Autotransplant with and without induction chemotherapy in older multiple myeloma patients: long-term outcome of a randomized trial

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Haematologica 2016
Volume 101(11):1398-1406

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Received: July 1, 2016.

Accepted: August 3, 2016.

Pre-published: August 4, 2016.

doi:10.3324/haematol.2016.151860

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/101/11/1398

ABSTRACT

Autologous transplantation is controversial for older patients with multiple myeloma. The role of age-adjusted high-dose melphalan and the impact of induction chemotherapy cycles is still unclear. A total of 434 patients aged 60-70 years were randomly assigned to 4 cycles of standard anthracycline-based induction chemotherapy or no induction. For all patients, double autologous transplantation after melphalan 140 mg/m^2 (MEL140) was planned. The primary end point was progression-free survival. Of 420 eligible patients, 85% received a first transplant and 69% completed double transplantation. Treatment duration was short with a median of 7.7 months with induction chemotherapy cycles and 4.6 months without induction. On an intention-to-treat basis, median progression-free survival with induction chemotherapy cycles (207 patients) was 21.4 months *versus* 20.0 months with no induction cycles (213 patients) (hazard ratio 1.04, 95% confidence interval 0.84-1.28; *P*=0.36). *Per* protocol, progression-free survival was 23.7 months *versus* 23.0 months (*P*=0.28). Patients aged 65 years or over (55%) did not have an inferior outcome. Patients with low-risk cytogenetics [absence of del17p13, t(4;14) and 1q21 gains] showed a favorable overall survival and included the patients with sustained first remission. MEL140 was associated with a low rate of severe mucositis (10%) and treatment-related deaths (1%). Based on hazard ratio, the short treatment arm consisting of mobilization chemotherapy and tandem MEL140 achieved 96% of the progression-free survival, demonstrating its value as an independent component of therapy in older patients with multiple myeloma who are considered fit for autologous transplantation. (*clinicaltrials.gov identifier: 02288741*)

Introduction

High-dose chemotherapy with autologous stem cell transplantation (ASCT) is considered the standard treatment for younger patients with multiple myeloma (MM).[1-3] In older patients, however, its role is less clear and remains controversial.[4-6] As a consequence, many older but otherwise fit patients are excluded from the procedure. This may have contributed to a survival disadvantage.[7]

Concerns about toxicity or an inferior outcome in comparison to younger patients continue to inhibit the application of high-dose therapy with ASCT in older patients, although its use has increased considerably in recent years.[8,9] Only limited data are available as these patients are under-represented or missing entirely from the large recent prospective multicenter transplantation trials which mostly apply an age cut off of 65 years.[10-17] The little information there is concerning higher age groups is based on retrospective single center experience. These mostly report limited numbers of patients.[18-23] Registry data are lacking details of toxicity and outcome but demonstrate improvements in overall survival (OS) over the years.[8,9]

Melphalan 200 mg/m^2 (MEL200) represents the standard high-dose regimen for the younger patient population.[24] The frequent reluctance to apply MEL200 in patients over the age of 65 years is related to concerns about potential higher toxicity. As an alternative to MEL200, an age-adjusted melphalan dose of 140 mg/m^2 (MEL140)[25] can be given in patients over 60 years of age; the intention is to decrease severe mucositis and other toxicities and thereby to enable older patients who are not considered eligible for MEL200 to proceed to ASCT. Reports show that this strategy has now become part of current clinical routine.[9,18,20,21,23] The proportion of patients receiving an age-adjustment of the melphalan dose is steadily increasing within the higher age groups when considering patients over the age of 60, over 65 and over 70 years.[9,20,21,23] If age-adjustment were to be applied consistently, many more older patients could be considered candidates for ASCT.

Two randomized clinical trials investigated intermediate-dose melphalan (MEL100) with ASCT in older patients.[5,26] Data from a prospective randomized trial specifically reporting the efficacy and toxicity of MEL140 in older patients has been lacking; this study aims to provide this missing information.

Historically, stem cell therapy is preceded by 3-6 cycles of induction chemotherapy. This strategy is considered to be important but since the progression-free survival (PFS) achieved after ASCT is achieved from the complete treatment, the contribution of induction chemotherapy alone still has to be defined. In the prospective phase III trial presented here, we addressed: 1) the role of conventional induction chemotherapy cycles prior to high-dose chemotherapy by randomization between anthracycline-based induction (the standard therapeutic approach when the trial started) and no induction cycles; and 2) the real toxicity and efficacy of tandem MEL140 with and without induction chemotherapy in a large older patient population.

Methods

Patients and study design

This randomized multicenter trial was planned by the German Multiple Myeloma Study Group (DSMM) and was conducted at 40 sites. Eligible patients had newly diagnosed stage II or III MM according to Durie and Salmon and were 60-70 years of age. Additional criteria for inclusion were an Eastern Cooperative Oncology Group performance status of 0-2, adequate organ function, and absence of uncontrolled infection. Enrollment began in August 2001 and ended in August 2006.

Patients with no previous chemotherapy or a maximum of one cycle were randomly assigned between conventional induction chemotherapy cycles and a short course of dexamethasone only (Figure 1A). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the local ethics committees at each participating center. Patients were required to provide written informed consent before enrollment. The study was registered at *clinicaltrials.gov identifier: 02288741*.

Treatment plan

In the induction arm, patients received 4 cycles of conventional anthracycline-dexamethasone-based regimens: vincristine-doxorubicin-dexamethasone (VAD),[27] idarubicin-dexamethasone (ID),[28] cyclophosphamide-doxorubicin-dexamethasone (CAD).[29] In the no induction arm, patients received only 40 mg oral dexamethasone on days 1-4 and 8-11 for symptom control. For the subsequent stem-cell mobilization, age-adjusted (75% dose) ifosfamide-epirubicin-etoposide (IEV) with granulocyte-colony stimulating factor (G-CSF) was recommended.[30] The target dose for stem cell collection was 6x10^6 CD34-positive cells/kg (two transplants and one back-up). The standard dose for each transplantation was 2x10^6 CD34-positive cells/kg. High-dose melphalan at a total dose of 140 mg/m^2 (MEL140) was given in two doses of 70 mg/m^2 on days -3 and -2. ASCT was performed on day 0. A second MEL140 course was planned two months after the first. No maintenance treatment was given but regular bisphosphonate administration was recommended.

Sample size and statistical aspects

The primary study end point was PFS calculated from the time point of randomization. To detect a 10-month advantage in PFS for the induction arm [24-34 months, corresponding to a hazard ratio (HR) of 0.71] with a power of 80% and based on a one-sided type I error rate of 0.05, at least 132 patients were required *per* randomization arm.

Toxicity of treatment was evaluated using Common Toxicity Criteria (v.2.0, 1999), the definition of remission followed European Group for Blood and Marrow Transplantation (EBMT) criteria.[31] Except for the primary end point, all analyses were descriptive or explorative in nature, providing two-sided *P*-values without referring to a specified error level. No adjustments were made for multiple testing. Proportions were eventually compared using Fisher's exact or χ^2 test. All time-to-event end points were calculated by the Kaplan-Meier method. Survival curves were compared using the log-rank test. HR with confidence intervals were derived from Cox models.

Results

Patients

Figure 1 shows the study design and the consort diagram. A total of 434 patients were enrolled into the study protocol and were randomized. Fourteen patients (3%) were excluded from analysis. Accordingly, 420 patients could be analyzed with respect to the primary end point: PFS. The median follow-up period was 5.2 years (range 0-10.1 years). Details of consecutive treatment steps were

documented in 416 patients. Baseline characteristics of patients are shown in Table 1.

Induction chemotherapy

In the induction arm (n=207 patients), 98% received one of the recommended induction regimens (idarubicin-dexamethasone 67%, vincristine-doxorubicin-dexamethasone 25%, cyclophosphamide-doxorubicin-dexamethasone 6%), 2% received dexamethasone alone. A median of 4 cycles (range 1-7 cycles) were given for a median of 3.9 months (range 0.3-12.3 months). In the no induction arm, the 2 cycles of 4x40 mg dexamethasone were given for a median of 0.7 months (range 0-5.7 months) before stem cell mobilization was initiated.

Stem-cell mobilization and ASCT

A total of 385 patients (92%) were treated with stem cell mobilization chemotherapy: ifosfamide-epirubicin-etoposide in 89%, cyclophosphamide-doxorubicin-dexamethasone in 5%, cyclophosphamide in 4%, cyclophos-

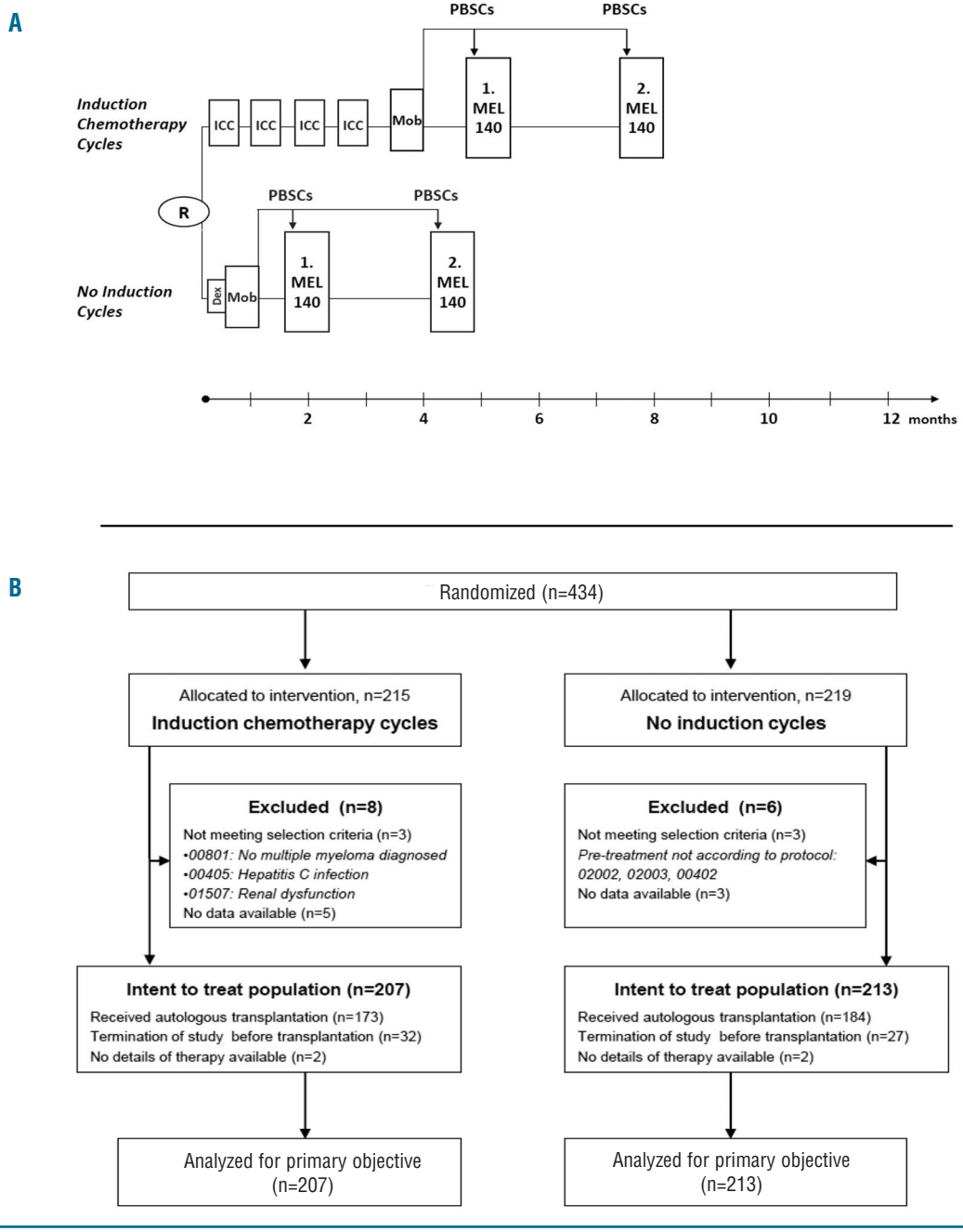

Figure 1. Study design and consort diagram. (A) Study design. Patients were randomized (R) to the two study arms: 1) induction chemotherapy cycles; and 2) no induction cycles. (B) Consort diagram. Inclusion, randomization, treatment and follow up of enrolled patients. PBSCs: peripheral blood stem cells; ICC: induction chemotherapy cycles; Dex: dexamethasone; Mob: mobilization chemotherapy; MEL140: high-dose melphalan.

Table 1. Patients' characteristics.

