Autologous Stem Cell Transplantation After First Remission Induction Treatment in Multiple Myeloma: A Report of the French Registry on Autologous Transplantation in Multiple Myeloma

By Jean-Luc Harousseau, Michel Attal, Marine Divine, Gerald Marit, Véronique Leblond, Anne-Marie Stoppa, Jean-Henri Bourhis, Denis Caillot, Marc Boasson, Jean-François Abgrall, Thierry Facon, Claude Linassier, Jean-Yves Cahn, Thierry Lamy, Xavier Troussard, Nicole Gratacos, Bernard Pignon, Gilles Auzanneau, and Régis Bataille

Eighteen French centers reported 133 autologous stem cell transplantations performed after first remission induction in multiple myeloma. The source of stem cell was marrow (81 cases), blood (51 cases) or marrow plus blood (1 case). The immediate outcome after transplantation was 49 (37%) complete remissions (CRs) (13 maintained, 36 achieved), 61 (46%) partial remissions, 17 failures and 5 toxic deaths. With a median follow-up of 35 months, the median remission duration was 33 months, the median time to treatment failure was 22 months. The median survival was 46 months overall, 54 months for the 103 patients responding to primary treatment, and 30 months for the 30 nonresponders. In univariate analysis, the outcome was influenced by age, Ig isotype, initial β2 microglobulin level, response to initial chemotherapy, plasma cell marrow involvement at the time of harvest, albumin and β2 microglobulin level at the time of transplantation, and CR achievement after transplantation. In multivariate analysis, the most important prognostic factor was the quality of response after transplantation. The conditioning regimen and the source of stem cell had no significant impact on immediate and long-term results. Maintenance therapy with interferon α did not appear to prolong remission duration or survival. Autologous stem cell transplantation is an effective consolidation for patients responding to primary treatment and a salvage therapy for some nonresponding patients. This approach has to be compared to conventional chemotherapy in prospective randomized studies. The critical impact of CR achievement on survival implies new strategies to increase the CR rate.

© 1995 by The American Society of Hematology.

PATIENTS AND METHODS

Patients

One hundred seventy-nine patients with MM who received ASCT in 18 French centers from 1984 to 1991 have been reported to the French Registry on autologous transplantation in MM. Some of these patients have been included in recently published series. Each investigator willing to participate in this registry analysis has reported all consecutive transplants performed in his own center within this period. Of these 179 patients, 46 have undergone ASCT after first or subsequent relapse. We have focused on the other 133 patients who have undergone ASCT as part of front-line therapy after initial tumor cytodestruction with various conventional (109 patients) or intensive (HDM 140 mg/m² without any hematopoietic support: 24 patients) chemotherapy regimens. According to the response to this initial chemotherapy, the 133 patients were classified into two groups.

Group 1 (responders). In this group of 103 patients, the initial chemotherapy obtained at least a 50% reduction of the serum M component or urinary M protein excretion according to the Chronic Leukemia Myeloma Task Force. Seventy-eight patients were in early response (=6 cycles of chemotherapy) and 25 patients were in stable remission (plateau phase after more than 6 cycles of chemotherapy).

Group 2 (nonresponders). This group consisted of 30 patients who did not respond to the initial chemotherapy.

In 5 cases, ASCT was decided after failure of only one line of chemotherapy whereas the other 25 cases were considered as truly primary refractory MM (failure of at least 2 lines of chemotherapy). The initial characteristics of the patients are shown in Table 1. The incidence of IgG isotype was lower in group 1 (48% v 73%; P = .025). The incidence of Durie-Salmon stage III was higher in group 1 (90%) than in group 2 (63%) (P = .001). The median interval between diagnosis and ASCT was longer in group 2 (9 v 7.5 months; P = .02). At the time of stem cell collection, the percentage of plasma cells in the marrow was higher in group 2 (0% to 40%; median, 16%) than in group 1 (0% to 42%; median, 3.5%) (P = 0.002). The incidence of patients with >15% plasma cells was 56% in group 2 versus 14% in group 1 (P = .0001).


Address reprint requests to Jean-Luc Harousseau, MD, Department of Hematology, Hôtel-Dieu, BP 1005, 44035 Nantes Cedex 01, France.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1995 by The American Society of Hematology.

