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


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Supported by a major grant from the Programme Hospitalier de Recherche Clinique. BE-8 was kindly provided by OPI, 6 chemin de l’industrie, Dardilly, 69570, France. The authors want to thank Hervé Avet-Loiseau for FISH analysis and reviewing the manuscript.

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All the authors are members of IFM and were involved in conception and design of the study, provision of study patients, manuscript review and approval. PM and JLH were involved in data analysis and manuscript writing.
Abstract

The combination of high level of beta-2-microglobulin (β2m) and chromosome 13 deletion allows to identify 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-IL6 monoclonal antibody (BE-8) as part of the second conditioning regimen in a multicenter prospective randomized trial of tandem autologous stem cell transplantation (ASCT). The first ASCT was prepared by melphalan 200 mg/m2, and the second one by melphalan 220 mg/m2 plus dexamethasone with or without BE-8 infusion. Two hundred and nineteen patients were included in this trial and 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) 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 46% in arm A vs 51% in arm B (p = .90), median EFS 35 months in arm A vs 31 in arm B (p = .39). In high-risk patients the dose-intensity of melphalan 420 mg/m2 leaded to encouraging results, but the addition of anti-IL6 monoclonal antibody to the second conditioning regimen did not improve neither OS nor EFS.
Introduction

Autologous stem cell transplantation (ASCT) is currently considered as the standard of care for younger patients with multiple myeloma (MM) (1-2). Melphalan 200 mg/m2 (mel200) is considered to be the optimal conditioning regimen (3). The randomized IFM94 trial showed that double transplantation significantly improved both overall survival (OS) and event-free survival (EFS) compared with a single ASCT (4).

In newly diagnosed MM patients, a number of biological markers or genetic abnormalities have been shown to adversely influence the outcome after ASCT, including high levels of beta-2 microglobulin (β2m), CRP or LDH, increased plasma cell labelling index, hypodiploidy, chromosome 13 deletion (Δ13), translocation (4;14), or a combination of these factors (2, 4-8). In a retrospective trial of 110 patients treated with high-dose therapy (HDT) followed by ASCT (7), Facon et al have shown that patients presenting with both high β2m and Δ13 (identified by FISH) at the time of diagnosis had a poor outcome with a median survival and progression-free survival (PFS) of 25 and 15 months, respectively. On the contrary, when Δ13 was not documented and β2m was low, the median survival time was not reached at 111 months and the median PFS time was 37 months. Patients with either a high β2m or a Δ13 had an intermediate outcome, with a median survival and PFS times of 47 and 26 months respectively. Thus the combination of these two biological markers at diagnosis allowed to identify a high-risk subgroup of patients, representing approximately 25 to 30% of the de novo patients less than 65 years.

To treat this subgroup of high-risk patients presenting with both Δ13 and high β2m at the time of diagnosis, the IFM group designed in 1999 two specific trials. When an HLA-identical sibling donor was identified at diagnosis, patients were offered dose-reduced allogeneic stem cell transplantation after a single melphalan-based (melphalan 200 mg/m2 : mel200) ASCT:
Patients and methods

Eligibility

The IFM 99-04 trial was conducted from April 2000 to August 2004. Patients less than 65 years of age, with Durie-Salmon stage I (one bone lesion), II, or III myeloma, who had both initial biologic features A13 (FISH analysis) and $\beta2$m level > 3 mg/L were eligible. FISH analysis (7) 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 less than 50 percent), chronic respiratory disease (indicated by a vital capacity or carbon monoxide diffusing capacity less than 50 percent of predicted), abnormal liver function (indicated by a serum bilirubin level more than 2mg per deciliter [35 µmol per liter] or an alanine aminotransferase or aspartate aminotransferase level more than four times the upper limit of normal), psychiatric disease, and availability of an HLA-identical sibling (inclusion criterion in the IFM99-03 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 Institutional Review Board of each participating centre (listed in Appendix), approved and registered by the official French agency for health security, and patients gave written informed consent.

