Bone marrow transplant in multiple myeloma

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Abstract

Multiple myeloma is a common disease among older people, accounting for 10% of all hematologic cancers. Its causes are unknown and its extent, clinical course, complications and sensivity to drugs vary widely. Conventional chemotherapy is palliative: less than 5% of patients survive for ten years, and of these, almost all suffer multiple relapses. This review focuses on the results of high dose chemotherapy in the treatment of multiple myeloma, with bone marrow transplant or peripheral blood stem cell support.

Key words: multiple myeloma, bone marrow transplant, intensive chemotherapy, allogenic bone marrow transplant, autologous bone marrow transplant, peripheral blood stem cells.

Introduction

Multiple Myeloma (MM) is a B cell malignancy that affects mainly the elderly population aged between 60 and 65. This disease encompasses a wide range of clinical entities, whether localized or disseminated, mild or aggressive. Conventional therapy is essentially palliative rather than curative. Complete remission achieved through standard programs, including alkylating agents and glucocorticoids, occurs in 10% to 15% of patients with low tumor mass. The average survival time is three years, although 5% to 10% of patients may survive for ten years.[1,4,6]After the results obtained with the intensification of polychemotherapy, using bone marrow transplant as a supportive therapy in patients with other hematologic neoplasms that are usually considered incurable (e.g., some leukemias and lymphomas), controlled studies were begun, to assess the results of this approach in patients with MM. The aim of this paper is to show and, in some cases, compare the results published to date. Initially, a summary is presented of the "conventional" therapeutic approach that is recommended for these patients.

Intermittent cycles of melphalan-prednisone (MP) have been the first therapeutic choice since the 1960s, achieving a remission (defined as a reduction of serum paraprotein production by at least 75%, a reduction of Bence-Jones proteinuria by at least 95% and less than 5% plasma cells in the bone marrow) in approximately 40% of patients. The average duration of the cycle was two years, with an average survival rate of approximately three years. However, less than 10% of patients survived more than ten years, and there was no evidence of cure. Other treatments were then attempted, with the most studied polychemotherapy regimens being those that included vincristine-cyclophosphamide-BCNU-melphalan-prednisone (VBMCP) and alternating cycles of vincristine-melphalan-cyclophosphamide-prednisone and vincristine-BCNU-adriamycin-prednisone (VMCP/VBAP). A randomized trial comparing VBMCP and MP showed that the former was superior in producing objective responses – 72% versus 51%. Although the survival times were practically the same – thirty months versus twenty-eight months – because older patients with poorer general condition were less tolerant to VBMCP, the ability to maintain and produce better results in all other patients using VBMCP was unquestionable: A five-year survival rate of 26% versus 19%.

The VMCP/VBAP regimen proved to be similar to the VBMCP regimen in terms of producing objective responses, but the survival was higher.[2,6] The regimen that included vincristine-adriamycin-dexamethasone (VAD) was also administered as an induction treatment, and a 15% higher response was observed in relation to the regimens used up until then. Nevertheless, neither the remission time nor the survival time were very long. In general, two cycles of any of

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these regimens (VBMCP, VMCP/VBAP or VAD) were sufficient to determine whether MM was responding favorably, with the induction of this response usually being rapid.[2,4] Dexamethasone monotherapy regimens were also effective, but the VAD induced complete remission more frequently. Interferon-alpha was also used as monotherapy, and proved to be an important cytoreductive treatment in patients without prior treatment and with low tumor mass. Its association with conventional regimens - alkylating agents and glucocorticoids – appeared to increase the remission rate obtained, when comparing the results with those in the MP regimen. The survival rate was similar in both cases. Interferon-alpha rarely benefited cases in which the disease remained refractory or resistant several years after diagnosis. The only benefit from its use was the recovery of biologically active immunoglobulin production in some patients, with a consequent recovery of humoral immunity.[2,4,6]

