

Advances in Allogeneic Transplantation for Multiple Myeloma Using Bone Marrow and Peripheral Blood Stem Cells

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INTRODUCTION

Centers within the European Group for Blood and Marrow Transplantation (EBMT) have performed allogeneic bone marrow transplantation for multiple myeloma since 1983,¹⁻⁴ and transplant results are regularly reported to the EBMT myeloma registry. Previous reports from this registry as well as from other centers⁵⁻⁷ have shown that allogeneic transplantation is associated with high transplant-related mortality compared with autologous transplantation; in EBMT studies, however, the relapse rate after allogeneic transplantation was significantly lower than after autologous transplantation.⁸ Thus, if transplant-related mortality could be reduced, allogeneic transplantation would be a more promising approach for the treatment of younger patients than autologous transplantation. In 1995, the EBMT compared the outcome of allogeneic transplants during the periods 1983-1988 and 1989-1994 in the hope that better supportive treatment could have improved results. However, no significant time-dependent improvement in outcome could be seen.⁴ In 1994, the first allogeneic transplants using peripheral blood stem cells (PBSCs) were performed in multiple myeloma within EBMT centers. In 1999, a comparison between such transplants and bone marrow transplants was performed (Gahrton G, Svensson H, Cavo M, et al., unpublished data). A dramatic improvement in survival for all transplants during the period 1994-1998 vs. 1983-1993 was seen, with no significant difference between bone marrow transplants and PBSC transplants, and was due to a reduction in transplant-related mortality.

PATIENTS AND METHODS

The EBMT study (Gahrton G, Svensson H, Cavo M, *et al.*, unpublished data) comprised 690 multiple myeloma patients. All patients received the graft from HLA-matched sibling donors. During the period 1983–1993, 334 patients received a bone marrow graft, and 223 during the period 1994–1998. During the same time period (1994–1998), 133 patients received a peripheral blood stem cell graft.

The 3 groups were relatively well matched for age, sex, subtypes, stage at diagnosis, and response before transplantation. However, the median time from diagnosis to transplantation was significantly longer in patients transplanted during 1983–1993 (median, 14 months; range, 2–168 months) than in those transplanted during 1994–1998 (bone marrow: median, 10 months; range, 3–155 months; PBSC: median, 10 months; range, 3–155 months). Obviously, the follow-up time was longer for transplants performed during 1983–1993 (median, 73 months) than for transplants performed during 1994–1998 (bone marrow: median, 22 months; PBSC: median, 10 months).

The fraction of patients that had received only 1 treatment regimen before transplantation was significantly higher in transplants performed during 1994–1998 (bone marrow, 56%; PBSC, 68%) than in those performed during 1983–1993 (45%); conversely, the proportion of patients who had received 3 or more regimens was significantly lower during the later period (bone marrow, 14%; PBSC, 12%) than during the earlier one (25%).

The conditioning regimens varied between groups and within groups, with no significant difference between them. Regimens including only total body irradiation (TBI) and cyclophosphamide were most common, followed by melphalan-containing regimens. Busulfan plus cyclophosphamide was less common.

Prevention of graft-vs.-host disease (GVHD) was at the discretion of each center. The regimen most commonly used was cyclosporine plus methotrexate without T-cell depletion. T-cell depletion with or without additional treatment was less commonly used.

Complete remission following transplantation was defined for the purpose of this study as disappearance of abnormal immunoglobulins from serum and/or light chain from the urine using either conventional electrophoresis or immunofixation, as well as disappearance of apparent myeloma cells from the marrow, as previously described.⁴

RESULTS

Response to BMT

The probability of entering complete remission (CR) at 6 months after transplantation was 53%, 54%, and 50%, and at 2 years, 60%, 60%, and 54% for

the 1983–1993, 1994–1998 (bone marrow), and 1994–1998 (PBSC) groups, respectively, with no significant difference between the groups.

