Randomized Trial Experience of the Intergroupe Francophone du Myélome

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This article summarizes clinical results of the Intergroupe Francophone du Myélome (IFM) trials: high-dose therapy (HDT) supported with autologous stem cells improves survival, melphalan 200 mg/m^2 is the best preparative regimen, unpurged peipheral blood stem cells (PBSC) are the recommended source of stem cells to support HDT, and tandem transplants significantly improve survival. Although these results are encouraging, the current IFM 99 protocol will evaluate innovative strategies with the goal to improve long-term survival. ***Semin Hematol 38:226-230. Copyright © 2001 by W.B. Saunders Company.***

DURING THE LAST DECADE the Intergroupe Francophone du Myélome (IFM) initiated different randomized studies to determine the impact of high-dose therapy (HDT) on myeloma. The IFM 90 trial addressed the issue of HDT versus conventional chemotherapy. IFM 95 was designed to compare the two major preparative regimens used in myeloma: high-dose melphalan (HDM) plus total body irradiation (TBI) versus HDM alone. IFM 94 01 addressed the issue of the best source of stem cells to support HDT, bone marrow versus peripheral blood stem cells (PBSC). Finally, the IFM 94 02 protocol compared the results observed after a single versus a double autologous transplant. This article focuses on the updated results of these trials and discusses the current research areas of the IFM.

The IFM 90 Trial

Over the past 10 years, HDT has been developed to manage myeloma patients. When applied in newly diagnosed patients, autologous bone marrow transplantation (ABMT) was found to be safe (<5% toxic deaths) and effective consolidation therapy, with response rates ranging from 70% to 90% (including a 20% to 50% complete response rate) and median survival durations of 4 to 5 years.[1,2,9] The superiority of these results over those observed after conventional chemotherapy was difficult to assess because patient selection for ABMT is subject to considerable bias, including young age, good performance status, and normal renal function. Thus, prospective randomized trials were required to compare conventional chemotherapy and HDT. In 1990, the IFM initiated the first trial designed to address this issue. A previous analysis of this protocol with a median follow-up of 40 months concluded that HDT significantly improved response rate, event-free survival, and overall survival.[2] The new analysis of this protocol, with a median follow-up of 7 years from diagnosis, confirms these results.

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Patients and Study Design

Previously untreated patients aged under 65 years with Durie-Salmon (DS) stage II or III myeloma were eligible. A total of 200 patients were evaluable. Patient characteristics of each group were similar as regards gender, age, DS stage, isotype, and β_2-microglobulin level. Patients were randomized at diagnosis to receive either conventional chemotherapy or HDT. Conventional chemotherapy consisted of a combination of vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) alternating with vincristine, carmustine, doxorubicin, and prednisone (BVAP); cycles were administered at 3-week intervals for 12 months (18 cycles: C1 to C18). Recombinant interferon alfa (IFNα) was administered from C9 until relapse. In the HDT arm, patients received an unpurged ABMT (collected after four to six cycles of VMCP/BVAP) prepared with HDM (140 mg/m^2) and TBI (8 Gy delivered in four fractions over 4 days without lung shielding). IFNα was started after hematologic reconstitution post-ABMT.

The following response criteria were applied: complete remission (CR), defined as the absence of paraprotein on serum and urine electrophoresis and ≤5% plasma cells of normal morphology on bone marrow aspirate; very good partial response (VGPR), which indicated a 90% decrease in serum paraprotein; partial response (PR), or a 50% decrease in serum paraprotein and/or 90% decrease in Bence Jones protein (including patients with Bence Jones protein only); and minimal response, a 25% decrease in serum paraprotein.

High-Dose Therapy Improves Response Rate

HDT was found to improve response rate ($P < .001$), as 38% of patients enrolled in the HDT arm achieved a CR or a VGPR versus 14% of patients enrolled in the conventional chemotherapy arm.

High-Dose Therapy Improves Event-Free Survival and Overall Survival

In the conventional chemotherapy arm, the median durations of event-free and overall survival were 18 and 44 months, respectively. The 7-year event-free and overall survival rates were 8% and 25%, respectively. In the HDT arm, the median durations of event-free and overall survival were 28 and 57 months, respectively. Seven-year event-free and overall survival rates were 16% and 43%, respectively (Fig 1). HDT significantly improved both event-free survival ($P = .01$) and overall survival ($P = .03$).

