

Myeloma

Prognostic factors for survival after autologous transplantation: a single centre experience in 133 multiple myeloma patients

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Summary:

Autologous stem cell transplantation (ASCT) has an established role in the treatment of symptomatic multiple myeloma (MM). Our aim was to analyse the impact of selected prognostic parameters on the survival of patients with MM after ASCT. The new International Staging System (ISS) was also evaluated. A total of 133 MM patients were transplanted in our centre between 1995 and 2002. Following ASCT, 35% of patients were in complete remission (CR) and 60% were in partial remission (PR). The median progression-free (PFS) and overall (OS) survival from transplantation were 29.5 and 68.8 months, respectively. Transplant-related mortality (TRM) was 3%. On multivariate analysis, factors associated with significantly shorter OS were lack of CR after transplant ($P=0.002$, hazard ratio (HR): 3.1), stage 3 according to ISS ($P=0.001$, HR: 3.0) and age at transplant over 60 years ($P=0.035$, HR: 2.0). The status of disease before ASCT did not significantly affect PFS and OS after transplantation. We conclude that ASCT is a safe and effective procedure in MM patients, associated with low TRM. The survival after ASCT was dependent on response after ASCT, stage according to ISS and age.

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Multiple myeloma (MM) is a haematologic malignancy predominantly affecting the elderly, with median age at presentation of 65 years.¹

Reliable and simple staging of MM is important for accurate prognostic evaluation and for the comparison of data from different clinical trials. Attempts to improve the widely accepted Durie–Salmon (DS) staging system² have

led to the development of numerous new prognostic systems,^{3–5} which have not been universally accepted. Recently, Greipp *et al*^{6,7} presented a new International Staging System (ISS) for MM. It has shown promise in patients treated by conventional as well as high-dose chemotherapy and is based on a simple combination of serum β_2 -microglobulin and albumin values (stage 1 = β_2 -microglobulin <3.5 mg/l and albumin \geq 3.5 g/dl; stage 2 = β_2 -microglobulin <3.5 mg/l and albumin <3.5 g/dl, or β_2 -microglobulin \geq 3.5 mg/l to <5.5 mg/l; stage 3 = β_2 -microglobulin \geq 5.5 mg/l).

When compared with standard-dose chemotherapy for MM, high-dose chemotherapy with autologous stem cell transplantation (ASCT) has been found to be significantly superior in terms of complete remission (CR), CR duration, progression-free survival (PFS) and overall survival (OS).^{8–12}

We have retrospectively analysed 133 patients with MM undergoing ASCT in our centre. The aims of our analysis were (1) to evaluate both ISS and DS systems in our set of patients; (2) to ascertain the feasibility and toxicity of the transplant procedure; (3) to evaluate the influence of some clinically important parameters (age, gender, type of MM, stage of MM, responses before and after ASCT, selected laboratory values at transplant) on PFS and OS after transplant in order to define the subgroups of patients with different prognosis.

Patients and methods

Patients and treatment

From January 1995 to December 2002, 133 patients with newly diagnosed symptomatic MM with stages I–III according to DS underwent ASCT at the Department of Internal Medicine – Haematology, Masaryk University Hospital, Brno. All patients with stage I according to DS had two or three risk factors of early progression according to Facon *et al*¹³ and some of them had one, but symptomatic bone lesion.

Patients had adequate stem cell collection and met all the eligibility criteria of the ASCT protocol that included age up to 70 years, good performance status before transplant (Karnofsky >70%) and acceptable cardiac (ejection fraction >50%), pulmonary (spirometry >50% of normal) and hepatic (bilirubin and transaminases <2 × upper

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limit) functions. All patients were informed about benefits and risks associated with stem cell collection and ASCT and signed an informed consent.

Patients were treated by four cycles of VAD (vincristine, doxorubicine, dexamethasone). Radiotherapy was performed in 40 patients (30%) with symptomatic skeletal lesions mostly in the region of the spine, pelvis and femoral bones.

