Annotation

ALLOGENEIC BONE MARROW TRANSPLANTATION IN MULTIPLE MYELOMA

Allogeneic bone marrow transplantation has now been used since the early 1980s for treatment of patients with multiple myeloma (Highby et al, 1982; Ozer et al, 1984; Gahrton et al, 1986; Tura et al, 1986). The rationale for using allogeneic bone marrow transplantation is firstly that the myeloma cell is highly sensitive to both irradiation and many cytotoxic drugs, secondly that high-dose therapy followed by bone marrow rescue was shown to have the potential to cure patients with other haematological malignancies, in particular acute leukaemia and chronic myelocytic leukaemia (Champlin et al, 1985; Zwann et al, 1984; Thomas et al, 1986), and thirdly that the marrow graft may by itself have a graft-versus-tumour effect (Weiden et al, 1981; Horowitz et al, 1990).

To these arguments one can add that conventional chemotherapy does not seem to be able to cure multiple myeloma (Alexanian et al, 1969). The overall median survival is less than 3 years, and although several attempts have been made to use multi-drug combination chemotherapy (Gregory et al, 1992), with or without interferon treatment (Melstedt et al, 1991; Quesada et al, 1986; Cooper et al, 1993; Österborg et al, 1993), none of these new attempts have been able to cure patients with multiple myeloma, and the median survival has only been marginally affected.

Early attempts at bone marrow transplantation

The first attempts to perform allogeneic bone marrow transplantation in multiple myeloma were made in the early 1980s (Highby et al, 1982; Ozer et al, 1984; Gahrton et al, 1986; Tura et al, 1986). In a series of three patients published by the Huddinge group (Gahrton et al, 1986) one patient who was resistant to melphalan + prednisolone treatment went into a complete haematological remission which lasted for 4 years. She then relapsed but is still alive. The Bologna group reported one of their early patients to be alive in complete remission 67 months post transplantation (Tura et al, 1989).

These early transplants were followed by allogeneic transplants throughout the world. Now 37 centres report their allogeneic transplants to the registry of the European Group for Bone Marrow Transplantation (EBMT) (Gahrton et al, 1995).

Number of bone marrow transplants performed

The EBMT registry now has reports of more than 300 allogeneic bone marrow transplants. Analysis has as yet only been made of 162 patients who were reported until early 1993 (Gahrton et al, 1995). The International Bone Marrow Transplant Registry (IBMTR) has 244 patients with allogeneic transplants reported (Durie et al, 1994). A substantial fraction, probably more than half of the patients, are the same as reported to the EBMT registry. The Seattle group has published information on 20 of their patients (Bensinger et al, 1992), but has at different congresses reported a further 40 patients and has since then probably transplanted about 100 patients. Thus, more than 500 patients have probably received an allogeneic transplant for multiple myeloma.

BMT using sibling donors

EBMT registry study. 162 patients who received an allogeneic bone marrow transplant from 1983 to early 1993 have been analysed. Although the patients are highly heterogeneous both concerning stage, time to transplant, status at conditioning, lines of treatment before conditioning, conditioning methods, and GVHD prophylaxis methods, the results imply that allogeneic bone marrow transplantation has a place in the treatment of multiple myeloma.

Patients were transplanted up to the age of 59, and the median age was 43 years. The youngest patient was 23 years.

The complete remission rate, survival, and duration of complete remission following bone marrow transplantation were studied. Complete remission was defined as no detectable immunoglobulins or light chains by conventional electrophoresis in serum or urine, respectively. In addition, no apparent myeloma cell should be present in the marrow.

With this definition, 44% of all patients entered a complete remission. However, the complete remission rate of patients that could be evaluated for response, i.e. those who had their marrow fully repopulated with haemopoietic cells, was 60%. Important prognostic factors for obtaining a complete remission was the stage of the disease at diagnosis, irrespective of the time when the transplant was performed, the number of lines of treatment and the status at the time of conditioning. Also, it appeared that females had a better response rate than men, IgG myeloma responded more poorly than IgA and Bence-Jones myeloma, and patients with β2-microglobulin values > 4 mg/l tended to respond more poorly than those with lower β2-microglobulin values. The overall actuarial survival was 32% at 4 years, and 28% at 7 years.

Survival advantages were clearly associated with response advantages, i.e. patients who were diagnosed in stage I, those who had received only one line of treatment and who were in complete remission at the time of transplantation had the best survival. Also, females, patients with IgG myeloma, and those who had low β2-microglobulin, had a favourable prognosis concerning survival.

A multivariate analysis of the different factors was attempted. However, the material was probably too small for
such an analysis. Although there were tendencies in the multivariate analysis for an independent prognostic impact of those factors that were significant in the univariate analysis, they did not come out significantly.

Attempts in this study were also made to investigate the importance of treatment-related factors. However, the great number of conditioning methods used made such a comparison difficult. The more commonly used conditioning methods were total body irradiation + cyclophosphamide according to the original Seattle protocol or its variants (Thomas et al, 1975a, b). Other methods used were total body irradiation + melphalan, or total body irradiation + cyclophosphamide and additional chemotherapeutic agents. A smaller fraction of the patients received only cytotoxic drugs, most commonly bursulfan + cyclophosphamide (Bu-Cy). There was no significant difference between any of these treatment modalities. Bu-Cy did not show any superiority to any of the other treatment modalities. If anything, it tended to be associated with poorer survival. This is in agreement with a recent study by the Nordic Group for Bone Marrow Transplantation, which shows that side-effects, such as haemorrhagic cystitis and veno-occlusive disease, are more frequent following Bu-Cy conditioning of other haematological disorders, and also that survival in patients with advanced haematological disease is poorer with Bu-Cy than with total body irradiation (Ringdén et al, 1994).