Prognostic Factors for Overall Survival

The prognostic factors for survival are summarized in Table 1. In multivariate analysis, when considering all 200 patients, overall survival was related to β_2-microglobulin level ($P < .001$).

To better appreciate the impact of ABMT on survival, we analyzed the group of patients aged under 60 years (n = 122). Most actually received ABMT, when randomized in arm B (82%). In multivariate analysis, survival was related to treatment arm ($P = .02$; Fig 2) and to β_2-microglobulin level ($P < .001$).

To include the response to treatment among the variables tested for their impact on survival, we analyzed the subgroup of patients surviving more than 1 year after diagnosis (n = 178). In multivariate analysis, response to treatment was strongly related to survival ($P < .001$; Fig 3).

Conclusions of the IFM 90 Trial

The IFM 90 trial showed that HDT was significantly superior to the VMCP/BVAP regimen regarding response rate, event-free-survival, and overall survival. Thus, HDT represents a real improvement and should be considered in the management of younger patients. Another important contribution of the IFM 90 trial was the demonstration that achievement of CR was the most important prognostic factor for survival ($P < .001$) and therefore should be the major objective in the management of younger patients. Finally, although the trial demonstrated that HDT significantly improved the EFS, the 7-year postdiagnosis event-free survival rate was only 16% for patients enrolled in the HDT arm and no plateau was observed. Thus few patients, if any, will be cured. Strategies to further improve these results were thus warranted.

Table 1. IFM 90: Prognostic Factors for Survival

	All Patients	≤60 Years	Survivors ≥ 1 Year
Age	NS	—	<0.01
DS stage	NS	NS	NS
M component	NS	NS	NS
Plasmocytosis	NS	NS	NS
β_2-microglobulin	<.001	<.001	<.05
Treatment (A/B)	NS	.02	NS
Response	—	—	<.001

Abbreviation: NS, not significant; DS, Durie-Salmon.

The IFM 95 Trial

The choice of a better preparative regimen was a logical approach to improve the results observed in the IFM 90 trial. As with other malignancies, the superiority of one high-dose regimen over another has not yet been demonstrated. The analysis of the French registry of HDT for myeloma showed no significant differences between patients treated with melphalan 140 mg/m^2 plus TBI 8 Gy and patients receiving a higher dose of TBI or combinations of several alkylating agents.[9] However, the Royal Marsden group reported an impressive 70% CR rate using a higher dosage of melphalan: 200 mg/m^2.[6] This conditioning regimen without TBI was associated with a low incidence of extramedullary toxicity. In 1995, the IFM initiated a prospective randomized trial comparing this regimen versus TBI plus melphalan 140 mg/m^2.[10]

Patients and Study Design

A total of 399 previously untreated patients aged under 65 years with DS stage II or III myeloma were eligible and enrolled. Initial treatment consisted of three cycles of the vincristine, doxorubicin, and dexamethasone (VAD) regimen, and 298 responding patients underwent PBSC collection. Patients with a sufficient graft collection and a good performance status (n = 282) were randomized to

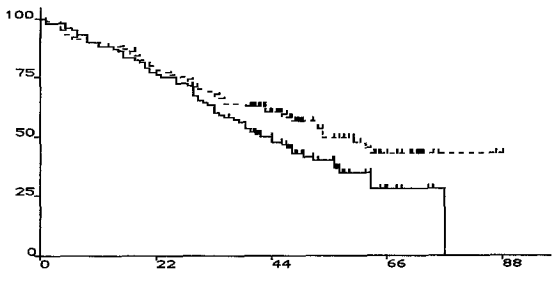

Figure 1. IFM 90: overall survival according to treatment arm. (—) Arm A, conventional chemotherapy; (·····) arm B, ABMT.

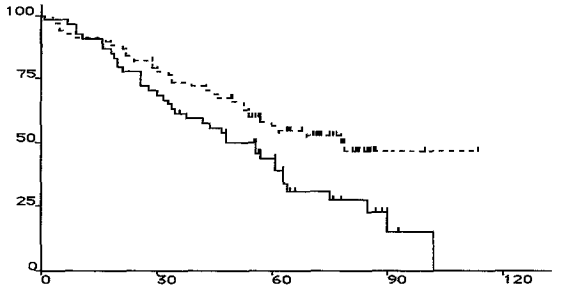

Figure 2. IFM 90: overall survival according to treatment arm for patients aged <60 years. (—) Arm A, conventional chemotherapy; (·····) arm B, ABMT.