**Study protocol (Figure 1 & 2)**

After registration in the study, patients were initially treated with a continuous intravenous infusion of 0.4 mg of vincristine and doxorubicin 9 mg/m2 over a 24-hour period for four consecutive days, with 40 mg of oral DXM per day on days 1 through 4 (VAD regimen). Three or four cycles of VAD were administered at four-week intervals. After initial chemotherapy, patients with a performance status below World Health Organization grade 3 and adequate cardiopulmonary, hepatic and renal functions underwent peripheral blood stem cell (PBSC) collection. Stem cells were collected after G-CSF priming (10 µg/kg/d for 6 days). Daily apheresis was continued until at least 5 x 106 CD34 cells per kilogram were collected in order to perform the tandem transplant program. After PBSC collection, patients received a first ASCT prepared by mel200. After this first ASCT, patients were then randomly assigned to one of the two HDT groups. Randomization was stratified according to the center and carried out by fax. In arm A, patients received a second ASCT prepared by the
combination of DXM 40 mg/day during 4 days plus mel220 infused over 30 min 48 hours before stem cell reinfusion. In arm B, patients received a second ASCT prepared by the combination of mel220, DXM and the addition of a B-E8 administered as previously described (12) (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; progressive disease was defined as a 25% increase 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 complete response and as a 50% increase above the plateau level of paraprotein in two samples obtained 4 weeks apart in a patient who had had a response.

FISH analysis

FISH analysis of 13q and 14q32 abnormalities has been 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 two HDT modalities, the first one using mel220 + DXM (arm A) and the second one using mel220 + DXM + anti-IL6 moAb (arm B). Secondary end-points were to compare both arms regarding OS and EFS, to study the feasibility and the toxicity of a tandem transplant with 2 different dosages of melphalan (mel200, and mel220). Assuming the complete response rate to be 25% in the DXM + mel220 arm, the study required 200 patients to have 80 percent power to detect an absolute improvement of 15% in the complete response rate in the mel220 + DXM + anti-IL6 moAb arm. The recruitment target was 200 randomized patients. Two interim-analysis were planned, the first one after the first 50 patients in order to check feasibility and toxic death rate, and after 140 randomized patients to check OS and EFS. The board of the IFM group agreed to stop the trial in September 2004 when there was a total of 165 patients randomized, considering the total lack of difference regarding primary and secondary end-points of the study.

Overall survival 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. Event-free survival was calculated from the date of diagnosis to the date of progression, relapse or death. Data on patients who had not had 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), biological (isotype, β2m, CRP, creatinine, hemoglobin, albumin, calcium), cytogenetic (14q32 rearrangement) characteristics at presentation. Comparison of frequencies between groups were performed using the \( \chi^2 \) and fisher’s exact tests. Median values were compared by Wilcoxon’s rank-sum test. Survival 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 base-line characteristics of the 219 patients. A total of 53 (24.2%) enrolled patients did not proceed to randomization because of disease progression (n = 17), 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), pulmonary failure (n = 2). Thus, 166 (75.8%) patients were randomised (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 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 + VGPR 16% after VAD induction therapy, 34% after the first ASCT, and 51% after the second ASCT.

The treatment related mortality 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).
Overall survival and event-free survival

Figure 3 depicts OS from diagnosis for the whole group of 219 patients enrolled in the trial. At the reference date of 15 May, 2005, the median OS was 41 months, and the 56-month survival 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). Overall survival 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 < .0001, figures 3 & 4).

Randomized patients

Baseline characteristics were identical in the 2 treatment arms, except for age at diagnosis: median age 56 years in arm A vs 59 years in arm B, p = .05 (Table 1).

Toxicity of the second conditioning regimen

Table 3 shows the toxicity of mel220 + DXM +/- anti-IL6 moAb. The median duration of hospitalisation was identical, 22 days, in both arms of the trial. No adverse side-effect was reported due to anti-IL6 moAb infusion. No veno-occlusive disease was reported. The duration of neutropenia and the number of transfusions were identical in both groups. The incidence of grade 3 and 4 mucositis (WHO scale) was similar in both groups, 54% in arm A vs 49% in arm B. One patient in arm A and 2 patients in arm B respectively died of infectious complications.