0006-4971/95/8511-0003$3.00/0

Blood, Vol 85, No 11 (June 1), 1995: pp 3077-3085
Table 1. Initial Characteristics of the Patients

<table>
<thead>
<tr>
<th></th>
<th>ALL (N = 133)</th>
<th>Group 1 Responding Pts. (N = 103)</th>
<th>Group 2 Nonresponders (N = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>78/55</td>
<td>64/39</td>
<td>14/16</td>
<td>NS</td>
</tr>
<tr>
<td>Age (median)</td>
<td>26-66 (52)</td>
<td>26-66 (52)</td>
<td>35-66 (53)</td>
<td>NS</td>
</tr>
<tr>
<td>Type of MM (IgG/IgA/BJ/others)</td>
<td>71/33/24/5</td>
<td>49/30/19/5</td>
<td>22/3/5</td>
<td>.025*</td>
</tr>
<tr>
<td>Light chain (k/λ subtypes)</td>
<td>81/41</td>
<td>62/32</td>
<td>19/9</td>
<td>NS</td>
</tr>
<tr>
<td>Stage III (%)</td>
<td>108/128 (84.5%)</td>
<td>91/101 (90%)</td>
<td>17/27 (63%)</td>
<td>.001</td>
</tr>
<tr>
<td>Initial β2-microglobulin level mg/L (median)</td>
<td>1.16 (2.8)</td>
<td>1.16 (2.8)</td>
<td>1.3-6.7 (2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>47/99 (47.5%)</td>
<td>37/78 (47%)</td>
<td>10/21 (47.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of previous chemotherapy cycles (median)</td>
<td>1-19 (5)</td>
<td>1-19 (4)</td>
<td>3-19 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Interval diagnosis-ASCT (median in months)</td>
<td>1-151 (8)</td>
<td>1-151 (7.5)</td>
<td>2-91 (9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Interval first chemotherapy-ASCT (median in mos)</td>
<td>1-51 (7)</td>
<td>1-34 (7)</td>
<td>4-51 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>≤6 mo</td>
<td>48 (36%)</td>
<td>41 (40%)</td>
<td>7 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;1 yr</td>
<td>103 (77.5%)</td>
<td>80 (77.5%)</td>
<td>23 (76.5%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

* IgG versus non IgG.
† This value was available in 99/133 cases.

ASCT

The source of stem cell was bone marrow in 81 cases, peripheral blood in 51 cases, bone marrow and peripheral blood in 1 case (Table 2). Bone marrow was never in vitro manipulated. PBSC collection was performed during hematopoietic reconstitution after intensive chemotherapy, high-dose cyclophosphamide23 or high-dose CHOP (cyclophosphamide, adriamycin, vincristin, prednisone) regimen,22 but without any hematopoietic growth factor. The number of cytapheresis ranged from 2 to 9 (median, 5).

The conditioning regimen was either chemotherapy alone in 33 cases (HDM 140 mg/m² in 25 cases, chemotherapy combinations in 8 cases) or TBI plus chemotherapy (HDM 140 mg/m² in 71 cases, HDM plus other chemotherapies in 29 cases). TBI was delivered in different ways: 8 Gy in 4 fractions over 4 days (44 patients), 10 Gy in a single dose (18 patients), 12 Gy in 6 fractions over 3 days (30 patients), and others (8 patients). Patients were nursed in laminar air flow rooms according to the available facilities in each center. Gut decontamination antibiotics and transfusions were used as indicated in each transplant unit.

Response to ASCT was assessed after the criteria defined by Gore et al. Patients were regarded as having achieved complete remission (CR) when no paraprotein was measurable by serum proteins electrophoresis, when no Bence Jones proteinuria was detectable on urine electrophoresis, and when BM aspiration showed less than 5% plasma cells. As this study is multicentric and retrospective, the