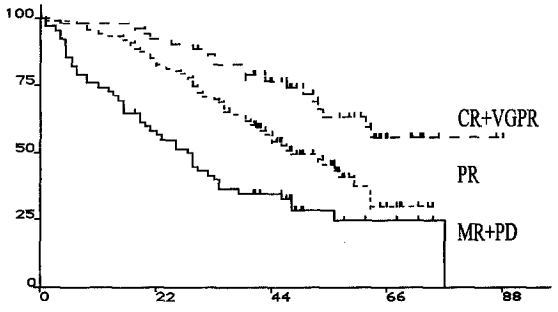

Figure 3. IFM 90: overall survival according to response to treatment. CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; PD, progressive disease.

receive TBI plus melphalan 140 mg/m^2 (arm A; n = 140) or melphalan 200 mg/m^2 (arm B; n = 142). Patient characteristics of each group were similar as regards gender, age, DS stage, isotype, β_2-microglobulin level, and C-reactive protein.

Melphalan 200 mg/m^2 Decreases Transplant-Related Toxicity

Melphalan 200 mg/m^2 was found to significantly reduce hematologic toxicity, transfusion and intravenous antibiotic requirements, severe mucositis, and duration of hospitalization. Five toxic deaths occurred in the TBI arm versus none in the HDM 200 mg/m^2 arm (Table 2).

Response Rate

The CR rate was comparable in the two arms (29% in arm A *v* 35% in arm B), but the rate of CR plus VGPR was slightly increased in arm B (55% *v* 43%, $P = .06$).

Event-Free and Overall Survival

With a median follow-up of 20 months from transplant, the median event-free survival durations were comparable (21 months in arm A *v* 20.5 months in arm B). However, the 45-month probability of overall survival was 66% in arm B versus 45% in arm A ($P = .05$) due to a better survival after relapse for patients enrolled in arm B (Fig 4).

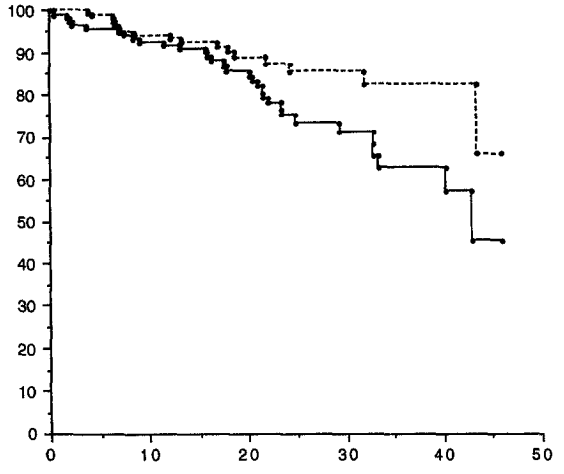

Figure 4. IFM 95: overall survival according to treatment arm. (—) Arm A, melphalan 140 mg/m^2 + TBI; (·····) arm B, melphalan 200 mg/m^2.

Conclusions of the IFM 95 Trial

The IFM 95 trial demonstrates that melphalan 200 mg/m^2 significantly decreases transplant-related toxicity and is associated with a better overall survival than melphalan 140 mg/m^2 plus TBI. Melphalan at the higher dose is thus the recommended preparative regimen in myeloma.

The IFM 94 01 Trial

The optimum source of hematopoietic stem cells to support HDT—bone marrow or PBSC—is frequently debated.[1,3,8] Peripheral blood progenitors, collected after priming with chemotherapy and/or hematopoietic growth factors, can accelerate hematopoietic reconstitution.[8] Thus, peripheral blood is currently preferred to support HDT. However, the impact of this choice on long-term event-free and overall survival was unknown, and the IFM therefore initiated the first prospective randomized trial to compare bone marrow and PBSC in myeloma.

