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Treatment of multiple myeloma

JÉSUS F. SAN MIGUEL,* JOAN BLADÉ CREIXENTI,° RAMÓN GARCÍA-SANZ,*
**Department of Hematology of the "Hospital Universitario de Salamanca", °Department of Hematology of the "Hospital Clínic Universitari de Barcelona (IDIBAPS)", Spain*

ABSTRACT

Background and Objective. Multiple myeloma (MM) accounts for about 10% of all hematologic malignancies. The standard treatment with intermittent courses of melphalan and prednisone (MP) was introduced more than 30 years ago and, since then there has been little improvement in event-free and overall survival (EFS & OS). The aim of this article is to review: 1) the role of initial chemotherapy (ChT), maintenance treatment with α-interferon and salvage ChT, 2) the results of high-dose therapy (HDT) followed by allogeneic or autologous stem cell transplantation (allo-SCT and auto-SCT), and 3) the most important supportive measures.

Evidence and Information Sources. The authors of this review have been actively working and contributing with original investigations on the treatment of MM during the last 15 years. In addition, the most relevant articles and recent abstracts published in journals covered by the Science Citation Index® and Medline® are also reviewed.

State of the Art and Perspectives. The importance of avoiding ChT in asymptomatic patients (smoldering MM) is emphasized. The criteria and patterns of response are reviewed. MP is still the standard initial ChT with a response rate of 50-60% and an OS of 2-3 years. Combination ChT usually increases the response rate but does not significantly influence survival when compared with MP. Exposure to melphalan should be avoided in patients in whom HDT followed by auto-SCT is planned, in order to not preclude the stem cell collection. The median response duration to initial ChT is 18 months. Interferon maintenance usually prolongs response duration but in most studies does not significantly influence survival (a large meta-analysis by the *Myeloma Trialists' Collaborative Group* in Oxford is being finished). In alkylating-resistant patients, the best rescue regimens are VBAD or VAD. In patients already resistant to VBAD or VAD and in those in whom these treatments are not feasible we recommend a conservative approach with alternate day prednisone and pulse cyclophosphamide. While HDT followed by autotransplantation is not recommended for patients with resistant relapse, patients with primary refractory disease seem to benefit from early myeloablative therapy. Although results from large randomized trials are still pending in order to establish whether early HDT intensification followed by auto-SCT is superior to continuing standard ChT in responding patients, the favorable experience with autotransplantation of the *French Myeloma Intergroup* supports this approach. However, although the complete response rate is higher with intensive therapy, the median duration of response is relatively short (median, 16 to 36 months), with no survival plateau. There are several ongoing trials comparing conventional ChT with HDT/autoSCT in order to identify the patients who are likely to benefit from one or another approach. With allo-SCT there is a transplant-related mortality ranging from 30 to 50% and also a high relapse rate in patients achieving CR. However, 10 to 20% of patients undergoing allo-SCT are long-term survivors (>5 years) with no evidence of disease and, consequently, probably cured. The use of allogeneic peripheral blood stem cells (PBSC) in order to speed the engraftment and also the use of partially T-cell depleted PBSC which can decrease the incidence of graft-versus-host disease are promising approaches. In the setting of allo-SCT, donor lymphocyte infusion is an encouraging strategy in order to treat or prevent relapses. Finally, important supportive measures such as the treatment of anemia with erythropoietin, the management of renal failure and the use of bisphosphonates are reviewed.

Key words: multiple myeloma, therapy, polychemotherapy, transplantation, supportive therapy

Correspondence: Jesús F. San Miguel, Department of Hematology, Hospital Universitario de Salamanca, Paseo de San Vicente, 58-182, 37007 Salamanca, Spain.
Phone: international +34-923-291384 • Fax: + 34-923-294624 • E-mail: sanmigiz@gugu.usal.es

In spite of the different drug combinations tried in multiple myeloma (MM), progress in event free and overall survival has, at most, been modest. At present, conventional melphalan and prednisone (MP) continue to be regarded as the gold standard. The response rates obtained with MP or other polychemotherapeutic regimens are around 50 to 70%, with less than 5% complete remissions, and moreover, almost all patients who do respond will ultimately develop chemoresistance and relapse. These poor results led to the search for alternative treatment strategies. In 1983, McElwain and Powles[1] demonstrated that dose escalation of intravenous melphalan could overcome primary resistance to conventional doses of alkylating agents, resulting in a significant increase in the response rate. This pilot study also indicated the feasibility of high-dose treatment in patients with MM and was the basis for fur-

ther investigations into the intensification of therapy. Nevertheless, high doses of chemotherapy resulted in a prolonged marrow aplasia associated with a relatively high frequency of fatal infectious episodes. Therefore, the subsequent goal was to reduce such consequences through bone marrow stem cell (BMSC) support – either autologous or allogeneic. In this review we will first discuss the role of conventional chemotherapy and maintenance treatment with interferon and then we will analyze the results obtained with autologous and allogeneic transplantation and finally the most relevant strategies for supportive therapy will be reviewed.

Conventional chemotherapy

General considerations

Patients who should not be treated. The majority of patients with MM require chemotherapy at the time of diagnosis because of symptomatic disease at presentation. However, not all patients fulfilling the diagnostic criteria of MM require cytostatic therapy. In this regard, patients with smoldering multiple myeloma (SMM) (serum M-protein >30 g/L and proportion of bone marrow plasma cells > 10%)[2] must not be treated even if the M-component and the percentage of bone marrow plasma cells are considerably higher than the cut-off required for the definition of SMM, provided that they do not develop bone pain, anemia, hypercalcemia, renal insufficiency or recurrent bacterial infections. In addition, when the tumor mass is relatively high (i.e., serum M-protein of 40 to 50 g/L and proportion of bone marrow plasma cells in the range of 30 to 40%), the hemoglobin level is usually below the normal limit. In this setting, a moderate degree of anemia is not a criteria for initiation of treatment in otherwise asymptomatic myeloma. As the diagnosis of SMM is sometimes difficult to prospectively establish, a decision on no treatment might be reinforced by a low plasma cell labeling index, normal serum β2-microglobulin and normal MRI of the spine.

There is also an small proportion of patients with *non-responding, non-progressive* myeloma. In our experience, these patients usually present with a high serum M-protein concentration, particularly of IgG type, a high proportion of bone marrow plasma cells, moderate anemia, bacterial infections or symptoms of mild hyperviscosity, but they have no lytic bone lesions, hypercalcemia, renal insufficiency or extramedullary plasmacytomas. These patients are usually treated with chemotherapy because of anemia or recurrent infections. If no change in their paraprotein level and clinical status is observed after 4 to 6 courses of chemotherapy, these patients should not be given further chemotherapy until evident disease progression occurs. It is of note that, although these patients are normally classified as *non-responders* it has been recognized that in fact they have a prolonged survival because of temporarily *non-progressive* disease.[3,4]

Criteria of response. In contrast to that occurring in acute hematologic malignancies, conventional chemotherapy for MM, although inducing different degrees of partial response, rarely results in complete remission (i.e., disappearance of the M-protein and fewer than 5% bone marrow plasma cells). The first criteria of response were developed by the *Committee on the Chronic Leukemia Myeloma Task Force* (CLMTF). According to the CLMTF, the main parameter for objective response was a 50% reduction in the amount of the serum and urinary M-proteins.[5] The Southwest Oncology Group (SWOG) proposed a system in which the objective response was based on a reduction of at least 75% in the serum M-protein synthesis rate and a decrease of at least 90% in the light chain urinary protein excretion sustained for at least two months.[6] Patients with clinical improvement but in whom the M-protein decrease was lower than 50% (CLMTF criteria) and those with a decrease in the M-protein synthesis between 50 and 74% (SWOG criteria) were considered as having indirect or partial responses. Both, the CLMTF and the SWOG criteria have been extensively used in clinical trials, although frequently with modifications on the original proposals. In 1980, the concept of a plateau phase, consisting of a period of stability after chemotherapy lasting for at least 4 to 6 months, in which tumor progression does not occur despite the persistence of measurable disease with a stable serum M-protein and a significant number of bone marrow plasma cells, was introduced in the response evaluation of MM.[7] Since the survival of patients with MM who achieve the plateau phase with disease stabilization is similar irrespective of whether they fulfil the objective response criteria, or just those of a partial response, this latter group of patients should also be considered as responders and consequently managed as such.[8-10] In some recent studies the achievement of complete response (disappearance of the M protein in serum and urine and less than 5% bone marrow plasma cells) is being considered.[11,12] In this regard, the emergence of new treatment approaches, particularly high-dose therapy followed by autologous or allogeneic stem cell rescue, is resulting in a much higher tumor reduction with complete response rates ranging from 25 to 75%. Although this high response rate is encouraging, longer follow-up is required to establish the real impact of this greater tumor reduction on survival. The EBMT (*European Group for Blood and Marrow Transplantation*), IBMTR (*International Bone Marrow Transplant Registry*), and ABMTR (*Autologous Bone Marrow Transplant Registry*) have developed a new proposal for definition of response, relapse and progression in MM, particularly after high-dose therapy.[13]

Response patterns and their influence on survival in multiple myeloma. Patients with MM display different patterns of response.[14] Thus, between 40% and 50% of patients with MM show an objective response to

chemotherapy, while an additional 10 to 20% attain a clinical improvement or partial response (CLMTF, SWOG criteria). As already mentioned, there is an small proportion of patients who have no response but in whom the disease does not progress: *non-responding, non-progressive disease*.[3,4] When the patients are asymptomatic and the maximal degree of response is sustained for at least 4 months it is considered that the disease is in the plateau phase. The attainment of response in MM is usually slow. In this sense, most patients with MM achieve the response between 2 and 6 months after the initiation of conventional chemotherapy. Moreover, in some cases the response not is observed until more than 6 months, or even more than one year, beyond the initiation of treatment. In contrast, about 10% of the patients show a rapid response to chemotherapy (< 2 months). For many years, it was considered that a rapid response to chemotherapy was followed by a quick relapse and subsequent short survival.[15,16] However, Boccadoro *et al*.[17] found that a rapid response, by itself, is not an indicator of poor prognosis. Rapid responders with a labeling index (LI) > 2% had a median response duration and survival of 12 and 16 months, respectively. In contrast, rapid responders with a LI < 2% had a median response duration of 26 months and the median survival was still not reached at 47 months.[17] Thus, early response is only a poor prognostic factor when it is associated with a highly proliferative tumor. In patients with low LI the early response is due to an intrinsic chemosensitivity of the myeloma cells, unrelated to the cell proliferation. About 25 to 30% of the patients with MM do not respond to chemotherapy and have progressive disease.

