microg/kg/day GM-CSF was administered according to the protocol. Platelet transfusions were given when the platelet count was less than 20E9/L or in cases of bleeding with low platelet count. Packed red blood cells were transfused to maintain the haemoglobin level over 80 g/L. The patients were discharged when the absolute neutrophil count reached greater than 0.5E9/L, if they were afebrile and without complications.

The impact of gender, age, status of disease at graft, previous radiotherapy, the number of previous cycles of chemotherapy, and the post-graft GM-CSF use, on the length of aplasia was explored. The study groups appear to have been comparable at baseline in terms of major demographic, risk and disease status factors. Thus, the role of potential confounding factors was relatively low.

Effectiveness results
The probability of overall survival after PBSC transplantation was 79% (lower dose) versus 85% (higher dose), (p=0.86). The probability of event-free survival after PBSC transplantation was 68% (lower dose) versus 69% (higher dose), (p=0.81).

The results were similar if the day of diagnosis was used as the start of the follow-up.

The group receiving the CD34+ dose higher than 5E6/kg achieved a more rapid engraftment. For the higher dose versus the lower dose, the length of grade 4 neutropenia was 10.2 versus 11.6, (p=0.07), leucopenia was 9.3 versus 11.8, (p=0.001), and thrombopenia was 6.0 versus 10.4, (p=0.02).

Gender, age, status of disease, prior radiotherapy, and the number of previous cycles of chemotherapy, did not affect the length of aplasia. Independently post-graft GM-CSF administration did not show any effect on the length of aplasia. However, after adjusting for it, a CD34+ cell count higher than 5E6/kg appears to have been a significant factor for early neutrophil, (p=0.01) and leucocyte, (p=0.02) recovery.

Clinical conclusions
No difference in the overall survival and event-free survival was observed between the patients receiving CD34+ doses up to 5E6/kg and those receiving doses higher than 5E6/kg. The higher dose group showed a significantly earlier haematopoietic engraftment.
Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary measure of benefits was used in the economic analysis. Thus, a cost-consequences analysis was carried out.

Direct costs
The costs were analysed from the perspective of a health care provider for individual patients. These included the costs of hospitalisation, medications (anti-infectious agents, haematopoietic growth factors), blood products and leucapheresis. The unit costs were reported for some items. The individual patient's follow-up was less than 2 years, and thus, no discounting of the costs was necessary. The hospitalisation costs were calculated per diem using the accounting system of one of the participating hospitals (Besancon University Hospital, 1998). These included the personnel costs, management and logistic costs, and small equipment and medical costs. The cost of apheresis (harvest, quality control, processing, cell conservation and thawing the cells to graft) was obtained from the local Blood Bank tariff, and the costs of GM-CSF were added (1999 tariff). The costs of anti-infectious agents per diem were derived from a sample of 21 patients (4 centres) using unit drug prices from the Besancon Hospital Pharmacy wholesale prices. The price year was 1999.

Statistical analysis of costs
A Student's t-test or Welch's t-test were used to compare the cost results.

Indirect Costs
No indirect costs were included in the analysis.

Currency
US dollars ($). The exchange rate used was US$1 = 5 French francs.

Sensitivity analysis
A number of univariate and multivariate sensitivity analyses were performed to study the effect of the following:

- simultaneous variation of the length of hospitalisation and the number of platelet transfusions;
- variation of the unit costs of hospitalisation, drugs and apheresis by 50%, and the use of USA unit costs data;
- the exclusion of very low (less than 2E6/kg) and very high (more than 15E6/kg) CD34+ cell counts;
- the successive fixing of a cut-off point of CD34+ cell dose to 4.5E6/kg and 5.5E6/kg.

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

Cost results
All the resource use parameters favoured a CD34+ dose higher than 5E6/kg.

The hospital length of stay was 25.9 (+/-6.3) days for the lower CD34+ dose group and 22.6 (+/-4) days for the higher dose group, (p=0.02). The units of platelet transfusion required were 3.9 (+/-2.9) for the lower dose group and 2.8 (+/-1.2) for the higher dose group, (p=0.04). Anti-infection treatment was given for 15.5 (+/-6.1) days for the lower dose group and 11.5 (+/-5.6) days for the higher dose group, (p=0.015). The units of red blood cell transfusion required were 3.6 (+/-2.9) for the lower dose group and 3 (+/-2.3) for the higher dose group.
The use of a CD34+ dose higher than 5E6/kg resulted in an overall mean cost-savings of $4,210, (p=0.01). This was mainly due to the decreased costs of hospitalisation (mean saving of $3,010, p=0.02) and the decreased use of blood transfusion products (mean saving of $815).

The mean increase of the harvest costs was $168.

The results were stable to the assumptions in the sensitivity analyses with respect to unit costs, the exclusion of extreme values of CD34+ cell dose (savings of $3,790), and changing the cut-off point for CD34+ content to 4.5 (savings of $4,300) or to 5.5 (savings of $4,730). To obtain similar total costs in the two groups, the length of hospitalisation had to be 3 days longer and the platelet transfusions twice as much, in the group with a CD34+ cell dose higher than 5E6/kg.

**Synthesis of costs and benefits**
Not relevant.

**Authors’ conclusions**
The comparison of the two patient groups showed no differences in the overall survival or the event-free survival. However, a cell determinant (CD)34+ cell dose higher than 5E6/kg resulted in a total cost-saving of $4,210 per patient. A CD34+ cell dose higher than 5E6/kg appeared to be optimal for clinical and economic considerations in non-Hodgkin’s lymphoma (NHL) patients undergoing peripheral blood stem cell (PBSC) transplantation in front-line therapy.

**CRD COMMENTARY - Selection of comparators**
The authors justified their decision to compare two ranges of CD34+ cell doses on the grounds that this represents a research question still unresolved in current patterns of treatment. You should assess whether the measurement of specific ranges of CD34+ cell doses represents a current issue in your own setting.

**Validity of estimate of measure of effectiveness**
The study sample was conveniently selected from an existing clinical trial arm. It seems to have been representative for the question of interest. Although the patient groups were shown to be comparable at baseline, the study design was of a retrospective and non-randomised nature. This could have had an impact on the validity of the results. The authors tested for possible confounders but few details were reported. Power calculations were not performed. These issues tended to limit the internal validity of the study.

**Validity of estimate of measure of benefit**
The authors did not find differences in the overall and symptom-free survival, although statistically significant differences were found for the remaining outcome measures. The authors did not derive a summary measure of health benefit and the analysis was, therefore, of a cost-consequences design. Consequently, the costs of the interventions were compared but no cost-effectiveness ratio was calculated.

**Validity of estimate of costs**
The costs were well handled. All the relevant cost categories from the perspective of the hospitals seem to have been included in the analysis. The costs and the quantities were reported separately for some items. Statistical analyses of the quantities were reported. The prices were derived using data from one of the study centres. Statistical analyses of the costs (overall and by resource use category) were reported. The costs for the drugs and blood products were derived from wholesale prices and official tariffs. Thus, it appears that charges rather than true costs were used. Sensitivity analyses on the major unit prices, and different sets of the unit costs, were performed.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was implicitly addressed through sensitivity analyses. The authors did not present their results selectively and discussed some limitations of their study. First, the study was based on a clinical trial that was not related to the research question. Second, the lack of a centralised CD34+ measurement. Third, the large variations in the unit costs across the hospitals and countries.

**Implications of the study**
The authors suggest that a CD34+ cell dose higher than 5E6/kg is optimal for clinical and economic considerations in NHL patients undergoing transplantation in front-line therapy.

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