High-Dose Therapy in Patients with Multiple Myeloma

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ABSTRACT

Is it possible to cure patients with myeloma? Whether more tumor cytoreduction with various stem cell transplants, resulting in a sufficiently high incidence of complete remission, would be a key step towards long-term disease control followed by cure needs to be seen. With advances in supportive care and therapeutic approaches for treating patients with myeloma, both clinicians and patients need to be mindful of the fact that standard melphalan-prednisolone is associated with poor outcome, and therefore advanced age or poor renal function should not exclude majority of patients with myeloma from on-going high-dose therapy trials which result in complete remissions that are associated with a good quality of life. This article reviews the role of high-dose therapy in patients with myeloma.

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INTRODUCTION

Treatment for multiple myeloma today is where it was for acute leukemia in the 1960s and 1970s when the aim was to attain complete remission (CR), which would transform into prolonged overall survival (OS) and cure. The Royal Marsden group was the first to establish a dose-response effect for melphalan in patients with multiple myeloma.[1] Use of high-dose melphalan (HDM, 140 mg/m^2) made it possible to overcome resistance to lower doses of melphalan and to induce CRs in approximately 32% of patients.[2,3] This prompted further studies of high-dose chemotherapy or radiotherapy followed by autologous stem cell transplantations.[4,5] Although it has now been demonstrated that intensive regimens result in an increased response with an improved OS, this approach is seldom curative since responses are followed by relapse even after allogeneic bone marrow transplantation.[6,7] Different strategies have been developed to improve the results of high-dose therapy in patients with myeloma, including use of alternating conditioning regimens, peripheral blood stem cells (PBSCs) as a source of stem cells, purging techniques to decrease graft contamination by the myeloma cell, increased dose intensity by tandem transplants, and finally the allogeneic matched or unmatched stem cell transplantation.

This review will discuss ongoing and published studies in patients with myeloma that allow a more precisely defined role of autologous and allogeneic stem cell transplantation in myeloma to be defined.

AUTOLOGOUS STEM CELL TRANSPLANTATION

Conditioning Regimens

Quite a few high-dose regimens have been used by different centers starting with McElwain and Powles who used melphalan 140 mg/m^2. Although this regimen had a high transplant-related mortality (TRM) without stem cell support, it induced CRs in the range of 32%. Barlogie[4] and Selby et al[5] showed that stem cell support considerably reduced TRM. Cunningham et al[8] then showed that increasing the melphalan dose to 200 mg/m^2 could induce a higher rate of CR associated with a low TRM if stem cells were used for rescue. Doses as high as 220 mg/m^2 have been used with acceptable toxicity.[9] A combination of total body irradiation (TBI) with HDM 140 mg/m^2 has been extensively used. However, the European Group for Bone Marrow Transplantation (EBMT) registry recently showed that a non-TBI preparative regimen was independently associated with a better survival,[10] because of the higher TRM in TBI containing regimens. Also, in a historical comparison of patients receiving tandem transplants, it was demonstrated that HDM 200 mg/m^2 was superior to lower doses of melphalan combined with TBI.[11] We have also shown the superiority of HDM 200 mg/m^2 compared to other high-dose regimens (Figs 1 and 2).[6]

A French randomized trial (IFM95) compared outcome and toxicity of conditioning regimens containing either HDM 200 mg/m^2 or HDM140 mg/m^2 +TBI in patients up to 65 years of age. Its preliminary analysis has shown that TBI-containing regimens are more toxic and not superior.[12]

Source of Stem Cells

Marrow was originally used to decrease the TRM associated with high-dose treatment but as soon as it was shown that stem cells could be mobilized into peripheral blood these cells have been used almost exclusively in the

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Progress in the supportive care of autologous transplantation means that patients up to the age of 75 are now eligible for the procedure.

Evidence-based data supports the use of melphalan in patients with renal dysfunction.

With the use of autologous peripheral stem cell rescue, there are lower costs due to faster engraftment post transplant.

Improvement in supportive care has decreased the transplant-related mortality in patients undergoing an allogeneic transplant.