In summary, patients with a slow objective or partial response, early responders with low LI as well as those with *non-responding, non-progressive* disease have a better prognosis with a median survival of about 4 years. In contrast, non responding patients with progressive disease and early responders with high LI have a poor prognosis with a median survival of less than one year. In our experience, response to chemotherapy is the most important prognostic factor.[18]

Initial chemotherapy

Before the introduction of alkylating agents, median survival of patients with MM was less than one year.[19] Since its introduction by Alexanian *et al.* thirty years ago,[20] the combination of melphalan and prednisone (MP) has constituted the standard therapy for patients with MM.[14] With this regimen the overall response rate is 50 to 60% and the patients' median survival ranges between 2 and 3 years. Cyclophosphamide is as effective as melphalan,[21,22] but has been less employed in the treatment of MM. Melphalan is usually administered at a dose of 0.25 mg/kg/day for four days, along with 60 mg/m^2 of prednisone every 4 to 6 weeks depending on the hematologic tolerance. Because of the variability in the melphalan absorption, this drug must be given while the patient is fasting and the dose should be adjusted until mild midcyle cytopenia occurs. In patients with renal failure the initial dose of melphalan should be reduced by 25 to 50% to prevent severe myelotoxicity. If renal function improves or no excessive toxicity is observed, full doses must be administered in the following courses. It has been stressed that combination chemotherapy could produce a faster response with a quicker decrease in light-chain production thereby avoiding further renal damage.[23] However, in our experience the survival of patients treated with single alkylating agents plus prednisone was similar to that of those treated with combination chemotherapy. An alternative approach for these patients might be the administration of the VAD regimen (vincristine and adriamycin in a four-day continuous infusion plus high-dose dexamethasone) which produces a more rapid response than MP and other more conventional regimens with low hematologic toxicity.[24,25] In MM patients with cardiac disorders and renal failure another approach is the use of cyclophosphamide (1 g/m^2 every 3 weeks) and dexamethasone (as used in VAD).

Although the introduction of melphalan constituted an important advance in the management of MM, the survival of patients with this disease still remains unsatisfactory. Numerous attempts to improve the results obtained with the standard MP regimen have been made. Several combinations of melphalan (M) with cyclophosphamide (C), prednisone (P), carmustine (BCNU) (B), vincristine (V), and adriamycin (A) have so far been employed, the most common associations being VBMCP (M-2 protocol), BMCP, VCMP, VBAP, and VCAP.

The results of a non-randomized trial performed at the Memorial Hospital in New York with the M-2 protocol, showing a 78% objective response rate and a median survival of 38 months, were encouraging.[26] However, four prospective randomized trials comparing the same M-2 protocol[27-29] or one slight variant[30] with MP, failed to show any significant survival advantage for patients treated with the combination chemotherapy, and in only one of them the combined regimen produced a significantly higher response rate (74 vs. 53%).[29] In other prospective randomized trials, the results with BCP[31] or MCBP,[32-34] were similar to those achieved with MP, except in the study by Harley *et al.*[33] where poor-prognosis patients survived significantly longer when treated with MCBP, while those with good prognosis fared better when given MP.

In 1983, the SWOG reported significant improvements in both the response rate and survival for patients treated with VCMP/VBAP or VCMP/VCAP as compared with those receiving MP.[35] In a large series recently reported by the MRC, the ABCM regimen also increased both the proportion of patients reaching the plateau phase and the survival, in comparison with

melphalan alone.[8] However, other randomized studies found no significant differences in survival of patients treated with adriamycin-containing regimens or MP,[34,36-39] although in one of them a significantly higher response rate in favor of combination chemotherapy was observed.[39] In a non-randomized series of 72 patients with MM who were younger than 40 years, combination chemotherapy produced a higher response rate with no significant influence on survival.[40] The *Italian Multiple Myeloma Study Group* has recently stressed that conventional induction treatments do not influence overall survival in MM.[41] The study by McIntyre *et al.*,[42] showing that the use of a 70-day tapering course of prednisone alone in good-risk myeloma patients which results in a 44% objective responses, has stimulated the investigation of high-dose dexamethasone in previously untreated patients. This primary treatment is simple and safe and yielded a 43% objective response.[43] However, its use either as single agent or in combination with chemotherapy (VAD) as front line therapy, has not resulted in significant prolongation of survival.[12,25] In several trials, melphalan has been administered intravenously.[33,34,44] There is no evidence that pulsed intravenous low dose melphalan is superior to oral melphalan in the treatment of MM.[33,34,44] Intravenous melphalan produces a higher frequency of allergic reactions and is associated with higher myelotoxicity, particularly in patients with renal function impairment.[44] In summary, it seems that combination chemotherapy can improve the response rate but without creating a significant improvement in survival.

In two pilot studies the administration of MP or VBMCP plus IFN-α2b in previously untreated patients resulted in a response rate, respectively, of 80% and 74%.[45,46] Following these promising results, several randomized studies comparing chemotherapy versus chemotherapy plus IFN were carried out. In two of them a higher response rate to the chemotherapy plus IFN arm was observed.[47,48] A third study showed a significantly higher complete remission rate in patients treated with BVMCP/INF-α2b as compared to those given BVMCP alone, although the overall response rate to chemotherapy was similar to that observed with chemotherapy plus IFN.[49] Other studies have shown no increase in response rate in favor of the chemotherapy plus IFN arm.[50-55] Regarding survival, a significant survival prolongation for the MP/IFN combination versus MP alone was reported in one small series.[47] No other studies showed significant prolongation of survival for patients treated with chemotherapy plus IFN compared with those receiving chemotherapy alone.[48-55]

One of the reasons for the poor outcome of patients with MM is the short duration of response. In this regard, the median duration of response in all the above mentioned studies ranged between one and a half and two years. It is of note that the response duration in MM seems to be independent of both the induction treatment and the degree of initial response.[39] This has also been observed when more intensive regimens, such as VAD[12] or high dose melphalan are used.[11] Furthermore, the duration of response after high-dose therapy/autotransplantation exceeds the response duration achieved with conventional chemotherapy by only a few months,[56] and all patients eventually relapse. In fact, the actuarial probability of being in continued first response at five years after chemotherapy or autotransplantation ranges between 14 and 28%.[56,57] A meta-analysis of eighteen published trials involving 3,814 patients comparing MP versus combination chemotherapy suggested that patients with good prognosis do better with MP, whereas those with poor prognosis, as well as patients with IgA myeloma, fare better with the combined treatment.[58] The results, which are still confidential, of another meta-analysis of 27 trials also comparing MP versus combination chemotherapy and including 6,633 patients, based on the individual patients' data from the *Myeloma Trialists' Collaborative Group* in Oxford have just been submitted for publication.[59]

Duration of initial chemotherapy and maintenance treatment

After several months of treatment, myeloma patients responding to chemotherapy enter into the so-called plateau phase, characterized by the persistence of residual disease that does not decrease, regardless of whether or not patients are receiving more chemotherapy.[7] Clinically and biologically this phase is very close to the quiescent state observed in monoclonal gammopathy of undetermined significance (MGUS) or SMM. The crucial difference between MGUS and MM in stable plateau phase is that in MM the residual malignant cells will lead to relapse in virtually all cases, while only about 25% of MGUS-individuals with evolve to MM, usually after a long period of stability.

The ideal duration of initial chemotherapy is unknown. In several randomized trials[16,60,61] no difference in survival was found between patients receiving maintenance therapy, usually MP, and those who were not given maintenance therapy. In addition, chemotherapy maintenance increases the risk of myelodysplasia or secondary leukemia.[32] Sequential hemibody irradiation for response consolidation has also been tried with disappointing results.[62] Initial chemotherapy should be given for a minimum of 4 to 6 months after the plateau phase is achieved and for a period of at least one year.