Peripheral blood stem cells (PBSC) were collected during 1–3 consecutive leukaphereses, following high-dose cyclophosphamide 2.5 or 5 g/m², with subsequent G-CSF at 5 or 10 µg/kg/day from day 3 to the last day of leukapheresis.

The conditioning regimen consisted of melphalan 200 mg/m² in most cases (125 patients, 94%). The dose of melphalan was reduced to 140 mg/m² in patients with renal impairment at the time of transplant and in patients with serious complications during previous treatment (eight patients, 6%). All patients received G-CSF 5 µg/kg/day from day 7 after transplantation until neutrophil recovery. Ciprofloxacin and fluconazole were administered prophylactically until neutrophil engraftment.

The maintenance treatment using interferon alpha (IFN) or IFN alternating with dexamethasone (IFN/DEX) was used in 129 patients who were randomised to two of these arms of maintenance therapy. The first group received IFN 3 × 10⁶ units three times weekly subcutaneously until progression or relapse (65 patients, IFN group). The second group was treated using IFN 3 × 10⁶ units three times weekly alternating with dexamethasone 40 mg on days 1–4, 10–13 and 20–23 in 3-month intervals until progression or relapse (64 patients, IFN/DEX group). A recent interim analysis has shown that there were no significant differences in OS or PFS between the IFN and IFN/DEX groups.¹⁴

Staging and response criteria

Staging was carried out according to the DS staging system and the new ISS as described previously.^{2,6,15} EBMT criteria were used for the evaluation of disease response.¹⁶ Complete response (CR) was defined as the absence of detectable M-protein component in serum or in urine by immunofixation analysis, associated with <5% plasma cells in the bone marrow. Partial response (PR) was defined as at least 50% reduction of the initial M-protein level and a reduction of Bence-Jones (BJ) proteinuria by greater than 90% and to <0.2 g/24 h. As a part of the PR group, very good partial response (VGPR) with at least 90% reduction of the initial M-protein level was evaluated; VGPR is not included in EBMT criteria.

Patients with reduction of initial M-protein between 25 and 49% and a reduction in BJ proteinuria by 50–89%, but exceeding 0.2 g/24 h, were considered as showing minor response (MR). Patients with responses not satisfying the criteria for CR, PR or MR were classified as having had no response (NR). Progressive disease was defined as an increase in serum or urinary monoclonal protein by 25% or a 25% increase in bone marrow infiltration in nonsecretory myeloma. Relapse was defined as the recurrence of M-protein or bone marrow plasmacytosis, if relapse was from CR, or a 25% increase from minimal tumour mass if relapse was from PR.

Statistical analysis

Data were analysed as of August 2003. Computations for the statistical methods were performed using the STATISTICA[®] (version 6.1) software package and SAS version 7. The Kaplan–Meier method was used to estimate PFS and OS probabilities, with differences compared by the log-rank test. All statistical analyses were two-sided and performed at the 5% significance level. PFS and OS were defined as the time from ASCT to progression, death or most recent follow-up. However, OS from the time of diagnosis was also evaluated. The multivariate analysis was performed for significant univariate variables using the Cox regression modelling.

Results

Patient characteristics and staging

Patient characteristics are shown in Table 1. The median age at transplant was 55 years (range: 31–69 years). Four age groups were evaluated: 30 patients (23%) with age at transplant under 50 years, 38 patients (28%) with age 51–55 years, 35 patients (26%) with age 56–60 years and 30 patients (23%) with age above 60 years.

Clinical stages at the start of chemotherapy according to DS² were as follows: stage I in 16 patients (12%), stage II in 17 cases (13%) and stage III in 100 cases (75%). Among the 100 patients with DS III, there were 94 patients with multiple osteolytic lesions. The size and number of bone lytic lesions varied considerably in the DS III subgroup.

Clinical stages at the start of chemotherapy according to ISS^{6,15} were the following: stage 1 in 48 patients (38%), stage 2 in 56 cases (45%) and stage 3 in 21 cases (17%). Initial values of β₂-microglobulin and albumin were not available for eight patients. Patients with clinical stage III according to DS had stage 1 according to ISS in 28% of cases, ISS stage 2 in 50% of cases and ISS stage 3 in 22% of cases.

