Cost-effectiveness of a transplantation strategy compared to melphalan and prednisone in younger patients with multiple myeloma


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 high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) to treat patients with multiple myeloma.

Before transplantation, patients were given HDC consisting of 4 to 6 cycles of vincristine, doxorubicin and dexamethasone (VAD). This comprised 0.4 mg/day vincristine and 9 mg/m² per day doxorubicin on days 1 to 4, plus 40 mg/day dexamethasone on days 1 to 4 and 15 to 18, repeated every 28 days.

After the initial chemotherapy, cyclophosphamine 2.5 g/m² and granulocyte-colony stimulating factor (G-CSF) 5 to 10 microg/kg per day (rounded to nearest 300 or 480 microg vial size; typically for 10 days) were administered for stem cell mobilisation. High-dose conditioning therapy, including total body irradiation (200 cGy/day), was given for 4 days on an outpatient basis. The patients were hospitalised 3 days before transplantation and received melphalan (140 mg/m²) during the first day of hospitalisation. After that, the patients received stem cell reinfusion.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 65 years or younger with untreated myeloma. Patients were not eligible for the HDC+ASCT group if they had preference for another therapy, had undergone prior treatment with an alkylator-based chemotherapy, had received treatment based on a research protocol using stem cell factor, or had smouldering myeloma or amyloidosis. Patients in the M+P group were selected from among those who were already registered in a trial and were receiving either M+P (after being randomised once they were shown to respond to initial therapy), or were selected but not randomised. Patients were eligible for the M+P group if they had sufficient information about the chart and had not previously received an allogeneic transplant. No patients in any of the groups could be older than 65 years at the moment of initial treatment.

Setting
The setting was a hospital. The economic study was carried out at the Hamilton Regional Cancer Centre (HRCC) in Hamilton (ON), Canada.

Dates to which data relate
The effectiveness and resource use data appear to have been collected between May 1987 and June 1992, and between December 1996 and June 2000 (although it was unclear whether this was for the selection of patients only, or also for data collection). The price year was 2001.
**Source of effectiveness data**
The effectiveness data were derived from a single study.

**Link between effectiveness and cost data**
The cost data seem to have been collected on the same sample as that used for the effectiveness analysis. The costing appears to have been collected prospectively for the HDC+ASCT patients, and retrospectively for the M+P patients.

**Study sample**
No power calculations were reported to have been performed in the planning phase of the study in order to assure a certain power. Patients in the HDC+ASCT group were selected among those referred to the centre for consideration of ASCT, and were treated with dexamethasone-based chemotherapy (dexamethasone alone or VAD). In total, 52 patients were included in the effectiveness analysis, of which 36 were in the ASCT group and 16 in the M+P group. The authors did not report evidence that the study sample was representative of the study population.

**Study design**
This was a historical cohort study carried out in a single centre. The patients were not randomised to either HDC+ASCT or M+P. The patients were followed up from the time of initial therapy until death for M+P patients, or from initial therapy until death or end of the study for HDC+ASCT patients. The median follow-up was 22.6 months (range: 2.9 - 88.5) for the M+P group and 14.8 months (range: 0.7 - 41.6) for the HDC+ASCT group. The authors stated that 6 of the HDC+ASCT patients did not actually receive a transplant because of toxicity with initial chemotherapy (4 patients) and disease progression prior to the transplant (2 patients).

**Analysis of effectiveness**
The authors stated that the basis for the effectiveness analysis was intention to treat.

The primary health outcomes assessed in the effectiveness analysis were:

the mean survival for both treatment groups,

the number of patients in the HDC+ASCT group who had complications that needed admission to the intensive care unit (ICU), and

the number who died in the HDC+ASCT group due to toxicity of the treatment.

The groups were shown to be comparable at analysis in terms of age at the time of initial treatment, gender, Durie-Salmon stage, serum creatinine and calcium, haemoglobin, paraprotein level, immunoglobulin heavy and light-chain class and the extent of lytic bone disease. However, the authors reported that patients in the HDC+ASCT group seemed to have more severe bone disease and more advanced disease than patients in the M+P group, although the differences were not statistically significant.

