Comparison of T-cell-depleted and non-T-cell-depleted unrelated donor transplantation for hematologic diseases: clinical outcomes, quality of life, and costs


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
Two approaches for prophylaxis against acute graft-versus-host disease (GVHD) in stem-cell transplantation from an unrelated donor were examined. The two approaches were T-cell depletion (TCD) and immunosuppressive medications (ISTs).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients undergoing unrelated donor transplantation for haematologic diseases. Patients with acute leukaemia in first complete remission or stable-phase chronic myelogenous leukaemia were labelled as low-risk patients, while patients with all other diseases were categorised as high-risk patients.

Setting
The setting was a hospital. The economic study was carried out at the Dana-Farber Cancer Institute in Boston, USA.

Dates to which data relate
The effectiveness and resource use data were gathered from January 1997 through December 1999. The price year was 2000.

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

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

Study sample
Power calculations to determine the sample size were not reported. A sample of 146 consecutive eligible patients was retrospectively included in the analysis over the study period. Forty-eight patients received TCD and 98 patients received IST. The median age in the TCD group was 48 years (range: 21 - 60), 38% were older than 50 years, and 46% were low-risk patients. The median age in the IST group was 42 years (range: 20 - 61), 28% were older than 50 years, and 24% were low-risk patients.
Study design
This was a retrospective case-control study, which was carried out in a single centre. The patients were allocated to the study groups, based on recommendation by the attending physician and patient preferences after a discussion of the risks and benefits of each method. After transplantation, patients in both groups received similar infectious disease prophylaxis and immune-suppressive medication tapers. The median follow-up was 18 months. Loss to follow-up was observed only in the quality of life study, where only 25 (52%) TCD and 53 (54%) IST patients provided valid data.

Analysis of effectiveness
All of the patients whose records were reviewed were taken into account when estimating the effectiveness. However, in the quality of life study only those who completed the questionnaire were included in the analysis. The primary health outcomes were:

the cumulative incidence of relapse at one year,
the cumulative incidence of grades II to IV acute GVHD at 100 days,
the cumulative incidence of extensive chronic GVHD at one year,
event-free survival at one year,
survival at one year,
organ toxicity (pulmonary, veno-occlusive disease, renal/bladder, infectious),
cause of death (relapse, GVHD, pulmonary, infection, other), and
quality of life.

Clinical data were extracted from the clinical transplant database. Quality of life was estimated using the SF-36 questionnaire, the Quality of Life Index (QLI), and a rating scale (RS). The SF-36 questionnaire comprised 8 domains (physical functioning, role limitations, bodily pain, general health perceptions, vitality, social functioning, and emotional well-being) and 2 composite scales (physical and mental functioning). The authors compared survival, estimated using the Kaplan-Meier method, in a Cox regression analysis. This analysis was adjusted for patient age (50 years or less versus over 50 years), gender matching (female donor and male patients versus all other combinations), degree of human leukocyte antigen match (matched versus mismatched), patient cytomegalovirus serostatus (seronegative versus seropositive), and disease risk (low versus high). The study groups were comparable at baseline in terms of their demographics and several clinical conditions. However, there were more low-risk patients and less mismatched donor situations in the TDC group than in the IST group. Further, there were more patients with acute leukaemia in the TDC group, and more patients with chronic myelogenous leukaemia and myelodysplastic syndrome in the IST group.

Effectiveness results
The cumulative incidence of relapse at one year was 16% (+/- 5) in the TCD group and 15% (+/- 4) in the IST group.

The cumulative incidence of grades II to IV acute GVHD at 100 days was 46% (+/- 7) in the TCD group and 36% (+/- 5) in the IST group.

The cumulative incidence of extensive chronic GVHD at one year was 9% (+/- 4) in the TCD group and 9% (+/- 3) in the IST group.

The event-free survival at one year was 42% (+/- 8) in the TCD group and 47% (+/- 5) in the IST group.

The survival at one year was 46% (+/- 8) in the TCD group and 49% (+/- 5) in the IST group.
Pulmonary toxicity occurred in 15% of the patients in the TCD group and 28% in the IST group.

Veno-occlusive disease occurred in 8% of the TCD group and 22% of the IST group.

Renal/bladder toxicity occurred in 8% of the TCD group and 10% of the IST group.

Infectious toxicity occurred in 8% of the TCD group and 11% of the IST group.

The death rate due to relapse was 16% in the TCD group and 31% in the IST group.

The death rate due to GVHD was 12% in the TCD group and 18% in the IST group.

The death rate due to veno-occlusive disease was 44% in the TCD group and 39% in the IST group.

The death rate due to infection was 32% in the TCD group and 23% in the IST group.

The death rate due to other causes was 24% in the TCD group and 24% in the IST group.

Only the difference in organ toxicity due to veno-occlusive disease reached statistical significance.

In terms of quality of life, the authors stated that there were no statistically significant differences among those who participated in the quality of life study and those who refused to participate.

There were generally no statistically significant differences between the two study groups in any of the quality indices and dimensions. The exception was the 'pain' dimension of the SF-36, which was significantly higher in the TCD group (100) than in the IST group (74), (p=0.03).

The Cox regression analysis showed that only the age of 50 years or less, and low-risk status predicted survival.