Survival, Treatment-Related Mortality, and Relapse

The median overall survival was 10 months for transplants performed 1983–1993 and 50 months for bone marrow transplants during 1994–1998 and was not reached for PBSC transplants during 1994–1998. The survival rates at 2 years were 40%, 57%, and 57%, and at 3 years, 35%, 55% and 57%, respectively. The 4-year survival rates were 32% and 50% for bone marrow transplants performed 1983–1993 and 1994–1998, respectively, and could not be estimated with enough confidence for PBSC transplants. The 5-year, 8-year, and 10-year survival rates could be estimated with enough confidence only for bone marrow transplants during 1983–1993: 28%, 21%, and 18%, respectively. Six patients survived >10 years following transplantation. The difference in survival between transplants performed during 1983–1993 and during 1994–1998 was highly significant ($P<.0001$), whereas there was no significant difference between bone marrow and PBSC transplants during 1994–1998.

A breakdown into 3 time periods—ie, comparing 1983–1988, 1989–1993, and 1994–1998—showed no significant difference in survival between the 2 earlier time periods but a significant difference between the latest 5-year period and each of the earlier periods (Figure 1). Thus, the entire improvement in survival has occurred since 1994. The improvement in overall survival from 1994 to 1998 compared with 1983–1993 was entirely due to a reduction in treatment-related mortality. This was 38% and 21% at 6 months and 46% and 30% at 2 years for bone marrow transplants performed during 1983–1993 and 1994–1998, respectively, with no significant difference between bone marrow and PBSC transplants from 1994–1998.

The relapse rate in patients who had entered a complete remission did not differ significantly between the time periods and was 19%–24% at 2 years after transplantation.

Acute and Chronic GVHD

The frequency of acute and chronic GVHD did not differ significantly between the periods or between bone marrow and PBSC transplants. However, the short follow-up for PBSC transplants hampers any firm conclusion as to possible differences in chronic GVHD.

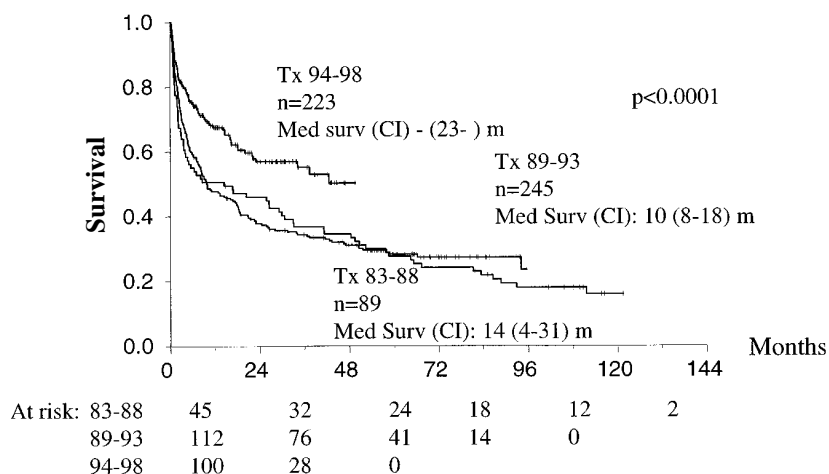


Figure 1. Allogeneic transplantation in multiple myeloma. Overall actuarial survival after bone marrow transplantation according to the time of transplantation. The Kaplan-Meier curves show a significantly better survival among patients who received transplants from 1994 to 1998 than among those who received transplants during 1983–1988 or 1989–1993. CI, confidence interval; m, months; Med Surv, median survival; Tx, transplant.