Table 1 Patient characteristics

	No	Percent
Patients	158	100
Age at transplant (median, range)	55 (31–69)	
<i>Gender</i>		
Male	80	60
Female	53	40
<i>Type</i>		
IgG	80	60
IgA	30	23
IgD	2	1
BJ	18	14
Nonsecretory	3	2
<i>Pretransplant response status</i>		
Complete response	10	8
Partial response/very good partial response	88/35	66/26
Minimal response	21	16
No response	12	9
Progression	2	1

Serum creatinine at diagnosis was >2 mg/dl in 12 patients (9%).

A total of 10 patients (8%) were transplanted in complete response, 88 (65%) in partial response and 21 (16%) in minor response. From 88 patients who achieved PR were 35 patients with VGPR. A total of 12 patients (9%) underwent transplant with nonresponding disease and two patients (1%) with the disease in progression.

Haematopoietic recovery and transplant-related toxicity

The median number of CD34+ cells infused was 4.7×10^6 /kg (range: 0.9 – 22.3×10^6 /kg). The median time to platelet recovery ($>50 \times 10^9$ /l) was 13 days (range: 10–56 days), while the neutrophil engraftment ($>0.5 \times 10^9$ /l) was achieved at a median time of 13 days (range: 10–27 days).

The TRM was 3% (4/133 patients). The causes of death were septicaemia (two patients), haemorrhage (one patient) and heart failure (one patient). No WHO grade 3 or 4 pulmonary, renal or liver toxicity were seen.

The consumption of blood products after transplant was low, the median of platelet transfusion was 1 (range: 0–18) and the median of red blood cell transfusion was 1 (range: 0–22). The number of days with fever between the day of transplant and engraftment ranged from 0 to 28 days (median 2.6 days). The most common and severe toxicity in our group of patients was mucositis. Grades 3–4 mucositis requiring parenteral nutrition and opioid analgesia developed in 30% of the patients.

Response rate and survival

We evaluated the best response according to EBMT criteria in the first 6 months after transplantation. Among 129 patients suitable for treatment response after transplant, 45 patients (35%) were in CR, 78 patients (60%) were in PR, five patients (4%) in MR and two patients (1%) had no response. From 78 patients who achieved PR were 34 patients with VGPR.

The median follow-up from transplant was 50.3 months. The median PFS from transplant was 29.5 months and the median OS from transplant was 68.8 months (Figure 1). The median survival from diagnosis of MM was 75.4 months.

Factors associated with PFS and OS after ASCT

Age was identified as a significant prognostic factor in our set of patients. We compared PFS and OS post transplant for four age groups (≤ 50 years, 51–55 years, 56–60 years, > 60 years). No significant differences were found in PFS among the age groups. However, patients with age ≤ 55 years had significantly longer OS after transplant than patients with age > 55 years (median OS 71.9 vs 47.9 months, $P=0.013$). The difference was even greater in the higher age group. The group of patients with age > 60 years had significantly shorter survival after ASCT than other groups with age ≤ 60 years (median OS 25.7 vs 71.0 months, $P=0.002$) (Figure 2).

The TRM was higher in patients > 60 years (2/30, 7%) compared with patients ≤ 60 years (2/103, 2%) in our set.

No other differences in the causes of death between these two age groups were observed; deaths in both groups were mostly related to MM without significant differences between patients > 60 years (70%) and patients ≤ 60 years (81%).

Survival after transplant was influenced by clinical stage according to ISS (Figure 3). The median OS of patients with ISS stage 3 was 23.6 months, with ISS stage 2 57.5 months and with ISS stage 1 72.8 months. Patients with ISS stage 3 had significantly shorter PFS and OS than others ($P=0.007$, $P=0.005$) in our group of patients. The differences in PFS and OS between ISS stages 1 and 2 were not significant.