Table 2. Characteristics of ASCT: Comparison Between BM and Peripheral Blood

<table>
<thead>
<tr>
<th></th>
<th>ALL No. of Evaluable Patients</th>
<th>BM No. of Evaluable Patients</th>
<th>Peripheral Blood No. of Evaluable Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at ASCT (median)</td>
<td>133 26-66 (52)</td>
<td>81 26-66 (55)</td>
<td>51 36-65 (49)</td>
<td>.001</td>
</tr>
<tr>
<td>Bone Marrow Plasma Cell Infiltration at the time of SC collection (median)</td>
<td>95 0-42 (5)</td>
<td>77 0-42 (5)</td>
<td>17 0-35 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>No of CFU GM (10⁶/K) (median)</td>
<td>93 0.2-81.4 (6.1)</td>
<td>44 0.2-72 (5.4)</td>
<td>48 0.8-84.4 (6.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin level at TX (median mg/L)</td>
<td>94 22-60 (36)</td>
<td>66 23-60 (37.5)</td>
<td>28 22-48 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>β2 microglobulin level at TX (median mg/L)</td>
<td>76 1.2-10 (2.4)</td>
<td>49 1.2-9.8 (2.4)</td>
<td>26 1.4-10 (2.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>133 25 (19%)</td>
<td>81 21 (26%)</td>
<td>51 4 (8%)</td>
<td>.02</td>
</tr>
<tr>
<td>HDM alone</td>
<td>8 (6%)</td>
<td>4 (5%)</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>Other CT</td>
<td>71 (53%)</td>
<td>53 (65%)</td>
<td>17 (33%)</td>
<td></td>
</tr>
<tr>
<td>HDM + TBI</td>
<td>29 (22%)</td>
<td>3 (4%)</td>
<td>26 (51%)</td>
<td></td>
</tr>
<tr>
<td>Other CT + TBI</td>
<td>133*</td>
<td>81</td>
<td>51</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TX, transplantation; CT, chemotherapy; NS, not significant.

* One patient received both BM and PBSCs.
absence of paraprotein was not confirmed in all cases by immuno-
fixation. Patients were in partial remission (PR) if there was a
50% decrease in M component or BM infiltration, compared with
pretransplant values. Patients who did not achieve CR or PR were
regarded as failures. Among the 110 patients achieving at least a
partial remission after ASCT, 65 received a maintenance therapy
with recombinant interferon α (IFNα; 3 MU/m² three times a week)
for a median time of 17 months (range, 1.5 to 52.5 months).

Statistical Analysis

Response rates were compared by the chi-squared test. Quantita-
tive values were compared by the Wilcoxon rank-sum test. Overall
survival (OS) was defined as the time from ASCT to death or to
last visit. Relapse-free survival (RFS) was evaluated in patients
achieving at least a PR after ASCT from the time of remission
achievement until relapse or until last visit. Relapse was assessed
according to criteria defined by Mandelli et al. Time to treatment
failure (TTF) was defined as the time from ASCT to any type of
failure (failure of ASCT, relapse or death). Actuarial survival curves
were plotted after the Kaplan-Meier method and differences between
the curves were analyzed with the log-rank test. In univariate analy-
sis, the following parameters were analyzed for their impact on the
clinical outcome (CR rate, RFS, OS and TTF): sex, age at the time
of ASCT, heavy chain type (IgG versus non IgG, IgA versus non
IgA), light-chain isotype, Durie-Salmon stage at diagnosis (stage III
versus stage I-II), β2-microglobulin level at diagnosis (cut-off values:
3 mg/L, 6 mg/L), number of chemotherapy courses given before
ASCT (≤6, >6) primary treatment with HDM, interval between first
chemotherapy and ASCT (≤6 months >6 months, ≥1 year
>1 year), percentage of BM plasma cells at the time of stem
cell collection (≥6% <6%, ≥15% <15%), albumin and β2
microglobulin levels at the time of ASCT, conditioning regimen
(TBI v no TBI, TBI < 10 Gy v TBI ≥10 Gy, TBI plus HDM v
TBI plus combination chemotherapy), source of stem cells (marrow
versus PB), and results of previous chemotherapy (group 1 v group
2, CR v PR). For RFS and OS, two other parameters were considered:
quality of response achieved after ASCT and maintenance treatment
with IFNαs in responding patients. Multivariate analysis of factors
influencing survival curves was made by the Cox proportional hazard
model. In the multivariate analysis, all variables significant at the
0.1 level in univariate analysis were considered, except the β2 micro-
globulin level at the time of transplantation, because this parameter
was available in only 75 patients. The median follow-up time for
the survivors is 35 months (range 22 to 84 months).

RESULTS

Overall Toxicity

The median duration of neutropenia (0.5 × 10⁹/L) was 17
days (range, 6 to 150 days). Only four patients received
granulocyte colony-stimulating factor (G-CSF) or granulo-
cyte-macrophage colony-stimulating factor (GM-CSF) after
ASCT. The median duration of thrombocytopenia (30 × 10⁹/
L) was 23 days (range, 4 days to more than 1 year). Fifteen
patients (11%) experienced long-lasting (more than 30 days)
neutropenia and 26 (20%), a very prolonged thrombocyto-
penia (more than 60 days). Seven patients could never have a
full hematopoietic reconstitution. Five patients died from
procedure-related complications (three veno-occlusive dis-
eseases and two interstitial pneumonitis).