Causes of Death

At follow-up in 1999, 250 of the 340 patients (74%) transplanted during 1983–1993, 84 of the 233 patients (38%) transplanted with bone marrow during 1994–1998, and 44 of the 133 patients (33%) transplanted with PBSCs during 1994–1998 had died. Interstitial pneumonitis and bacterial/fungal infections were significantly more common causes of death in bone marrow transplants performed from 1983–1993 (14% and 17%, respectively) than for the period 1994–1998 (7% and 7%, respectively). Other causes of death such as original disease, new malignancy, acute or chronic GVHD, viral infections, adult respiratory distress syndrome (ARDS), capillary leak syndrome, rejection/poor graft, organ failure, disseminated intravenous coagulation, veno-occlusive disease (VOD), hemorrhage, and cardiac toxicity did not differ significantly. There was no significant difference in the causes of death between bone marrow and PBSC transplants performed during 1994–1998.

DISCUSSION

Our registry study shows (Gahrton G, Svensson H, Cavo M, et al., unpublished data) that the overall survival after allogeneic bone marrow transplantation for

multiple myeloma has improved significantly over a recent 5-year period (1994–1998) compared with transplants performed during the previous 5 and 11 years. This is in contrast to earlier analyses made by the EBMT that failed to show improvement in outcome with time.⁴ Thus, the improvement has occurred during the later 5 years from 1994 onward.

The study also shows that the improvement is due to a lower transplant-related mortality during the latest 5-year period. Acute GVHD does not appear to have changed during this period—the incidence of both overall and severe GVHD was about the same. However, there was a significant reduction in deaths caused by either interstitial pneumonitis or bacterial and fungal infections. There are several possible reasons for the reduction in interstitial pneumonitis, including better treatment of cytomegalovirus infection and perhaps changes in dosage of cytotoxic drugs and fractionation of TBI.

Earlier transplantation (10 months from diagnosis during the latest time period and 14 months during the earlier time period) has probably played an important role in reducing deaths due to bacterial and fungal infections. Earlier transplantation results in a lower number of treatment regimens before the transplant. Previous studies have shown that fewer regimens before the transplant is the second most important favorable prognostic parameter for survival in multivariate analysis.⁴ The use of peripheral blood stem cells instead of bone marrow did not change the overall outcome per se. The transplant-related mortality was similar to that of transplantation with bone marrow cells during the same time period. Although the engraftment rate was more rapid using peripheral blood stem cells, it did not translate into reduced transplant-related mortality or significantly lower death rate due to bacterial or fungal infections.

The relapse rate does not appear to have improved with either bone marrow cells or peripheral blood stem cells. However, longer follow-up is needed for firm conclusions. Allogeneic transplantation still appears to be the most promising way to obtain cure in patients with multiple myeloma. Although occasional molecular remissions can be obtained with autologous transplantation, these are usually transient, and the frequency and durability of molecular remissions is higher using allogeneic transplantation.^{9–12} Also, there is the possibility to use donor lymphocyte transfusions to treat patients with persistent disease or relapses following previous complete remissions.^{13–16} Recently, nonmyeloablative conditioning followed by allogeneic transplantation has proven to be feasible and is associated with low transplant-related mortality.^{17–19} However, the relapse risk is unknown. The EBMT, therefore, will compare nonmyeloablative transplantation following autologous transplantation in patients with a matched sibling donor to autologous transplantation alone in patients who lack such a donor.

SUMMARY AND CONCLUSIONS

Results of allogeneic bone marrow transplantation for multiple myeloma have improved dramatically since 1994. Overall survival has improved from a median of 10 months for patients transplanted during 1983–1993 to 50 months for patients transplanted during 1994–1998. The improvement is due to a significant reduction in transplant-related mortality that was 38% at 6 months during the earlier period but only 21% during the later period. Transplantation with peripheral blood stem cells has been performed since 1994, and the results are similar to transplantation with bone marrow during the same time period. Reduced transplant-related mortality appears to be due to fewer deaths from bacterial and fungal infections and interstitial pneumonitis, in turn as a result of earlier transplantation and less prior chemotherapy. Relapse rate is mainly unchanged, but molecular remissions occur in a significant number of patients, some of them long-term survivors.

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