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autologous transplant setting. The advantages of PBSCs are that the number of tumor cells are lower in blood than in marrow, although circulating clonotypic cells have been detected by polymerase chain reaction (PCR) and immunophenotyping,[13-16] and that engraftment is more rapid and consequently transplant-related morbidity and costs are lower.[13-19]

We have previously shown in a group of 63 newly diagnosed myeloma patients that those given PBSCs had significantly faster engraftment, resulting in a reduced need for platelet transfusions and intravenous antibiotics, and ultimately a significantly faster discharge from hospital.[19] Consequently, the cost of PBSC transplant was significantly lower than that of bone marrow transplant in a cost-minimization analysis.[18]

A French randomized study (IFM 94) addressed this as well, and showed that use of PBSC significantly reduces the mean duration of neutropenia (P=0.001) and thrombocytopenia (P=0.01), though event-free survival (EFS) and OS were not significantly different between the two arms.[12]

A more controversial issue is the optimal method for stem cell mobilization.[20] The most common procedure includes the combination of high-dose cyclophosphamide (HC-CTX) (2.5 to 7 g/m^2) and G or GM-CSF.[21-25] In a randomized study, although the combination of HC-CTX with G-CSF generated a higher number of CD34 cells as compared with only G-CSF, there was no difference in the number of patients from whom sufficient numbers of stem cells for transplantation were collected. Additionally, in the HC-CTX arm, significantly higher toxicity (neutropenia and anemia) was observed, resulting in higher costs.[26]

Graft Contamination

Even if the patient is in complete hematologic remission following cytoreductive therapy at the time of leukapheresis, contamination with significant numbers of monoclonal plasma cells has always been found.[14] PCR-based techniques have demonstrated that PBSC harvests are frequently contaminated with malignant cells.[27] The immunoglobulin heavy chain gene fingerprinting method has shown myeloma cell contamination in 44% to 70% of PBSC samples collected after high-dose therapy.[27-29] Contamination can be decreased by positive selection of CD34 positive cells or by cleaning infused cells from myeloma cells by purging with myeloma cell-specific antibodies.[30-33] Though the prognostic significance of detecting malignant cells is unknown, Gertz et al have shown that detection of monoclonal plasma cells in PBSC was associated with a shortened relapse-free survival after transplantation.[34]

The lack of prognostic significance of graft contamination by plasma cells has already been reported in the context of autologous bone marrow transplantation.[35,36] That PBSC transplantation when compared with bone marrow transplantation does not prolong EFS

FIGURE 1. LOG-RANK COMPARISON OF OVERALL SURVIVAL OF HIGH-DOSE MELPHALAN (N=112) VS OTHER HIGH-DOSE PATIENTS (N=29).

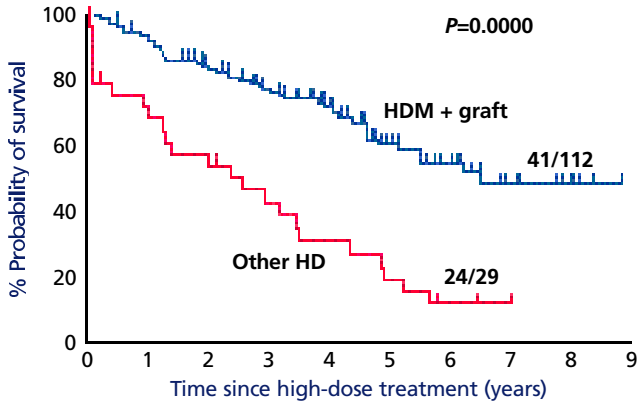

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FIGURE 2. LOG-RANK COMPARISON OF PROGRESSION-FREE SURVIVAL OF HIGH-DOSE MELPHALAN (N=112) VS OTHER HIGH-DOSE PATIENTS (N=29).