Response to ASCT

The remission status after ASCT could be evaluated in
132 of the 133 patients and is shown in Table 3. Thirteen
patients (10%) who were regarded as having achieved CR
with conventional chemotherapy (4/109) or with HDM with-
out ASCT (9/24) remained in CR. After ASCT, 36 patients
(27%) achieved CR and 61 (46%) obtained a PR. There were
17 (13%) failures and 5 (4%) toxic deaths. Thus, the overall
response rate and the CR rate were 83% and 37%, respec-
tively (including patients already in CR before ASCT). The
rate of CR achievement was significantly higher in group 1
than in group 2 (33% v 7%; P = .008). In univariate analysis,
among all the other parameters (see Statistical Analysis)
tested for their influence on CR achievement, only plasma
cell infiltration at the time of stem cell collection was statisti-
cally significant (Table 4). Patients with 15% or more plasma
cells in the BM had a 8% CR rate versus 32% for patients
with less than 15% plasma cell (P = .04).

RFS

For the 110 patients who achieved at least a PR, the me-
dian remission duration was 33 months and the actuarial
probability of remaining in remission at 4 years was 35%
(±6%) (Fig 1A).

RFS was longer for patients being in CR after ASCT than
for patients achieving only PR (median, 37 v 22 months),
but the difference did not reach the significant level (log-
rank last P = .07) (Fig 1B).

In univariate analysis, three factors had a significant impact
on remission duration: (1) initial β2 microglobulin level,
<6 mg/L versus ≥6 mg/L (P = .003) (Fig 2A) or <3 mg/
L versus ≥3 mg/L (P = .05); (2) plasma cell infiltration
at the time of stem cell collection, <6% versus ≥6% (P = .01); and (3) heavy chain isotype IgA versus non IgA (0.01).
In multivariate analysis, plasma cell infiltration and initial
β2 microglobulin remained statistically significant (P = .003
and P = .01, respectively).

Overall Survival

For the entire group of 133 patients, the median survival
was 46 months and the actuarial probability of being alive
at 5 years was 43% (±7%) (Fig 3). There was a borderline
difference in favor of group 1 (median survival, 54 v 30
months; P = .06) (Fig 4A). In univariate analysis, the para-
eters significantly influencing the OS duration were β2 micro-
globulin level at the time of ASCT (<6 mg/L or ≥6 mg/
L (P = .03) and albumin level at the time of ASCT ≥30 g/
L or ≥30 g/L (P = .01). The type of response achieved after
ASCT was also a significant prognostic factor. The median
survival of the 49 patients who had a clinical CR before or
after ASCT was 60 months, versus only 33 months for the
78 patients who did not achieve CR (excluding the five toxic
deaths) (P = .003). The difference remained significant when
comparing CR and PR (Fig 4B). The 61 patients who
achieved only a PR had a median survival of 42 months (P = .04).
In multivariate analysis, the quality of response after
ASCT was the only significant parameter (P < .0001).
Table 3. Response to ASCT

<table>
<thead>
<tr>
<th>Type of Remission Induction</th>
<th>HDM</th>
<th>Conventional CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR Responders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR maintained (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR achieved (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| No. of evaluable patients   | 132 | 13 | 89 | 102 | 30 | 24 | 108 |
| CR maintained (%)           | 13 (10) | 13 (100) | 13 (13) | 9 (37.5) | 4 (3.5) |
| CR achieved (%)             | 36 (27) | 34 (38) | 34 (33) | 2 (7) | 34 (31.5) |
| PR (%)                      | 61 (46) | 45 (50.5) | 45 (44) | 16 (53) | 11 (46) | 50 (48) |
| Failure (%)                 | 17 (13) | 7 (8) | 7 (7) | 10 (33) | 2 (8) | 15 (14) |
| Toxic death                 | 5 (4) | 3 (3.0) | 3 (3) | 2 (7) | 5 (4.5) |

Abbreviations: TT, treatment; CT, chemotherapy.