It remained to be proven whether the maintenance treatment using interferon-alpha (3-5x106U subcutaneously three times per week) in patients who responded to the conventional therapy increased the survival rate, compared to those patients who did not receive any additional treatments. When compared with the MP regimen as a maintenance treatment, interferon-alpha proved to be a valid option, since the MP regimen caused secondary myelodysplasia and acute leukemia in 2% of patients.[2,6]

In patients with refractory MM, or those who suffered a relapse within one year, acceptable tumor cytoreductions were observed from the start of the VAD regimen. Dexamethasone at high doses was also effective, but VAD obtained more frequent remissions (in approximately 40% of cases). In patients who were resistant to the primary treatment, both VAD and dexamethasone induced remissions in 25% of cases[2,4]. In cases where there was resistance to VAD, the choices were very limited. It was known that some adriamycin-resistant cell lines had a MDR (Multidrug Resistance) phenotype, resulting from the deletion of the long arm of chromosome 7. The result was the efflux of vincristine and/or doxorubicin out of the neoplastic cells. In an attempt to reverse this effect, calcium channel blockers (namely, verapamil) were used, which annulled this effect *in vitro*. In a small study involving twenty-two VAD resistant patients, verapamil was used concomitantly, and five remissions were observed. Another alternative was the use of intravenous melphalan in doses five times higher than the conventional dose. A response was observed in a third of patients, with an average duration of four months.[2,4] Alexanian & Dimopoulos used high doses of cyclophosphamide (3g/m^2) with etoposide (900mg/m2) and GM-CSF (Granulocyte-macrophage colony stimulating factor) in 65 VAD resistant patients with MM. The response rate observed was 35%, with 6% early mortality and average remission of eight months.[2]

Until very recently, patients with MM were not subjected to increased chemotherapy doses, since most of them were elderly and usually in poor clinical condition. Allogenic bone marrow transplant (allo-BMT) seemed to be a promising approach only for younger patients. However, it had various limitations: the advanced age of most patients, as mentioned above, the lack of compatible donors, and the high mortality rate associated with the graft-versus-host reaction. These premises meant that taking age into account, only 20%-25% of patients with MM were potential candidates, and of these, only 30%-40% had a compatible donor. For most patients with MM, increasing the dose, with autologous bone marrow transplant (auto-BMT) support, appeared to be the only possible therapy for achieving better survival rates. The complete remission rate was lower, but the one-year disease-free survival time was as high as 85%. In addition, the associated mortality was much lower (less than 10%). A rational explanation for this type of therapy in a bone marrow-derived cell malignancy was based on the fact that only a small proportion of these cells were capable of self-renewal.

Allogenic transplant

Allo-BMT using HLA compatible donors appeared to be a promising method for the treatment of some patients with MM. In the largest series of patients reported, the complete remission rate was around 43%. Of these, 50% were alive and free of disease after forty-eight months. Compared to auto-BMT, allo-BMT also had the advantage of an absence of tumor cells in the graft that could be responsible for a relapse. On the other hand, one of the main disadvantages of this therapeutic approach was the peritransplant mortality, and the possibility of a graft-versus-host reaction.[3,5,6,7,8]

In October 1993, Oscar F. Ballester published a review article summarizing the results obtained from

TABLE I

Characteristics of patients submitted to allo-BMT

Group	No. of patients	Average age	Phase III	Refract. D.	C/TBI	S/TBI
Italian[8] – 1991	27	41	75%	48%	70%	30%
EBMTG[7,8] – 1991	90	42	67%	54%	90%	10%
SEATTLE[8] – 1992	20	39	75%	50%	0%	100%

TBI – total body irradiation; Refract. D. – refractory disease; EBMTG – European Group for Bone Marrow Transplant.

TABLE II

Results of patients submitted to allo-BMT

Group	No. of patients evaluated	CR RT	CR Time (months)	Survival (months)	Forecast. S. => CR (months)
Italian – 1991	19 (70%)	58%	60	43% (24m)	63% (84m)
EBMTG[7] – 1991	67 (74%)	58%	48	50% (26m)	75% (72m)
SEATTLE – 1992	15 (75%)	80%	?	36% (16m)	?