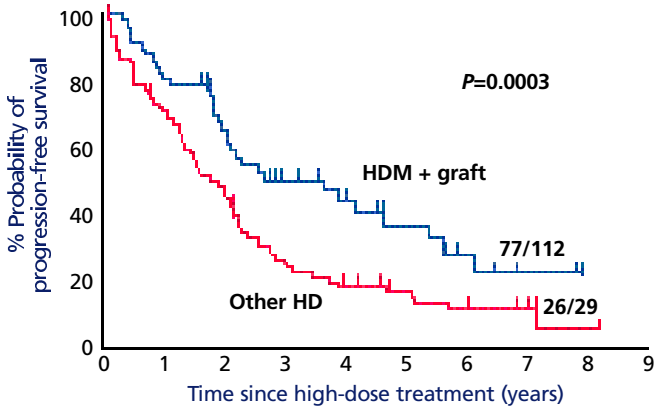

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TABLE 1. RESULTS OF AUTOLOGOUS TRANSPLANTS IN PATIENTS WITH REFRACTORY MYELOMA

Author (reference)	N	Resistance	CR (%)	TRM	Median EFS (months)	Median OS (months)
Vesole[40]	56	Primary	30	10	9	20
Selby[2]	15	Primary	13	13	7	10
Alexanain[41]	26	Primary	15	8	17	42
	23	Late	0	17	5	18
Tricot[42]	31	After Tx	22	—	—	78% alive at 18 months
Fermand[43]	8	Primary	25	12	71% at 2 years	88% at 2 years

CR=complete remission; TRM=transplant-related mortality; EFS=event-free survival; OS=overall survival.

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and OS despite a lower tumor load could mean that relapse is mainly due to the myeloablative regimen's lack of efficacy in eradicating the malignant clone and not to the graft contamination.[12]

Outcome with autologous transplantation

TRM with autologous transplantation has fallen from 20% initially to less than 5% in more recent series, probably due to better patient selection and the shift from bone marrow to peripheral blood as the source of stem cells, which has led to faster engraftment.[8] This explains the rapid expansion of autologous stem cell transplantation, which is now offered to multiple myeloma patients up to age 75 years and which means that most patients with myeloma may be candidates for autotransplantation.[37,38]

Until now, only one study has randomized patients to either conventional chemotherapy or high-dose treatment followed by autotransplantation, and it showed benefit for the transplanted group.[39] Later follow-ups have indicated that the differences have been sustained and are significant for response rate ($P<0.001$), EFS ($P=0.01$), and OS ($P=0.03$).[12] This is the only randomized study and it clearly shows the superiority of autotransplantation vs conventional chemotherapy for younger patients.

Autologous stem cell transplants for refractory multiple myeloma

Patients with refractory myeloma were the first candidates for exploring the use of autologous stem cell transplant. The results, as shown in Table 1, indicate that, though there were acceptable CR rates, the duration of responses was short.[2,40-43] Vesole et al have reported that the use of double transplants in primary refractory myeloma patients may lead to a median progression presurvival and an OS of 21 and 47 months, respectively, which indicates that tumor resistance may be overcome with high-dose chemotherapy.[40] It may be important to identify patients with refractory myeloma even earlier so as to minimize the emergence of new resistant cell clones.

What about patients who relapse after autotransplantation? Tricot et al have followed 94 of these patients to evaluate the efficacy of further therapy.[42] A new transplant performed as primary salvage treatment was associated with significant survival prolongation compared with conventional chemotherapy salvage. In relapsed transplanted patients, the appearance of a high presalvage beta-2 microglobulin (β2M) >2.5 and relapse <12 months after the first transplant were unfavorable factors for OS.

Autologous transplantation as consolidation therapy

In multiple myeloma the CR rate with conventional chemotherapy ranges from 5% to 17%. A few patients will live well with the disease for many years but the overall expected survival is short with conventional chemotherapy and there are no cures. In patients with chemosensitive disease who were transplanted after a short period of induction therapy, remarkably high CR rates and prolonged EFS and OS rates have been achieved. Table 2 summarizes some of the most relevant published studies using this strategy either with autologous bone marrow or PBSCs.[6,8,22,39,44-49] Overall response rate is around 90% with CRs between 25% and 70%. The variability in the CR rates could possibly be due to different criteria used for response assessment. Immunofixation should be mandatory to document disappearance of serum paraprotein and urinary Bence-Jones