The most promising approach in the maintenance treatment of MM is the administration of interferon-α (IFN-α). The results of INF-α maintenance on response duration and survival are, however, still controversial.[63] There are five randomized studies showing a significant benefit from INF-α maintenance with a prolongation in response duration, ranging from 5 to 12 months in favor of the INF-α arm.[53,64-67] In con-

trast, other trials have not shown longer response duration in patients maintained with IFN-α.[68,69] There are two other trials, recently published in abstract form, comparing the use of IFN-α versus no treatment in patients in plateau phase after the initial chemotherapy. In both studies IFN-α maintenance significantly improved progression-free survival.[70,71] Concerning survival, most studies have shown no significant differences in patients maintained with IFN-α as compared with the observation groups.[52,65,67-71] However, two studies showed a significant survival prolongation in favor of the IFN maintenance in patients in objective response after the initial chemotherapy.[53,64] In addition, a third study showed a survival benefit of borderline significance for the IFN maintenance group when the statistical analysis was performed after the adjustment for chance imbalances in baseline prognostic factors.[66]

The inconveniences of IFN treatment, particularly toxicity, that can result in a decrease in the quality of life and the financial cost should be considered when prescribing IFN maintenance. Concerning patients' preferences, in an interview study, the majority of patients would accept a treatment with the toxicity and financial cost of IFN, if at least a 6-months gain in relapse-free or overall survival was expected.[72] In an attempt to establish the role of IFN, both in induction and maintenance treatments, a large meta-analysis, based on the individual patients' data of patients included in 24 IFN-α trials is being finished by the *Myeloma Trialists' Collaborative Group* in Oxford.

Two studies have shown encouraging results with the association of IFN plus glucocorticoids as maintenance treatment of MM.[68,73] In line with this observation, the preliminary results of a trial by the *Italian Myeloma Study Group* comparing maintenance with IFN alone versus IFN plus dexamethasone show a significantly longer survival in patients receiving IFN plus dexamethasone.[74]

The results of IFN maintenance after high-dose therapy followed by stem cell rescue will be discussed in the autologous transplant section of this review.

Treatment of resistant multiple myeloma

Patients with MM who either fail to respond (primary refractory) or become refractory to the alkylating treatment (relapsing refractory) have a low response rate to subsequent chemotherapy and a short survival. With the combination of vincristine, BCNU, adriamycin, and prednisone (VBAP), response rates of about 25%, as well as survival prolongation for responding patients, have been reported.[4,75] A modification of the VBAP regimen, in which prednisone was replaced by dexamethasone (VBAD), produced an overall response in more than one third of the patients, the response rate being significantly higher in primary resistant patients than in those becoming resistant after a prior response.[76] The highest response rate in patients with MM resistant to alkylating agents has been reported with four-day continuous infusion of vincristine and adriamycin, along with high-dose dexamethasone.[77] The major shortcomings of this regimen are that vincristine and adriamycin have to be given via a central venous catheter and the significant steroid toxicity manifested by infections, myopathy and gastrointestinal bleeding. Furthermore, the median duration of response is less than one year. High-dose glucocorticoids, particularly dexamethasone, have also shown antitumor activity in refractory MM with an expected response rate of 20 to 25%.[78] In this regard, VAD or dexamethasone alone were equally effective in the treatment of patients with primary refractory myeloma, while VAD was better than dexamethasone alone in relapsing refractory patients.[78] A combination of etoposide, dexamethasone, cytarabine and cisplatin (EDAP) produced 40% of responses in heavily pretreated patients, but the myelosupression of this regimen was extremely severe and the patients' median survival short.[79] There are other regimens consisting of cyclophosphamide/etoposide,[80] cyclophosphamide/teniposide/dexamethasone,[81] or cyclophosphamide/dexamethasone/idarubicin/etoposide,[82] usually given with growth factors, which produce a high response rate but the duration of response and survival are short. These regimens usually produce severe myelosupression and are costly. It is important to highlight that, when considering the treatment of resistant myeloma, the inconveniences of therapy, particularly toxicity, that can decrease the quality of life, and cost must be weighed against a questionable prolongation of survival when compared with more conservative approaches. Hemibody irradiation can produce transient subjective improvement and decrease in the M-component size, but the hematologic toxicity is severe.[83]

The results of treatment of relapsing or resistant MM with IFN, used as a single agent, have been disappointing, with an overall response rate ranging from 10 to 20%.[65] San Miguel *et al.*[84] treated 51 refractory patients with IFN-α2b plus high-dose dexamethasone. Thirty-seven of them completed the 3 months induction period and 18 (48%) achieved an objective or partial response. In contrast, Alexanian *et al.*[85] reported that the combination of either dexamethasone or VAD chemotherapy with IFN-α did not improve the response duration and survival when compared with historical results using dexamethasone or VAD chemotherapy alone.

Monotherapy with many different agents (hexamethylmelamine, high-dose cytarabine, clorozotozin, mitoxantrone, vincristine, vindesine, m-AMSA, VM-26, deoxycoformycine, epirubicin, 2-clorodeoxyadenosine) has been tried with disappointing results.[86,87] The vinca alkaloid vinorelbine has shown antitumor activity in MM (unpublished data) and is being investigated in association with dexamethasone in prospective trials. A multicenter study of oral idarubicin

versus idarubicin plus dexamethasone is currently in progress.

The failure of MM patients to respond to VAD may be due to the expression of the multidrug resistant phenotype. Multidrug resistance (MDR) is characterized by the expression of glycoprotein p-170 encoded by the MDR-1 gene. Cells with p-170 glycoprotein expression achieve lower intracellular drug concentration. Attempts to prevent or overcome the MDR in resistant myeloma with verapamil or quinine have been disappointing.[88] It was reported that clinical resistance to VAD could be modulated by adding cyclosporine to the chemotherapy regimen.[89] However, in a subsequent study no association could be demonstrated between response to VAD and MDR-1 expression, suggesting that in MM there are other mechanisms of resistant apart from MDR.[90,91] The efficacy of the association of VAD with the cyclosporine analog PSC 833, which is a potent chemosensitizer and is less nephrotoxic and immunosuppressive than cyclosporin A, in refractory myeloma is investigated.

The administration of anti-interleukin-6 antibodies to 10 patients with advanced MM resulted in the inhibition of CRP production and in a decrease in the plasma cell LI. However, this treatment had no effect on the patients' clinical status or in the amount of M-protein.[92]

In summary, in patients with MM resistant to alkylating agents, VBAD or VAD seems to be the more appropriate rescue regimen. In patients already resistant to a rescue regimen with VAD or VBAD as well as in those in whom these treatments are not feasible (very advanced age, poor performance status, severe pancytopenia, cardiac disorders) we recommend a conservative approach with alternate day prednisone (30 mg), and pulsed dose cyclophosphamide (800 to 1200 mg) every 2 to 3 weeks. This approach rarely produces objective responses but it is a palliative treatment that can temporarily control the disease with a very low toxicity.[93,94]

Autologous hemopoietic stem cell transplantation

Introduction

Due to the limitations inherent to allogeneic stem cell transplantation (SCT), such as age, donor availability and high toxicity, autologous-SCT has become an encouraging alternative approach that allows the use of myeloablative therapy with low toxicity and mortality. Indeed, the mortality rate has fallen from 20% in the initial series to < 5% in more recent series, probably due to better patient selection and also to the shift from BM to PB as the source of stem cells which has led to faster engraftment. This explains the rapid expansion in the use of autologous-SCT which is now offered to MM patients up to 70 years which means that theoretically half of myeloma patients may be candidates for such therapeutic approach.[95-102]

Here, we will review the role of auto-SCT in two different situations: 1) as rescue therapy for refractory (primary resistant and relapsed) MM patients, and 2) as intensification treatment for patients who have shown initial response to conventional chemotherapy. Technical aspects such as the conditioning regimens, source of stem cells, impact of purging and residual disease will also be discussed.

Auto-SCT for refractory MM

Patients with refractory MM were the first candidates for exploring the value of auto-SCT. The overall results indicate that although intensive therapy induces a high rate of CR, the duration of responses

Table 1. Autologous stem cell transplantation in refractory multiple myeloma.

Author ref.	n	Type of resistance	Conditioning regimen	CR	Total response	Toxic deaths	Progression free survival		Overall survival	
							Median	at 2 yr.	Median	at 2 yr.
Vesole[106]	72	Primary	Various*	11%	62%	8%	21 m	–	47 m	–
	63	Late	Various*	8%	59%	14%	8 m	–	15 m	–
Alexanian[97]	26	Primary	Various*	15%	65%	8%	17 m	31%	42 m	72%
	23	Late	Various*	0%	61%	17%	5 m	0%	18 m	23%
Selby[104]	15	Primary	MF140	13%	63%	13%	7m	0%	10 m	32%
Tricot[109]	31	After Tx	Various	22%	–	–	–	–	78% alive at 18 months	
Vesole[107]	56	Primary	MF200 + IFN	30%	35%	10%	9 m	–	20 m	-
Fermand[103]	8	Primary	MF140 + hydroxyurea + VP16 + TBI	25%	88%	12%	NR	71%	NR	88%

Abbreviations: yr.: years; m: months; MF: Melphalan; Tx: Transplant; IFN: Interferon; TBI: Total Body Irradiation.
Various: MF100 without transplantation, MF100 or Thiotepa + TBI, MF200. NR: not reached.*

is short.[97,103-106] This high relapse rate together with the high costs of transplants have put into question the suitability of such an approach for this cohort of patients. It is important, however, to recognize that under the term *refractory* MM very different subsets of patients are included: primary resistant, sensitive relapses and resistant relapses. According to the data of M.D. Anderson Cancer Center[96] and the experience of Fermand *et al*.,[103] autologous-SCT is useful in patients with primary resistant disease (65% to 88% responses with 80% of patients alive at two years) (Table 1). In line with these positive observations, Vesole *et al*.[106,107] have reported that the use of a double transplant in primary refractory MM patients may lead to a median PFS and OS of 21 and 47 months, respectively. These data indicate that tumor resistance could be overcome with high dose chemotherapy. For this reason it is particularly important to identify patients with primary resistant myeloma promptly in order to avoid the emergence of new resistant cell clones or more aggressive tumor subclones during disease evolution. In addition prolonged chemotherapy damages the progenitor cells, and this may preclude stem cell collection and can also increase the risk of secondary MDS/AML.[108] The benefit of transplantation is not so clear in patients at relapse, either sensitive or resistant, since transplants performed during late phases of the disease (i.e., more than one year after diagnosis) have yielded very poor results.[97,106] Nevertheless, preliminary results from two randomized studies (detailed description on next section, see refs. #122 and 123) designed to compare auto-SCT versus chemotherapy, but reserving the possibility of salvage transplant for patients who relapse in the chemotherapy arm, suggest that if the rescue transplant is performed at a relatively early period, it can be successful.

