

High Dose Therapy Followed by Autologous Peripheral Blood Stem Cell Transplantation as a First Line Treatment for Multiple Myeloma: a Korean Multicenter Study

We conducted a phase II multicenter trial to estimate the response and survival of patients with newly diagnosed multiple myeloma to high dose melphalan therapy followed by autologous peripheral blood stem cell transplantation. Eligible patients who had undergone induction with vincristine, adriamycin and dexamethasone (VAD) should have adequate cardiac, pulmonary and renal function (creatinine <2 mg/dL). Melphalan at 200 mg/m² was used as a conditioning regimen. Eighty patients were enrolled from 13 centers. The median age of the patients was 53 yr (range; 20 to 68 yr). The initial stage was IA/IIA/IIB/IIIA/IIIB in 3/8/1/54/14 patients, respectively. Beta₂-microglobulin, CRP and LDH were increased in 74, 42 and 34% of the patients examined. Cytogenetic data were available in 30 patients, and 6 patients showed numeric or structural abnormalities. Two therapy-related mortalities occurred from infection. Among the 78 evaluable patients, CR/PR/MR/NC/PD were achieved in 48/26/2/1/1 patients, respectively. After a median follow-up of 30 months, the median overall and event-free survivals were 66 months (95% CI: 20-112) and 24 months (95% CI: 18-29), respectively. This study verifies the efficacy and feasibility of high dose melphalan therapy with autologous stem cell transplantation in newly diagnosed multiple myeloma.

Key Words : Multiple Myeloma; Transplantation Autologous; Peripheral Blood Stem Cell Transplantation

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INTRODUCTION

Multiple myeloma accounts for 14% of the incidence among of hematologic malignancies and is frequently involved in old age (1), and the incidence of multiple myeloma has shown a tendency to increase since the 1980s in Korea (1, 2). This increase may be the result of the larger old population and improved detection methods.

The effective treatment of myeloma began in the 1960s with the introduction of alkylating agents, of such as melphalan and cyclophosphamide (3). Moreover, during the past four decades, a number of pharmacological agents have been tried for myeloma treatment. These have included other alkylating agents (BCNU), topoisomerase inhibitors (doxorubicin and etoposide), glucocorticoids (prednisolone and dexamethasone),

and anti-tubulin agents (vincristine). The combination of melphalan and prednisolone used to be considered the mainstay of myeloma treatment, and produced response rates (RR) of 50-60%. Median remission duration and overall survival (OS) were 18 and 30-36 months, respectively (4), but complete response (CR) was less than 5%, and no more response was observed after 6 to 12 cycles of chemotherapy (5). Other investigator reported that the ten-year survival rate was 2.2% (6). To cure myeloma and improve survival, many protocols and new modalities of treatment have been developed, and one of these approaches is high dose therapy (HDT). McElwain and Powles (7) reported that high doses of melphalan could induce a high rate of response even in patients with disease refractory to conventional doses of the drugs. To shorten the myelosuppressive period and reduce therapy related mortality, Bar-

logie *et al.* used autologous blood stem cell transplantation (ASCT) after high dose therapy, and found that this resulted in reduced myelotoxicity (8). The Intergroupe Français du Myélome was the first to conduct a randomized trial, which demonstrated the superiority of HDT with ASCT, as compared to conventional chemotherapy (9). In the trial (IFM90), HDT was found to significantly improve the response rate, and 38% of patients enrolled in the HDT arm achieved a CR or a very good partial remission versus only 14% of patients enrolled in the conventional chemotherapy arm ($p < 0.001$). HDT also significantly improved event-free survival (EFS) (5-yr EFS 28% versus 10%, $p = 0.01$), and OS (5-yr OS 52% versus 12%, $p = 0.03$) in comparison to conventional therapy. In another randomized French trial (10), 190 patients aged 55 to 65 yr were randomized to receive conventional chemotherapy or HDT. Although the results of HDT appeared comparable to those achieved in the IFM90 trial, no significant difference was found in the OS of the 2 arms due to unexpected survival in the conventional chemotherapy arm (median 55 months with HDT versus 50 months with conventional chemotherapy). It should be noted that in this conventional chemotherapy arm, 17 patients received HDT at the time of relapse. By the very fact, HDT represents a significant improvement, and is currently proposed as part of the front line therapy for patients up to 70 yrs of age.