Patients and Study Design

From October 1994 to March 1997, 403 previously untreated myeloma patients younger than 60 years of age

Table 2. IFM 95: Transplant-Related Toxicity

	Arm A (Mel + TBI; n = 140)	Arm B (Mel 200; n = 142)	*P*
Duration of neutropenia, days (median)	4-34 (10)	4-34 (8)	<.001
Duration of thrombocytopenia, days (median)	0-110 (7)	0-30 (7)	<.001
No. of platelet transfusions (median)	0-30 (2)	0-18 (1)	<.001
No. of red blood cell transfusions (median)	2 (0-22)	2 (0-9)	<.001
Duration of hospitalization, days (median)	12-77 (23)	11-47 (19)	<.001
Duration of intravenous antibiotics, days (median)	0-60 (11)	0-30 (8)	<.001
Cardiac toxicity grade 3/4 (%)	5 (3.6)	1 (0.7)	.21
Mucositis grade 3/4 (%)	71 (51)	42 (30)	<.001
Pulmonary toxicity grade 3/4 (%)	9 (6.4)	2 (1.4)	.06
Renal toxicity grade 3/4 (%)	5 (3.6)	3 (2.1)	.7
Liver toxicity grade 3/4 (%)	2 (1.4)	1 (0.7)	.99
Toxic death (%)	5 (3.6)	0	.07

were randomly assigned at diagnosis to receive a single autologous transplant prepared with HDM (140 mg/m^2) and TBI (8 Gy) or a double autologous transplant: the first prepared with melphalan (140 mg/m^2) and supported with blood stem cells, and the second prepared with HDM (140 mg/m^2) and TBI (8 Gy). Three months after diagnosis, patients from both arms were also randomized to receive bone marrow (collected after three initial cycles of VAD) or PBSC (collected with granulocyte colony-stimulating factor [G-CSF] after three initial cycles of VAD) to support melphalan and TBI. Three months after diagnosis, 343 patients were randomized to receive bone marrow (n = 163) or PBSC (n = 180) transplants. The characteristics of patients in each group were similar.

Results

Eighteen percent of patients randomized to receive bone marrow received PBSC. Although analyzed on an intent-to-treat basis, the use of PBSC nevertheless was found to significantly decrease the incidence of hematologic toxicity (Table 3). No significant difference was observed between the treatment groups with respect to response rate or event-free survival. A trend in favor of PBSC was observed in terms of overall survival (P = .07) (Fig 5). For the 180 patients randomized to receive PBSC, CD34$^+$ selection was allowed. One hundred thirty patients received an unselected graft and 50 a selected one. No significant differences in terms of hematologic reconstitution, response rate, or survival were observed.

Conclusions of the IFM 94 01 Trial

This trial demonstrated that the use of PBSC reduces the duration of aplasia and transfusion requirements with a borderline improvement in overall survival. PBSC should be the recommended source of stem cells to support HDT in myeloma.

The IFM 94 02 Trial

Repeated cycles of intensive therapy supported with autologous transplant have been investigated.[4,5,11,12] The administration of two courses of HDM supported with hematopoietic stem cells was feasible in more than 70% of patients and could increase the CR rate in one study.[11] However, the impact of such a therapy on overall survival warranted further evaluation. To address this issue, the IFM initiated a prospective and randomized study to compare single versus double transplantation.

Table 3. IFM 94 01: Bone Marrow Versus PBSC

	Bone Marrow	PBSC	P
No. of patients	163	180	
Days with neutropenia (<500/μL)	12	10	.001
Days with thrombopenia (<50,000/μL)	21	12	.001
No. of red blood cell transfusions	3	3	NS
No. of platelet transfusions	7	4	.01
6-year event-free survival	21%	26%	NS
6-year survival	37%	50%	NS

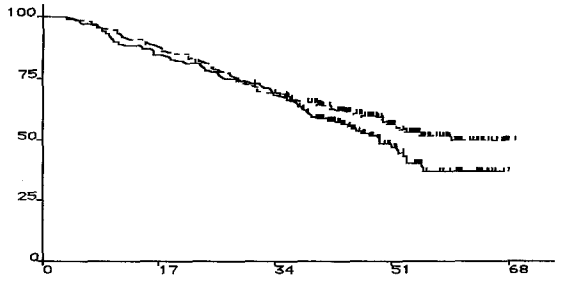

Figure 5. IFM 94 01: overall survival according to treatment arm. (——) Arm A, bone marrow; (·····) arm B, PBSC.