CR – complete remission; RT – rate; Intend. S. – Intended Survival; EBMTG – European Group for Bone Marrow Transplant.

137 patients.[8] The clinical characteristics, conditioning regimen and results are show in *Table 1 and 2*.

The data related to patients with poor prognostic factors at the outset:

- Phase III in 66%-75% of cases;
- Previous polychemotherapy;
- 50% of refractory patients at the time of bone marrow transplant.

The conditioning regimens consisted in mono or polychemotherapy associated with Total Body Irradiation (TBI) in 100 of the 137 patients. The use of TBI was associated with a higher frequency of interstitial pneumonia.

16% (n=23) of the patients died due to complications related to myelosuppression. Only 73% (n=101) of the patients could be evaluated after the bone marrow transplant (*Table 2*).

It was observed that 61% of the patients evaluated had complete remission; patients with previous chemo-sensitivity had more frequent remission. The average survival was similar in the Italian and EBMTG groups. The follow-up time for the Seattle group was not significant at the time of publication.

The primary causes of death in the patients evaluated were graft-versus-host reaction and interstitial pneumonia. In only ten patients (10%) was the cause of death progression of the disease or relapse.

Generally, the results indicated that the therapy with high dose chemotherapy associated with allo-BMT were capable of inducing complete remission in a significant number of patients with MM. Even taking into account the associated mortality, this type of therapeutic approach appeared to determine a higher response rate, longer survival and longer disease-free interval.

In terms of the most suitable timing, it was observed that in general, delaying allo-BMT led to poorer results, due to the presence of larger tumor mass and increased resistance to chemotherapy. On the other hand, greater tolerance, more tumor control and fewer complications were observed in the patients transplanted earlier on.[5]

In 1993, J.M. Bird and colleagues evaluated, at the molecular level, the possibility of the existence of minimal residual disease in five patients who underwent allo-BMT using Polymerase Chain Reaction (PCR) techniques. All the patients were PCR positive before the allo-BMT and during the first year after transplant, suggesting that early positivity is common and has no predictive value in terms of relapse. Three patients were subsequently evaluated: one patient became negative one year after transplant, another two years after transplant and a third patient 4.5 years after transplant. The ability to demonstrate clonal evolution through this technique was later found in a fourth patient, who suffered a relapse. Thus, an absence of detectable disease was observed at the molecular level in three patients with complete and prolonged remission.[9]

These data suggest that a cure for MM may be a realistic objective. Allo-BMT is available to only a small group of patients; however, in these patients it should be considered as the treatment of first choice.[6,7,8]

TABLE III

Auto-BMT in Multiple Myeloma

Group	No. P.	Age (average)	Phase	Treatm. Induction	Died	R.	Surv. (average)	Surv. Forecast
Gore et al[10] – 1989	50 28*	51	IA-5 IB-4 IIIA-33 IIIB-8	VAMP + HDM	14	74% (50% CR)	41 m	–
ATTALet al[12] – 1992	35 31*	54	III	VMCP/VAD + HDM/TBI	1*	43% (40% PR)		85% (38m) 81%* (42m)
Harousseau et al[13] – 1992	97 35*	51	* CR-12 PR-22 Rfr-1*	HDM/TBI=>17 or HDM=>18	2*	34%	24/41*	28,5%* (60m)
Jagannath et al[11] – 1990	55*	53	CR-34 Rfr-21	HDM/TBI=>37 or Tiotp/TBI=>18	18	>75% 100%	40m	80% (60m) no calc.
Dimopoulus et al[14] – 1993	40*	49	I II III	TBC	5	53%	–	–
Reece et al[15] – 1993	14*	49		Busulfan /cyclophospham. /Melphalan	3	43%	19m	–

– Patients submitted to allogenic bone marrow transplant. No. P. – number of patients; m – months; R – response; CR – complete remission; PR – partial response; TBC – Thiotepa/Busulfan/Cyclophosphamide; * This patient had complete remission after autologous bone marrow transplant.