Since auto-SCT is performed with increasing frequency for MM and relapses are very frequent, we should now also consider a new type of refractory MM: patients that relapse after autotransplantation. Tricot *et al*.[109] have reported on 94 of these patients in order to evaluate the efficacy of further therapy. A new transplant performed as primary salvage therapy was associated with a significant survival prolongation as compared to salvage with conventional chemotherapy. Nevertheless, a patient selection bias may occur within this cohort of patients, i.e., cases with poor PS and advanced age may not be considered candidates for transplantation. In addition, in Tricot's study[109] it was found that in relapsed transplanted patients, the presence of both a high pre-salvage β2M (>2.5) and an early relapse after the first transplant (<12 months), were unfavorable factors for OS.[109]

Auto-SCT as consolidation/intensification therapy

In acute leukemias and lymphomas it is well established that the first step for cure is the achievement of complete remission (CR). In MM, the rate of CR with conventional chemotherapy is very low (<5%).[58] As soon as initial studies in refractory MM showed that toxicity of high dose therapy followed by stem cell support was low, this strategy began to be used as consolidation/intensification therapy in order to obtain a response of higher quality after a short program of conventional chemotherapy (3 to 4 courses) – *induction therapy*. Tables 2 and 3 summarize some of the most relevant published series using this strategy either with autologous BM or PBSC. The overall response rate is around 90% and, more importantly, between 25% and 70% of these responses – median 50% – are CR.[103,110-118] This variability in the CR rate may be partially due to the criteria used for response assessment and in this sense immunofixation should be mandatory in order to assure the disappearance of the paraprotein. In addition, it should be taken into account that in some patients the clearance of the paraprotein may be relatively slow – up to 6 months or even more –,[119] and that oligoclonal Ig bands may emerge as a result of the expansion of a reactive cell clone. The increase in CR rates has been accompanied by a prolongation in PFS of up to 3 years in some series (Tables 2 and 3), thereby increasing the PFS usually obtained with conventional chemotherapy by six to ten months. Although in most series the follow-up is not long enough for a correct estimation of overall survival (OS), the projected median survival is about 5 years with around 70% of patients alive at 3 years (Tables 2 and 3).[110-114,116-118]

Nevertheless, despite the apparent advantage of the results of auto-SCT over conventional chemotherapy, the results must be interpreted with caution since the transplant series includes a patient bias: ≤ 70 years, good performance status (PS), chemosensitive disease and exclusion of early deaths. In fact, the *Spanish PETHEMA Cooperative Group*[56] reported that of 487 patients treated with conventional chemotherapy (VCMP/VBAP or melphalan/prednisone), the 77 cases that were < 65 years old, with good PS and initial response to chemotherapy (candidates for intensification with transplantation but who were conventionally treated) displayed a median survival of 5 years, similar to that reported with auto-SCT. In order to avoid misinterpretations due to patient selection bias, Barlogie *et al.*[120] compared their results with auto-PBSCT with a pair matched group of patients retrospectively selected from the SWOG trials (treated with conventional therapy) and observed significant benefits for the transplant group. However, there is no doubt that the most appropriate way to perform such comparisons is through well-designed randomized trials. The only randomized study so far reported is that conducted by the *Intergroupe Français du Myeloma*,[57] updated at the 1997 ASH meeting.[121] The design of the study, based on 200 patients, included four courses of conventional treatment with VMCP/VBAP after which the patients were randomized to receive either eight

Table 2. Autologous bone marrow stem cell transplantation.

Author ref.	No.	Situation at Tx	Conditioning regimen	% of CR	% of total responses	Toxic deaths	Progression free survival			Overall survival		
							Median (months)	at 3 yr.	at 5 yr.	Median (months)	at 3 yr.	at 5 yr.
Gore[113]	503	post-VAMP	MF-200 + ASCT (28) MF140 alone (22)	50%2	74%	14%	18	20%	–	NR	78%	–
Harousseau[114]	35	Untreated Responsive	MF140 & ASCT MF140±TBI & ASCT	34%1/2	94%	6%	25	30%	0%	41	68%	29%
Attal[115]	31	Responsive to VCMP	MF-140+TBI+IFN	48%1	94%	3%	NR	53%	–	NR	85%	–
Jagannath[111]	19	Responsive to VAD	MF-140 + TBI	37%2	95%	5%	20	–	–		70%	54%
	18	Responsive to VAD	MF-200 (x2)	44%2	89%	0%	NR	75%	–	NR	89%	–
Cunningham[117]	53	Post-VAMP	MF-200	75%1	98%	2%	>20	–	–	>60	65%	–
	84		MF-200±IFN	77%1	–	0%	NR	60%	50%	NR	–	87%
Harousseau[144]	61	Responsive	MF-140 + TBI	36%1/2	82%	2%	28	28%	–	42	50%	–
	20	Primary refractory										
Alexanian[96]	45	Responsive to VAD	MF-140 + TBI	45%2	89%	11%	NR	58%	–	50	77%	–
Barlogie[110]	34	Responsive to VAD	MF-140 + TBI	27%2	92%	6%	24	–	–	66	67%	–
IFM[133]	200	Responsive	Single/Double Tx	33%		–	57% at 2 yr.			67% at 2 yr.		
Bjørkstrand[183]	189	143 responsive 46 unresponsive	MF ±TBI ± Cy (156) Various (33)	40%	86%	13%	23	28%	21%	34	45%	38%
Attal[59]	100	Post-VCMP/VBAP	MF-140 + TBI + IFN	22%1	81%	2%	28	40%	28%	57	75%	52%

Tx: Transplant; MF: Melphalan; ASCT: Autologous Stem Cell Transplantation; NR: Not reached; TBI: Total Body Irradiation; IFN: Interferon; CY: Cyclophosphamide.
1. CR not confirmed by immunofixation; 2. CR confirmed by immunofixation; 3. Calculations on intention to treat; 4. Those patients who achieved CR where previously treated with IFN.

Table 3. Autologous peripheral blood stem cell transplantation.

Author ref.	No.	Mobilization regimen	Conditioning regimen	% CR	% of global responses	Toxic deaths	Progression free survival			Overall survival		
							Median (months)	at 3 yr.	at 5 yr.	Median (months)	at 3 yr.	at 5 yr.
Fermand[103]	39	Mega-CHOP	MF-140 + TBI	51%	100%	15%	–	–	–	60 m	65%	–
Fermand[122]	63	Mega-CHOP	HDC+TBI	20%	100%	11%	43	53%	42%	59 m	75%	54%
Jagannath[111]	119	Cy 6 g/m²+GM-CSF	MF200	31%	–	2%	37	–	–	NR	70%	62%
Harousseau[144]	51	Cy 7 g/m² or Mega-CHOP	MF140+TBI	37%	84%	6%	34	47%	35%	52 m	63%	40%
Marit[146]	51	Cy 7 g/m²+GM	MF140+TBI	44%	98%	2%	–	–	–	–	52%	–
Jagannath[131]	231	Cy 6 g/m²+GM	Double Tx°	38%	81%	7%	42	39%	–	65	53%	–
Björkstrand[116]	15	GM-CSF	Double Tx°	53%	93%	7%	NR	62%	–	NA	80%	–
EBMT[124]	79	Various	Double Tx	65%	–	–	38	–			71% at 4 yr.	
Harousseau[123]	60	VCMP+MF+G-CSF	MF + TBI	40%	93%	–	–	–			79% at 2 yr.	
Schlossman[187]	78	Various	MF or Cy + TBI Purged SC	35%	95%	1%	25	–	<20%	51 m		40%
Alegre[125]	259	Various	MF200 or MF+TBI	51%	91%	4%	23	–	–	35 m	–	–

MF: melphalan; TBI: total body irradiation; Cy: cyclophosphamide; Tx: transplant; m: months; NR: not reached; yr.: Year; SC: Stem cells; –: data unavailable;
HDC: carmustine (120 mg/m²), etoposide (250 mg/m², x3) and melphalan (140 mg/m²) ± – in 26 patients – cyclophosphamide (60 mg/kg) .
°First transplantation with MF200 and second with MF140+TBI.

additional courses of VMCP/VBAP or high-dose therapy (melphalan 140 mg/m^2 plus TBI) followed by autologous BMT. The results show that auto-BMT used as consolidation therapy is significantly superior to chemotherapy in terms of CR (22% vs. 5%, p<0.0001), PFS (median 28 vs. 18 months p<0.02) (24% vs. 15% at 6 years p<0.01) and OS (median 57 vs. 42 months, p<0.03; 43% vs. 21% at 6 years, p<0.03). Preliminary results of another randomized trial conducted by Fermand *et al.*,[122] including 167 patients led to slightly different results, since no significant differences were observed between the transplant and the conventional VCMP arms (median OS of 58 months vs. not reached p=0.8) (OS at 2 years 80 % vs. 62 %). However, it should be noted that in this study, as previously mentioned, relapsing patients from the chemotherapy arm could be salvaged with auto-SCT. In fact, this study raises the question of the alternative approach of reserving the transplant until the time of first relapse after chemotherapy. On the other hand, in Fermand's study[122] the transplant arm was associated with a longer period of time without any chemotherapy, which suggests that such a therapeutic strategy may be clinically beneficial, and they actually recommend early rather than late transplant for young patients with symptomatic MM. At the *VI International Workshop on Multiple Myeloma*, Harousseau *et al.*[123] presented preliminary data of a randomized trial designed to explore the optimal timing of autologous transplantation. Patients received front line therapy with a combination of 3 cycles of conventional chemotherapy plus high-dose melphalan (140 mg/m^2) and G-CSF without stem-cell support. Responding patients were randomized to receive either an autologous BMT conditioned with melphalan + TBI (60 cases), or maintenance therapy with IFN (55 cases), reserving, in this second arm, the autologous transplant as salvage therapy for relapses should they occur. In the IFN group, 23 patients have already received the auto-BMT. Although the follow-up is still short, the actuarial 2-year-survival (79%±6 vs. 76%±2) does not show a significant difference between the two approaches. Several national trials (USA, Scandinavia, UK and Spain) comparing conventional chemotherapy versus early high-dose therapy intensification are in progress, which will, it is to be hoped, help to clarify the role of auto-SCT as intensification therapy in MM.