The median OS of patients with DS stage I was 67.6 months, with DS stage II 71.0 months and with DS stage III 71.3 months. Differences in survival among patients with clinical stages according to DS system were not statistically significant.

Patients with MR and NR before transplant had lower CR rate (9%) after transplant compared with patients who achieved CR or PR before transplant (CR rate 36%). We compared the group achieving CR prior to transplant with others, the group achieving CR+PR with others, the

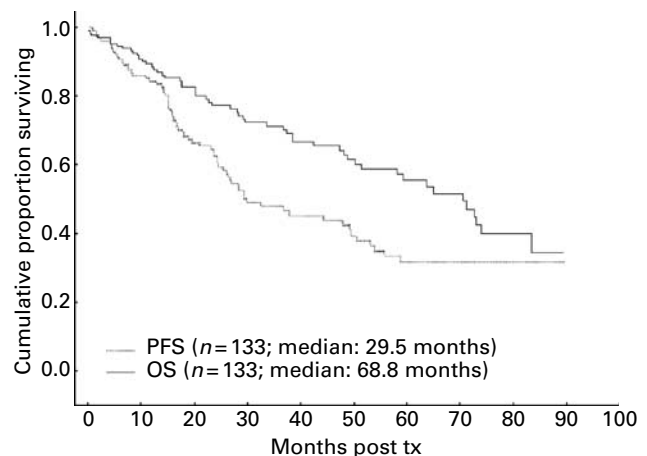


Figure 1 PFS and OS after transplantation for all 133 patients.

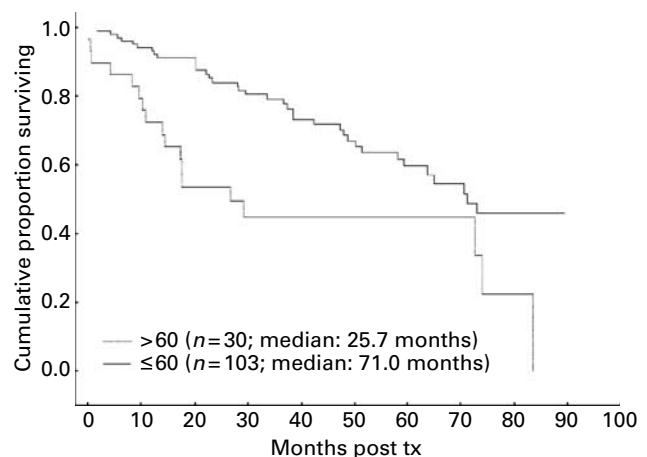


Figure 2 Survival by age.

group achieving CR+VGPR with others and the group achieving MR+NR with the group achieving CR+PR. There was no significant difference in PFS and OS between patients with MR or NR and patients in PR or CR before transplantation. We transplanted only two patients with progression before transplant; both patients died shortly after transplantation (2 and 5 months) to disease progression.

Patients who achieved CR after transplant had significantly longer PFS and OS than others ($P < 0.001$) (Figure 4).

We also evaluated a possible correlation between the type of M-protein and PFS and OS. The patients with type IgA M-protein had shorter PFS (median PFS 16.2 months vs 36.8 months, $P = 0.030$), but the differences in OS between IgA and non-IgA type are not statistically significant ($P = 0.077$).

Selected other clinical and laboratory parameters were evaluated in univariate analysis with the aim to find factors that influence PFS and OS. We used similar cutoffs of some laboratory variables as was published by Tricot *et al*¹⁷ and by Barlogie *et al*.¹⁰

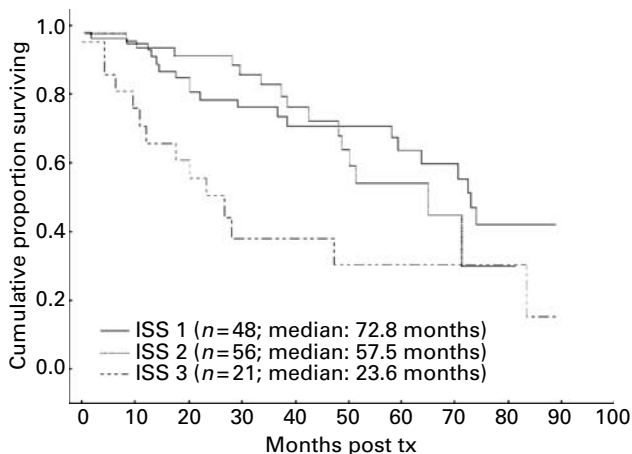


Figure 3 Survival by stage according to International Staging System.