No data is available upon HDT in previously untreated myeloma in Korea. Therefore, a phase II multicenter trial of HDT with ASCT as a first line treatment for multiple myeloma in newly diagnosed patients was conducted. This study aimed, to estimate the CR rate and survival, to assess the safety and feasibility of HDT and to document the prognostic factors of response in the Korean population.

PATIENTS AND METHODS

Patients

Between April 1997 and March 2002, 80 patients were enrolled in this study from 13 centers in Korea. The eligibility criteria were as follows: a) symptomatic multiple myeloma with measurable M-protein, b) age < 70 yr, c) an ECOG performance status of 0-3, d) adequate cardiac, pulmonary, and renal function before the mobilization (systolic cardiac ejection fraction $\geq 50\%$, FEV₁ $\geq 60\%$ and creatinine < 2.0 mg/dL), e) VAD induction chemotherapy before enrollment (VAD: vincristine 0.4 mg by continuous intravenous (i.v.) infusion for 4 days (total 1.6 mg) and adriamycin 9 mg/m² by continuous i.v. infusion for 4 days (total 36 mg/m²) and dexamethasone 40 mg once daily p.o. on days 1-4, 9-12, and 17-20 every 5 weeks).

Prior local radiotherapy was permitted. All patients gave informed consent and the study was approved by an individual institutional review boards.

Response Criteria

Response to VAD induction and HDT were evaluated according to the EBMT criteria (11). CR was defined as the absence of M component on immunofixation (or immune electrophoresis) for 6 weeks and 5% or fewer plasma cells in the bone marrow, with no increase in the size or number of bone lesions and the disappearance of soft tissue plasmacytomas; Partial response (PR) was defined as $\geq 50\%$ decrease of serum M component and/or a $\geq 90\%$ decrease of urine M component for 6 weeks, or a $\geq 50\%$ reduction of soft tissue plasmacytomas with no increase in size or number of bone lesions. Minimal response (MR) was defined as a 25-49% decrease of serum M component and/or a 50-89% reduction in urine M component, which still exceeded 200 mg/day for 6 weeks, and/or a 25-49% reduction of soft tissue plasmacytomas with no increase in the size or number of bone lesions. No change (NC) was defined as not meeting the criteria of either minimal response or progressive disease, and progressive disease (PD) was defined as a $\geq 25\%$ increase of serum M-protein, which must have represented an absolute increase of at least 0.5 g/dL, and/or a $\geq 25\%$ increase of urine M-protein, which must have represented an absolute increase of at least 200 mg/day and have been confirmed by at least one repeated test, and/or a $\geq 25\%$ increase in bone marrow plasma cells, which must have represented an absolute increase of at least 10%, and/or a definite increase in the size of plasmacytomas or bone lesions, and/or the development of a new bone lesions, plasmacytomas, or hypercalcemia (corrected calcium level > 11.5 mg/dL). Relapse was defined as the reappearance of M component on immunofixation or routine electrophoresis, confirmed by at least one further test, or $\geq 5\%$ of plasma cells in the bone marrow, or the development of new bone lesions, plasmacytomas or hypercalcemia, or a definite increase in the size of residual bone lesions.

Mobilization and Transplantation

Protocols for peripheral blood stem cells (PBSCs) mobilization were decided according to each investigator's policy. The minimum recommended CD34⁺ cell dose was 2.0×10^6 /kg. HDT was performed with melphalan (100 mg/m² i.v. infusion over 30 min on two consecutive days -3 and -2; total 200 mg/m²) at least 4 weeks after mobilization. Stem cells were infused 2 days after the final melphalan dose. G-CSF 5 μ g/kg daily subcutaneous (s.c.) was started from day 1 until the ANC achieved 1,000/ μ L for 3 consecutive days. Prophylactic antibiotics, antifungal and antiviral agents were used according to the participating center's policy. Transfusion and nutritional support were supplied via a central venous catheter. If neutropenic fever developed, broad-spectrum antibiotics were administered immediately after cultures of blood and/or specimens of suspicious foci of infection had been taken. Hematologic and non-hematologic toxicities were graded according to the modified WHO criteria.

Post-transplant Follow-up

Response was evaluated 4 weeks after ASCT. Protein electrophoresis and immunofixation (or immune electrophoresis) of serum and/or urine were performed concomitantly with bone marrow aspiration and biopsy. If CR had been achieved, the patient was seen once per month for two months, the once every 2 months on 3 occasion, and every 3 months thereafter. If CR had not been achieved, the patient was seen once per month until CR. At each follow-up visit, patients underwent a history taking and a physical examination, and complete blood count, platelet count and liver function testing. Serum and/or urine protein electrophoreses were screened. If the relapse or progression was confirmed, the further therapy was at the direction of the participating physicians.

Statistical Analysis

Data obtained up to and including September, 2002 were analyzed. Response rates were compared using the chi-square test or Fisher's exact test. All tests were two-sided. Therapy-related mortality (TRM) included any deaths within 60 days of transplantation. Event-free survival (EFS) was calculated for all patients from the date of induction until the time of disease progression, relapse, or death, or until the date the patient was last known to be in remission. OS was defined as the time from induction until death or the date the patient was last known to be in remission. CR duration was evaluated from the time of CR until relapse. Actuarial survival and CR duration curves were plotted according to Kaplan and Meier's method, and the prognostic factors were compared using the log-rank test. Analysis was performed on an intent-to-treat basis. All calculations were performed upon SPSS system, version 10.0.

Table 1. Patients and disease features at diagnosis

Characteristics	Patients No.	Percentage
Sex (M/F)	44/36	55/45
Age (median; range, yr)	53; 20-68	
>50	44	54
ECOG PS (1/2/3)	52/20/8	65/25/10
Stage (IA/IIA/IIIB/IIIA/IIIB)	3/8/1/54/14	4/10/1/68/18
M component (median; range)	4.9; 0.6-14.3 g/dL	
G/A/light chain/D	41/21/12/6	51/26/15/8
κ/λ	42/38	53/47
BM plasma cell >30%	52	65
Hemoglobin <8.5 g/dL	41	51
Platelet <150,000/ μ L	28	35
Serum calcium >11.5 mg/dL	8	10
Lytic bone lesions \geq 3	42	53
LDH >UNL (checked patients)	22 (64)	34
CRP >0.5 mg/dL (checked patients)	19 (45)	42
β_2 -MG >UNL (checked patients)	58 (78)	74

Stage, Durie-Salmon stage; BM, bone marrow; UNL, upper normal limit.

RESULTS

Patients Characteristics

Table 1 shows the base-line characteristics of the 80 patients at diagnosis. At that time, bone marrow cytogenetics, CRP, LDH, and beta₂-microglobulin (β_2 -MG) were not checked in 62, 48, 26, and 9% of the patients. Six among the 30 patients checked for cytogenetics showed abnormalities (Table 2). After a median 4 (range; 2-6) cycles of VAD, the responses were 13 CR (16%), 59 PR (74%), 4 MR (5%), 2 NC (2.5%) and 2 PD (2.5%).

Treatment courses

The protocols used for the mobilization of PBSCs were cyclophosphamide (CTX) with G-CSF (or GM-CSF)/CTX and etoposide with G-CSF/VAD with G-CSF/G-CSF only in 70/6/2/2 patients. One patient refused HDT after mobilization because of poor economy. The median interval between diagnosis and transplantation was 6 months (3-20) in the remaining 79 patients. Transplantation within 1 yr after diagnosis was performed in 77 patients. Median infused mononuclear cells and CD34⁺ cells were 4.6×10^8 /kg (0.2-24.0) and 4.2×10^6 /kg (1.5-32.0), respectively. A second infusion of PBSCs was performed in 2 patients for delayed engraftment. Two therapy-related mortalities occurred due to infection on days 27 and 30. Before HDT, these two patients were in CR. One patient had received a second infusion of stem cells but had not achieved engraftment at time of death. The remaining 77 patients showed ANC recovery (>500/ μ L) on day 11 (7-31) after HDT commencement. Transfusion independency of platelets (>20,000/ μ L) showed on day 12 (8-60) in 76 patients. One patient continued to be dependent upon platelet transfusions up to 19 months after transplantation despite myeloid engraftment. The median transfused packed RBCs and platelet concentrates were of 2 (0-17) and 24 (0-420) units. There was no correlation between CD34⁺ cell dose (more or less than

Table 2. Cytogenetic abnormalities of six patients

Sex	Age (yr)	Cytogenetic findings
M	61	46, XY[12]/46, XY, inv(1)(p11q21)[6]
M	55	46, XY[17]/46, XY, t(7:14)(q12;q32)[3]
M	48	43, XY, -8, -18, -20[1]/47, XY, +21[1]/46, XY[4]
F	62	46, XX, del(1)(q32), t(11:14)(q13;q32)[2]/46, XX[1]
F	49	45, X,-X, +1, der(1:16)(q10;p10), dic(1:6)(p11;p25), t(6:14)(p21;q32), -13[6]/48, idem, +der(14)t(6:14), +15, +21[8]/45, X,-X,+1, +del(1)(p11), der(1:5)(q10;p10), t(6:14)(p21;q32), -13[2]/46, XX[4]
F	51	46, X-X, der(1)t(1:?) (q21:?), der(5)t(5:10)(q33;q11.2), add(6)(q21), add(7)(p13), t(8:14)(q24.1;q32), -10, der(11)t(11:?) (p15:?), t(11:14)(q13;q32), -16, -17, -20, +mar1, +mar2, +mar3, +mar4[6]

M, male; F, female.

Table 3. Responses after high dose therapy on an intent-to-treat analysis

Types of response	Patients No.	Percentage
CR	48	60
PR	26	33
MR	2	3
NC	1	1
PD	1	1
TRM	2	3
Total	80	100

CR, complete response; PR, partial response; MR, minimal response; NC, no change; PD, progressive disease; TRM, therapy related mortality.

Table 4. Non-hematologic toxicity of grade 3 or 4 in 79 patients

Toxicity	Grade 3	Grade 4	Percentage
Infection	40	2*	53
Mucositis	13	3	20
Nausea	16	1	21
Vomiting	12	-	15
Diarrhea	4	-	5
Hepatotoxicity	1	-	1
Renal toxicity	-	1	1

*Related to mortality.

$3.0 \times 10^6/\text{kg}$) and the rapidity of engraftment.

Responses

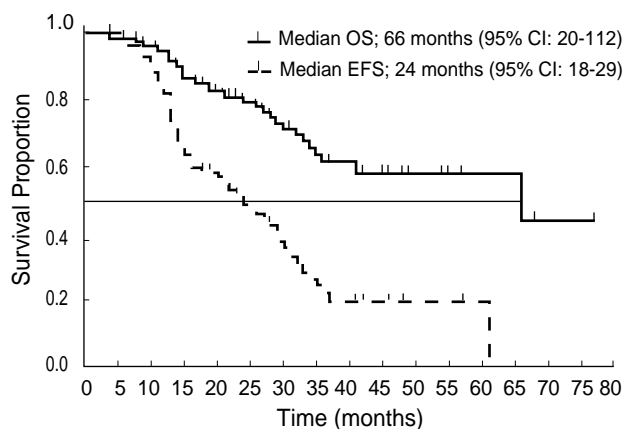
Table 3 demonstrates the responses of the patients. The CR rate after HDT was 60% by an intent-to-treat analysis. CR was induced by HDT in 36 patients, and the remaining 12 patients continued in CR. The median duration of CR was 17 months (95% confidence interval (CI):10-25). CR after transplantation was negatively associated with the serum β_2 -MG level ($p=0.03$). CR after HDT was found to be marginally related to cytogenetic status in 33 patients ($p=0.08$).

Non-hematologic Toxicity

Toxicities greater than grade 3 are summarized in Table 4. Types of fever in 42 patients were as follows; 24 of unknown origin, 11 microbiologically documented infections (MDI) and 7 clinically documented infections (CDI). Sites of the MDI were central venous catheter, blood, gastrointestinal tract, skin, ear, and urinary tract in 3, 3, 2, 1, 1, and 1 patient, respectively. The etiologic organisms were Gram-positive cocci in seven patients and Gram-negative rods in four.

Survival

After a median follow-up of 30 months, median OS and EFS were 66 months (95% CI: 20-112) and 24 months (95% CI: 18-29), respectively (Fig. 1). Lambda light chain

**Fig. 1.** Overall survival (OS) and event free survival (EFS) in total 80 patients.

($p=0.0009$), initial anemia ($p=0.004$), thrombocytopenia ($p=0.004$), and hypercalcemia ($p=0.01$) were associated with shorter OS. The poor prognostic factors for EFS were initial thrombocytopenia ($p=0.03$) and hypercalcemia ($p=0.05$).

DISCUSSION

This study has several limitations. The first is the timing of enrollment. At the start of this trial, many investigators had difficulty in obtaining patients' consents. Reasons were mainly economic problems with no guarantee of insurance, and the fear of the toxicity of ASCT. Therefore, most patients were enrolled after induction chemotherapy, and therefore, the true response rate and toxicity of VAD could not be measured. Moreover, patients with high-risk might have dropped out during the induction. The second is that we lacked base-line data in most patients. Delayed enrollment made the collection of initial characteristics difficult, and the evaluation of prognostic factors influencing response and survival could be performed only by univariate analysis. The third is that there was no uniform protocol for mobilization or for infection prophylaxis. Although neither serious myelotoxicity nor life-threatening infection occurred, except in the two TRMs, the ideal methodology of ASCT in myeloma could not be inferred.

VAD induction chemotherapy was chosen because of non-cross resistance with melphalan. The CR rate after VAD was 16%, which was lower than other reports (12), but overall RR (91%) and median time to CR (3.6 months) were comparable with that reported previously (12, 13). The main limitation of VAD induction was the need of the admission for continuous infusion.

The other points concerning HDT with ASCT for myeloma are as follows; the timing of the transplantation, the conditioning regimen, single versus tandem transplants, purging of stem cells, and maintenance therapy. Since ASCT is also a useful salvage therapy for primary refractory myeloma and for

chemosensitive relapses, the optimal timing is not yet known. Fermand et al. reported the results of a randomized study showing no significant difference in OS between early ASCT and late ASCT (14). Other supportable data are required on this topic. The optimal conditioning regimen for ASCT also has not been determined. After the introduction of total body irradiation (TBI) (8), many conditioning regimens have been tried. One randomized study, comparing high-dose melphalan 200 mg/m² with high-dose melphalan 140 mg/m² plus TBI in newly diagnosed myeloma (15), found that high-dose melphalan (200 mg/m²) was significantly less toxic (shorter duration of neutropenia and thrombocytopenia, lower incidence of grade >3 mucositis, and no toxic deaths versus 5 in the TBI group). Although the response rate and the EFS were identical, OS was superior for high-dose melphalan (200 mg/m²). Therefore, high-dose melphalan at 200 mg/m² should be preferred to high-dose melphalan at 140 mg/m² plus TBI. Higher doses of melphalan alone or in combination with an anti-IL-6 antibody have also been explored with encouraging results (16).

The impact of tandem transplantation was well documented by the largest trial of the Little Rock group (13). In 231 of newly diagnosed patients, the CR rate increased from 26% after the first transplant to 41% after the second transplant. However, several randomized trials except one upon single versus tandem transplants have failed to prove the superiority of double transplants (17-20). Because the data of three negative results obtained to date still appear immature, longer follow-up is needed. Sensitive immunofluorescence studies or PCR based techniques have demonstrated that virtually all PBSCs are contaminated with malignant cells. Two randomized studies compared CD 34⁺ selected PBSCs with unselected PBSCs. Engraftment was not different in the two groups, and also failed to prolong EFS or OS (21, 22).

Interferon- α may be effective in minimal residual disease after HDT. One randomized trial showed that progression-free survival (PFS) and OS were significantly better in an interferon- α maintenance arm with a median follow-up of 52 months, but these differences disappeared with prolonged follow-up (23). Since the cure of myeloma with a single course of HDT followed by interferon- α is unlikely, new strategies to control minimal residual disease after HDT are necessary.

As in a IFM90 trial (9) and total therapy with tandem transplants (13), no plateau of the survival curve was observed in this study. It means that HDT alone has limitations for the cure of myeloma. Using a larger cohort of 1,000 consecutive patients, Desikan R et al. confirmed that the independent favorable features were an absence of chromosome 13 deletion, low β_2 -MG, low CRP level and less than 12 months of prior conventional chemotherapy (24). Plateauing of the EFS and OS curves were noted in 45% and 60% of patients with all of these favorable characteristics. In another retrospective analysis of 110 patients treated with HDT, the detection of chromosome 13 abnormalities (-13, 13q-) by FISH was the most powerful adverse prognostic factor (25). The combination of FISH

analysis, β_2 -MG and the IgA isotype produced a very powerful staging system in the context of HDT.

Therefore, risk-based approaches are needed after the making of an accurate scoring system in myeloma. The mainstay of these approaches should be HDT with ASCT. In addition, new molecularly targeted agents, allogeneic stem cell transplantation, and microenvironment modifiers offer additional tools for such approaches.

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