Autologous transplant

Evidence that auto-BMT could determine complete remission in some patients with recurrent MM led some research groups to try this type of therapy.[2,6]

Table 3 shows the most representative works carried out since the 1980s.

The groups of Gore et al[10] and Attal et al[12] studied patients who had not previously undergone treatment; in the groups treated by Harousseau et al,[13] Jagannath et al,[11] and Dimopoulous et al.[14] some patients had undergone multiple polychemotherapy regimens. The last group studied (Reece et al[15]) was a group of patients whose grafts had been submitted to purging (bone marrow purification with removal of myeloma cells, in this case with 4-hydroperoxycyclophosphamide).

Other research groups used circulating progenitor cells, assuming that the grafting of these cells is usually faster, and the likelihood of contamination by the circulating tumor cells is considerably smaller.[16,17]

Having demonstrated that the circulating progenitor cells increase after a short period of therapeutic aplasia, the patients were submitted to a chemotherapy regimen (mobilization regimen) which led to a short period of cytopenia. After hematologic recovery (increase in the number of neutrophils and platelets), cells were collected by leukocyte aphaeresis, with separation of the progenitor cells using blood cell separation devices. Progenitor cells were collected daily, then frozen and cryopreserved. The samples were analyzed daily, to detect macrophage and granulocyte progenitors (cfu-gm/ Granulocyte-Macrophage

TABLE IV

Use of circulating progenitor cells in multiple myeloma

Group	No.	Age (average)	Mobil. Reg.	Treatm. Regimen	Post-BMT mort.	A. R.	Follow up (months)	Results
Fernand et al[16] – 1989	8	41	CHOP (high doses)	Carmustine (120mg/m2) Etoposide/ (250mg/m2) Melphalan/ (140mg/m2) + TBI	1	>90% (Alive) 2 CR	13 (m)	88% Alive Min. D. 4 Relap.-2 CR-1
Jagannath et al[17] – 1992	60	50	HD-CTX + GM-CSF	Melphalan (200mg/m2) or Melphalan (140mg/m2) + TBI	3	>75% (68% cases)	12 (m)	85% Alive

No. - number of patients; Mobil. Reg. – circulating progenitor cell mobilization period; CHOP (high doses) – Cyclosphosphamide (1500mg/m^2) / Adriamycin (90mg/m^2)/ Vincristine (1,4mg/m^2)/ Prednisone; Treatm. Regimen – treatment regimen; HD-CTX – high doses of Cyclosphosphamide (6mg/m^2, into five doses); GM-CSF – granulocyte-macrophage colony-stimulating factor; Post-BMT mort.– post-transplant mortality; A.R. – accumulative response in the first group with reduction of tumor mass above 90% in surviving patients, above 75% in 68% of patients in the second group; CR – complete remission; Min. D. – minimum disease; Relap. – relapses.

Colony-Forming units). In the group of patients studied by Fermand et al,[16] only the circulating progenitor cells were reinfused after the treatment. In the group of patients studied by Jagannath et al[17], in addition to the circulating progenitor cells, auto-BMT was also performed.

The patients' characteristics, mobilization treatments (with circulating progenitor cells), pre-transplant regimens and results obtained can be more clearly understood by looking at *Table 4*.

It is very difficult to compare the results, which are initially encouraging. It was observed, for example, that the disease-free interval was longer in patients in whom auto-BMT was carried out as a consolidation therapy, with complete remissions reaching 50%. However, a high dose therapy was usually administered to patients with advanced or refractory disease, or who had suffered a relapse. Taking into account the potential myelotoxicity of these regimens, it is imperative to evaluate the prognostic factors in order to decide between consolidation therapy and saving a patient who is in a condition of refractory or resistant disease.

Compared with allo-BMT, auto-BMT offers the following advantages:

- It can be used in patients aged up to 70 years;
- Low mortality;
- Shorter hospital stays;
- Lower cost.

Regarding additional immunomodulation, some studies appear to indicate that there is some advantage in the use of interferon-alpha after bone marrow transplant, since the number of relapses was lower. The use of other immunomodulators, such as interleukin-2, is under investigation.

Prognosis

The behavior of this type of neoplasm is much more complex than would be expected, given the relative uniformity of the dominant plasmacytoid cells, which represent the terminal phase of normal B cell differentiation. However, phenotypic, molecular and genetic data suggest that a myeloma progenitor cell appears early on in the hematopoietic development, which would explain the differences in phenotypic tumor expression, e.g., the presence or absence of the MDR phenotype (previously mentioned). Some studies on flow cytometry in nucleic acids provide some important prognostic data: no patient whose tumor cells were hypodiploid DNA responded to the standard MP or VAD therapy; patients with high intracellular RNA generally had the best response rates. Both nuclear DNA and RNA were stable during the course of the disease, declining only during relapse.[2,4] It is also generally agreed that a large tumor mass is associated with a shorter survival, and that the serum

TABLE V

Important variables in the prognosis of patients with MM

Area of action	Adverse pre-treatment variable
RESPONSE	Aneuploidy DNA Low RNA Large tumor mass High beta-2 microglobulin MDR Expression*
RELAPSE TIME	Low RNA High beta-2 microglobulin Large tumor mass High LDH
SURVIVAL	High beta-2 microglobulin Large tumor mass High LDH Low RNA * Aneuploidy DNA *

beta-2 microglobulin level reflects both tumor mass and renal function. Later, Barlogie considered the factors shown in *Table 5* as important variables in the prognosis of MM. Some of these data were then unequivocally correlated with the findings obtained in a series of 100 patients (retrospective analysis).[4]

In summary, although there are no randomized studies, the following are favorable prognostic factors in MM:[1,6,8]

1- host-related factors: aged fifty years or under, good level of activity.

2 – disease-related factors: aneuploidy DNA; morphology of plasma cells (non blastic); beta-2 microglobulin under 2.5mg/L; low LDH; light chain; chemo-sensitivity, IgG isotypes.

Conclusion

There is evidence that treatment with high doses of chemotherapy followed by allogenic bone marrow transplant can cure some patients with MM. Therefore, it should at least be considered for patients aged 55 years or under, where there is a compatible donor. The most suitable timing would be: consolidation therapy in patients with poor prognostic factors at onset, and therapy to save patients in the first relapse with favorable prognostic factors. Treatment of multiple myeloma with the same treatment followed by autologous bone marrow transplant did not show good results. This type of treatment may be administered with relative safety and good responses in both consolidation therapies in patients with poor prognostic factors at onset and in chemo-sensitive patients with recurrent MM.

In both allogenic and autologous bone marrow transplant, there is no consensual evidence regarding stem cell induction or mobilization regimens, or the need for bone marrow purging. Further studies are awaited.

But one conclusion seems correct: bone marrow transplants are a temporary solution towards new advances and developments in Medicine. With the advances in knowledge of growth factors, bone marrow transplants may come to be replaced by sequential hematopoietic growth factors, namely: stem-cell factor, interleukin-1, interleukin-3, interleukin-3/GM-CSF and interleukin-6. Some of these factors make myeloma cells dormant in kinetically active cells and, therefore, more sensitive to cytotoxic agents. The stem-cell factor interleukin-1, and G-CSF, may also have radioprotective and probably chemoprotective effects, enabling the use of supra-lethal doses. The most appropriate post-transplant immunomodulation has yet to be defined.

Another possibility is the development of specific, targeted immunotherapy to target the specific myeloma idiotype. Further progress will come from a better understanding on the nature of malignant cells and the ability to isolate them from normal hematopoietic progenitor cells.[1,6]

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