Although as we have previously mentioned, intensification therapy with auto-SCT has led to an increase in CR rates and prolongation in PFS and OS in some series, relapses are still the major challenge. The most widely used strategy for prolonging response is the employment of IFN after auto-SCT. In a randomized study including 84 patients, Cunningham *et al.*[117] showed that PFS was significantly longer in patients under IFN maintenance than in those not receiving IFN (46 vs. 27 months, p<0.03) and this resulted in a significant prolongation in OS. Several other non-randomized studies[120,123] as well as the European[124] and Spanish[125] BMT registries have also shown the benefit of IFN in similar cohorts of patients. Moreover, in order to improve the duration of response some groups[126] have combined IFN and dexamethasone, due to the apparent synergism of these two drugs.[68,84] In addition bisphosphonates can also be attractive drugs for MRD eradication, due to their possible anti-tumor activity.[127] Other experimental strategies to reduce the incidence of relapses after autologous transplantation are being investigated and include: 1) the use of cyclosporine to induce a GvHD-like process in an attempt to generate a graft-versus-myeloma effect,[96,128] induction of a T-cell immune response against idiotypic determinants on the myelomatous cell clone, or vaccination using autologous dendritic cells pulsed *ex vivo* with tumor-specific idiotypic protein.[129,130]

Double transplants

The favorable results and low toxicity of PB-SCT have stimulated the search for new transplant programs in an attempt to increase the response rate and to reduce the relapse rate. The feasibility of using two courses of myeloablative therapy was first demonstrated in high-risk refractory MM patients,[106,131] and several double transplant programs were subsequently activated for newly diagnosed MM patients. The widest experience in this field has been accumulated by Barlogie *et al.* at the University of Arkansas[102] and is based on over 500 patients and a *total therapy program* including: three non-cross-resistant induction regimens (VAD x2, HD-CTX + GM-CSF with subsequent PB stem cell collection and EDAP) followed by a first transplant with melphalan 200 mg/m^2 and a second transplant with melphalan 140 mg/m^2 + TBI or again melphalan 200 mg/m^2. The updated results reported in December 1997 at the ASH meeting[131] showed that 71% of enrolled patients (231 subjects) proceeded to the second transplant within 5 months. The treatment related mortality was 7%. The CR rate increased from 15% at the end of induction to 29% and 38% after the first and second transplant, respectively. The median PFS and OS in patients receiving the two transplants was 42 and 65 months, respectively. From multivariate analysis the occurrence of two transplants emerged as the most important prognostic factor, even more relevant than cytogenetics.

The Spanish co-operative group GEL/TAMO[132] use the same regimen for the first transplant, but cyclophosphamide, BCNU and VP16 for the second. Out of 42 patients, 85% achieved CR with OS of 54+ months and only 5% toxic deaths.

The EBMT[124] has collected 79 patients who completed two transplants and compared them with a cross-matched series of patients who received a single transplant. The CR rate was slightly better in the double transplant group (65% vs. 49% p=0.01) as was the median PFS (38 vs. 24 months, p=0.01). The OS for patients receiving double or single transplants was

71% vs. 47% at 4 years post-transplantation (p=0.16).

At present the IFM group[133] is conducting a randomized trial comparing, after 3-4 cycles of VAD, single transplant (melphalan 140-TBI) with double transplant (melphalan 140 mg/m^2 in the first procedure and melphalan 140-TBI in the second). Four hundred untreated MM patients have been enrolled and a partial analysis of the first 200 patients with a median follow-up of 2 years shows no differences in CR rate (32% vs. 33%), EFS (54% vs. 57% at two years) or OS (71% vs. 67% at two years).

Source of stem cells, mobilization schemes and number of CD34 cells

The issue of the optimal source of stem cells – bone marrow or peripheral blood – is not a subject of debate since the use of peripheral blood has been adopted universally. The advantages of PB are: i) the numbers of tumor cells are lower in PB than in BM,[134-137] although circulating clonotypic cells have been detected by PCR and immunophenotyping and ii) engraftment is more rapid and consequently transplant related morbidity and costs are lower.[138-140] This fact was confirmed at the 1997 ASH meeting by the *French Intergroup*[123] through a randomized study comparing BM (78 cases) and PB (84 cases). PBSCT was associated with a significant reduction in the duration of aplasia and transfusion requirements, without impact on survival.

A more controversial issue is the optimal method for stem cell mobilization.[141] As shown in Table 3 the most common procedure includes the combination of high dose cyclophosphamide (HC-CTX) (2.5-7g/m^2) and G or GM-CSF.[142-146] The Spanish group has, however, recently demonstrated the efficacy of using G-CSF with no chemotherapy for stem cell collection with almost no toxicity.[125] Concordant with this latter data, the Arkansas group[147] has shown, through a randomized study, that although the combination of HC-CTX with G-CSF generated a higher number of CD34 cells as compared to only G-CSF, there was no difference in the number of patients from whom sufficient numbers of stem cells for transplantation were collected. Moreover, in the HC-CTX arm a significantly higher toxicity (neutropenia and anemia) was observed, resulting in higher costs for the procedure. Demier *et al.*[148] reported that the combination of CTX (4 g/m^2) and etoposide (200 mg/m^2/day, 3 days) with G-CSF (10 mg/kg/day) is superior to CTX plus G/GM-CSF or G-CSF alone. In addition, they observed that a higher dose of G-CSF (16-32 µg/kg/day) can be useful in MM patients failing an initial mobilization regimen. There is now clear evidence that the duration of previous chemotherapy, exposure to alkylating agents or nitrosoureas, or prior radiotherapy are important predictors of PBSC yield.[56,148] Accordingly, our strategy is to reserve combination treatments for patients heavily pre-treated or for cases in which CD34 selection is planned, and to use G-CSF alone for the remaining patients.

The number of CD34$^+$ cells necessary to ensure engraftment varies depending on both the method used for CD34 quantification and the clinical setting. In our experience the figures are usually overestimated because the CD34 counts are not restricted to the CD34$^+$ cells with high intensity of fluorescence although these are probably the most important for engrafment.[149] Moreover, Tricot *et al.*[118] reported that patients previously treated for long periods (>2 years) require double the number of CD34$^+$ cells to ensure a stable engraftment (5×10^6 CD34 cells/kg).

Conditioning regimen

A major goal for transplantation is to identify the myeloablative therapy that best combines low toxicity with high anti-tumor effect. The most widely used schemes include: 1) high dose melphalan (200 mg/m^2) as a single agent or 2) combination of total body irradiation (TBI) (800 to 1350 cGy) associated with melphalan (140 mg/m^2). The benefit of adding TBI is not clear according to the published data, which often proves to be somewhat contradictory.[110,116,118,142,150-152] For instance, in 1993, the Arkansas Group suggested that addition of TBI increased the efficacy of melphalan,[150] while two years later the same group reported a slight benefit for patients conditioned with melphalan alone, particularly in terms of a lower toxicity.[110,118] Goldschmidt *et al*.[151] have shown that the rate of CR or PR is not significantly different upon using TBI+HD melphalan or HD melphalan alone. Interestingly, at the European registry it was found that the use of TBI is associated with poor outcome.[152] In double transplants the conventional scheme includes the use of high dose melphalan in the first transplant and TBI plus melphalan in the second.[116,142] Nevertheless, an interesting recent report presented at the 1997 ASH meeting by the Arkansas group,[153] compared melphalan 200 mg/m^2 with melphalan-TBI or melphalan-cyclophosphamide as conditioning regimens for the second transplant in patients who are already in PR after the first transplant. Results indicate a significant benefit in terms of OS and EFS for patients treated with melphalan-200. The lack of radiotherapy facilities at some centers will hamper the design of large randomized trials which would be the only appropriate way to clarify the role of TBI in the preparative regimen.

Several alternative regimens are being investigated in MM. Since busulfan may have a similar activity to TBI for myeloablation, regimens combining melphalan and busulfan[154,155] have been designed, showing an efficacy similar to high dose melphalan, although the series of patients and follow-ups are too short to reach firm conclusions. Other reported regimens[156-160] are shown in Table 4 and include the combination of thiotepa, busulfan and cyclophosphamide;[156,157] dacarbazine, cyclophosphamide, carmustine and etoposide;[158] busulfan, and melphalan;[154,155] busulfan,

cyclophosphamide and TBI[159] or carboplatin, cyclophosphamide and etoposide.[160] Probably one important task for the large co-operative groups will be to investigate the optimal ablative regimen through appropriate randomized trials.

Tumor cell contamination

The two major obstacles when comparing autologous with allogeneic SCT are the possible contamination of stem cells with myelomatous cells and the lack of graft vs. myeloma effect. There is evidence that autologous harvested cells, obtained from either BM or PB, are contaminated by myelomatous cells (including both PC and clonal B lymphocytes). Thus, at the *VI Workshop on Multiple Myeloma*, Corradini *et al.* confirmed previous studies[135] showing that using allele-specific oligonucleotide (ASO)-PCR, 96% of the collections (24 out of 25) were contaminated by clonal tumor cells. Using IgH fingerprinting, which is around two logs less sensitive than other PCR techniques, Bird *et al.*[161] found contamination in 60% (14/32) of the samples. In line with these observations, both Witzig *et al*.[162] and Pope *et al*.[163] have reported contamination by immunologic methods in 60% of the cases. As previously mentioned, studies comparing PB vs. BM collections have shown that the former are usually less contaminated by tumor cells (from 2 to 2×10^5 fewer myelomatous PCR+ cells, median 100 times less).[136,137] Accordingly, PB would be the source of choice for stem cell harvest. However, questions regarding the influence of the mobilization regimen and time of collection still need to be clarified. It has been suggested that the number of malignant cells increases in the last days of apheresis (e.g. days 5 and 6) while the highest proportions of normal hematopoietic progenitor cells are collected early during apheresis (within the first two days),[164] but studies in this field are still scanty.

Because tumor cells are present in virtually all PBSC harvests, it is conceivable that autografted myeloma cells contribute to relapse after auto-transplants. In order to reduce contamination, two possible approaches can be used: 1) depletion of malignant cells with monoclonal antibodies (MoAb) directed against antigens expressed on the malignant cells in which the MoAb are conjugated with complement, immunotoxins or magnetic beads, and 2) positive selection of $CD34^+$ cells. The first approach is rather complicated since the myelomatous clone includes a spectrum from mature PC, identified by markers such as CD38 and CD138, up to immature B cells that express the CD19 and CD20 antigens. Accordingly, several cocktails of MoAb have been used: anti CD10, CD19, PCA-1 or anti-CD10, CD19, CD20, CD23 and although they were able to produce a tumor reduction of at least 3 log, PCR analysis confirmed the persistence of residual clonal cells within autografts.[165,166]

Regarding CD34 selection, although Pilarsky's group reported that the $CD34^+$ cell fraction may harbor a small subset of clonal myelomatous cells,[167] most studies indicate that $CD34^+$ cells are not part of the malignant clone as assessed by PCR or immunophenotypic analysis[135,164,168-170] and therefore their selection would offer an adequate purging strategy. Preliminary studies showed that $CD34^+$ selection led to between 1.5 and 6.0 (median 3.1) log reduction in tumor cell contamination.[126,171] Moreover, it has been shown that in half of the patients who undergo CD34 selection, tumor cells become undetectable according to sensitivity of the PCR-assay.[171] This positive result has stimulated several trials using this approach both in Europe and USA, but the initial impression is that the impact of $CD34^+$ selection on disease outcome will be marginal, although definitive results are still pending. If these observations are finally confirmed, they would indicate that relapses in MM are mainly due to the lack of efficacy of the myeloablative regimens in eradicating the malignant

Table 4. Other conditioning regimens.

Author[ref]	No.	Type of diseasae	Conditioning regimen	% CR	Global response	Toxic deaths	Progression free survival			Overall survival		
							Median (months)	at 1 yr.	at 3 yr.	Median (months)	at 1 yr.	at 3 yr.
Reece[154]	8	untreated	Bu+MF+Purged BM	25%	88%	12%	NR	100%	–	NR	88%	–
Dimopoulos[157]	40	various	Thiotepa+Bu+Cy	25%	65%	13%	NR	72%	–	NR	–	–
Alegre[155]	24	responsive	Bu+MF	58%	38%	4%	NR	74%	–	NR	100%	86%
Bensinger[179]	63	44 refractory 19 responsive	Bu+Cy±TBI	30%	66%	25%	–	–	30%	–	–	46%
Schiller[174]	37	responsive	Bu+Cy+CD34 selection	15%	87%	0%	67% at 1 yr.			68% at 1 yr.		
Adkins[158]	31	relapsed or refractory	Cy+BCNU+VP16+DTIC	52%	68%	18%	–	42%	–	–	70%	–
Long[160]	34	responsive	Cy+VP16±TBI or BCNU	34%	87%	6%	–	–	26%	–	–	36%

Bu: busulfan; MF: melphalan; BM: bone marrow; Cy: cyclophosphamide; TBI: total body irradiation; DICT: dacarbazine.

clone, and not to the graft contamination that was theoretically eliminated by the CD34+ selection. Moreover, most, if not all autografted patients remain PCR+ after autologous-SCT,[135,172] while molecular remission, assessed by IgH fingerprinting, has been reported with double transplant programs,[116] which again points out the important role of chemotherapy for eradicating residual tumor cells. Interestingly, PCR negativity can be achieved by allogeneic BMT[173] which suggests that the graft-versus-myeloma effect may play an important role in eliminating minimal residual disease and therefore immunization strategies that would mimick this effect following autografting should be actively investigated.[128,129]

Finally, when considering CD34+ selection it is important to balance the potential therapeutic benefit of tumor cell depletion against the delay observed in hemopoietic[174] and particularly immune recovery.[175]

Prognostic factors

When discussing a new therapeutic option it is always important to have models to predict which patients are more likely to benefit from its use, thus avoiding the financial and emotional burden imposed on those unlikely to respond. In this area, it would also be desirable to have predictive models to individualize the choice between chemotherapy and autologous SCT in MM patients as well as between allogeneic and autologous transplants in young patients.

An obvious question when using high dose chemotherapy is whether prognostic factors differ from those identified under conventional chemotherapy. Preliminary data suggest that they are similar. The Arkansas University group[150,176] initially identified low β_2M levels, low CRP, less prior therapy, and Ig isotype other than IgA as independent favorable variables for overall survival (OS) and disease free survival (DFS). In addition, age <50 years, ECOG <2, and stages I/II were also positive factors, but only in univariate analysis. In a more recent study, the same group showed that abnormalities in chromosomes 11q and 13 were associated with a poorer outcome in patients receiving tandem autologous transplants: EFS (21 vs. 50 m. p=.0001) OS (34 vs. +62, p=.001).[120,177] In a landmark analysis, CR was a significant favorable parameter for both EFS and OS (p=.0001). At the EBMT,[178] it was found that stage I, to be in CR before transplant, one line of therapy, age < 45, and low β_2M were all favorable factors. In the experience of Bensinger *et al*.[179] low β2M levels, less than 3 years from diagnosis to transplant, fewer cycles of chemotherapy and absence of previous radiotherapy were identified as favorable prognostic factors. Similar results were obtained in the Spanish registry:[125] longer overall survival was associated with one line of therapy, response status pre-transplantation and use of IFN maintenance. Interestingly, neither the use of TBI in the conditioning regimen nor the use of growth factors alone for stem cell mobilization had prognostic influence. Controversial results exist on the influence of LI, since Boccadoro[180] suggested that its adverse effect disappears with high dose therapy, while at the Mayo Clinic, Gertz *et al.*[181] have recently shown that a high LI as well as the presence of circulating monoclonal PC in the blood stem cell harvest were all associated with shortened survival after transplantation. Interestingly, in both studies, β_2M retained its adverse prognostic influence. Other new prognostic factors such as IL-6, sIL-6R or CRP are under evaluation in ongoing studies and may also help to identify the patients most likely to benefit from autologous transplant.

Allogeneic transplantation in multiple myeloma

Allogeneic BMT is an attractive option in MM patients, since it offers the possibility of using myeloablative therapy followed by rescue with healthy stem cells which have not been exposed to chemotherapeutic agents and are free of contaminating tumor cells. In addition, the potential graft-versus-myeloma effect of allogeneic cells may contribute to the elimination of residual tumor cells that have been resistant to the conditioning regimen, increasing the chances of cure in MM patients.[182]

Clinical results with allogeneic bone marrow transplantation

Since MM frequently affects patients of advanced aged (median age around 65 years) and only 25-35% of patients have a related donor, allogeneic BMT can only be offered to a low percentage of patients with MM, not more than 10%. Consequently, the number of cases so far reported is still relatively small. However, through national and international registries, the results of three series including more than one hundred transplanted patients have been reported (Table 5).[110,183-195] Although the marked heterogeneity of these series makes the evaluation of the results difficult, it is remarkable that all these series show a high transplant-related mortality (TRM), (>40%). Some centers have recently reported a TRM as low as 8% (Table 5), but in the two largest series from single centers, Seattle[186] (80 patients) and Little Rock[185] (97 patients), there is an early mortality (within the first 60-90 days after transplantation) of 22% and 26%, and the overall TRM is 54% and 57%, respectively (Table 5). The major causes of TRM are bacterial and fungal infections, interstitial pneumonitis and acute GvHD, which in the experience of the EBMT were responsible for 18%, 17% and 10% of the deaths, respectively.[196,197] In addition, studies with long follow-ups have shown that chronic GVHD is also an important factor.[183,185,186]

Efforts have been made to establish whether the conditioning regimen could be a reason for this high toxicity. It has been suggested that preparative regimens including TBI are associated with higher TRM.[185]

Table 5. Sibling HLA-matched allografts for multiple myeloma.