Response rate

The response rates after the second ASCT were strictly identical in both arms of the study (Table 2): CR 31% in arm A vs 35% in arm B, p = .62, CR + VGPR 50% in arm A vs 53% in arm B, p = .42. The number of patients with a PR was also similar in both arms (p = .44).
**Overall survival and event-free survival**

The median follow-up time for living patients who were randomized was 24 months (9-59). The EFS was identical in both arms of the study, median 35 months in arm A vs 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 vs arm B, 46% vs 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: β2m level > 8 mg/L (median survival 30 months in the group of 47 patients with β2m > 8 vs 47 months for the 172 remaining patients, p = .002 and median EFS 22 months vs 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 β2m > 8 vs not reached for the 136 remaining patients, p = .04 and median EFS 24 months vs 36, p = .08). On the other hand in this population of 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 (ISS) (13) was not predictable for survival, but the inclusion criterion β2m > 3 mg/L interferes with the definition of ISS1 (in which patients must present with β2m < 3.5 mg/L).
**Discussion**

Until now, no study has been specifically designed to study the impact of HDT on a subset of high-risk de novo MM patients. Barlogie et al 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 unfavourable karyotype (Δ11/13) and elevated β2m (> 4) experienced both shorter OS and EFS (median 2.1 and 1.7 years dated from the time of the first cycle of VAD, respectively) as compared with others (median 7.0+ and 4.2 years, respectively, p = .0001, for the remaining 206 patients, 161 with β2m < 4 mg/L and 45 with β2m > 4 mg/L but absence of Δ11/13) (Table 4) (14). More recently the same group reported the outcome of 1475 MM patients scheduled to receive tandem transplants, and showed in a multivariate analysis that Δ13/hypodiploid karyotype, pretransplant level of β2m > 2.5 mg/l and pretransplant levels of albumin < 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 three groups of patients with very different outcomes. The median EFS for patients with none (596 patients), one (562 patients) and ≥ 2 (317 patients, 21%) poor prognostic factors were 30, 22 and 11 months (P < 0.001), while the OS for the same groups of patients were 59, 41 and 16 months respectively (p < 0.001) (Table 4). The IFM group has shown similar prognostic implications for the combination of β2m and Δ13 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 β2m and Δ13. The IFM99-04 trial is the first prospective randomized trial of tandem ASCT in such patients.

The aims of the IFM99-04 trial were first to check the interest of anti-IL-6 moAb as part of the second conditioning regimen in a tandem transplant program, and secondly to
address the issue of a dose-escalation of melphalan using mel200 for the first transplant, and mel220 for the second one.

Our study shows that the addition of anti-IL-6 moAb to the second conditioning regimen did not improve neither OS nor 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 a 85% response rate after the induction chemotherapy and the first ASCT, without elevated in vivo IL-6 production in patients. This antibody, which has a true activity in vivo in high proliferative disease such as plasma cell leukaemia (11), 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 as mentioned above (7, 14, 15). This could be attributed to the dose-intensity of mel420 (mel200 plus mel220), a tandem sequence that is tolerable. A clear relationship between dose and response in patients treated with melphalan for MM has been described almost twenty years ago (16,17). 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 (9). When we used mel220 in patients with primary refractory disease or patients who relapsed after a prior HDT, the response rate was 85%, with a 2-year survival rate of 67% (10). The escalation of melphalan dosage has also been investigated by another group in North America who reported in an abstract form 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 non-hematopoietic tissues (18). Fourty 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 favourably with the tandem mel140, mel140 + 8 Gy total body irradiation of this latter study (4). A similar median EFS of 33 and 31 months has also been described in the double transplant arm of the MAG95 trial (19), and of the Bologna trial (20), respectively. In these 3 latter studies, IFM94 MAG95 and Bologna trials, patients with de novo MM were included regardless β2m level or 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 chromosome 13 abnormality and β2m level > 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 (6). These results, using a tandem dose-intensified approach, are also apparently better than those recently reported by the group of Princess Margaret Hospital (8). 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 transplant program.

In conclusion, in the first prospective trial of tandem ASCT in patients with high-risk MM, we have shown that the addition of anti-IL6 moAb as part of the second conditioning regimen in a tandem transplant program does not improve survival. In this situation dose-intensity of 420 mg/m2 melphalan leads to a median survival of 41 months. Innovative, more effective, treatment approaches are warranted, or under evaluation, such as modification of induction regimen using thalidomide or proteasome inhibitor (21-24), or maintenance therapy using thalidomide analogs.

