Hematopoietic stem cell transplantation in the treatment of multiple myeloma

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Multiple myeloma is a malignant clonal plasma cell disorder that accounts for about 10% of all hematological malignancies. Conventional melphalan-based chemotherapy produces less than 5% of complete remission rates, with less than 5% of patients surviving 10 years or more. The VAD regimen is very effective to induce cytoreduction, but does not prolong event free survival or overall survival. High-dose therapy with autologous bone marrow or peripheral blood stem cell support induces complete remission in 30%-50% of patients, with a very low transplant related mortality (<5%). Both event free survival and overall survival are prolonged with High-dose therapy, but relapses continue to be a major problem. A subset of patients (chromosome 13 abnormalities and high level of beta2-microglobulin at diagnosis) at high risk of relapse has been identified. Double transplants and post-transplant strategies, with the use of alpha interferon, thalidomide, or combined chemotherapy, are additional measures used to reduce the incidence of relapse. Allogeneic transplants can induce durable molecular remissions. However, the very high (30%-50%) transplant-related mortality limits the application of this procedure. The emerging concept of non-myeloablative transplants may be a very attractive alternative to improve these results. This strategy may be associated with lower transplant related mortality, and yet provide a graft versus myeloma effect, potentially increasing event free survival and overall survival.

Keywords: Multiple myeloma, hematopoietic stem cell transplantation

Introduction

Multiple myeloma is a malignant clonal plasma cell disorder accounting for about 1% of all cancers and 10% of hematological malignancies (1). The main characteristic of the disease is the clonal proliferation of plasma cells, and the production, in the majority of cases (with the exception of non-secretory myeloma), of a monoclonal heavy and/or light chain immunoglobulin (M-protein). The main clinical and laboratorial features of the disease include bone pain and fractures, renal failure, hypercalcemia, anemia, and susceptibility to infection (2).

Multiple myeloma was first treated successfully with melphalan in 1962 (3). Prior to the introduction of alkylating agents, the median survival of myeloma patients was less than one year. Approximately 60% of patients respond to initial treatment with conventional chemotherapy, but the median survival is only 3 years. Complete remissions (CR) are less frequent than 5%, and the long-term survival (10 years)
is less than 10%. These results have not been improved with combination of multiples agents such as VMCP/VBAP. (4) The VAD (vincristine, doxorubicin and dexamethasone) protocol is very useful to induce a rapid cytoreduction, but the duration of response, event-free survival (EFS) and overall survival (OS) remain the same observed using melphalan and prednisone (5).

**High dose chemotherapy without stem cell support. The Royal Mardsen Experience**

The application of high-dose chemotherapy was introduced in the early 1980s by the Royal Mardsen (U.K.) Group. A phase II study was conducted in 63 newly diagnosed patients with myeloma between November 1981 and April 1986. All patients received high-dose melphalan (140 mg/m$^2$) without stem cell support. The overall response rate was 82%, with 32% of CR, much higher than the 5% obtained with conventional chemotherapy (6). Unfortunately, the treatment-related mortality was high (16%). The median overall survival of the whole group was 4 years, and the median event free survival was 16 months.

**IFM 90: The first randomized trial**

The “Intergroupe Francophone du Myélome” conducted a randomized trial to compare conventional versus high dose chemotherapy with stem cell support for newly diagnosed stage 2 and 3 multiple myeloma patients. Patients were randomized at diagnosis. Conventional chemotherapy was VMCP (vincristine, melphalan, cyclophosphamide and prednisone) / VBAP (vincristine, carmustine, doxorubicin and prednisone). Patients in the conventional arm received a total of 12 cycles, and the high-dose chemotherapy group received the same induction conventional chemotherapy for four to six cycles, followed by autologous bone marrow collection. The patients received high-dose therapy (HDT) consisting of melphalan 140 mg/m$^2$ and total body irradiation (8 Gy). Both groups received alpha interferon until relapse or progression. A total of 200 patients were evaluable. Patients' baseline characteristics of both groups were similar regarding age, gender, stage, isotype and beta2-microglobulin level. CR was defined as the absence of paraprotein on serum and urine electrophoresis and less than 5% plasma cells on marrow aspirate. Very good partial response (VGCR) was defined as a reduction of 90% in the paraprotein level. HDT significantly improved response rates compared with conventional chemotherapy (CT): 38% of patients in the HDT arm achieved CR or VGPR versus 14% of patients in the CT arm (p< 0.001). EFS and OS were also improved by HDT. The median duration of EFS and OS were 18 and 44 months in the CT arm versus 28 and 57 months in the HDT arm. The 7-year EFS and OS rates were 8 and 25% in the CT arm versus 16 and 43 % in the HDT arm (p=0.01 and 0.03, respectively).

In conclusion, the IFM 90 trial showed a significant improvement in terms of response rate, EFS and OS for patients treated with HDT, but the 7-year EFS was only 16% and no plateau was observed in the HDT arm. Therefore while autologous stem cell transplant must be part of the treatment of all patients with multiple myeloma, new strategies are needed in order to improve these results (7).

**The University of Arkansas Experience. “Total Therapy I” Phase 2 Study**

The University of Arkansas (UAMS) group has explored an innovative approach for patients with newly diagnosed multiple myeloma. The “Total Therapy I” included an initial induction conventional chemotherapy phase (VAD for 3 or 4 cycles), followed by bone marrow or peripheral blood stem cell collection. Cyclophosphamide (4g/m$^2$) plus hematopoietic growth factor were used to mobilize stem cells. After stem cell collection, a non-cross-resistant regimen (EDAP - etoposide, dexamethasone, doxorubicin and cisplatin) was used to enhance cytoreduction before HDT. A first high-dose melphalan 200 mg/m$^2$ was administered, followed by a second course 3 to 6 months later.

For patients who did not achieve at least a partial response with the first HDT, a modified
(melphalan 140 mg/m² + TBI) conditioning regimen was offered. After the transplant phase, patients received alpha-2 interferon until relapse or progression. Total Therapy I was evaluated in 231 patients in a non-randomized fashion. The median age was 51 years (26-71 years), 50 patients were 60 years or older, and 9% had creatinine >2.0 mg/dl. Ninety-percent of patients completed the phase of induction therapy, 84% received one HDT and 71% received two courses of HDT with stem cell support. A remarkable finding was the progressive increase in the response rates after each phase of the protocol. The CR rate was 5% after VAD, 30% after the first transplant, and 41% after the second transplant. An intent-to-treat analysis for all 231 patients found 5-year median EFS of 42 months, and OS of 58 months.

Transplant-related mortality was 1% after the first and 4% after the second transplant. Good prognostic factors were the absence of unfavorable cytogenetic abnormalities (11q- and del13), and low levels of beta-2 microglobulin (8).

The results of total therapy were compared in a case control study with patients treated with standard therapy, according the Southwest Oncology Group (SWOG). Patients were matched for age, beta-2 microglobulin and creatinine level. Total therapy was superior in terms of response (PR rate 85% versus 52%, p=0.0001) median duration of EFS (49 versus 20 months, p=00001) and OS (62 versus 46 months, p=0.003) (9).

**Is more better? Single x Double Transplants**

The concept of intensifying at a maximum possible level the treatment of multiple myeloma and obtaining a status of complete remission may be the key to obtain cure for this disease. CR has a positive effect in terms of EFS and OS (10). The group of the University of Arkansas assumes that a double-transplant is the best way to intensify the treatment, and has utilized this strategy as a part of the Total Therapy.

The French Group (IFM) has explored this strategy performing a randomized study. In the IFM 94, 403 newly diagnosed patients under the age of 60 years were treated. Patients were randomized to receive a single autotransplant (Arm A) using melphalan 140 mg/m² plus TBI (8 Gy) or a double autotransplant, the first using melphalan 140 mg/m² and the second melphalan 140 mg/m² plus TBI (8 Gy). For stem cell support, patients were submitted to a second randomization in which peripheral blood stem cell transplant was compared to bone marrow stem cell transplant. Therefore, four subgroups were constituted: A1 - single transplant and BM, A2 - single transplant and PBSC, B1 - double transplant and BM, B2 - double transplant and PBSC. Baseline characteristics and risk factors were similar among the four groups. The response rates (CR + VGPR) were significantly different: A1 - 43%, A2 - 50%, B1 - 50%, and B2 - 61% (p< 0.05). The EFSs were: A1 - 19%, A2 - 20%, B1 - 27%, B2 - 35% (p <0.01), and the OSs were: A1 - 35%, A2 - 40%, B1 - 43%, and B2 - 60% (p <0.05). The authors concluded that double autotransplants supported by PBSC seemed to improve response rate, EFS and OS (11).

**Timing of transplant**

Another controversial point was the more appropriate time to perform HDT with stem cell support in the course of the disease (early versus late). The single randomized trial comparing both strategies was published by Fermand et al. One hundred and eighty-five patients were treated; 91 received HDT and an autotransplant after a short induction with conventional chemotherapy (early transplant), and the second group of 94 patients received HDT, which was performed only in occasion of relapse or progressive disease (late transplant). The results were similar regarding transplant-related mortality and OS, but patients transplanted earlier received less courses of chemotherapy and remained asymptomatic for longer periods than patients transplanted later (12).

**Conditioning regimens**

The large majority of HDTs for multiple myeloma are based on the combination of melphalan and TBI and/or melphalan alone in a variable range of doses (140 mg/m² to 220 mg/m²). In addition, many other combinations that
included others alkylating agents were used, but none presented a clear advantage over melphalan (13). In a retrospective study the Spanish Registry for Transplantation compared three HDT regimens for multiple myeloma: melphalan 200 mg/m$^2$, melphalan 140 mg/m$^2$ plus TBI, and melphalan 140 mg/m$^2$ plus busulfan 12 mg/kg. The 3 regimens were similar in terms of transplant-related mortality, but a trend for better EFS was observed in the group treated with busulfan (14).

The French Group performed a randomized trial (IFM 95) comparing two different regimens of HDT for newly diagnosed multiple myeloma. A total of 282 evaluable patients were evaluated. In Arm A, 140 patients were treated with melphalan 140 mg/m$^2$ plus 8 Gy TBI, and in Arm B, 142 patients were treated with melphalan 200 mg/m$^2$. The toxicity was much lower in the group of patients treated without TBI: the duration of neutropenia and thrombocytopenia, and hospitalization time were significantly shorter, and fewer transfusions were needed. In addition, the incidence of severe mucositis was higher in the group treated with TBI. Five toxic deaths occurred in the TBI arm versus none in the no-TBI group. The median duration of EFS was similar (21 versus 20.5 months) but the OS at 45 month was significantly higher in the group with no TBI (65.8% versus 45.5%, p=0.05). The authors concluded that melphalan 200 mg/m$^2$ was less toxic and significantly decreased the transplant-related mortality, with a better OS (15).

Post-transplant strategies

HDT increases the response rate and prolongs EFS and OS of multiple myeloma patients. Unfortunately, very few patients, if any, are cured with this strategy. Therefore, the concept that transplant is the final treatment modality and no other therapy is required is not applied to multiple myeloma, as it is for other diseases, such as large-cell lymphomas. In multiple myeloma, transplant must be considered one of various phases of treatment, a concept much closer to the treatment of acute lymphoid leukemia. Therefore, the exploration of post-transplant strategies is of paramount importance in order to improve the results. A classical approach, as used in conventional therapy, is maintenance with alpha-interferon. A randomized trial in the post-transplant setting was performed: 85 patients were randomized to receive alpha-interferon (3 millions UI three times a week) until relapse or progression versus no additional treatment. With a median follow-up of 52 months, the median progression-free survival (PFS) in the group treated with alpha-interferon was 46 months, compared to 27 months in the control arm (p=0.0025). However, in a second and much longer follow up analysis, the advantage in terms of survival disappeared (16).

Another strategy of post-transplant consolidation was evaluated by the group of the University of Arkansas. A combination chemotherapy called DCEP (dexamethasone, cyclophosphamide, etoposide and cisplatinum) was used as consolidation after transplant (4 cycles). This regimen had been utilized previously with success for the treatment of relapse after transplant (17). Seventy-one patients received DCEP as a part of post-transplant consolidation chemotherapy. Patients receiving this regimen were compared with a historical control group of 142 patients, matched for unfavorable chromosomal abnormalities and beta-2 microglobulin levels. Patients who received DCEP had superior EFS (37 versus 15 months, p=0.002) and OS (34 versus 13.5 months, p=0.004) (18).

The role of allogeneic stem cell transplant

The role of allogeneic transplantation for patients with multiple myeloma remains controversial. The major problem is the 30% to 50% transplant-related mortality rate in the first 100 days (19). However, patients who survive after the first year have a good possibility to remain disease-free. A graft versus myeloma effect can induce true molecular remissions and prolong DFS and OS (20). One of the largest series published analyzed data from the European Bone Marrow Transplantation Group (EBMT). There were more than 1300 patients
transplanted, and the first transplant was performed in 1983 (21). In 1996, the EBMT performed a retrospective study comparing 189 allogeneic transplants with 189 case-matched autologous transplants controls. The median overall survival was significantly better for autologous patients (34 versus 18 months). However, the relapse rate was lower in allogeneic patients (50% versus 70%). Transplant-related mortality was much higher in allogeneic (41%) compared to autologous patients (13%) (22). A more recent EBMT analysis compared 225 allogeneic patients transplanted from 1994 to 1998 and 339 patients transplanted from 1983 to 1993. There was a decrease in the transplant-related mortality in the group more recently transplanted (total mortality 50% versus 30% and early mortality 30% versus 20%). The actuarial survival at four years was 50% compared to 30% in the previously transplanted group. A better control of transplant complications and good selection of patients transplanted early in the course of disease contributed to these results (23).

The emerging concept of nonmyeloablative transplants may be the key to improve results in the therapy of myeloma patients. This strategy may be associated with lower transplant-related mortality and yet provide a graft versus myeloma effect (24). There are many ongoing studies exploring the concept of nonmyeloablative transplants in high risk newly diagnosed, as well as in relapsed patients. The University of Arkansas Group published recently a phase-two study exploring a nonmyeloablative melphalan-based conditioning regimen. Thirty-one multiple myeloma patients received allografts from HLA-matched siblings (n = 25) or unrelated donors (n = 6). Patients received melphalan 100 mg/m$^2$ as conditioning regimen. Cyclosporine at a dose of 3 mg/kg was administered to all patients, starting on day -1. Patients transplanted from unrelated donors received methylprednisolone 1mg/kg/day starting on day +5. In absence of graft versus host disease (GVHD), cyclosporine was tapered over 1 month, starting on day 60 after transplant. Donor lymphocyte infusions with dose-escalating CD3+ lymphocytes was done to enhance the graft versus myeloma effect, and establish full chimeric engraftment for patients with no GvHD on days 21, 42 and 112. A high incidence of GvHD motivated modifications in the protocol. Cyclosporine was continued until day +120, and decisions regarding DLI were based on results of chimeric and disease status. By day +100, 25 patients (89%) were full donor chimeras, 1 was mixed chimera, and 2 had autologous reconstitution. Acute GvHD was observed in 18 patients (58%), and 10 progressed to chronic GvHD (58%). At a median follow-up of 6 months, 19 patients (61%) achieved complete/near complete remissions. Twelve patients (39%) died (3 patients from progressive disease, 3 from early and 6 from late transplant-related mortality). The median OS was 15 months. The authors concluded that mini-allograft induced an excellent disease control, but GvHD remains a significant problem (25).

Another interesting strategy exploring the concept of mini-allograft was proposed in a multicenter study (Fred Hutchinson, Seattle; City of Hope, Duarte; Stanford University, California and University of Leipzig, Germany). Thirty-two patients with a median age of 55 (range 39-71) years, with previously treated stage II/III multiple myeloma were enrolled. Patients received a first autograft prepared with melphalan 200 mg/m$^2$. Forty to 120 days later, patients received an allograft from an identical HLA sibling donor (PBSC) after a conditioning regimen with 200 cGy TBI. Immunosuppression was done with mycophenolate mofetil for 28 days and cyclosporine for a minimum of 56 days. One patient died from cytomegalovirus pneumonia after an autologous transplantation. There were no toxic deaths after the allograft. All patients engrafted with 90% of donor T-cell chimerism by day +28, and 99% by day +84. The OS was 81%. Forty-five percent of patients developed acute GvHD and 55% chronic GvHD requiring therapy. The total response rate was 84% (CR 53% and PR 31%). The authors concluded that despite being used in advanced disease and older patients, this novel regimen reduced dramatically the toxicity, maintaining a potent anti-tumor activity. (26)
O transplante de células precursoras hematopoéticas no tratamento do mieloma múltiplo
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Resumo

O mieloma múltiplo é uma neoplasia clonal maligna das células plasmáticas, com uma prevalência de 10% do total das hemopatias malignas. Esquemas quimioterapêicos convencionais utilizando o melfalano produzem menos de 5% de remissões completas, com 5% dos pacientes sobrevivendo por 10 anos ou mais. O esquema VAD é muito eficaz para induzir uma rápida citorredução, mas não é capaz de prolongar a sobrevida livre de eventos (SLE) ou a sobrevida global (SG). Quimioterapia em altas doses seguida de transplante autólogo de células progenitoras hematopoéticas (TCPH) induz a remissões completas em 30 a 50% dos pacientes, com uma baixa mortalidade relacionada ao procedimento (<5%). Tanto a SLE como a SG são prolongadas após TCPH, mas a recaída da doença continua sendo o maior fator limitante ao sucesso terapêutico. Um subgrupo de pacientes (alteração do cromossoma 13 e beta 2 microglobulina elevada no diagnóstico) com alto risco de recaída, já foi identificado. Duplo transplante autólogo e estratégias terapêuticas pós transplante, como o uso de alfa-interferon, talidomida e poliquimioterapia (DCEP) são medidas adicionais utilizadas com o intuito de reduzir a incidência das recaídas. O transplante alogénico pode induzir a remissões moleculares prolongadas. Entretanto, a elevada mortalidade relacionada a este procedimento (30 a 50%) tem se revelado um fator limitante a sua maior utilização. O transplante não mieloablativo pode ser uma alternativa válida ao transplante alogénico convencional. Esta estratégia tem uma menor mortalidade relacionada ao procedimento, mantendo no entanto o efeito do enxerto versus mieloma, que pode levar a um prolongamento da SLE e da SG.

Palavras-chave: Mieloma múltiplo, transplante de células progenitoras hematopoéticas

References


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