Group ref	Patients	Regimen	Early deaths*	Transplant related deaths	Complete remission°	Progression Free survival	Overall survival
IBMTR[110]	208	various	41%	–	35%	35% at 3 yr.	40% at 3 yr.
EBMT[183]	189	Cy + TBI ± MF	20%	41%	49%	30% at 3 yr. 20% at 5 yr.	38% at 3 yr. 30% at 5 yr.
SFGM[184]	137	various	–	43%	51%*	33 months	28% at 5 yr.
Little Rock[185]	97	various	26%	54%	26%	12% at 3 yr.	18% at 3 yr.
Seatle[186]	80	Bu + Cy ± TBI	22%	57%	38%	20% at 4.5 yr.	24% at 4.5 yr.
Boston[187]	52	MF + TBI	8%	8%	29%	40% at 3 yr.	20% at 4 yr.
Bologna[188]	62	Bu + Cy TBI + MF	18%	42%	34%	38% at 5 yr.	15% at 8 yr.
Vancouver[189]	26	Bu + Cy ± MF Cy + TBI	19%	35%	56%	40% at 3 yr.	47% at 3 yr.
Royal Marsden[190]	24	MF or CY + TBI Bu + Cy	46%	54%	42%	46% at 2 yr.	42% at 3 yr.
Baltimore[191]	23	Bu + Cy	22%	26%	61%	43% at 3.5 yr.	48% at 3 yr.
Toronto[192]	22	Cy + TBI Bu + Cy	27%	54%	45%	21% at 3 yr.	30% at 3 yr.
Nottingham[193]	13	TBI + MF	15%	23%	78%	69% at 3 yr.	69% at 3 yr.
Wayne[194]	10	Cy + TBI	20%	20%	40%	–	42% at 3 yr.
Halifax[195]	10	Bu + Cy + MF	10%	30%	60%	50% at 2 yr.	60% at 2 yr.

*Bu: busulfan; MF: melphalan; Cy: cyclophosphamide; TBI: total body irradiation; *deaths occurred before 60 to 100 days post-transplantation; °percentages calculated over the total number of patients (including those considered as not evaluable by the authors).*

However, in the Seattle experience, the frequency of veno-occlusive disease was higher in patients who received busulfan and cyclophosphamide than with other regimens which usually included TBI.[198]

Although the CR rate obtained in most series is relatively high (26 to 78%) (Table 5), most patients eventually relapse. Thus, in the EBMT registry the predicted progression free survival for those patients achieving CR after allogeneic BMT was only 34% at 6 years, with only nine out of 162 patients remaining in continuous CR more than 4 years after transplantation.[196] The results from other registries are similar (Table 5), as are the results from single center reports, in which PFS of the whole series ranges from 20% at 4.5 years in Seattle[186] and Boston[187] to 12% at 3 years in Little Rock.[185] With those relapse rates, together with the high TRM, it is not surprising that the overall survival (OS) is relatively short. Thus, in the EBMT registry, the reported OS is around 30% at 5 years (28% at 7 years),[183] and seems to be similar in single center studies, ranging between 18% and 38% at three years (Table 5).

The information about syngeneic transplantation in MM is scanty. The widest experience comes from Seattle,[199] where 11 patients were treated: two of them remain disease free at 9 and 15 years post-transplantation.

Reducing transplant-related toxicity

As we have previously stated, in the past years a high TRM has been reported. This could be mainly due to poor patient selection and late timing of the procedure. GVHD and infections are also important factors contributing to TRM which deserve further efforts in order to reduce the toxicity of the procedure.[200-202]

In other disorders it has been shown that the use of growth factors (either for the mobilization of donor stem cells or for reducing the aplasia period) is associated with a reduction in the number of neutropenic days and the need for antibiotics.[203,204] Moreover, the employment G-CSF has allowed the development of new strategies for allografting, such as the use of allogeneic peripheral blood stem cells (allo-PBSC) obtained by leukapheresis after stimulation of the donor progenitor cells.[205] The Italian group transplanted ten MM patients with allo-PBSC, who took a median of 13 days to recover 0.5 granulocytes $\times 10^9$/L, with 10% of deaths before day +100 and 20% total TRM;[206] the short recovery time contributed to a reduction in the risk of serious infections.

Ex vivo treatments of the stem cells harvested can also be of value in order to reduce transplant related toxicity. In the series from Little Rock,[185] T-cell depletion was associated with a favorable outcome. In an update of their series,[165,207] the Dana Farber group in Boston reported a TRM of only 8% in 52 MM

patients transplanted with allogeneic T-cell ($CD6^+$) depleted cells.[187] These encouraging results support the use of *ex vivo* manipulations of allogeneic stem cells in MM, not only through T-cell negative selection but also through $CD34^+$ positive selection, which also leads to a T-cell depletion. However, the PFR was relatively low in this series (20% at ≥4 years), which may be due to a partial loss of the graft-versus-myeloma effect, indicating that a balance between reduction of GVHD and maintenance of GVM effect should be achieved.

In summary, we now have several tools which are expected to decrease the allo-BMT toxicity, and make this therapeutic approach more feasible.

Reducing the risk of relapse (graft-versus-myeloma effect)

Several clinical reports have demonstrated that patients with MM after allogeneic BMT can achieve clinical remissions using donor lymphocyte infusions (DLI). This has been the definitive proof of the existence of a graft-versus-myeloma (GVM) effect.[208-211] DLI were able to induce clinical remissions in 4 allografted patients who had relapsed, even in a case with extramedullary plasmacytomas.[209-211]

These findings have prompted several trials using DLI to treat, or even to prevent, relapses in MM.[187,212,213] However, it should be taken into consideration, that in acute leukemias DLI were associated with an increase in the incidence and severity of GVHD,[126,127] and, as previously mentioned, GVHD is a major lifethreatening complication in MM. Nevertheless, there is already evidence that suggests a different mechanism for GVL and GVHD, which makes it possible to seek out strategies that could reduce GVHD without affecting the GVL effect, such as $CD8^+$ T-cell depletion. Thus, the group from the Dana Farber Cancer Institute,[187] has treated seven MM patients, who were in relapse after allogeneic $CD6^+$ T-cell depleted BMT, with donor $CD4^+$ cells ($CD8^+$ T-cell depleted). One patient died due to progressive disease 3 weeks after DLI and six are alive after a mean of 39 weeks from DLI (10-72 weeks). In five of them, the myeloma responded, including three complete remissions. Of the four responders, one did not develop GvHD while the other three had cutaneous GvHD, and two of them also had liver involvement. These results illustrate that using appropriate T cell selection, the GVM effect can be preserved while the GvHD is partially abrogated.

An additional strategy for improving the outcome in MM patients after allogeneic BMT is to a induce specific immune response against tumor cells in order to treat the minimal residual disease which may remain after transplantation. Kwack *et al*.[216] immunized a donor against the patient's idiotype protein and were able to transfer this donor immunity to the patient at the time of allografting. The effect was mainly evidenced through the recovery of a $CD4^+$ T-cell line in the patient derived from the donor (demonstrated by *in situ* hybridization), which proliferated specifically to idiotypic protein used as an immunogen.

Finally, other strategies to avoid relapses after allogeneic BMT, such as immunotherapy or maintenance treatment, can also be applied to MM. In this way, the EBMT registry has already provided data which would support the use of interferon as maintenance therapy in MM after BMT.[217]

These attractive new strategies have provided the basis for future experiments directed towards inducing a GVM specific effect which could reduce the high relapse rate still present in MM after allo-BMT.

Prognostic factors for allografted MM patients

Due to the high toxicity of allogeneic BMT, identification of prognostic factors associated with favorable outcome would be very useful in order to identify those patients who could be cured or who could obtain a real benefit from such a therapeutic option. To this end, several studies have been carried out. The largest is that of the EBMT registry,[196] in which favorable pre-BMT variables for both response to and survival after BMT were female sex, IgA myeloma, low serum β_2-microblobulin, stage I at diagnosis, having received one line of previous treatment and being in CR prior to BMT. In contrast, no significant differences were seen regarding age (≥40 or <40 years), time from diagnosis to transplantation or conditioning regimen. In the Seattle series,[186] the following adverse prognostic factors were recognized: transplantation more than one year after diagnosis, β_2-microglobulin >2.5 mg/L, female patients transplanted from male donors, having received more than eight cycles of chemotherapy, and Durie-Salmon stage III disease at the time of BMT. The group from Little Rock has also recently published their results from 97 MM allografted patients.[185] They found that a poor overall survival was associated with a LDH >190 U/L pre-BMT and total body irradiation used in the conditioning regimen. These findings seemed to be due to the association of high LDH values with resistant disease and to the toxicity of TBI. A short event-free survival was associated with LDH >190 U/L and strategies in which graft T-cell depletion was not included, while a poor response to the therapy was related to β_2-microglobulin >2.5 mg/L and LDH >190 U/L. Interestingly, the use of prior autografts did not result in poorer results after the allo-BMT, which could be a good reason for indicating first an auto-SCT and then, if relapse occurs, proceeding with allogeneic BMT.

Allogeneic or autologous stem cell transplantation?

