Tandem autologous stem cell transplantation in high-risk de novo multiple myeloma: final results of the prospective and randomized IFM 99-04 protocol


The combination of high levels of $\beta_2$-microglobulin ($\beta_2$-m) and chromosome 13 deletion allows identification of a high-risk subgroup of patients with de novo multiple myeloma (MM). In this population of patients, we have evaluated the impact of a murine anti-interleukin 6 (anti–IL-6) monoclonal antibody (BE-8) as part of the second conditioning regimen in a multicenter prospective randomized trial of tandem autologous stem cell transplantation (ASCT). Conditioning for the first ASCT was accomplished with melphalan 200 mg/m$^2$ and for the second one with melphalan 220 mg/m$^2$ plus dexamethasone with or without BE-8 infusion. This trial included 219 patients, of whom 166 were randomized, 85 without BE-8 (arm A) and 81 with BE-8 (arm B). The median overall survival (OS) and event-free survival (EFS) times of the whole group of patients were 41 and 30 months, respectively. Response rates, OS, and EFS were not different between the 2 arms of the trial. OS at 54 months was 46% in arm A and 51% in arm B ($P = .90$); median EFS was 35 months in arm A and 31 in arm B ($P = .39$). In high-risk patients the dose intensity of melphalan at 420 mg/m$^2$ led to encouraging results, but the addition of anti–IL-6 monoclonal antibody to the second conditioning regimen did not improve either OS nor EFS. (Blood. 2006; 107:397-403)

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with a high response rate of 87.5%,9,10 B-E8 is a murine anti–IL-6 mAb that can suppress the proliferation of myeloma cells in vivo.11 To improve the response achieved with mel220 without increasing the toxicity of HDT, we previously conducted a phase 2 trial evaluating the combination of B-E8 with DXM and mel220 followed by ASCT in 16 patients with MM.12 The conditioning regimen was feasible, and a strong inhibition of IL-6 activity evaluated by quantification of CRP was observed in all patients and was correlated with the high complete remission (CR) rate achieved with this combination therapy. Thus, to study the impact of B-E8 therapy as part of second conditioning regimen, we have conducted in high-risk MM a multicenter prospective randomized trial of tandem autologous transplantation with mel200 followed by mel220 and DXM with or without B-E8 infusion, the IFM 99-04 trial. We present the results of this trial in 220 previously untreated patients.

Patients, materials, and methods
Eligibility
The IFM 99-04 trial was conducted from April 2000 to August 2004. Patients younger than 65 years of age, with Durie-Salmon stage I (one bone lesion), II, or III myeloma, who had both initial biologic features Delta13 (FISH analysis) and beta2-m level greater than 3 mg/L were eligible. FISH analysis7 and beta2-m studies were carried out centrally at the University of Nantes (H. Avet-Loiseau). The criteria for exclusion were prior treatment for myeloma, another cancer, abnormal cardiac function (indicated by a systolic ejection fraction < 50%), chronic respiratory disease (indicated by a vital capacity or carbon monoxide diffusing capacity < 50% of predicted), abnormal liver function (indicated by a serum bilirubin level > 2 mg/dL [35 μM] or an alanine aminotransferase or aspartate aminotransferase level more than 4 times the upper limit of normal), psychiatric disease, and availability of an HLA-identical sibling (inclusion criterion in the IFM 99-03 trial). The study was carried out in accordance with the Declaration of Helsinki, approved prior to initiation by the local Institutional Ethics Committee of the University Hospital of Nantes, then by the Institutional Review Board of each participating center (listed in the “Appendix”), and approved and registered by the official French agency for health security; patients gave written informed consent.

Study protocol
After registration in the study (Figure 1), patients were initially treated with a continuous intravenous infusion of 0.4 mg vincristine and doxorubicin 9 mg/m² over a 24-hour period for 4 consecutive days, with 40 mg oral DXM/d on days 1 through 4 (VAD regimen). Three or 4 cycles of VAD were administered at 4-week intervals. After initial chemotherapy, patients with a performance status below World Health Organization (WHO) grade III and adequate cardiopulmonary, hepatic, and renal functions underwent peripheral-blood stem-cell (PBSC) collection. Stem cells were collected after priming with granulocyte colony-stimulating factor (G-CSF; 10 μg/kg/d for 6 days). Daily apheresis was continued until at least 5 × 106 CD34 cells/kg were collected to perform the tandem transplantation program. After PBSC collection, patients underwent a first ASCT conditioned by mel200. After this first ASCT, patients were then randomly assigned to one of the 2 HDT groups. Randomization was stratified according to the center and carried out by fax. In arm A, patients underwent a second ASCT after conditioning by the combination of DXM 40 mg/d during 4 days plus mel220 infused over 30 minutes 48 hours before stem-cell reinfusion. In arm B, patients underwent a second ASCT after conditioning by the combination of mel220, DXM, and the addition of B-E8 administered as previously described7 (Figure 2). No maintenance therapy was given after the second ASCT.

Assessment of response
The response criteria have been defined previously.4 A complete response was defined as the lack of detectable paraprotein by serum and urine electrophoresis and 5% or fewer plasma cells with normal morphologic features in a bone marrow aspirate. A very good partial response was defined as a 90% decrease in the serum paraprotein level; a partial response was defined as a 50% decrease in the paraprotein level or a 90% decrease in the level of Bence Jones protein (including patients with Bence Jones protein alone) or both; a minimal response was defined as a 25% decrease in the paraprotein level; stable disease was defined as no change in the paraprotein level; and a relapse was defined as the reappearance of paraprotein, the recurrence of bone marrow infiltration, or both in a patient who had had a complete response and as a 50% increase above the plateau level of paraprotein in 2 samples obtained 4 weeks apart in a patient who had had a partial response.

FISH analysis
FISH analysis of 13q and 14q32 abnormalities was performed on highly purified human myeloma cells as previously described.6,7

Statistical analysis
The primary end point was to compare the CR rates achieved by 2 HDT modalities, the first one using mel220 plus DXM (arm A) and the second one using mel220 plus DXM plus anti–IL-6 mAb (arm B). Secondary end points were to compare both arms regarding OS and EFS and to study the feasibility and the toxicity of a tandem transplantation with 2 different dosages of melphalan (mel200 and mel220). Assuming the complete response rate to be 25% in the DXM plus mel220 arm, the study required 200 patients to have 90% power to detect an absolute improvement of 15% in the complete response rate in the mel220 plus DXM plus anti–IL-6 mAb arm. The recruitment target was 200 randomized patients. Two interim analyses were planned, the first one after the first 50 patients to check feasibility and toxic death rate, and the second after 140 randomized patients to check OS and EFS. The board of the IFM group agreed to stop the trial in September 2004 when a total of 165 patients had been randomized, considering the total lack of difference regarding primary and secondary end points of the study.

OS was calculated from the date of diagnosis to the date of death from any cause. Data on patients who were alive at the time of analysis were censored in the survival analysis on the last date they were known to be alive. EFS was calculated from the date of diagnosis to the date of

Figure 1. IFM 99-04 trial profile. VAD indicates vincristine-doxorubicin-dexamethasone [VAD] regimen.
progression, relapse, or death. Data on patients who had not shown progression or relapse were censored on the last date they were known to be alive and event-free. Analysis of prognostic factors for survival was performed including usual clinical (age, sex), biologic (isotype and β2-m, CRP, creatinine, hemoglobin, albumin, and calcium levels), and cytogenetic (14q32 rearrangement) characteristics at presentation. Comparison of frequencies between groups were performed using the χ² and Fisher exact tests. Median values were compared by the Wilcoxon rank sum test. Survivl was estimated by the Kaplan-Meier product-limit method, and curves were compared by the stratified log-rank test. A cut-off date of May 15, 2005 was used for survival analysis.

Results

Overall results

From April 2000 to September 2004, 219 patients from 48 centers met eligibility criteria and received at least one course of VAD. Table 1 shows the baseline characteristics of these 219 patients. A total of 53 (24.2%) enrolled patients did not proceed to randomization because of disease progression (n = 17), the patient’s decision (n = 10), death during VAD therapy (n = 6), death during the first ASCT (n = 2), protocol violation (n = 4), severe ongoing infection (n = 9), inadequate stem-cell collection (n = 1), cardiac failure (n = 2), and pulmonary failure (n = 2). Thus, 166 (75.8%) patients were randomized (85 patients in arm A and 81 patients in arm B) and were treated according to the whole protocol.

Response to therapy and toxic death rate

Table 2 shows the response after the VAD induction regimen and after the first and the second ASCT. At each step of the protocol, the CR and very good partial response (VGPR) rates increased: CR plus VGPR 16% after VAD induction therapy, 34% after the first ASCT, and 51% after the second ASCT.

The treatment-related mortality rate was 5%; 6 patients (3%) died during the induction therapy with VAD, 2 patients died during the first ASCT, and 3 patients (2%) died during the second ASCT (1 in arm A and 2 in arm B).

OS and EFS

Figure 3 depicts OS from diagnosis for the whole group of 219 patients enrolled in the trial. At the reference date of May 15, 2005, the median OS was 41 months, and the 56-month survival rate was 44.4%. The median EFS from diagnosis for the whole group of 219 patients was 30 months, and the 5-year EFS was 0% (Figure 4). OS and EFS of the 166 patients who were randomized were better as compared with those of the 53 patients who could not proceed to randomization (median, 47 and 35 months, respectively, versus 17 and 12 months, respectively, P < .001; Figures 3-4).

Randomized patients

Baseline characteristics were identical in the 2 treatment arms, except for age at diagnosis, which was a median age of 56 years in arm A and 59 years in arm B, P = .05 (Table 1).

Toxicity of the second conditioning regimen

Table 3 shows the toxicity of mel220 plus DXM with or without anti–IL-6 mAb. The median duration of hospitalization was identical, 22 days, in both arms of the trial. No adverse side effects were reported due to the anti–IL-6 mAb infusion. No veno-occlusive disease was reported. The duration of neutropenia and...
the number of transfusions were identical in both groups. The incidence of grades III and IV mucositis (WHO scale) was similar in both groups, 54% in arm A versus 49% in arm B. One patient in arm A and 2 patients in arm B died of infectious complications.

**Response rate**

The response rates after the second ASCT were identical in both arms of the study (Table 2): CR 31% in arm A and 35% in arm B, \( P = .62 \), and CR plus VGPR 50% in arm A and 53% in arm B, \( P = .42 \). The number of patients with a partial response was also similar in both arms (\( P = .44 \)).

**OS and EFS**

The median follow-up time for living patients who were randomized was 24 months (range, 9-59 mo). The EFS was identical in both arms of the study, median 35 months in arm A versus 31 in arm B, and 0% at 59 and 57 months, respectively, \( P = .39 \) (Figure 5). The OS was not statistically different in arm A versus arm B, 46% versus 51% at 54 months, respectively, \( P = .90 \) (Figure 6).

**Prognostic factors for survival**

In a statistical analysis of all 219 patients, a single factor was associated with an adverse outcome for both OS and EFS: a \( \beta_2 \)-m level greater than 8 mg/L (median survival 30 months in the group of 47 patients with \( \beta_2 \)-m > 8 versus 47 months for the 172 remaining patients, \( P = .002 \) and median EFS 22 months versus 35, \( P = .01 \)). When the analysis was performed on the group of 166 randomized patients, this parameter remains statistically significant for both OS and EFS (median survival 30 months in the group of 30 patients with \( \beta_2 \)-m > 8 versus not reached for the 136 remaining patients, \( P = .04 \) and median EFS 24 months versus 36, \( P = .08 \)). On the other hand, in this population with high-risk disease, albumin level, platelet count, or other presenting features did not statistically influence survival as single parameters. Neither t(4;14) nor t(11;14), the main translocations involving the 14q32 chromosomal region, significantly modified the outcome of the whole group of patients. As compared with patients who did not present with t(4;14) at diagnosis, the median OS and EFS of patients with t(4;14) were 37 and 23 months, respectively, versus 45 (\( P = .41 \)) and 35 months (\( P = .34 \)), respectively. Results were similar when the analysis was performed on the group of 166 randomized patients; the median OS and EFS of patients with t(4;14) were 37 and 27 months, respectively, versus 46 (\( P = .61 \)) and 35 months (\( P = .46 \)), respectively. The International Staging System \(^3\) (ISS) was not predictable for survival, but the inclusion criterion \( \beta_2 \)-m greater than 3 mg/L interferes with the definition of ISS1 (in which patients must present with \( \beta_2 \)-m level < 3.5 mg/L).

**Discussion**

Until now, no study has been specifically designed to study the impact of HDT on a subset of patients with high-risk de novo MM. Barlogie et al \(^{14} \) were the first to report among 229 patients treated with tandem transplants (Total Therapy I) that a subgroup of 23 patients presenting with the combination of unfavorable karyotype (\( \Delta 11/13 \)) and elevated \( \beta_2 \)-m levels (> 4) experienced both shorter OS and EFS (median 2.1 and 1.7 years, respectively, dated from the time of the first cycle of VAD) as compared with others (median, 7.0 + and 4.2 years, respectively, \( P = .001 \), for the remaining 206 patients, 161 with \( \beta_2 \)-m levels less than 4 mg/L and 45 with \( \beta_2 \)-m levels greater than 4 mg/L but absence of \( \Delta 11/13 \)), as shown in Table 4. More recently, the same group reported the outcome of 1475 MM patients scheduled to receive tandem transplants and showed in a multivariate analysis that \( \Delta 13 / \text{ hypodiploid karyotype}, \) a pretransplant level of \( \beta_2 \)-m greater than 2.5 mg/L, and pretransplant levels of albumin less than 35 g/L were the most important negative factors for both EFS and OS (from the time of the first transplant). \(^{15} \) The application of these factors identified 3 groups of patients with very different outcomes. The median EFS for patients with none (596 patients), one (562 patients), and at least 2 (317 patients, 21%) poor prognostic factors were 30, 22, and 11 months (\( P < .001 \)), respectively, and the OS for the same groups of patients were 59, 41, and 16 months respectively (\( P < .001 \); Table 4). The IFM group has shown similar prognostic implications for the combination of \( \beta_2 \)-m and \( \Delta 13 \) detected by FISH analysis (Table 4). \(^{7} \) These findings led to the risk-adapted IFM99 protocols, with 2 specific trials for high-risk patients with both high \( \beta_2 \)-m and \( \Delta 13 \). The IFM 99-04 trial is the first prospective randomized trial of tandem ASCT in such patients.

The aims of the IFM 99-04 trial were first to check the interest of anti-IL-6 mAb as part of the second conditioning regimen in a tandem transplantation program, and second, to address the issue of a dose escalation of melphalan using mel200 for the first transplantation and mel220 for the second one.

Our study shows that the addition of anti-IL-6 mAb to the second conditioning regimen did not improve either OS or EFS. Even if we did not evaluate IL-6 or CRP levels (the surrogate marker of IL-6 production) in patients immediately before the infusion of the antibody, the main explanation for these negative results is probably that the majority of patients had responsive disease...
immediately before the second ASCT, with an 85% response rate after the induction chemotherapy and the first ASCT, without elevated invivo IL-6 production in patients. This antibody, which has a true activity in vivo in high proliferative disease such as plasma-cell leukemia, should be used preferentially in patients at the time of relapse, when elevated serum levels of IL-6 are detectable.

The major findings of our study are the encouraging OS and EFS rates, superior to the 2-year and 18-month survival and EFS rates previously described in high-risk patients. This could be attributed to the dose intensity of mel200 (mel200 plus mel220), a tandem sequence that is tolerable. A clear relationship between dose and response in patients treated with melphalan for MM was described almost 20 years ago. In a previous work we showed that pharmacokinetic parameters of mel220 were the same as those of mel140 or mel200, except for area under the plasma concentration curve which was, as expected, higher with mel220 as compared with mel140 or mel200. When we used mel220 in patients with primary refractory disease or patients who had a relapse after a prior HDT, the response rate was 85%, with a 2-year survival rate of 67%. The escalation of melphalan dosage has also been investigated by another group in North America who reported in an abstract the use in patients with MM of an increased dose of melphalan 280 mg/m² followed by a single ASCT performed as part of initial therapy along with amifostine to reduce toxicities to nonhematopoietic tissues. Forty patients with de novo MM responding to induction therapy received this conditioning regimen. No toxic death was reported, and with a short median follow-up of 13 months, 85% of the patients were alive without progressive disease. Of note, in our trial, despite the inclusion of poor-prognosis patients only, the median EFS for the whole group of 219 patients was 30 months, strictly identical to the median EFS of the double-transplant arm (200 patients) of the IFM94 trial, indicating that the tandem mel200, mel220 compares favorably with the tandem mel140, mel140 plus 8 Gy total body irradiation of this latter study. A similar median EFS of 33 and 31 months has also been described in the double-transplant arm of the MAG95 trial, and of the Bologna trial, respectively. In these 3 latter studies, IFM94, MAG95, and Bologna trials, patients with de novo MM were included regardless of chromosome 13 abnormality. Nevertheless, in these 3 trials, the median OS ranged from 58 to 73 months, which is much longer than the median OS of 41 months described in the present study (Table 4). The treatment of relapse was not standardized in our trial and OS data should be interpreted cautiously; nevertheless, this probably indicates that the duration of survival after relapse is short and that salvage treatments, despite the availability of agents such as thalidomide and more recently bortezomib, are less frequently active in this subgroup of patients with poor-risk MM, in relation with disease severity. In such patients relapse after tandem HDT is explosive and often refractory, particularly in patients with chromosome 13 abnormality and a β2-m level greater than 8 mg/L. The role of a maintenance therapy should be explored in this situation.

The 27-month EFS and 37-month OS rates of patients with t(4;14) who received the whole procedure look slightly better than those previously described by our group. These results, using a tandem dose-intensified approach, are also apparently better than those recently reported by the group of Princess Margaret.
Hospital. In their series of 128 patients treated with a single ASCT prepared by mel200, t(4;14) was identified as the only adverse prognostic factor for both progression-free and OS (median 9.9 and 18.3 months, respectively). Our data indicate that patients with t(4;14) should not be excluded from double transplantation programs.

In conclusion, in the first prospective trial of tandem ASCT in patients with high-risk MM, we have shown that the addition of induction regimen using thalidomide or proteasome inhibitors,21-25 or maintenance therapy using thalidomide analogs.

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Appendix

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References


Table 4. Results of studies in high-risk MM patients and of tandem ASCT

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*FISH analysis. †Progression-free survival. ‡Conventional cytogenetic.


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