**Effectiveness results**
The mean survival was 53.2 months for HDC+ASCT patients and 34.2 months for M+P patients.

Two HDC+ASCT patients had complications that needed ICU admission. One of the two died from treatment toxicity.

**Clinical conclusions**
Patients in the HDC+ASCT had longer mean survival than the M+P patients, although they also had complications that were not present in the latter group.
Modelling
An exponential survival curve was used to extrapolate the survival of HDC+ASCT patients to the long term, due to the fact that the follow-up for HDC+ASCT patients was shorter than that for M+P patients. It was assumed that HDC+ASCT patients relapsing would not be offered a second transplant, but would be treated with salvage chemotherapy similar to that given in the M+P group. The impact of pamidronate on skeletal events was assumed to be the same between the two groups.

Measure of benefits used in the economic analysis
The health benefit measure used in the economic analysis was the number of life-years gained with HDC+ASCT in comparison with M+P therapy. The authors obtained this value directly from the effectiveness analysis. They did not apply any quality-adjustment because, as they stated, no patient-derived utilities for myeloma patients undergoing ASCT have been described.

Direct costs
All the unit costs appear to have been reported. The resource quantities were reported separately from the costs. The direct costs included at analysis appear to have been those of the health service. These included chemotherapy costs, other supportive medication (G-CSF and pamidronate), chemotherapy administration, total body irradiation, stem cell costs, in-hospital costs and other costs. The chemotherapy costs were for prednisone, dexamethasone, melphalan, vincristine, doxorubicin and cyclophosphamine. Chemotherapy administration covered the chair time, nursing time and pharmacy time. The stem cell costs were for CD34 enumeration, stem cell processing, cryopreservation and stem cell reinfusion. The in-hospital costs were for the ward, ICU and ICU pharmacy. Other costs included viral testing, platelet transfusion, red blood cell transfusion, clinic visit and visiting nurse.

The drug costs and dispensing fees were obtained from the Ontario Drug Benefit Plan and the HRCC pharmacy, and physician fees were taken from the Schedule of Benefits of the Ontario Health Insurance Plan. The transfusion costs were obtained from two published Canadian studies, while the Ontario Case Costing Project provided the daily medical ward and ICU costs. Data from regional home care programmes were used to calculate the home care nursing costs. The reimbursement costs of the HRCC were used to calculate body irradiation costs. Therefore, the costs were estimated from actual data. The study reported the average costs. The Consumer Price Index was used to adjust the costs to year 2001. The base-case scenario did not discount the costs, although it would have been appropriate since the follow-up period was longer than 2 years. However, discounting was performed in the sensitivity analysis.

The authors reported that some capital costs were not included, but they did not justify their exclusion. They assumed the cost of diagnosis, pre-transplant treatment complications, terminal care, radiotherapy and surgical interventions to be the same between the two treatment groups.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
No indirect costs were included.

Currency
Canadian dollars (Can$).

Sensitivity analysis
Sensitivity analyses were performed. These varied both the costs and survival differences by 50%, in order to assess the robustness of the results under best- and worst-case scenarios. Discounting was performed in both the costs and benefits, using a 3 and a 5% rate.
Estimated benefits used in the economic analysis
The incremental benefit, in terms of months of life gained, of patients receiving HDC+ASCT in comparison with those receiving M+P, was 19.3 months. These benefits were measured from the time of initial therapy until death.

Cost results
The cost of HDC+ASCT treatment per patient was Can$32,320, while that for M+P was Can$1,803. The incremental cost per patient was Can$30,517. The costs of adverse effects were not dealt with in the costing.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER) was used to combine the costs and benefits. The ICER for the base-case analysis was Can$25,710 per life-year gained for HDC+ASCT compared to M+P. The best-case scenario showed a cost of Can$13,049 per life-year saved for HDC+ASCT compared to M+P. Under the worst-case scenario this was Can$63,954 per life-year saved. When the costs and benefits were discounted at a 3 and 5% discount rate, the ICERs were Can$27,807 and Can$29,372 per life-year gained, respectively.