In patients under 55 years of age with a compatible sibling donor, a challenging decision is whether to choose an autologous or allogeneic transplant. As we have seen in this review, the progression free and

overall survivals are not very different between allogeneic and autologous stem cell transplantation in MM, and in fact could be even worse in the former group. Nevertheless, up to date there have been no prospective, randomized studies comparing both strategies. The EBMT registry published a retrospective, case-matched, comparative study between 189 allografted and 189 autografted patients.[183] In this study, a lower relapse rate was found for allo-BMT compared to auto-BMT, which resulted in a trend towards better PFS, but this effect did not compensate for the higher TRM found in the former group (41% vs. 13%, p=0.0001) and the median OS was finally longer in the auto-BMT group (34 vs. 18 months, p=0.0003). However, considering only those patients who were alive more than one year post-transplantation (excluding the majority of toxic deaths), the allo-BMT achieved a better progression-free survival (p=0.02) and a trend towards better long-term survival (p=0.09). More recently, the group from Little Rock also compared autologous versus allogeneic BMT in a retrospective analysis of two selected matched populations, including 40 patients in each one.[218] Again, the survival was superior in the autologous group due to the TRM, which was 33% for the allografts and 5% in the autografts (p=0.003), without any difference in the CR rate between groups (35% auto, 43% allo; p=0.65). However, we should not forget that in these two studies, the allogeneic transplantations were usually performed without the above mentioned alternative approaches to reduce the toxicity of the grafts. Nevertheless, in the series of the Dana Farber group, although the TRM was significantly reduced upon using T-cell depleted products,[187] this did not translate into a significant benefit in PFS and OS in comparison with auto-SCT. Based on these results, it could be argued that the impact on survival of using uncontaminated allogeneic stem cells and the GVM effect is apparently marginal, and the counterbalance of the high TRM of allogeneic BMT would be an important argument in favor of autologous instead of allogeneic transplantation. However, it is important to remember that while PCR negativity can be achieved by allogeneic BMT, most, if not all autografted patients remain PCR+. At present, 10 to 20% of patients undergoing allogeneic transplantation are long survivors with no evidence of disease and are probably cured.

Still, all these findings are not enough to confirm which approach is better in MM, and the answer to this question will only be obtained after prospective randomized studies which compare the two sources of stem cells directly, particularly when using specific protocols to reduce GVHD.

Supportive therapy

As we have already discussed, the most important factor for prolonging survival in MM is a successful treatment that reduces the malignant tumor clone as much as possible. Nevertheless, it has become evident that some disease complications, which may be the first signs heralding the presence of MM and which may have an important prognostic impact, require other specific therapeutic measures.

Anemia

In most patients anemia usually improves when the myeloma responds to chemotherapy. If this is not the case, there are have two possibilities: red cell transfusion or erythropoietin (EPO). The first choice has several inherent risks: viral transmission, allergic reactions and iron overload. EPO increases BM erythroid function by stimulating the expansion of erythroid progenitor cells and decreasing BFU-E and CFU-E apoptosis. MM patients may have either insufficient EPO production or a diminished proliferative response of erythropoietic cells to normal or even high levels of EPO. These latter patients are unlikely to respond while the first group, which is associated with low EPO levels, will probably benefit from exogenous EPO replacement.

Several clinical trials have shown the value of recombinant human EPO in MM patients.[219-223] The response rate (assessed by an increase in Hb level of at least 2 g/dL and reduction of red-blood-cell transfusions) ranges between 52% and 80%. The usual dose is 5,000-10,000 U/day or 150-300 U/Kg three times weekly. Interestingly, in patients with normal platelet counts (good residual hematopoiesis), the dose of EPO required is usually lower. In responding patients, the dose of EPO can be reduced for maintenance treatment but disease progression and infectious episodes lead to a loss of EPO sensitivity. It should be remembered that iron supplementation is generally necessary during EPO treatment since iron depletion usually occurs.[224]

In spite of the benefits derived from EPO treatment, the relatively high price of EPO means that it is important to set criteria for optimizing clinical decision-making. In most studies the criteria for predicting response are coincidental.[219,220,225] Accordingly, in the algorithm derived from Cazzola's study,[219] patients with an EPO serum level <50 mU/mL at diagnosis, or those who show an increase in the Hb levels >0.3 g/dL after two weeks of treatment, have a probability of response of 72% and 80%, respectively.

Renal failure

One of the most important prognostic factors in MM is renal insufficiency. Renal failure in MM is often multifactorial but urinary light chain excretion and/or hypercalcemia are the most important factors, present in 90% of cases. Other causes include: amyloidosis, infiltration of kidney by PCs, hyperuricemia, infections, dehydration and the use of nephrotoxic antibiotics.[226] Moderate renal failure can generally be reversed by the combined use of active hydration (3-5 L/day), sodium bicarbonate, diuretics and allopurinol together with chemotherapy.[227] In

these patients, it is important to avoid nephrotoxic cytostatic drugs and antibiotics. In MM patients with severe renal failure (2-10% of cases), dialysis employed simultaneously with chemotherapy has resulted in a marked improvement in the renal function of some of the patients, to the point where dialysis can be discontinued in some cases. However, in most of these patients, long-term dialysis will be required.[228] This should be offered to patients with severe irreversible uremia in whom the myeloma has responded to chemotherapy, but not to patients with progressive MM. In a recent study, the factors associated with reversibility of renal failure were: serum creatinine level (< 4 mg/dL), amount of proteinuria (< 1 g/24 hours) and the presence of hypercalcemia (≥ 11.5 mg/dL).[229]

Bone lesions and bisphosphonates

The management of bone disease depends on the severity of the lesions and sometimes requires a multidisciplinary approach with collaboration of orthopedics and/or neurosurgeons.[227] Physical activity should be encouraged in order to avoid increased osteoporosis. Analgesics must be adapted to the degree of pain, from paracetamol up to morphine, and in severe back pain, due to vertebral compression fractures, they can be combined with non-steroid anti-inflammatory drugs and/or muscle relaxants. External spine supports (corsets, braces) may help patients with lumbar or thoracic vertebral compression fractures. Radiation therapy has two major indications: 1) relief of severe localized pain and 2) treatment of spinal cord compression. In the first case it is administered at a dosage of 3000cGy over 10 days. Radiotherapy may also be required in areas of extensive osteolysis at high risk of pathological fracture (e.g. femur or pelvis). In cases with paraplegia or signs of spinal cord compression, emergency radiographic examinations (MRI) should be performed in order to initiate radiotherapy immediately (< 24 hours) together with high dose steroids (pulses of dexamethasone at a starting dose of 25 mg every 6 hours during the first day, followed by a decreasing dose schedule). This avoids the need for laminectomy in most cases. This latter option should be reserved for patients who display severe acute compromised spinal cord function as the presenting feature of MM and whose diagnosis is uncertain. Intramedullary fixation with a nail followed by radiotherapy may be of value for fractures of long bones.

In the management of bone disease in MM, bisphosphonates have emerged as one of the most attractive therapeutic tools. Information on clinical trials with three of these compounds (etidronate, clodronate and pamidronate) is already available, but several other new and more potent bisphosphonates (alendronate, ibandronate and zolendronate) have already been generated. Etidronate has not shown a significant clinical benefit.[230,231] In a recent study, 232 clodronate has shown efficacy in the prevention of non vertebral fractures but others have only observed a marginal benefit.[233-236] It should be noted that the drug was taken orally and this may have resulted in a low bioavailability. By contrast, in a double blind placebo controlled trial including 377 patients, Berenson *et al.*[127] showed that pamidronate – 90 mg once monthly in a 4 hour iv. infusion for 21 months – led to a significant reduction in skeletal events (pathological fractures, radiation therapy requirement, hypercalcemia or spinal cord compression), a reduction in the proportion of cases with poor performance score and a significant decrease in bone pain. Moreover, in those patients who had received two or more lines of therapy, pamidronate treatment resulted in a significant prolongation in survival (20 vs. 14 months).[237] This benefit in survival may be related to the IL-6 inhibition induced by bisphosphonates[238,239] as well as by their possible apoptotic effect not only on osteoclasts but also on myeloma cells.[240-241]

Infections

Hospitalization and empirical treatment with broad-spectrum i.v. antibiotics should be immediately indicated for febrile granulocytopenic patients (< 500 granulocytes). Nephrotoxic antibiotics, particularly aminoglycosides, should be avoided, in favor of other alternatives. In patients with recurrent Gram-positive infections penicillin given prophylactically (daily oral dose) may be useful. Trimethroprim-sulfamethoxazole during the first two months after diagnosis has proved to be useful but toxic.

The use of pneumococcal vaccine remains controversial. The defective antibody response of MM patients and the frequent involvement of other organisms different from *S. pneumonia* are considered to be arguments against its use. However, considering its low toxicity, low cost and possible benefit for some patients, pneumococcal vaccine should be offered to all patients, but they should be informed of their potential inability to respond to it. Several studies have reported a decrease in the incidence and severity of infections in MM patients receiving prophylactic intravenous immunoglobulins. In a recent randomized, double-blind, trial conducted in 82 patients in plateau phase MM, Chapel *et al.* (1994) showed that monthly infusions of i.v. Ig (0.4 g/kg) significantly reduced the incidence of episodes of septicemia and pneumonia (0% vs. 24%) and serious infections (19 vs. 38 episodes along 450 patients-months on i.v. Ig). In our opinion, despite these results, due to its high cost, its role in prophylaxis of infection should be restricted to patients with very low Ig levels and recurrent infections.

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JFSM was the co-ordinator of the article and wrote the autologous transplant and supportive therapy parts of the review. JB was responsible for conventional treatment section and RG-S

for the allogeneic transplant one. All three authors reviewed the complete manuscript which was sent in its final form by JFSM. The authors thank Mark Anderson for his technical assistance.

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