**TTF**

As OS can be influenced by the results of salvage therapy given after failure of ASCT, we also looked at TTF (Table 4). The median time between ASCT and failure, relapse, or death was 22 months with an actuarial probability of being in first response at 5 years of 17% (±7%). In univariate analysis, the parameters influencing TTF were the response to initial chemotherapy (group 1 vs group 2, \( P = .004 \)); age

Table 4. Univariate Analysis of Parameters Influencing the Outcome After ASCT

<table>
<thead>
<tr>
<th>Age</th>
<th>CR Achievement (%)</th>
<th>Median RFS (mos)</th>
<th>Median Overall Survival (mos)</th>
<th>Median TTF (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 y (N = 52)</td>
<td>29.5 ( P = .53 )</td>
<td>36.0</td>
<td>54.8</td>
<td>33.3</td>
</tr>
<tr>
<td>≥50 y (N = 81)</td>
<td>36</td>
<td>27.0</td>
<td>42.0</td>
<td>17.2</td>
</tr>
<tr>
<td>Response to initial CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders (N = 103)</td>
<td>33 ( P = .008 )</td>
<td>33.0</td>
<td>54.0</td>
<td>31.0</td>
</tr>
<tr>
<td>Nonresponders (n = 30)</td>
<td>7 ( P = .32 )</td>
<td>26.0</td>
<td>30.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Initial β2 microglobulin level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 mg/L (N = 52)</td>
<td>29 ( P = .52 )</td>
<td>52.0</td>
<td>NR</td>
<td>22.0</td>
</tr>
<tr>
<td>≥3 mg/L (N = 47)</td>
<td>21 ( P = .05 )</td>
<td>22.0</td>
<td>33.4</td>
<td>16.0</td>
</tr>
<tr>
<td>&lt;6 mg/L (N = 82)</td>
<td>24 ( P = .003 )</td>
<td>19.0</td>
<td>NR</td>
<td>22.0</td>
</tr>
<tr>
<td>≥6 mg/L (N = 17)</td>
<td>29 ( P = .32 )</td>
<td>16.0</td>
<td>33.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Heavy chain isotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA (N = 33)</td>
<td>33 ( P = .44 )</td>
<td>23.0</td>
<td>30.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Non IgA (N = 100)</td>
<td>25 ( P = .01 )</td>
<td>37.0</td>
<td>46.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Plasma cell infiltration at SC collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6% (N = 48)</td>
<td>33 ( P = .18 )</td>
<td>39.0</td>
<td>61.0</td>
<td>32.0</td>
</tr>
<tr>
<td>≥6% (N = 47)</td>
<td>19 ( P = .01 )</td>
<td>25.0</td>
<td>31.0</td>
<td>16.0</td>
</tr>
<tr>
<td>&lt;15% (N = 71)</td>
<td>32 ( P = .60 )</td>
<td>33.0</td>
<td>60.0</td>
<td>31.0</td>
</tr>
<tr>
<td>≥15% (N = 24)</td>
<td>8 ( P = .09 )</td>
<td>20.0</td>
<td>31.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Albumin level at TX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 g/L (N = 14)</td>
<td>21.5 ( P = .36 )</td>
<td>10.0</td>
<td>14.0</td>
<td>8.0</td>
</tr>
<tr>
<td>&gt;30 g/L (N = 79)</td>
<td>28 ( P = .61 )</td>
<td>34.0</td>
<td>61.0</td>
<td>30.0</td>
</tr>
<tr>
<td>β2 microglobulin level at TX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mg/L (N = 69)</td>
<td>19 ( P = .11 )</td>
<td>27.0</td>
<td>2.0</td>
<td>22.0</td>
</tr>
<tr>
<td>≥6 mg/L (N = 6)</td>
<td>33 ( P = .03 )</td>
<td>7.0</td>
<td>25.0</td>
<td>7.0</td>
</tr>
<tr>
<td>CR achievement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (N = 49)</td>
<td>37 ( P = .07 )</td>
<td>60.0</td>
<td>42.0</td>
<td>22.0</td>
</tr>
<tr>
<td>PR (N = 61)</td>
<td>32 ( P = .01 )</td>
<td>60.0</td>
<td>42.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (N = 33)</td>
<td>25 ( P = .34 )</td>
<td>39.0</td>
<td>39.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Chemotherapy + TBI (N = 100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI &lt; 10 Gy (N = 44)</td>
<td>32 ( P = .69 )</td>
<td>31.0</td>
<td>46.0</td>
<td>22.0</td>
</tr>
<tr>
<td>TBI = 10 Gy (N = 56)</td>
<td>25 ( P = .69 )</td>
<td>30.0</td>
<td>46.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Source of SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM (N = 80)</td>
<td>22.5 ( P = .44 )</td>
<td>50.0</td>
<td>39.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Blood SC (N = 51)</td>
<td>33 ( P = .50 )</td>
<td>37.0</td>
<td>46.0</td>
<td>31.0</td>
</tr>
</tbody>
</table>

Abbreviations: CT, chemotherapy; SC, stem cell; TTF, time to treatment failure; TX, transplantation; NR, not reached.
conditioning regimen containing HDM. There was no significant difference in the outcome after ASCT between the 24 patients treated with HDM and the 103 treated without HDM. The overall response rate and the CR rate were 91.5% and 45.5% after primary treatment with HDM versus 81% and 35% after primary treatment with conventional chemotherapy. The median RFS, OS, and TTF were 22 and 33 months ($P = .10$), 41 and 46 months ($P = .69$) and 20 and 23 months ($P = .35$), respectively.