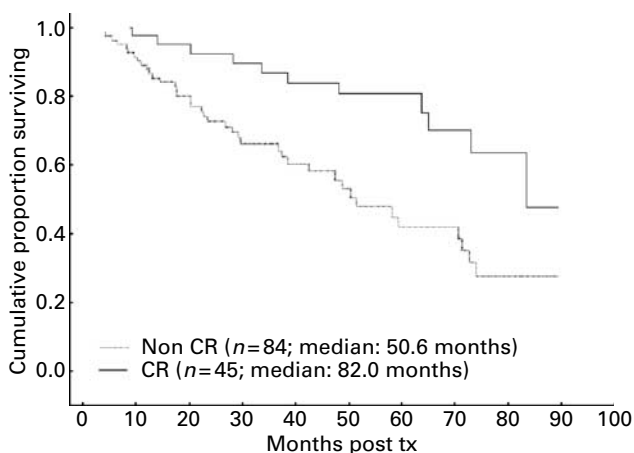


Figure 4 Survival by response after transplantation.

The results from our univariate analysis are summarised in Table 2. Prognostic factors influencing OS with statistical significance ($P < 0.05$) identified in the univariate analysis were stage 3 according to ISS, age and status of disease after transplantation. Selected variables were entered into multivariate final model. The results of multivariate analysis are presented in Table 3. The factors associated with significantly shorter survival according to multivariate analysis were non-CR status after transplant (hazard ratio (HR): 3.1, $P = 0.002$), stage 3 according to ISS before transplant (hazard ratio 3.0, $P = 0.001$) and age at transplant over 60 years ($P = 0.035$, HR: 2.0).

Discussion

We found no significant correlations between DS staging system and survival after transplantation. We observed that patients with ISS stage 3 had significantly shorter OS than others (HR: 3.0, $P = 0.001$) in our group of patients, but the differences in PFS and OS between ISS stages 1 and 2 were not significant. The variability between ISS and DS system is not surprising, because various parameters are used in both systems. Greipp *et al*⁶ presented that 44% DS stage III patients (2299/5181) are evaluated as stage 1 or 2 in the ISS. ISS was very useful in our DS III patients to define the subgroup with poor prognosis (ISS 3).

The vast majority of 133 patients in our study received the same conditioning (melphalan 200 mg/m² in 93% cases) and all patients had transplantation during the first year after diagnosis of MM. In comparison to other published trials,^{18,19} we found no significant differences in the number

Table 2 Univariate analysis

	PFS (P-value)	OS (P-value)
Thrombocytes at transplant (≤ 130 vs > 130)	0.682	0.323
CRP at transplant (≤ 4 mg/l vs > 4 mg/l)	0.080	0.217
Calcium at transplant (≤ 11.0 g/dl vs > 11.0 g/dl)	0.607	0.766
Lactate-dehydrogenase (LD) at transplant (≤ 190 IU/l vs > 190 IU/l)	0.322	0.084
Gender (male vs female)	0.713	0.526
Ig type (IgA vs others)	0.030	0.077
Stage according to ISS (3 vs 1+2)	0.007	0.005
Age at transplant (≤ 55 vs others)	0.541	0.013
Age at transplant (> 60 vs others)	0.424	0.002
Response prior to transplant (CR vs others)	0.329	0.116
Response prior to transplant (MR+NR vs CR+PR)	0.504	0.782
Response after transplant (CR vs others)	< 0.001	< 0.001
Radiotherapy prior to transplant (yes vs no)	0.615	0.747

Bold values are statistically significant.

Table 3 Unfavourable prognostic factors for survival: multivariate analysis

Parameter	P-value	Hazard ratio	95% CI
Non-CR status after transplant	0.002	3.1	1.5–6.5
Age at transplant > 60	0.035	2.0	1.0–3.6
Stage 3 according to ISS	0.001	3.0	1.5–5.9

of days to the neutrophil and platelet recovery, in the consumption of blood products and in the number of days with fever after transplant.

The overall response rate after transplantation was 95% (CR + PR). The response rate is high and it is similar to that reported from other large studies.^{20,21} The TRM (3% in our study) was also similar to the findings of other groups.^{20,22,23}

Advanced age has been shown to be a negative prognostic factor in some trials using ASCT for MM.^{24,25} Majolino *et al*²⁴ reported that age emerged as an important prognostic factor at a cutoff value of 55 years, while other studies using a cutoff value of 65 years or even 70 years have suggested that age is not an exclusion criterion for the ASCT.^{26,27} Vesole *et al*²⁸ reported age less than 60 years among factors favourably affecting MM patient outcome. The French study IFM 90 indicated that patients over the age of 60 years have less favourable outcome after autograft.⁸ We have evaluated PFS and OS in four age groups of patients. We found that patients with ≤ 55 years of age at transplant had longer survival than patients with age > 55 years (median OS 71.9 vs 47.9 months). Patients with age at transplant > 60 years had shorter survival than patients with age ≤ 60 years (median OS 25.7 vs 71.0 months) in our set of patients. The analysis of deaths in various age groups was carried out, the higher TRM was found in patients with age at transplant > 60 years, and no other differences were observed.

The treatment of refractory MM is difficult. Dimopoulos *et al*²⁹ have published that refractory patients had better outcome after transplantation than after conventional chemotherapy. Terpos *et al*²⁰ reported no significant differences in PFS and OS in patients who achieved CR or PR prior to transplantation compared to patients with MR, NR or refractory disease prior to transplantation. However, according to other studies, patients with primary resistant disease gained only minimal advantage from high-dose therapy with autologous stem cell support.^{30,31} Vesole *et al*³² have reported low median OS (19 months) in 72 refractory myeloma-transplanted patients. In our series, there was no significant difference in PFS and OS in patients who had achieved CR or PR before transplant compared to patients with MR or NR before transplant. In our patients with MR or NR but not with symptomatic progressive disease, the survival was good, but the CR rate after transplant was low. The results of ASCT in our two patients with progression of disease before transplant are poor. According to our findings, the performance of ASCT in myeloma patients with symptomatic progressive disease has got no significant benefit.

We have found that patients who achieved post transplant CR had significantly longer PFS and OS than others. The correlation between the good therapeutic response after transplant and the survival is not completely clear. Some authors also believe that better responses after transplant are associated with improved survival.^{10,20,21} In contrast, Rajkumar *et al*³³ reported that the outcome following ASCT depends more on biological variables, such as plasma cell labelling index rather than on the CR status.

The median PFS and OS after transplantation were 29.5 and 68.8 months for our patients, and these values are

comparable to the results of other reported studies.^{8,20,25,34} Although the median OS from diagnosis was 75.4 months, the patients unfortunately continued to progress and die several years after ASCT. The PFS and OS curves failed to show a stable plateau. However, the increase of response rate and prolongation of PFS and OS was observed after ASCT with an estimated benefit of 1–2 years on OS against conventional treatment.^{8,12,18,35,36} New strategies to control minimal residual disease after ASCT are needed.³⁷ They may include maintenance chemotherapy, thalidomide, revimid, bortezomid or immunotherapy (eg peptide or DNA vaccines with or without *ex vivo* pulsed dendritic cells). These strategies are currently under evaluation.¹⁵

In conclusion, ASCT is a safe and effective procedure for MM patients, associated with low TRM. In our group of patients, the outcome of ASCT correlated with the response after ASCT, the age and the stage according to ISS.

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