Patients and Study Design

From October 1994 to March 1997, 403 untreated myeloma patients under the age of 60 years were randomized to receive a single autologous transplant (arm A) prepared with melphalan (140 mg/m^2) and TBI (8 Gy) or a double autologous transplant (arm B): the first prepared with melphalan (140 mg/m^2) and the second with melphalan (140 mg/m^2) and TBI (8 Gy). Patients were initially treated with three cycles of the VAD regimen. After these three cycles, patients who were eligible (n = 344; 87%) for a transplant (good performance status, normal cardiac and respiratory functions) underwent a second randomization: bone marrow versus blood (PBSC) to support the transplant prepared with melphalan and TBI. According to these two randomizations, four treatment groups could be compared: group A1 (n = 79), single transplant with bone marrow; group A2 (n = 88), single transplant with PBSC; group B1 (n = 85), double transplant with bone marrow; group B2 (n = 92), double transplant with PBSC. Patient characteristics of each group were similar. An intermediate analysis was performed in November 2000 with a median follow-up of 5 years from diagnosis.

Results

Eighty-one percent of patients received the first transplant and 75% in arm B received the second. The

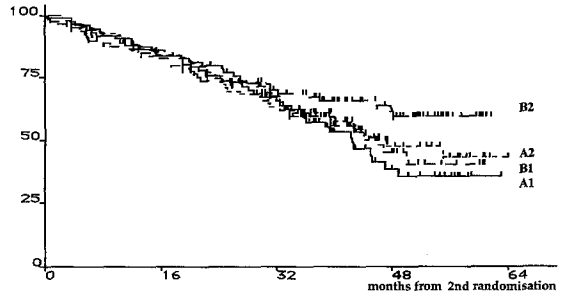

Figure 6. IFM 94 02: overall survival. (——) Arm A1, single transplant + bone marrow; (·····) arm A2, single transplant + PBSC; (·····) arm B1, double transplant + bone marrow; (·····) arm B2, double transplant + PBSC.

Table 4. IFM 99 Protocol (Factors: Δ13; β_2 > 3 mg/L)

0 to 1 Factor		2 Factors
	VAD × 3 Mel-140 + PBSC Mel-200 + PBSC	VAD × 3 Mel-200 + PBSC
IFM 99-02	IFM 99-03	IFM 99-04
• No maintenance • Pamidronate • Pamidronate + thalidomide	HLA-identical sibling Nonmyeloablative allogenic BMT	No HLA-identical sibling Mel-220 + PBSC ± anti-interleukin-6
	PBSC collection = IFM 99-01 →Cyclophosphamide (4 g/m²) + G-CSF →Stem cell factor + G-CSF	

Abbreviations: HLA, human leukocyte antigen; G-CSF, granulocyte colony-stimulating factor.

response rates (CR plus VGPR, >90%) differed significantly among the four groups: A1, 43%; A2, 50%; B1, 50%; and B2, 61% ($P < .05$).

The 5-year post-second randomization EFS also differed significantly among the treatment groups: A1, 19%; A2, 20%; B1, 27%; and B2, 35% ($P < .01$). Finally, 5-year post-second randomization survival differed significantly among the four groups: A1, 35%; A2, 40%; B1, 43%; and B2, 60% ($P < .05$) (Fig 6).

Conclusions of the IFM 94 02 Trial

Finally, double transplantation supported with PBSC was found to improve response rate, and event-free and overall survival in myeloma patients aged under 60 years. The final analysis of the protocol was to be performed in May 2001.

Conclusions and Current IFM 99 Trial

The IFM 90 trial demonstrates a significant superiority of HDT (melphalan + TBI) over conventional chemotherapy regarding response rate, event-free-survival, and overall survival. The IFM 95 trial demonstrates that the use of melphalan 200 mg/m^2 significantly reduces transplant-related toxicity and improves overall survival compared with melphalan plus TBI. The IFM 94 01 protocol shows that the feasibility and toxicity of HDT can be improved with the combined use of hematopoietic growth factors and PBSC. The IFM 94 02 protocol strongly suggests that survival could be further improved using a tandem transplant strategy supported with PBSC. However, a recent analysis[7] of prognostic factors for survival after a single or a double transplantation still identified a population with a poor overall survival (<2 years): patients with both a high β_2-microglobulin level at diagnosis (>3 mg/L) and a deletion of chromosome 13. In the current IFM 99 trial, we decided to explore new strategies for this poor-prognosis group, including nonmyeloablative allogeneic transplantation or autologous transplantation with a higher dosage of melphalan plus anti–interleukin-6. For the other patients, we assessed the impact of thalidomide and biphosphonate as maintenance treatment after a tandem autologous transplant supported with PBSC (Table 4).

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