**Influence of the Conditioning Regimen**

The conditioning regimen did not appear to be correlated with CR achievement. CR was achieved in 8 of 32 evaluable patients (25%) prepared with chemotherapy only and in 28 of 100 patients (28%) prepared with chemotherapy plus TBI ($P$ value is not significant). The CR achievement rate was 32% (14/44) when TBI was delivered at the dose of 8 Gy versus 25% (14/56) when the total dose was 10 Gy or more.

**Fig 1.** (A) RFS of the 110 patients achieving at least a PR. (B) Comparison of RFS for patients achieving CR (♦) and PR (○) after ASCT (log-rank test, $P = .07$).

<50 or ≥50 ($P = .04$); the initial β2 microglobulin level, <6 mg/L or ≥6 mg/L ($P = .05$); the heavy chain type, IgA versus non IgA ($P = .04$); the marrow plasma cell infiltration at the time of stem cell collection (<6% v ≥6%, $P = .02$; <15% v ≥15%, $P = .02$); and the β2 microglobulin level at the time of ASCT, <6 mg/L versus ≥6 mg/L ($P = .02$).

In multivariate analysis, plasma cell infiltration was the only significant factor ($P = .018$).

**Influence of HDM Given as Remission Induction Treatment**

Of the 133 patients, 24 received HDM as part of their initial remission induction treatment. Twenty of them did respond to HDM and 9 (37.5%) were considered in clinical CR after HDM versus only 4 of 109 (3.5%) treated only with conventional chemotherapy ($P < .0001$). However only 2 of the 15 patients who were not in CR after HDM could achieve CR after ASCT. Thirteen of these 15 patients had a

**Fig 2.** (A) Impact of the initial β2 microglobulin level on RFS (log-rank test, $P = .002$). (B) Impact of IFNα maintenance therapy for patients in CR after ASCT (interferon, 29 patients; no interferon, 20 patients; log-rank test, $P = .10$).
There was no significant difference regarding median RFS, OS, and TTF when comparing conditioning regimens with or without TBI, or TBI < 10 Gy and TBI ≥ 10 Gy (Table 4).

Comparison Between BM and Blood Stem Cell Transplantation

The source of stem cell was BM in 81 cases and PB in 51 cases (1 patient received both marrow and blood). The 2 groups were comparable for all prognostic parameters except for age and type of conditioning regimen (Table 2). The median age was 55 years (range, 26 to 66) in the ABMT group and was 49 years (range, 36 to 65) in the PBSCT group (P < .001). In the ABMT group, the incidence of conditioning regimen without TBI was higher (31% v 16%, P = .08). Moreover, when TBI was delivered, the total dose was always ≥10 Gy in the PBSCT group, whereas it was only 8 Gy in 44 of 56 patients in the ABMT group (P < .0001). The number of nucleated cells infused was higher in the PBSCT group (median 3 X 10^6/kg v 1.6 X 10^6/kg; P < .001). The comparison of the numbers of colony-forming unit granulocyte-macrophage (CFU-GM) infused is more hazardous because the methods for CFU-GM cultures varied from one center to another.

The duration of neutropenia was significantly reduced in the PBSCT group (median, 13 v 20 days; P < .001). The duration of thrombocytopenia was slightly longer in the PBSCT (median, 26 v 22 days). There was no significant difference between ABMT and PBSCT in the outcome (CR rate, RFS, survival or TTF) (Table 4).

Influence of Maintenance Therapy With IFNa

Of the 110 responding patients (in CR or PR after ASCT), 65 received at least 1 month of maintenance therapy with IFNa. Their median remission duration was 34 months versus 30 months for the 45 patients who have not received this treatment (P = .48). When looking only at the 49 patients in CR after ASCT, there was a trend in favor of IFNa maintenance (Fig 2B). The median remission duration was 40 months for the 29 patients receiving IFNa versus 28 months for the 20 patients with no maintenance therapy (P = .10).

There was no significant difference in OS between maintenance and no maintenance with IFNa, both for the entire group of responding patients and for patients in CR after ASCT.