Clinical conclusions
The effectiveness analysis showed that the two prophylaxis methods led to similar clinical outcomes and survival.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used. Thus it would appear that a cost-consequences analysis was conducted. However, it is worth noting that although most of the outcome measures were not statistically different in the two study groups, the authors did not state that a cost-minimisation analysis was conducted.

Direct costs
Discounting was not applied since the costs were incurred over one year. The unit costs were not reported separately from the quantities of resources, and there was no breakdown of the cost items. The health service costs included in the economic evaluation were inpatient charges and total hospital days for the first year after transplantation. Professional charges and outpatient medical costs were not included in the analysis. The cost/resource boundary adopted in the study was not explicitly reported, but appears to have been that of the hospital. The costs and quantities were estimated using actual data derived from the hospital administrative database during January 1997 and December 1999. One patient was excluded from the analysis due to a research administrative error. All of the costs were inflated to year 2000 using the medical care component of the consumer price index.

Statistical analysis of costs
An analysis of variance was used to test for heterogeneity of the costs and length of hospital stay between the two study groups. The estimated costs were adjusted for patient age (50 years or less versus over 50 years), gender matching (female donor and male patient versus all other combinations), degree of human leukocyte antigen match (matched
versus mismatched), patient cytomegalovirus serostatus (seronegative versus seropositive), and disease risk (low versus high).

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analyses were conducted.

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

**Cost results**
The median hospital days within the first year were 34 (range: 19 - 127) in the TCD group and 46 (range: 18 - 176) in the IST group, (p=0.0006).

The total costs in the first year were $113,000 (range: 44,000 - 390,000) in the TCD group and $155,000 (range: 67,000 - 479,000) in the IST group, (p<0.0001).

The length of initial hospital stay was 26 days (range: 19 - 68) in the TCD group and 39 days (range: 18 - 84) in the IST group, (p<0.0001).

The costs of initial hospitalisation were $86,000 (range: 37,000 - 259,000) in the TCD group and $139,000 (range: 56,000 - 479,000) in the IST group, (p<0.0001).

The analysis of variance showed that the costs and hospital stay were significantly lower for both TCD patients (than IST patients) and patients with negative cytomegalovirus serological status (than those with positive serological status). In addition, they were significantly higher for both high-risk patients (than low risk-patients) and male patient to female donor (other than combinations).

**Synthesis of costs and benefits**
Not relevant as a cost-consequences analysis was conducted.

**Authors’ conclusions**
The study showed similar clinical outcomes, survival, and quality of life after T-cell depletion (TCD) and immunosuppressive medication (IST) bone marrow transplantation. However, the costs and length of hospitalisation were significantly lower in patients receiving TCD procedures, even after adjustments for clinical characteristics in the study population.

**CRD COMMENTARY - Selection of comparators**
The authors justified the selection of the comparators used in the analysis. TCD and IST represented the two broadest categories of prophylaxis against acute GVHD in the context of stem-cell transplantation. You should decide whether they are widely used technologies in your own setting.
Validity of estimate of measure of effectiveness
The analysis of effectiveness used a case-control study, which appears to have been appropriate for the study question. The study sample was representative of the study population. However, the authors stated that their findings may not be applicable to TCD of marrow accomplished through anti-C-D6 (a narrow specific antibody) and complement. The retrospective nature of the study and the method of patient allocation to the study groups (decided by the attending physician and the patients) may represent further limitations of the analysis. Although the quality of life analysis was conducted on a sub-sample of patients included in the whole effectiveness analysis, the authors stated that the sub-sample studied was representative of the overall study sample. The authors acknowledged that, although statistical analyses were conducted to reduce potential bias and confounding factors, some selection bias may have occurred and affected the conclusions of the analysis. The conclusions must, therefore, be interpreted with caution. Power calculations were not performed and there was no evidence that the initial study sample was appropriate for the study question. These issues may limit the internal validity of the analysis, especially in the quality of life study.

Validity of estimate of measure of benefit
No summary benefit measure was used in the economic analysis. The analysis was therefore categorised as a cost-consequences study.

Validity of estimate of costs
It appears that most of the categories of costs relevant to the perspective of the hospital (which was presumably adopted in the study) were included in the analysis. Some direct costs, such as professional charges and outpatient medical costs, were not included in the analysis. The authors stated that such costs were expected to mirror direct inpatient costs. The indirect costs were not included, but their impact was assumed to be low in comparison with the direct medical inpatient costs. The price year was reported, thus assisting reflation exercises in other settings, but the unit costs were not reported separately from quantities of resources. The source of the cost data was appropriately stated. Charges were converted into costs using the charge-to-cost ratio used at the study institution.

Other issues
The authors stated that the findings of their effectiveness study were comparable with other published observational studies. However, they did not address the issue of the generalisability of the study results to other settings. The external validity of the analysis was fairly limited, as no sensitivity analyses were conducted, although the authors did comment on some limitations of their study. For example, the small sample size and the likelihood of selection bias.

Implications of the study
The authors noted that the main implication of their study (the similar effectiveness of TCD and IST and the cost-savings associated with TCD) should be confirmed in future studies, focusing on quality of life issues and cost analyses.

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