Graft-versus-host prevention methods varied. No advantage could be seen using any particular GVHD-preventive method. T-cell depletion did not show any significant advantage concerning survival, although there was a tendency for less GVHD if T-cell depletion was used with or without combination with other GVHD-preventive methods. There was no detectable increase in the relapse rate in T-cell-depleted patients, as has been seen in chronic myelocytic leukaemia (Apperley et al, 1986).

Out of the 72 patients who entered a complete remission, five patients were still in complete remission > 4 years following transplantation. However, most patients appeared to relapse with time, although they had no signs of disease following transplantation. This would indicate that although patients are in haematological remission they may not be in a disease-free state. This is corroborated by recent findings that some patients who are in complete haematological remission still have clonal myeloma cells as detected by PCR-based methods, which detect clonal rearrangement in the immunoglobulin gene (Bird et al, 1993). However, some patients still may have had their disease eradicated, because in three out of five patients who were analysed by this method no clonal cells could be detected.

The Seattle experience. The Seattle group has used Bu-Cy for conditioning (Bensinger et al, 1992). They reported 12 complete remissions in 20 patients who were autografted. Eight patients died within the first 100 d after grafting, and four died later from graft-versus-host disease. Eight patients were alive at reporting in complete remission 6–42 months after transplantation. The actuarial disease-free survival was 32% at 3 years. Thus, the experience in Seattle is about the same as in the EBMT group. The material is clearly too small to evaluate if the Bu-Cy conditioning should be exchanged for TBI and cytotoxic drug combinations.

Allogeneic bone marrow transplantation using non-sibling donors. In the material so far analysed in the EBMT registry, only six patients have received marrow from non-sibling donors. Those that have been selected for such a transplant were usually in poor condition (Gahrton et al, 1991). Only three of these were unrelated donors. Five of the six patients died within 75 d and only one patient who received marrow from an unrelated donor is alive 200 d after transplantation. No conclusions can be made from these observations. Progress in unrelated donor transplantation and selection of more suitable patients may well show that unrelated donor transplantation is feasible for certain patient groups (Howard et al, 1990; Gahrton, 1991; Kernan et al, 1993).

BM T versus other treatment options in multiple myeloma. The present knowledge concerning allogeneic bone marrow transplantation does not give a clear view of its place in relation to other treatment options, such as autologous transplantation or chemotherapy. It seems obvious that allogeneic bone marrow transplantation due to relatively high treatment-related toxicity should not be used in stage I or those stage II patients who have a very slowly progressing disease. Such patients probably need no therapy at all. Thus, patients who do not require treatment according to the general view concerning treatment with conventional therapy are not candidates for allogeneic bone marrow transplantation.

For patients who respond to first-line treatment and have not yet received second-line treatment, allogeneic bone marrow transplantation seems to provide the best possibility for long-term survival, particularly if the diagnosis was made in stage I. However, transplant-related mortality is high in this group of patients also. Therefore it is not known whether autologous transplantation or chemotherapy is preferable.

Patients who do not respond to first-line therapy may well be candidates for bone marrow transplantation. This group of patients have fewer options with conventional chemotherapy and the marrow and probably also peripheral blood are contaminated with multiple myeloma cells. Therefore an autologous transplant would not have the potential to cure such patients.

For patients in later stages of the disease who have received several lines of treatment and do not respond, the prognosis is poor with bone marrow transplantation. On the other hand, in such patients conventional treatment or autologous transplantation is almost certainly useless. Some of the patients who have been transplanted with allogeneic marrow are long-term survivors, but the fraction is very small. It is possible that patients who are physically in a relatively good condition could be candidates, even though they are in an advanced stage of disease.

β2-microglobulin has been investigated only in a relatively small number of patients. However, it seems that it is also a powerful prognostic parameter in allogeneic bone marrow transplantation. However, since it has the same prognostic impact for patients treated with conventional chemotherapy (Cuzick et al, 1990; Durie et al, 1990), β2-microglobulin may not be of great importance for the selection of patients for allogeneic transplantation. Further studies will have to elucidate this problem.
Although patients relapse many years after allogeneic bone marrow transplantation (one patient has relapsed as late as 9 years following transplantation), allogeneic transplantation appears to be the most promising method to eradicate multiple myeloma. One patient in the EBMT material is still in complete remission 11 years following transplantation (Cavo et al., 1994). To improve results it appears most important to be able to delineate optimal conditioning methods. The difficult task is to find a method that does not damage the lung (with the increased risk of CMV pneumonitis) and at the same time is effective enough to eradicate the disease. Fractionated irradiation, lung shielding, and addition of new therapeutic drugs is being attempted. Improved GVHD preventive methods may be important. However, such methods may eventually, if more effective in preventing GVHD, increase the relapse rate. The effective treatment of CMV infection by ganciclovir and ganciclovir plus ribavirin and ganciclovir and ganciclovir plus ribavirin, increase the relapse rate. The effective treatment of CMV infection by ganciclovir and ganciclovir plus ribavirin, increase the relapse rate. The effective treatment of CMV infection by ganciclovir and ganciclovir plus ribavirin, increase the relapse rate.
Annotation

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