DISCUSSION

This study reflects the experience of a large group involving 18 French transplant centers. It confirms at the multicentric level the results of pilot studies performed in single centers in newly diagnosed patients.\textsuperscript{15-17} First, it clearly shows the feasibility of ASCT as part of front-line therapy in MM because the toxic-death rate was only 4%. The median duration of neutropenia was 17 days and was markedly
In this study, only patients transplanted before 1992 were analyzed. Thus, only four patients received G or GM-CSF after ASCT. The use of hematopoietic growth factors for stem cell collection or after ASCT could further enhance the neutrophil recovery. Thrombocytopenia was analyzed. Thus, only four patients received G or GM-CSF after G-CSF or GM-CSF priming could be beneficial even with the same definition of CR, the British investigators argued. The overall response rate was 83% and the CR rate was 37% including 10 patients already in CR before ASCT. The CR rate after ASCT partly depends on response criteria. When stringent criteria are applied and specifically when immunofixation is required for defining M component disappearance, the expected CR rate is probably below 30%, even after myeloablative TBI containing regimens. In this multicenter trial, immunofixation was not mandatory and we used the response criteria defined by Gore et al. The CR rate achieved in the present series appears to be somewhat lower than in the Royal Marsden experience. With the same definition of CR, the British investigators obtained 98% response and 75% CR in previously untreated patients. This difference could be explained by the preparative regimen because they have used higher doses of HDM (200 mg/m²). The dose of HDM could be critical because in another study, the same investigators obtained only 32% CR with a dose of 140 mg/m² in the same indication and with the same criteria of response.

The CR rate was influenced only by two parameters, the response to initial chemotherapy and the plasma cell marrow infiltration at the time of stem cell collection. Response to chemotherapy has been reported as a potent prognostic factor for ASCT in advanced MM. CR rates being higher for patients with sensitive relapses than for patients with resistant relapses.

We confirm that this parameter is also important earlier in the course of the disease, the CR rate being significantly higher for patients responding to their first remission induction treatment.

With a median follow up of 35 months, the median duration of response was 33 months and the actuarial probability of remaining in CR or PR at 4 years was 35%. The median OS was 46 months with a 43% actuarial probability of being alive at 5 years. These results compare favorably with those achieved with conventional chemotherapy because 84.5% of the patients had a stage III MM. However, it must be emphasized that this is a registry analysis. Even if all consecutive transplants performed in each center were registered, this sort of analysis introduces a selection of patients. Because of this selection bias, the apparent superiority of ASCT over conventional chemotherapy can only be proved by a randomized study. This study has been performed in France and the interim analysis performed on an intention to treat basis on the first 100 patients shows a significant advantage in favor of ABMT in terms of CR rate, remission duration and OS.

In case of remission (CR or PR) after ASCT, the remission duration was not significantly different between patients responding patients. Therefore, ASCT can be considered not only as a consolidation therapy for patients in remission after their first chemotherapy, but also as a salvage therapy for patients resistant to this treatment.

In univariate analysis, the outcome after ASCT appeared to be influenced by the initial characteristics of the patients (age, IgA isotype, β2 microglobulin level), by the status at the time of stem cell collection (response to initial chemotherapy, plasma cell marrow involvement) and by the characteristics at the time of transplantation (albumin and β2 microglobulin levels). The prognostic value of age, Ig isotype, and β2 microglobulin level in the context of intensive therapy have already been reported.

Until now, plasma cell marrow infiltration has never been reported as being a significant prognostic factor. Jagannath has even claimed that a greater extent of plasmacytosis is prognostically unimportant. However, it should be noted that in his study, the majority of transplanted patients had advanced MM. In previously untreated patients, Attal has already shown that graft plasmacytosis is correlated to progression-free survival in univariate analysis, but the P value was of borderline significance, probably because of a small number of patients. In multivariate analysis, this parameter did not reach the significant level. On a larger number of patients, we confirm that plasma cell marrow infiltration is correlated to CR achievement, duration of response, and TTF and is the only significant factor regarding TTF in multivariate analysis. Yet, for CR achievement, the difference is only significant at high levels of plasma cell marrow involvement (~15%). The prognostic impact of marrow plasmacytosis can indeed be the logical consequence of reinfusing malignant cells. However, another explanation could be more simply the close relation of this parameter to the response to initial chemotherapy because patients with a high percentage of plasma cells in the marrow are mostly in the group of nonresponders.