TABLE 2. RESULTS OF AUTOLOGOUS TRANSPLANTS AS CONSOLIDATION THERAPY IN PATIENTS WITH MYELOMA

Author (reference)	N	Prior therapy	Conditioning regimen	Stem cells	CR rate (%)	Median EFS (months)	Median OS (months)
Cunningham[8]	53	VAMP/CVAMP	HDM 200	BM	75	24	77
Harousseau[44]	133	Conventional (109) HDM140 (24)	HDM 140 HDM 140+TBI	PBSC BM	37	33	46
Alexanian[45]	45	VAD	HDM 140+TBI	BM	45	58% at 3 yrs	50
Attal[39]	100	VCMP/VBAP	HDM 140+TBI	BM	22	28	57
Anderson[46]	52	Conventional	HDM 140+TBI	Purged BM	40	30	50
Barlogie[47]	231	VAD/HDC/EDAP	HDM 200 x 2 HDM 200+HDM 140/TBI	PBSC	38 49 (if 2 Tx)	43	68
Lokhorst[48]	50	VAD/IDM	Cy+TBI	PBSC	24	36	63% alive at 36 mos
Powles[6]	112	VAMP/CVAMP	HDM 200	BM/PBSC	74	27	79
Bensinger[49]	63	NS	BuCy±TBI	BM PBSC	40	10	30
Fermand[22]	63	NS	Carmustine/VP16/ HDM 140+TBI*	PBSC	20	43	59

*Cyclophosphamide was added to the last 26 patients' regimen.

CR=complete remission; EFS=event-free survival; OS=overall survival; VAMP/CVAMP= cyclophosphamide, vincristine, doxorubicin, and methylprednisolone; HDM=high-dose melphalan; BM=bone marrow; PBSC=peripheral blood stem cell; TBI=total body irradiation; VCMP/VBAP=vincristine-cyclophosphamide-melphalan-predinisolone/vincristine-carmustine-doxorubicin-prednisone; VAD/HDC/EDAP=vincristine-doxorubicin-dexamethasone/high-dose cyclophosphamide/etoposide-dexamethasone-cytarabine-cisplatin; Tx=therapy; VAD/IDM = vincristine, adriamycin, dexamethasone/intermediate-dose melphalan; Bu=busulphan; Cy=cyclophosphamide; NS=not specified.

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protein. An increase in CR rate has been accompanied by an increase in EFS.

Autologous transplants in patients with renal failure

Patients with renal failure are generally excluded from high-dose therapy even though they have a poor prognosis with conventional chemotherapy. Tricot et al[50] and Kergueris et al[51] have shown that pharmacokinetics of high-dose melphalan is not affected by renal function and therefore HDM 200 mg/m^2 could be an appropriate regimen. Accordingly, renal insufficiency should not constitute a criterion for exclusion from transplantation, and only patients with poor performance status should be excluded as potential candidates. At the Royal Marsden, we have shown that it is feasible and safe to administer HDM 140 mg/m^2 to patients with severe renal failure (serum creatinine >4 mg/dL).[52]

Tandem autologous transplantation

Two autologous transplants in sequence were first performed in the early 1990s by Harousseau et al[53] and Bjorkstrand et al.[54] The early results indicated that patients who had not entered remission after the first autologous transplantation could experience remission following the second one. Barlogie et al have now entered 1,000 consecutive patients in a tandem high-dose therapy program and in their earlier reports suggested that the tandem transplants are superior to standard treatment.[55] However, these studies are selective, not randomized, and therefore inconclusive. EBMT attempted to retrospectively compare patients with single and double transplantation and showed a small but significantly better survival rate with two transplants (median OS 51 vs 49 months). Again, the patient groups were not strictly comparable and firm conclusions cannot be drawn.[56]

IFM 94 is a French study comparing one vs two autologous transplants in a randomized format. Among 405 untreated patients so far recruited, preliminary results show no significant differences in CR, OS, and 2-year postdiagnosis EFS between the two transplant modalities. However, the latest follow-up showed significantly better survival with double autologous transplantation in patients with low β2M, suggesting that the impact of double transplantation could be of interest for patients with low β2M at diagnosis.[12]

PROGNOSTIC FACTORS FOR AUTOLOGOUS TRANSPLANTATION

An obvious question when using high-dose therapy is whether the prognostic factors are different from those identified for conventional therapy. The data suggest that they are

"An obvious question when using high-dose therapy is whether the prognostic factors are different from those identified for conventional therapy. The data suggest they are quite similar."

quite similar. According to the EBMT, having stage I disease, being in CR prior to transplant, undergoing one line of therapy, being younger than 45, and having a low β2M were favorable factors. Also, the inclusion of TBI in the high-dose conditioning regimen produced a poorer survival than HDM alone.[57]

The Little Rock group initially identified low β2M levels, low C-reactive protein, less prior therapy, and Ig isotype other than IgA as independent favorable variables for OS and EFS. They showed later that abnormalities in chromosomes 11q and 13 were associated with a poorer outcome in patients receiving tandem autologous transplants.[35,58] Bensinger et al have shown that low β2M levels, <3 years from diagnosis to transplant, fewer cycles of chemotherapy, and absence of previous radiotherapy were favorable prognostic factors.[49] We have shown that the prognostic factors differ according to the immunologic subtype in context of high-dose therapy. In patients with IgG myeloma, age 52 years, β2M <2.7, and Hb >8.5 were independently favorable prognostic factors; for light-chain myeloma, good performance status and urine total protein <1 g/L had a significantly favorable impact on outcome.[59,60] Newer prognostic factors such as IL-6, sIL-6R, IL-1β, and CRP are under evaluation in ongoing studies .

INTERFERON AFTER AUTOLOGOUS TRANSPLANTATION

Interferon was shown to have efficacy in myeloma about 25 years ago.[61] Numerous studies have examined the role of interferon following autologous transplants. In a randomized study, we initially showed significantly superior survival following maintenance treatment with interferon-α2b (3 million units/m² three times a week) following induction with cyclophosphamide, vincristine, doxorubicin, and methylprednisolone (CVAMP) and consolidation with HDM 200 mg/m².[62] However, in an update, the significant survival advantage was lost, but there was still a tendency for better survival for patients on interferon, and patients in CR on interferon still had a significantly better OS.[63] The EBMT data also show that both OS and EFS were significantly better in the interferon group than in the group without interferon.[64] It was concluded that patients who were responsive to treatment, particularly those who entered a partial response, could benefit from posttransplant interferon treatment.

Two recent meta-analyses both indicate that there is a survival advantage of about 6 months with interferon, and they suggest that interferon therapy should be weighed against the quality of life benefit.[65,66]

ALLOGENEIC STEM CELL TRANSPLANTATION

Since myeloma frequently affects patients of advanced age (median age around 65 years) and only 25% to 35% of patients have a related donor, allogeneic transplant can only be offered to a small percentage of patients with myeloma (< 10%). The first attempt to treat multiple myeloma patients with high-dose treatment followed by an allogeneic transplant was made in the early 1980s.[67-70]

Conditioning regimens and response rate

The conditioning regimens for allogeneic transplantation have been cyclophosphamide 120 mg/kg+fractionated/unfractionated TBI, melphalan+TBI, busulphan+cyclophosphamide, and a few other combinations.[71-75] Table 3 summarizes the results of published

TABLE 3. RESULTS OF ALLOGENEIC TRANSPLANTS IN PATIENTS WITH MYELOMA

Author (reference)	N	Conditioning	TRM (%)	CR Rate (%)	EFS	OS
Bjorkstrand[76]	198	Various regimens	41	48	20% at 5 years	30% at 5 years
Bensinger[74]	80	BuCy±TBI	35	36	20% at 4.5 years	24% at 4.5 years
Mehta[77]	9	Various	50	26	27.5% at 3 years	12.8% at 3 years
Kulkarni[73]	33	Various	51	37	39% at 3 years	36% at 3 years
Schlossman[78]	52	Mel+TBI	8	29	12 months	24 months
Cavo[79]	62	BuCy, Mel+TBI	42	34	38% at 5 years	15% at 8 years
Lokhorst[48]	54	Cy+TBI	18	32	Not reached	Not reached
Marit[80]	137	Various	57	51	33.3% for CR patients	28 months

TRM= transplant-related mortality; CR=complete remission; EFS=event-free survival; OS=overall survival; Bu=busulphan; Cy=cyclophosphamide; TBI=total body irradiation; Mel=melphalan.

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studies.[73,74,76-80] About 50% of patients treated with these regimens achieve CR. The response is also dependent on the response prior to transplant. Although the overall response is about 50%, it decreases to 25% in patients who are refractory or in relapse after previous treatment.

Molecular remissions

Molecular remissions are frequently obtained with allogeneic transplantation. Corradini et al[81] performed molecular monitoring in 29 patients in CR, of whom 14 had received an allogeneic and 15 an autologous transplant. Clonal markers based on the rearrangement of IgH genes were generated for each patient and used for PCR detection of myeloma cells. Only one of the patients autografted but seven of the allografted ones entered a molecular remission. Hence, the chances for cure are greater with an allogeneic transplant.

Treatment-related mortality

Due to a high TRM, the OS and EFS results with allotransplants have been relatively poor in previously published studies. The major causes of TRM are bacterial and fungal infections, interstitial pneumonitis, and acute graft vs host disease, which, in the experience of EBMT, caused 18%, 17%, and 10% of deaths, respectively.[71,72] EBMT comparisons of allogeneic and autologous transplants performed before 1995 reported that autologous transplantation was superior to allogeneic.[76] Allogeneic transplants performed between 1983 and 1993 were recently compared with those done between 1994 and 1998 and showed a dramatic improvement in OS and EFS, especially for those in CR.[82] The early TRM and total mortality was 30% and 50% between 1983 and 1993 vs 20% and 30%, respectively, during 1994–1998. Possible reasons are decreased deaths due to interstitial pneumonitis (increased use of lung shielding), and bacterial and fungal infections (increased prophylactic approaches).

Reducing treatment–related mortality

Ex vivo treatments of the harvested stem cells can be of value in reducing TRM. A group from the Dana Farber Cancer Institute, in an update of their series, have reported a TRM of only 8% in 52 myeloma patients transplanted with allogeneic T-cell ($CD6^+$)-depleted cells.[78] Soiffer et al[83] have also shown that selective depletion of CD6+ve T lymphocytes from donor marrow prevents graft vs host disease. These encouraging results support the use of ex vivo manipulations of allogeneic stem cells in myeloma but it remains to be seen what effect these interventions will have on long-term EFS.

Relapses after allotransplantation and donor leucocyte infusions

Quite a few studies have demonstrated that patients with myeloma relapsing after an allogeneic transplant can attain clinical remissions using donor leukocyte infusions (DLIs). This has been the definitive proof of a graft myeloma (GVM) effect.[7,84,85] These findings have prompted trials using DLI to treat and prevent relapses in myeloma. Lokhorst et al[7] gave patients DLIs with T-cell doses ranging from 1×10^6/kg to 33×10^7/kg. Eight of 13 patients with relapsed multiple myeloma responded; four achieved CR and four partial remission. Schlossman et al[78,86] used CD4+ DLI (CD8-depleted) in six relapsed patients post CD6 T cell-depleted allogeneic transplant. One patient died due to progressive disease 3 weeks after DLI and five are alive after a mean of 39 weeks from DLI (range, 10 to 72 weeks). Three obtained a CR and two a partial remission.

New ways to promote the GVM effect by immune-based strategies need to be explored.

Prognostic factors for allogeneic transplantation

Among the largest of the studies, EBMT has reported that for both response and survival, the most important favorable pretransplant prognostic factors are to be female, to have received only one treatment regimen, to have IgA myeloma, low β2M, stage I disease at diagnosis, and to be in CR prior to transplant.[72] In the Seattle series, adverse prognostic factors were recognized as transplantation >1 year after diagnosis, β2M >2.5 mg/L, being female and transplanted from male donors, having received more than eight cycles of chemotherapy, and Durie-Salmon stage III disease at the time of bone marrow transplant.[74] We have shown that having received a previous autograft conferred a worse prognosis.[73]

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SYNGENEIC TRANSPLANTS

The information about syngeneic transplants in myeloma is scanty. An EBMT case-matched analysis between 25 syngeneic transplants and 125 allogeneic and 125 autologous cases, respectively, has shown that

survival following syngeneic transplantation tended to be superior to that of autologous transplantation and was significantly better than that of allogeneic transplantation.[87] The OS 4 years after syngeneic transplantation was 77%, after allogeneic transplantation 31%, and after autotransplantation 46%. The reason for the better outcome after syngeneic vs allogeneic transplantation was the lower TRM. The Seattle group[88] has treated 11 patients with syngeneic transplants: two of them remain disease free at 9 and 15 years after transplantation, two died of TRM, and seven died following progressive disease. A syngeneic donor, if available, should be the preferred method.

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NONMYELOABLATIVE TRANSPLANTATION

The concept of nonmyeloablative conditioning followed by an allogeneic transplant is based on the fact that engraftment can occur without myeloablation and that the graft has an antitumor effect.[89-91] To start with, mixed chimerism is obtained, and a possibly increased risk of relapse is thereafter counteracted by DLIs, either as prevention or as treatment at early signs of relapse. Various conditioning regimens being used include TBI 200 cGy, fludarabine/melphalan, and fludarabine/ATG/busulphan.[89-91] Ongoing trials indicate that earlier transplantation may give substantially better results with very low toxicity. Nonmyeloablative transplantation may well be an important alternative for some patients with multiple myeloma.

PHARMACOECONOMICS

In a recent retrospective cost-effectiveness analysis, Trippoli et al[92] found the incremental cost-effectiveness ratio of autologous bone marrow transplantation vs conventional melphalan-prednisolone therapy in multiple myeloma to be about $26,000 per life-year gained (in 1998 US dollars). However, due to the selection of patients in the trials analyzed, these authors probably overestimated survival for the patients who received transplants (7.28 years) and underestimated it (3.47 years) for control patients of similar age. Thus, the cost per quality-adjusted life-year for high-dose chemotherapy with autologous PBSC support is likely to be higher, somewhere between $30,000 and $40,000 (US dollars).

Jagannath et al demonstrated the feasibility and cost effectiveness of outpatient autotransplants in multiple myeloma.[93] Compared with inpatient treatment, the number of days in hospital was reduced from 15 to 9, causing a 40% reduction in procedural costs, We found that patients undergoing PBSC treatment had a much faster engraftment, so the outpatient management resulted in significant financial savings due to lower pharmacy (42%), hospitalization (50%) and pathology/laboratory charges (36%).[18] Outpatient transplants should facilitate easy access to myeloablative therapy, thereby improving CR and survival rates of myeloma patients.

CURING MYELOMA/ "OPERATIONAL CURE"

The evidence that myeloablative therapy with autotransplants can be administered safely to patients with myeloma up to the age of 75 years and can produce CRs in almost 50% is encouraging. In acute leukemias and lymphomas, the well-established first step for cure is the achievement of CR. The overall experience with high-dose therapy for myeloma indicates that drug resistance, characteristic of tumor cells even at diagnosis, can be overcome by dose intensification, although relapses still occur even after tandem autotransplants and allogeneic transplants.

From the prospectively maintained myeloma database at the Royal Marsden, we have been able to identify 14 patients who had a first CR lasting for more than 10 years either with HDM 140 mg/m^2 alone or with CVAMP followed by HDM 200 mg/m^2. Possibly, these patients were operationally cured as they fulfilled all the described criteria for CR and have a good performance status with a normal quality of life.[94] Although two patients relapsed at 10.1 and 11 years, there is a possibility that this group of patients will not die of myeloma but of other reasons, ie, they are "operationally cured" but living in symbiosis with their minimal residual disease. Application of recently introduced molecular techniques such as CDR III PCR should provide further insight into the dynamics of "molecular CR" and its association with better prognosis.

FUTURE DEVELOPMENTS

Based on recent phase III studies, patients may be risk stratified so that they benefit from different treatment strategies. Postallograft cytokine maintenance therapies, eg, interferon-α2b and IL-2[95,96] have been shown to be effective, and vaccination with tumor antigens or DNA[97-99] may possibly help to prevent relapse. The demonstration of a GVM effect

and the recent introduction of nonmyeloablative regimens for allogeneic stem cell transplantations open the possibility to explore new treatment strategies.[97,100] The optimal use of GVM after such transplants may be achieved by repeated DLI infusions until "molecular CR" has been obtained. Once this approach is standardized, its wide-scale application in patients up to the age of 65 years may be possible and donors may be recruited from matched unrelated donor banks.

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