Appendix

The following additional centres and investigators from The Intergroupe Francophone du Myélome participated in this study:

Amiens, Centre Hospitalier Général, V.Salles; Angers, Centre Hospitalier Régional et Universitaire, M.Dib; Avignon, Centre Hospitalier Général, G.Lepet; Bourg-en-Bresse, Centre Hospitalier Général, M.C.Perrin; Brussels, Belgium, Centre Universitaire Saint Luc, A.Ferrant; Clermont-Ferrand, Centre Hospitalier Régional et Universitaire, C.Chaletex; Dijon, Centre Hospitalier Régional et Universitaire, D.Caillot; Dunkerque, Centre Hospitalier Général, M.Wetterwald; Genève, Switzerland, Hôpital Universitaire, T.Matthès; Haine-Saint-Paul, Belgium, Centre Hospitalier Jolimont, P.Delannoy; La Roche sur Yon, Centre Hospitalier Général, M.Tiab; Le Havre, Centre Hospitalier Général, M.Zarnitsky; Lyon-Sud, Centre Hospitalier Régional et Universitaire, C.Dumontet; Marseille, Centre Paoli-Calmette, A.M.Stoppa; Metz, Centre Hospitalier Général, V.Dorvaux; Pau, Clinique des Pyrénées, D.Schlaiffer; Percy-Clamart, Hôpital des Armées, B.Souleau; Perpignan, Centre Hospitalier Général, X.Vallantin; Poitiers, Centre Hospitalier Régional et Universitaire, F.Guilhot;
Quimper, Centre Hospitalier Général, J.P.Vilque; Reims, Centre Hospitalier Régional et Universitaire, B.Kolb; Rennes-Sud, Centre Hospitalier Régional et Universitaire, B.Grosbois; Rennes-Ponchaillou, Centre Hospitalier Régional et Universitaire, C.Dauriac; Saint-Etienne, Centre Hospitalier Régional et Universitaire, J.Jaubert; Strasbourg, Centre Hospitalier Régional et Universitaire, F.Maloisel; Suresnes, Hôpital Foch, M.Janvier; Vannes, Centre Hospitalier Général, H.Jardel; Annecy, Centre Hospitalier Général, C.Martin; Institut Curie, Centre Anti-cancéreux, J.Decaudin; Laval, Centre Hospitalier Général, M.Jacomi; Boulogne-sur-mer, Centre Hospitalier Général, X.Agape; Caen, Centre Anti-cancéreux, A.M.Pény; Colmar, Centre Hospitalier Général, B.Audhuy; Villejuif, Institut Gustave Roussy, J.H.Bourhis; Brussels, Belgium, Institut Bordet, P.Bron; Bruges, Belgium, M.Lauvagie; Paris, Hôpital Saint-Louis, P.Brice; Draguignan, Centre Hospitalier Général, B.Valenza; Caen, Polyclinique du Parc, X.Levaltier; Le Mans, Centre Hospitalier Général, M.Duguet; Blois, Centre Hospitalier Général, P.Rodon.
References


Figure 1: IFM 99-04 trial profile

Enrollment

VAD

Stem cell collection

mel200 + ASCT n°1

Randomization

Arm A
DXM + mel220
+ ASCT n°2

Arm B
DXM +B-E8 + mel220
+ ASCT n°2
Figure 2: Conditioning regimen in arm B

B-E8: anti-iL-6-murine mAb (Diaclone Research / OPI – France)

DXM 40mg 40mg 40mg 40mg

G-CSF

100mg 50mg 50mg 50mg mel 220

Day

-6 -5 -4 -3 -2 -1 0 7

ASCT
Figure 3. Overall survival

No. At risk
Randomized 166 122 72 40 13
Non randomized 53 20 10 7 2

Probability of Survival

p < .0001

All patients, n = 219

Non randomized
Randomized

months
Figure 4. Event-free survival

- Non randomized
- Randomized
- All patients, n = 219

No. At risk

Randomized 166 122 72 40 13
Non randomized 53 20 10 72

p < .0001
Figure 5. Event-free survival

<table>
<thead>
<tr>
<th>No. At risk</th>
<th>Arm A</th>
<th>Arm B</th>
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<tr>
<td></td>
<td>85</td>
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Figure 6. Overall survival

\[ p = .90 \]
## Table 1. Patient’s characteristics

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<th>Arm A n = 85</th>
<th>Arm B n = 81</th>
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<tr>
<td>Age at diagnosis</td>
<td>58 (28-65)</td>
<td>56 (34-65)</td>
<td>59 (28-65)</td>
<td>.05</td>
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<tr>
<td>Sex (M/F)</td>
<td>114 / 105</td>
<td>41 / 44</td>
<td>47 / 34</td>
<td>.28</td>
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<tr>
<td>Isotype (G/A/BJ)</td>
<td>121 / 62 / 36</td>
<td>45 / 23 / 17</td>
<td>42 / 24 / 15</td>
<td>.93</td>
</tr>
<tr>
<td>Stage (I/II/III)</td>
<td>2 / 24 / 193</td>
<td>1 / 9 / 75</td>
<td>0 / 10 / 71</td>
<td>.98</td>
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<tr>
<td>β2m (mg/L)</td>
<td>4.9 (3.03-39.4)</td>
<td>4.6 (3.1-28.5)</td>
<td>4.8 (3.1-37.2)</td>
<td>.35</td>
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<tr>
<td>β2m &gt; 5.5 mg/L (ISS 3)</td>
<td>88 (40.2%)</td>
<td>29 (34.1%)</td>
<td>32 (39.5%)</td>
<td>.26</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38 (16.2-54)</td>
<td>38 (22.5-54)</td>
<td>37 (16.2-52)</td>
<td>.62</td>
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<tr>
<td>Albumin &gt; 35 g/L</td>
<td>134 (61%)</td>
<td>51 (60%)</td>
<td>51 (63%)</td>
<td>.47</td>
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<tr>
<td>Platelets (G/L)</td>
<td>211 (20-500)</td>
<td>216 (60-462)</td>
<td>204 (84-469)</td>
<td>.63</td>
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<tr>
<td>Hb (g/dL)</td>
<td>9.8 (4.7-14.7)</td>
<td>9.5 (5.1-14.7)</td>
<td>10.2 (4.7- &gt; 14.4)</td>
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<td>Ca (mM/L)</td>
<td>2.43 (1.87-4.5)</td>
<td>2.42 (1.96-4.5)</td>
<td>2.42 (1.87-4.03)</td>
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<td>CRP (mg/L)</td>
<td>6 (1-279)</td>
<td>7 (1-244)</td>
<td>2.42 (1.87-4.03)</td>
<td>.22</td>
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<td>t(11;14) Yes/No/Missing</td>
<td>21 / 124 / 74</td>
<td>5 / 55 / 25</td>
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<td>.11</td>
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<td>t(4;14) Yes/No/Missing</td>
<td>26 / 116 / 77</td>
<td>10 / 47 / 28</td>
<td>5 (1-137)</td>
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<td>Interval between VAD and 1st ASCT (days)</td>
<td>-</td>
<td>130 (95-252)</td>
<td>11 / 57 / 13</td>
<td>.61</td>
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<tr>
<td>Interval between 1st and 2nd ASCT (days)</td>
<td>-</td>
<td>90 (50-206)</td>
<td>10 / 58 / 13</td>
<td>.78</td>
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Table 2. Disease response

<table>
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<tr>
<th>Response</th>
<th>VAD n = 219 (100%)</th>
<th>ASCT n°1 n = 182 (100%)</th>
<th>ASCT n°2 Arm A n = 85 (100%)</th>
<th>ASCT n°2 Arm B n = 81 (100%)</th>
<th>p</th>
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<tr>
<td>CR</td>
<td>9 (4.1)</td>
<td>26 (14.3)</td>
<td>26 (30.6)</td>
<td>28 (34.6)</td>
<td>.62</td>
</tr>
<tr>
<td>VGPR</td>
<td>26 (11.9)</td>
<td>36 (19.8)</td>
<td>16 (18.8)</td>
<td>14 (17.3)</td>
<td>.84</td>
</tr>
<tr>
<td>PR</td>
<td>104 (47.5)</td>
<td>98 (53.8)</td>
<td>39 (45.9)</td>
<td>31 (36.5)</td>
<td>.44</td>
</tr>
<tr>
<td>Stable or MR</td>
<td>49 (22.3)</td>
<td>16 (8.8)</td>
<td>2 (2.4)</td>
<td>4 (4.9)</td>
<td>.43</td>
</tr>
<tr>
<td>Progressive</td>
<td>25 (11.4)</td>
<td>4 (2.2)</td>
<td>1 (1.2)</td>
<td>2 (2.5)</td>
<td>.61</td>
</tr>
<tr>
<td>Death</td>
<td>6 (2.7)</td>
<td>2 (1.1)</td>
<td>1 (1.2)</td>
<td>2 (2.5)</td>
<td>.61</td>
</tr>
</tbody>
</table>
Table 3. Toxicity of the second conditioning regimen

<table>
<thead>
<tr>
<th></th>
<th>Arm A n = 85</th>
<th>Arm B n = 81</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of G-CSF, d (median)</td>
<td>4 – 13 (6)</td>
<td>2 – 11 (6)</td>
<td>.70</td>
</tr>
<tr>
<td>Duration of neutropenia, d (median)</td>
<td>4 – 15 (8)</td>
<td>4 – 19 (7)</td>
<td>.88</td>
</tr>
<tr>
<td>Duration of thrombocytopenia, d (median)</td>
<td>2 – 100 (8)</td>
<td>0 – 200 (8)</td>
<td>.71</td>
</tr>
<tr>
<td>No. of platelet transfusions (median)</td>
<td>0 - 8</td>
<td>0 - 29</td>
<td>.63</td>
</tr>
<tr>
<td>No. of red blood cell transfusion (median)</td>
<td>0 – 10 (1)</td>
<td>0 – 9 (2)</td>
<td>.45</td>
</tr>
<tr>
<td>Duration of hospitalisation, d (median)</td>
<td>17 – 120 (22)</td>
<td>13 – 82 (22)</td>
<td>.68</td>
</tr>
<tr>
<td>Anti-IL6 toxicity</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac toxicity grade 3-4 (%)</td>
<td>1 (1.2)</td>
<td>2 (2.5)</td>
<td>.61</td>
</tr>
<tr>
<td>Mucositis grade 3-4 (%)</td>
<td>46 (54.1)</td>
<td>40 (49.4)</td>
<td>.64</td>
</tr>
<tr>
<td>Pulmonary toxicity grade 3-4 (%)</td>
<td>3 (3.5)</td>
<td>3 (3.7)</td>
<td>1</td>
</tr>
<tr>
<td>Renal toxicity grade 3-4 (%)</td>
<td>3 (3.5)</td>
<td>2 (2.5)</td>
<td>1</td>
</tr>
<tr>
<td>Liver toxicity grade 3-4 (%)</td>
<td>2 (2.4)</td>
<td>2 (2.5)</td>
<td>1</td>
</tr>
<tr>
<td>Toxic death (%)</td>
<td>1 (1.2)</td>
<td>2 (2.5)</td>
<td>.61</td>
</tr>
</tbody>
</table>
Table 4. Results of studies in high-risk MM patients, and of tandem ASCT.

<table>
<thead>
<tr>
<th>Study in high-risk MM pts (reference)</th>
<th>Criteria</th>
<th>No. of pts</th>
<th>Median EFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM (7)</td>
<td>β2m ≥ 2.5 and Δ13* 2m &gt; 4 and Δ11/13*** 2m &gt; 2.5 and Δ13/hypodiploid*** and albumin &lt; 35</td>
<td>22 / 168 23 / 229 317 / 1475</td>
<td>15** 20.4 11</td>
<td>25 25.2 16</td>
</tr>
<tr>
<td>Arkansas (14)</td>
<td>β2m &gt; 3 and Δ13</td>
<td>219</td>
<td>30</td>
<td>41</td>
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<tr>
<td>Arkansas (15)</td>
<td></td>
<td></td>
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<tr>
<td>IFM 99-04</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Tandem ASCT</td>
<td>de novo, &lt; 61 years</td>
<td>200</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>IFM 94 (4)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MAG 95 (19)</td>
<td>de novo, &lt; 59 years</td>
<td>115</td>
<td>33</td>
<td>73</td>
</tr>
<tr>
<td>Bologna (20)</td>
<td>de novo, &lt; 61 years</td>
<td>113</td>
<td>31</td>
<td>60</td>
</tr>
</tbody>
</table>

* : FISH analysis  
**: Progression-free survival  
*** : Conventional cytogenetic
Tandem autologous stem cell transplantation in high-risk de novo multiple myeloma: final results of the prospective and randomized IFM 99-04 protocol