Authors’ conclusions
The resulting incremental cost-effectiveness ratio (ICER) for high-dose chemotherapy and autologous stem cell transplantation (HDC+ASCT), compared to melphalan and prednisone (M+P), compares favourably with other interventions, even when the worst-case scenario is considered.

CRD COMMENTARY - Selection of comparators
The comparator (M+P therapy) was justified on the grounds that it was the standard therapy for patients not receiving transplantation in the authors' setting. However, in the discussion, the authors mention that this is not current practice among younger patients. Therefore, it is not entirely clear why they used this strategy as the comparator for the analysis. You should decide if this is a widely used health technology in your own setting and for the same target population.
Maintenance interferon therapy may not have been included in the study as an alternative comparator, because the authors reported one study showing health improvements with standard chemotherapy when compared to interferon.

Validity of estimate of measure of effectiveness
The design of the study employed a historical cohort. This may not have been appropriate for the objective of the study, as the sample population receiving M+P was selected and followed-up some years before the intervention group. This difference in time may have led to differences in health outcomes due to confounding variables. The groups were shown to be comparable in terms of age, gender and other characteristics related to the disease, although, as the authors stated, no other co-morbid illnesses were considered at analysis. Further, the HDC+ASCT patients had more severe bone disease and more advanced disease than the M+P patients, although the differences were not statistically significant. The lack of statistical significance may have been due to the small sample size considered at analysis. The authors also recognise that the selection process may have introduced bias into the effectiveness analysis, since patients were randomised in the previous trial if they responded to initial therapy. An additional point worthy of note is that survival for HDC+ASCT patients was extrapolated to a longer period than the follow-up period using an exponential survival curve. The results obtained therefore depend on the accuracy of this method to estimate the survival gains for HDC+ASCT patients. These facts may have introduced uncertainty into the reliability of the conclusions, thus affecting the internal validity of the study.

Validity of estimate of measure of benefit
The estimation of benefits was obtained directly from the effectiveness analysis. The authors justified this choice due to the lack of patient-derived utilities for myeloma patients undergoing HDC+ASCT, which made quality-adjustment of the survival impossible. In the sensitivity analysis, the health benefits were discounted at both 3 and 5%. There is considerable discussion in the field of health economics of whether or not benefits should be discounted.
Validity of estimate of costs
All the categories of costs relevant to the perspective adopted appear to have been included in the analysis. The authors stated that some capital costs were excluded, but they did not justify this exclusion, and nor did they assess how it may have affected the results obtained. The unit costs were reported in detail, resource utilisation was reported separately from the costs, and the price year was reported. These facts would assist in reflation exercises to other settings. No statistical analyses of the quantities or costs were performed, but the authors carried out sensitivity analyses to assess the robustness of the results. The authors stated that they could not collect indirect cost data, but recognised that these costs are very important when medical care is shifted from the inpatient to the outpatient setting. Discounting was not performed in the base-case analysis, although it would have been appropriate because the follow-up period was longer than 2 years. Nevertheless, the authors performed discounting in the sensitivity analysis.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. They reported several ICERs obtained by published studies and discussed some of the characteristics and caveats these studies presented. They also showed that the results from one of these studies, in terms of gains in life expectancy, were similar to those obtained in the present study. The issue of the generalisability of the results to other settings was not addressed.

Implications of the study
The authors report that this study complements prior economic evaluations about HDC+ASCT versus standard chemotherapy, in that it used actual costs and survival data from patients included in the study, rather than from different sources of data. The authors recommend further research to develop patient-derived utilities for this group of patients. They also recommend the collection of indirect costs, which would allow the effects of shifting these patients from inpatient to outpatient settings to be assessed.

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