In the present series, albumin level at the time of transplantation also appeared to be correlated with survival. Albumin level has already been described as a potent prognostic indicator in MM. As albumin synthesis by the liver can be inhibited partly by interleukin-6 (IL-6), low albumin levels could be correlated to high IL-6 activity. The crucial role of IL-6 as a potent stimulant of in vitro plasma cell proliferation has been shown. In vivo, the biologic importance of IL-6 has been shown directly by IL-6 level determination and indirectly suggested by the prognostic value of C reactive protein (CRP) levels. In this retrospective multicenter study, CRP or IL-6 levels could not be evaluated on a large number of patients, but albumin level could be a reflection of IL-6 activity and low albumin levels could correspond to more severe MM.

The results of ASCT did not appear to be significantly influenced by the modalities of the procedure. Unexpectedly, we failed to show any prognostic importance of the conditioning regimen. The CR rate, RFS, OS, and TTF were correlated neither to the use of TBI nor to the total dose of TBI.

Several investigators consider that PB could be a better source of stem cells because blood contamination is possibly
However, in the present study, we could not find any significant prognostic difference between ABMT and PBSCT, even if patients in the group of PBSCT were younger and received more TBI. Pilot studies using BM purged with chemotherapy or with monoclonal antibodies have also been published, but their results are still preliminary. More recently, Berenson et al have shown, by polymerase chain reaction (PCR) analysis using patient specific Ig gene primers, that CD34+ progenitors selected by immunoadsorption were not contaminated by tumor cells and a first clinical study using a selection of CD34+ hematopoietic stem cells has just been reported. The biologic value of these approaches will be shown only by careful PCR analysis of minimal residual disease in the infused stem cells and in the patient after ASCT, or by gene marking of autologous stem cells. The clinical relevance of an effective method of purge will be assessed only by randomized studies.

We were unable to find a significant advantage of IFNα maintenance therapy. Therefore, we cannot confirm the favorable results obtained by Cunningham et al in a randomized study comparing observation and IFNα after ABMT. However, in this study, the advantage of IFNα was significant only for patients achieving CR after ABMT. In our analysis, the number of CR may be too low to show a difference at the significant level, but there is a trend in favor of IFNα maintenance in the subgroup of patients in CR after ASCT.

Finally, in multivariate analysis, the most important factor influencing survival was the quality of response achieved by ASCT. Patients in apparent CR had a median survival of 67 months versus 33 months for patients who did not achieve CR (and 47 months for patients achieving only a PR). In a previous study on double-intensive therapy, we have already shown that the response to the first course of HDM has a great impact on survival. In a pilot study of ABMT for previously untreated patients, one of us also reported that the duration of response was affected by the magnitude of response. In the British study, the high CR rate after ABMT was translated into an apparent prolongation of survival because 63% of the patients were alive at 54 months. Thus, achievement of at least apparent CR appears to be critical for survival. In this present series, CR achievement is dependent on the result obtained before ASCT. Therefore, more intensive strategies have to be developed to increase the proportion of patients susceptible to achieve apparent CR. We have already tried a double-intensive treatment, but as the first treatment with HDM was supported neither with hematopoietic growth factors nor with stem cell administration, the toxicity was severe, and even in patients with de novo MM, the exclusion rate for the second course was high. Our current analysis confirms that primary treatment with HDM does not confer any advantage compared with conventional chemotherapy. Moreover, for patients not in CR after first course of HDM, achievement of CR after conditioning regimens including the same dose of HDM appears to be a rare event. Barlogie et al have used a program called Total Therapy consisting of an intensive induction treatment with three non-cross-resistant regimens followed by two autotransplants. This program is supported by hematopoietic growth factors and is relatively well tolerated with no episode of long-lasting cytopenia. CR rates appear to increase after each intensive treatment. The value of this approach in survival prolongation is still unknown. We are currently comparing the impact of two versus one ASCT in a prospective randomized trial.

ACKNOWLEDGMENT

We thank L. Bataille and C. De Cervens for technical assistance, and B. Racape and N. Raimbault for preparation of the manuscript.

REFERENCES

AUTOGLOGOUS TRANSPLANTATION IN MYELOMA


From www.bloodjournal.org by guest on October 22, 2017. For personal use only.
Autologous stem cell transplantation after first remission induction treatment in multiple myeloma: a report of the French Registry on autologous transplantation in multiple myeloma

JL Harousseau, M Attal, M Divine, G Marit, V Leblond, AM Stoppa, JH Bourhis, D Caillot, M Boasson and JF Abgrall

Updated information and services can be found at:
http://www.bloodjournal.org/content/85/11/3077.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml