High-dose Therapy followed by Autologous Haematopoietic Stem Cell Transplantation in Multiple Myeloma

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Abstract

***Introduction and Objectives**: The median survival of patients with multiple myeloma (MM) after conventional chemotherapy is 3 years or less. Previous studies have shown that high-dose therapy, supported by haematopoietic stem cell rescue, improves survival of patients with MM. We analysed the outcome of 29 myeloma patients who had autologous haematopoietic stem cell transplantation (AHSCT) in our institution over an 8-year period. **Materials and Methods**: Between May 1993 and August 2001, 29 patients with MM underwent high-dose therapy followed by unpurged AHSCT. There were 16 male and 13 female patients. The median age of the patients was 52 years (range, 31 to 67 years). All patients had at least a partial remission after initial chemotherapy. The preparative regimen for the AHSCT was melphalan 200 mg/m^2 in 25 patients, melphalan-total body irradiation in 1 patient, and busulphan-cyclophosphamide (BuCy) in 3 patients. Twenty-three patients received peripheral blood stem cells (PBSCs) autograft, 3 patients received bone marrow autograft and 3 patients received both. **Results**: Treatment-related death occurred in only 2 patients (7%). The median time to neutrophil engraftment was 11 days (range, 8 to 22 days). With a median follow-up period of 18.5 months, the 5-year overall survival (OS) and event-free survival (EFS) rates were 71% and 21%, respectively. The OS was found to be superior to a group of historical controls who were treated with conventional chemotherapy without transplantation (71% vs 19%; **P = 0.014). **Conclusion**: In conclusion, high-dose therapy followed by AHSCT is safe and beneficial for patients with MM.*

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Key words: Bone marrow transplant, Chemotherapy, Plasma cells malignancy

Introduction

Multiple myeloma (MM) is a disorder in which malignant plasma cells accumulate in the bone marrow and produce an immunoglobulin, usually monoclonal IgG or IgA.[1] The incidence of MM in Singapore is 1 to 2 per 100,000 per year with a median age of 65 to 70 years at diagnosis. MM accounts for 1% of all cancers and 10% of all haematological malignancies in Singapore.[2]

For the last 30 years, the mainstay of treatment in MM has been melphalan and prednisolone.[3] With this treatment or other combination chemotherapy, stringently-defined complete remission (CR) rates have not exceeded 5% and median survival has not extended beyond 3 years.[3,4]

Evidence of a dose-response effect for alkalyting agents has prompted studies using high-dose therapy regimens followed by transplantation of syngeneic, allogeneic, or autologous bone marrow or peripheral blood stem cells (PBSCs).[5-9] Since MM is predominantly a disease of the elderly, with a median age of onset of 65 years,[10] allograft in this regard, with its high treatment-related mortality, becomes an unacceptable option for most patients. Attal et al[11] have demonstrated in a randomised trial that greater survival could be achieved in patients with high-dose therapy followed by autologous bone marrow transplantation as compared to those treated with conventional chemotherapy.

Since 1993, we have performed high-dose therapy followed by transplantation using autologous bone marrow, PBSC, or both in 29 patients with MM. In this single institution study, we analysed the treatment outcome of chemoresponsive patients with MM who received intensification with high-dose therapy followed by autologous haematopoietic stem cell transplantation (AHSCT), compared to that of those who were treated with

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conventional chemotherapy.

Patients and Methods

Patients

Eligibility criteria for high-dose therapy included symptomatic MM, an upper age limit of 70 years, adequate cardiac function (systolic ejection fraction ≥50%), adequate hepatic function (serum bilirubin <35 μmol/L, serum aminotransferase <4 times normal value) and good performance status of not more than grade 2 according to the criteria of the Eastern Cooperative Oncology Group (ECOG). Between May 1993 and August 2001, 29 patients with MM seen in our institution were enrolled into this study. The study was approved by the institutional ethics committees and written informed consent was obtained from all patients.

Initial Chemotherapy and Stem Cell Harvesting

Peripheral blood stem cells were obtained using conventional cytapheresis methods from patients in the stable plateau phase of MM after initial chemotherapy. The priming chemotherapy regimen used for PBSC mobilisation consisted of intravenous cyclophosphamide (Cy) 4 g/m^2 administered in 2 divided doses over 2 days. This is followed by subcutaneous administration of granulocyte colony-stimulating factor (G-CSF) 5 μg/kg beginning on day 5 and 10 μg/kg beginning on day 10 until the final cytapharesis. When the total white blood cell counts were equal or greater than 1,000/μL or when circulating CD34+ cells count exceeded 11/μL, cytapheresis was performed as described previously.[12] Daily cytapheresis of approximately 10 L of blood was continued until at least 5 x 10^6 CD34+ cells/kg were collected. Each cytapheresis product was processed, frozen, thawed and washed according to standard techniques. In addition, autologous bone marrow was obtained after informed consent in patients yielding less than 1 x 10^6 CD34 cells/kg.

Treatment Protocol

Three high-dose therapy regimens were used as preparative regimen before AHSCT:

1) melphalan 140 mg/m^2 and total body irradiation (TBI) (1200 cGy in 6 fractions over a 3-day period);
2) melphalan alone (200 mg/m^2); and
3) busulphan-cyclophosphamide (busulphan 16 mg/kg orally over 4 days, cyclophosphamide 120 mg/kg in 2 divide doses intravenously over 2 days). The busulphan-cyclophosphamide regimen was used in patients who had renal impairment with serum creatinine of more than 2 mg/dL (176.8 μmol/L) or creatinine clearance of less than 40 mL/min.

All patients received granulocyte-macrophage colony-stimulating factor (GM-CSF) at 10 μg/kg/d beginning at day +1 and continue until the absolute neutrophil count exceeded 1 x 10^6 cells/μL.

All patients were treated in conventional single, non-laminar air flow rooms using standard reverse isolation procedures. Oral prophylatic antibiotics were administered to all patients. Intravenous antibiotics were instituted in place of oral antibiotics if fever exceeded 38°C. All blood products were leukoreduced via filtration to prevent transmission of cytomegalovirus and gamma-irradiated (2,500 cGy) to prevent transfusion-associated graft-versus-host disease.

Following transplantation, maintenance therapy with alpha-interferon (α-IFN) was commenced at 3 million U (miU) subcutaneously twice to thrice weekly when granulocyte counts exceeded 1,500 cells/μL and platelet counts exceeded 100,000/μL. This was continued until disease relapse.

Treatment Response Criteria

Response to therapy was classified using standard criteria as previously described.[13] Briefly, CR was defined as:

1) disappearance of the original monoclonal immunoglobulin in serum and urine assayed using immunofixation methods for a minimum of 6 weeks,
2) the presence of <5% plasma cells in the bone marrow,
3) no increase in size or number of lytic lesion bone lesions, and
4) the disappearance of soft tissue plasmacytomas.

Partial remission (PR) was defined as:

1) >50% reduction in the level of serum monoclonal protein, maintained for at least 6 weeks,
2) the reduction in 24 h urinary light chain protein excretion either by >90% or to <200 mg, maintained for a minimum of 6 weeks,
3) >50% reduction in the size of soft tissue plasmacytomas, and
4) no increase in size or number of lytic lesion bone lesions.

A very good PR was defined as a decrease of 90% in the serum paraprotein level and a minimal PR as a decrease of 25% of the serum paraprotein level. Stable disease was defined as no change in the paraprotein level.

Progressive disease (for patients not in CR) required one of the following criteria:

1) >25% increase in the level of serum monoclonal protein, which also had to be an increase of at least 5 g/L confirmed on a repeat assay,
2) >25% increase in the 24-hour urinary light chain protein excretion, accompanied by an absolute increase of at least 200 mg/24 h; which was confirmed on a repeat assay,

3) >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, accompanied by an absolute increase of at least 10%,
4) definite increase in the size of existing bone lesions or soft tissue plasmacytomas,
5) development of new bone lesions or soft tissue plasmacytomas, and
6) development of hypercalcaemia (corrected serum calcium >11.5 mg/dL or >2.8 mmol/L) not attributable to other causes.

Relapse from CR required at least one of the following:

1) the reappearance of serum or urine paraprotein on the immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution,
2) ≥5% plasma cells in a bone marrow aspirate or on trephine bone biopsy,
3) development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions, and
4) development of hypercalcaemia (corrected serum calcium >11.5 mg/dL or >2.8 mmol/L) not attributable to other causes.

Grading of Toxicity

Acute and subacute toxicities were graded according to the World Health Organisation (WHO) grading system for toxic reactions to drugs and therapies.[14]

Patient Controls

For comparison of outcome with AHSCT, 29 MM patients with the same clinical features were identified and selected from the historical cohort of patients to serve as case controls (Table I). This historical control group of 86 patients with MM diagnosed between 1988 and 1992 were treated with conventional chemotherapy, predominantly with melphalan and prednisolone combination. The 29 closely "paired mates" receiving standard chemotherapy were selected to match for age ($P = 0.5$), β_2-microglobulin levels ($P = 0.9$) and serum creatinine level ($P = 0.7$). These three parameters have been recognised as the dominant prognostic variables in previous studies.[15,16]

Statistical Analysis

Patient characteristics were summarised using proportions and medians. Overall survival (OS) was calculated from the day of autologous stem cell infusion to the date of death or last visit. Event-free survival (EFS) was calculated from the date of autologous stem cell infusion until the time of progression of disease, relapse, death, or the date the patient was last known to be in remission. Curves for OS and EFS were plotted according to the Kaplan-Meier[17] method and were compared using the log-rank test.[18]

Results

Patient Profile

A total of 29 MM patients underwent high-dose therapy

TABLE I: PATIENT CHARACTERISTICS AT THE TIME OF DIAGNOSIS

Characteristic	Category	AHSCT	Chemotherapy
Gender			
Male		16 (55%)	19 (66%)
Female		13 (45%)	10 (34%)
Median age (y) (range)		52 (31-67)	57 (30-68)
Stage (Durie and Salmon)	I	3 (10%)	1 (3%)
	II	2 (7%)	7 (24%)
	III	24 (83%)	21 (72%)
M-protein class	IgG	16 (55%)	18 (62%)
	IgA	6 (21%)	8 (28%)
	Light chains only	6 (21%)	3 (10%)
	Non-secretory	1 (3%)	0 (0%)
Haemoglobin (g/dL) [median (range)]		9.4 (5-14)	9.0 (4.2-13.9)
Serum creatinine (μmol/L) [median (range)]		88 (50-281)	88 (45-401)
Serum β_2-microglobulin (mg/L) [median (range)]		3,131 (1,084-15,923)	4,408 (2,919-6,797)
Cytogenetics	Normal	15	*
	Abnormal	8	*
	Not available	6	*

AHSCT: autologous haematopoietic stem cell transplantation

* Data on cytogenetics were not available for all historical control group

followed by unpurged haematopoietic stem cell infusion (Table I). The patients' characteristics are summarised in Table I. The median age of these patients was 52 years (range, 31 to 67 years). Seven (24%) patients had achieved CR and 22 (76%) patients had achieved PR following initial conventional chemotherapy at the time of high-dose therapy plus AHSCT. The median time from diagnosis to AHSCT was 13 months (range, 5 to 102 months).

Patients had received a median of 2 regimens (range, 1 to 5) before AHSCT. The initial treatment consisted of VAD[19] (vincristine, adriamycin and dexamethasone) in more than 86% of the patients. Fifteen (55%) patients received more than one regimen before the PBSC mobilisation. Thirteen (44.8%) patients received only one line of induction chemotherapy.

High-dose therapy consisted of melphalan 140 mg/m^2 and TBI (12 Gy in 6 fractions over a 3-day period) in 1 (3%) patient and melphalan alone (200 mg/m^2) in 25 (86%) patients. Three (10%) patients were given busulphan-cyclophosphamide (busulphan 16 mg/kg orally over 4 days, cyclophosphamide 120 mg/kg in 2 divide doses intravenously over 2 days) because of renal impairment. Their serum creatinine at transplantation ranged between 185 and 245 μmol/L.

Haematological Toxicity and Engraftment Kinetics

All patients experienced severe grade 3 to 4 haematological toxicity requiring transfusion support. The median duration of neutropenia (absolute neutrophil count <0.5 x 10^9/L) was 7 days (range, 0 to 19 days). The median duration of grade 3 thrombocytopaenia (platelet <20 x 10^9/L) and grade 4 thrombocytopaenia were 6 days (range, 1 to 26 days) and 2 days (range, 0 to 12 days), respectively.

The median time to absolute neutrophil count >500/μL was 11 days (range, 8 to 22 days) and platelets more than 20,000/μL was 12 days (range, 8 to 35 days). The median duration of hospitalisation was 26 days (range, 18 to 49 days).

TABLE II: ACUTE NON-HAEMATOLOGICAL TOXICITY

Side effects	Grade I-II No. of episodes	Grade III- IV No. of episodes	Total
Gastrointestinal			
Mucositis	6	9	15
Nausea and emesis	11	14	25
Diarrhoea	15	5	20
Hepatic	0	0	0
Renal	3	2	5
Neurological	0	0	0
Infectious	0	26	26
Cardiac	0	1	1
Total	35	57	92

Twenty-four (83%) patients had autologous PBSC infusion alone. The median number of CD34+ cells infused was 8.97 x 10^6 CD34+ cells /kg (range, 2.14 to 32.25 x 10^6 CD34+ cells/kg). Three patients (10%) required infusion of both PBSC and bone marrow cell because of insufficient CD34+ cell yields from PBSC harvesting. The median PBSC dose was 1.25 x 10^6 CD34+ cells/kg (range, 0.03 to 1.46 x 10^6 CD34+ cells/kg) and the median nucleated cell dose was 2.95 x 10^8/kg (range, 1.95 to 5.37 x 10^8/kg). Two (7%) patients, because of financial reasons, opted for autologous bone marrow collection over PBSC collection. These 2 patients were rescued with autologous bone marrow with a median nucleated cells dose of 2.72 x 10^8/kg (range, 2.70 to 2.74 x 10^8/kg).

Non-haematological Toxicity

As shown in Table II, neutropaenic sepsis occurred in 26 (79%) patients. The median duration of fever (which was >38°C) was 6 days (range, 0 to 13 days). Nineteen (66%) patients had fever associated with sterile isolates; whereas the remaining 7 (34%) patients had fever associated with positive microbial cultures. Only 1 (3%) patient died of pneumonia and acute respiratory distress syndrome during the early phase of transplantation before achieving neutrophil engraftment.

Gastrointestional toxicity, i.e. oral mucositis, nausea, emesis and diarrhoea, occurred in more than half of patients. Grade 3 renal toxicity was seen in 2 patients (7%) with renal impairment. One patient (3%) developed grade 4 toxicity, presenting as cardiac failure which required mechanical ventilatory and inotropic support in intensive care unit.

Response to Treatment

Complete response was achieved with initial chemotherapy in 7 of 29 patients (24%). The remaining 22 patients had PR, including 3 patients (10%) who had very good partial response. After transplantation, CR was induced in 7 (24%) additional patients. Conversion of PR to CR was seen at a median of 3 months (range, 1 to 18 months) after transplantation. In the remaining evaluable patients, PR was observed in 13 (59%) patients. Two patients had early death at D+129 and D+20, respectively, and were therefore not evaluable. Seven patients developed relapse or progression of disease at a median of 18 months (range, 5 to 50 months) following high-dose therapy and AHSCT. Of these, 3 patients succumbed to progressive disease whereas 4 are currently receiving salvage chemotherapy.

Alpha-Interferon Maintenance Therapy

Twenty (69%) patients received α-IFN 3 miU/m^2 thrice a week, commencing at a median of 10 weeks (range, 4 to

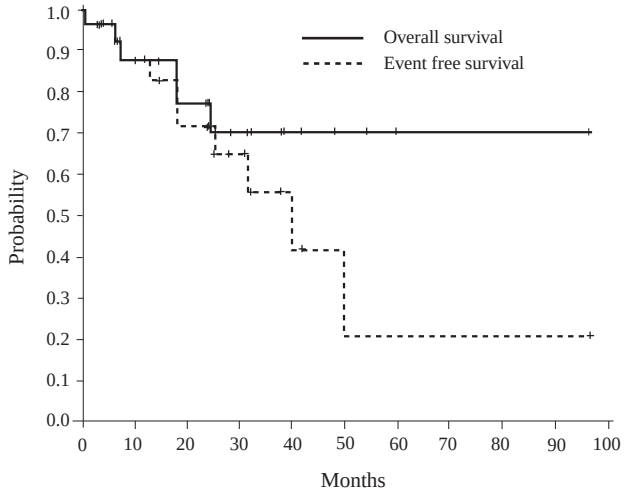

Fig. 1. Overall and event-free survival of 29 MM patients with AHSCT.

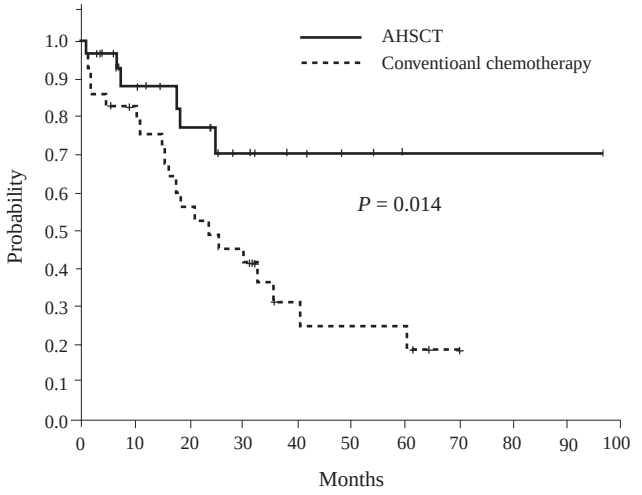

Fig. 2. Overall survival according to treatment group.

30 weeks) post high-dose therapy and AHSCT. The therapy was generally well tolerated. Two (10%) patients developed grade 2 thrombocytopenia and α-IFN had to be discontinued. Another 2 patients developed poor tolerance to α-IFN (1 patient developed grade 2 depression; and the other developed grade 2 myalgia). To date, 5 (25%) patients have either suffered relapses or disease progression while receiving α-IFN.

Treatment-related Death

Treatment-related deaths occurred in 2 patients. The first patient developed pneumonia and multiorgan failure on D+20 and the second patient developed pneumonia on D+129 after successful engraftment.

Event-free and Overall Survival

With a median follow-up period of 18.5 months (range, 0.7 to 96.8 months), the probabilities of EFS and OS over 5 years after transplantation were 21% and 71%, respectively (Fig. 1). The 5-year OS is significantly superior to the historical control group (71% vs 19%, $P = 0.014$) (Fig. 2).

Cause of Death

A total of 6 patients died; 3 from disease progression and complications related to MM, 1 from pneumonia in the peri-transplant period, 1 from pneumonia 4 months post transplantation and 1 from abdominal sepsis 2 years post-transplantation while in PR at the time of death.

Relapse and Salvage Therapy

Seven patients (24%) had relapsed or disease progression at a median time of 18 months from transplantation (range, 5 to 50 months). Three patients relapsed from CR whereas 4 patients had disease progression after achieving PR after high-dose therapy plus AHSCT. Of these, 4 patients had succumbed to the disease so far. The remaining patients are still receiving salvage chemotherapy. With a median follow-up of 4.4 months (range, 0.8 to 27.4 months) from the time of relapse, the probability of survival for 2 years after relapse was 57%.

Discussion

Conventional treatment for MM, first introduced in the 1960s, produces objective responses (>50% reduction of the monoclonal protein) in 50% to 60% of patients and results in a median OS of approximately 3 years.[3] The addition of other chemotherapeutic agents (carmustine, cyclophosphamide, vincristine) to the classic melphalan-prednisolone regimen has not improved survival.[20] The results of a number of trials, comparing melphalan and prednisolone vs combination chemotherapy, as well as two meta-analysis, concluded that combination chemotherapy does not prolong survival in MM.[21,22]

It is now more than 15 years since the late Tim McElwain and colleagues introduced high-dose therapy for MM.[23] The Royal Marsden group in the UK was the first to establish a dose-response effect for alkylating agents in MM. Administration of melphalan 140 mg/m^2, without stem cell support, induced true CR in approximately 35% of patients, which is much higher than the 5% CR rate as seen with conventional chemotherapy. However, high-dose therapy induced prolonged cytopaenias and was associated with a higher morbidity and mortality. This experience led future investigators to further escalate the doses of melphalan and to add stem cell support; initially with autologous bone marrow and subsequently PBSCT, in order to reduce the duration of cytopaenia and consequently reduce the toxicity of the procedure.

High-dose therapy followed by AHSCT has been increasingly used in the past 15 years in MM. Uncontrolled studies have shown that AHSCT is a useful salvage therapy

for refractory and relapsed MM, and a safe and effective consolidation therapy for patients responding to initial conventional chemotherapy.[24] However, because of selection bias in all these patients, the exact role of AHSCT in the manangement of newly diagnosed patients was not known. In 1990, the Intergroupe Francais du Myelome (IFM) initiated a randomised study comparing conventional chemotherapy and high-dose therapy followed by autologous bone marrow transplantation (ABMT).[11] The results of this landmark study showed a significantly higher EFS and OS in patients treated with high-dose therapy followed by ABMT compared to patients treated with conventional chemotherapy.

The results of the present study add further evidence to the fact that high-dose therapy plus AHSCT significantly improves OS and EFS. Although a randomisation between a conventional and high-dose therapy is the accepted strategy to unequivocally define the relative merits of different treatment patients, accrual of patients into randomised studies is difficult mainly because of three reasons:

1) lower incidence of MM compared with western countries;
2) the general reluctance of patients in accepting a new treatment option without a promising outcome, despite encouraging results of earlier pilot trials in published literatures; and
3) with the French studies published in 1996 showing the superiority of ASCT over conventional chemotherapy, it would be unethical to conduct a randomised control trial in which one group of patients would be denied the potential benefit of ASCT.

We decided to rely on historical controls for comparison of results of our cohort of patients. Appreciating the difficulty of drawing firm conclusions from historical controls, an effort was undertaken to account for differences in relevant prognostic factors by matching patients for the most important pretreatment parameters affecting EFS and OS after standard therapy (age, β_2-microglobulin, creatinine). Other potential prognostic factors, such as CRP, LDH and karyotypic abnormalities, were not available or available in small number of patients.

In our present study, majority of the patients (83%) received PBSC collected after priming with chemotherapy and haematopoietic growth factors (i.e. GM-CSF). The median time for neutrophil engraftment and platelet engraftment was both 11 days. PBSC is currently preferred over bone marrow as the source of stem cells in AHSCT for MM because of easier accessibility and availability, faster haematopoietic recovery and possibly lower tumour contamination.[25] However, the impact of this choice on long-term EFS and OS was unknown. The IFM trial is the first prospective randomised trial to compare bone marrow and PBSC in MM. It has demonstrated that the use of PBSC reduces the duration of aplasia as well as transfusion requirements and is associated with a borderline improvement in OS.[26]

The role of α-IFN as maintenance therapy post-AHSCT remains controversial and the experience is less impressive as compared with MM patients receiving conventional chemotherapy.[27] A few uncontrolled studies suggest that α-IFN induces a prolonged time to disease progression, as well as duration of survival after AHSCT.[28-30] In the only published randomised study comparing α-IFN maintenance treatment with no treatment in the post ASCT setting, there was an initial OS and progression-free survival (PFS) advantage in the α-IFN treated group, although this difference decreased with longer follow-up.[31] The European Group for Blood and Marrow Transplantation has recently reported a registry-based retrospective study addressing the same question;[32] suggesting that α-IFN maintenance treatment after AHSCT was associated with better OS and PFS. Moreover, treatment appeared to be most beneficial in patients who did not achieve CR. We elected to offer all patients who had achieved haematopoietic reconstitution after AHSCT, α-IFN maintenance therapy. The therapy was well tolerated by all except 4 (20%) patients whose therapy was discontinued because of both haematological and non-haematological toxicity. A total of 5 (25%) patients had relapse or disease progression despite receiving α-IFN maintenance therapy. However, the number of patients in the present study is too small to draw any meaningful conclusions. Further studies and longer follow-up are needed to identify the role of α-IFN post AHSCT.

Although the number of patients in our series is comparatively small, the OS of 71% compares favourably with most other series, which ranged between 52% and 70%.[11,33-35] All the patients in our series achieved at least PR (24% CR, 76% PR) before AHSCT. This may have accounted for, at least partially, the favourable survival of our patients compared to other series, one of which included patients who were chemoresistant.[33]

Conclusion

In conclusion, our study demonstrates the feasibility and safety of high-dose therapy plus AHSCT for treating patients with MM. The 5-year OS rate of 71% is comparable to those reported in larger series. However, disease progression and relapse remain the main problem. high-dose therapy followed by AHSCT is hence not curative for most patients with MM. Strategies to improve these results are warranted.

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