Characteristic	Randomization	
	Induction chemotherapy (n=207)	No induction (n=213)
Age, years		
Median	65	65
Range	(60-72)	(60-72)
Sex, n. (%)		
Male	119 (57)	117 (55)
Female	88 (43)	96 (45)
Durie and Salmon stage, n. (%)		
I	0 (0)	3 (1)
II	38 (18)	45 (21)
III	169 (82)	164 (77)
A	185 (89)	173 (81)
B	22 (11)	39 (18)
Undefined	–	1 (1)
M-component, n. (%)		
IgG	135 (65)	132 (62)
IgA	40 (19)	49 (23)
IgM	2 (1)	0 (0)
IgD	2 (1)	1 (1)
Kappa light chain only	21 (10)	18 (8)
Lambda light chain only	5 (3)	10 (5)
Non-secretory myeloma	2 (1)	3 (1)
Hemoglobin, g/dL		
Mean ± SD	11.3±1.8	10.9±1.8
Median	11.3	11.0
Range	6.3 - 16.1	5.7-15.8
Platelets, x10^9/L		
Mean ± SD	245±93	237±94
Median	240	227
Range	69-757	54-540
Serum creatinine, mg/dL		
Mean ± SD	1.1±0.4	1.4±1.1
Median	1.0	1.0
Range	0.6-3.3	0.4-9.6
β_2-microglobulin, mg/L		
Mean ± SD	4.6±5.0	5.1±5.4
Median	3.3	3.8
Range	0.2-46.7	0.9-54.6
< 3.0	85 (41)	71 (33)
≥ 3.0	110 (53)	124 (58)
Unknown	12 (6)	18 (9)
≥ 5.5 (*ISS stage III)	45 (22)	52 (24)
Lytic bone lesions, n. (%)		
Present	168 (81)	165 (77)
Absent	37 (18)	46 (22)
Unknown	2 (1)	2 (1)
Cytogenetics,° n./total (%)		
Adverse		
Deletion 17p13	9/116 (8)	10/104 (10)
Translocation (4;14)	17/112 (15)	2/100 (12)
Translocation (14;16)	2/ 98 (2)	5/ 93 (5)
Amplification +1q21.2	35/116 (30)	43/102 (42)
Other		
Translocation (11;14)	18/100 (18)	14/ 93 (15)
†Hyperdiploid myeloma	66/116 (57)	64/102 (63)
‡Deletion 13q14	56/161 (35)	53/148 (36)
Risk profile		
‖High	25/111 (23)	19/99 (19)
§Intermediate	26/111 (23)	32/99 (32)
¶Low	60/111 (54)	48/ 99 (48)

**ISS: International Staging System. †Hyperdiploid myeloma was assessed by the presence of gains of 9q34.2 ‡Data from either central or local cytogenetic laboratory.‖High: presence of t (4;14) and/or del 17p13.§Intermediate: presence of +1q21.2 and absence of t(4;14) and del 17p13.¶Low: absence of t (4;14), del 17p13 and +1q21.2 in patients with analysis of all these three characteristics. °Cut-off of aberrant cells: 20%; SD: standard deviation.*

phamide-etoposide in 1%, ifosfamide in 1%. Stem cells were collected in 376 patients. The recommended target value (≥6x10^6 CD34$^+$ cells/kg) and the required dose for a double transplantation (≥4x10^6 CD34$^+$ cells/kg) were achieved in 80% and 90% of patients, respectively. A total of 357 patients (85%) then went on to receive at least one transplant and 289 patients (69%) completed a double transplant. The main reasons for drop-out in the 68 patients (16%) who did not receive the second transplant were: progression of disease (21%), toxicity (22%), death (7%), patient refusal (18%), insufficient stem cell collection (7%).

Toxicity, deaths and second primary malignancies

The major grade III/IV non-hematologic toxicities were infection and mucositis (Table 2). Deaths up to 100 days from the last treatment occurred in 25 patients (6.0%) and death was due to: disease progression in 5 patients (1.2%), toxicity (infection, sepsis, renal failure, cardiac) in 20 patients (4.8%). In 20 of 25 cases, death occurred before the first MEL140. Transplant-related mortality (TRM) was very low: 1.4% after the first MEL140 and, notably, 0% following the second MEL140. Some cases of grade III/IV mucositis were seen during induction chemotherapy cycles (4%), but none were observed during the short dexamethasone pre-phase. Comparison of the induction and the no induction arms showed: 2% *versus* 6% grade III/IV mucositis after mobilization, 11% *versus* 16% after the first MEL140 course, 5% *versus* 7% for the second MEL140, respectively. Moderate rates of grade III/IV infections occurred during induction chemotherapy cycles or the dexamethasone pre-phase (17% *vs.* 4%), after mobilization (17% *vs.* 30%), and at a higher frequency after the first MEL140 (35% *vs.* 44%) and second MEL140 (38% *vs.* 34%). A second primary malignancy was reported (2 solid tumors, 2 acute myeloid leukemias) in 4 of 420 patients (1%).

Response rates

Response rates reflected differences in treatment and treatment progress between patients in the two arms (Table 3). There was an initial lag in response rate in the no induction arm. However, this recovered in the following treatment steps, and after the second MEL140 response rates were similar in the two arms.

Long-term outcomes after randomization

Median PFS for patients in the induction arm was 21.4 months compared to 20.0 months for patients in the no induction arm [hazard ratio (HR) for progression or death 1.04, 95% confidence interval (CI) 0.84-1.28; *P*=0.36] (Figure 2A). Therefore, based on this HR, 96% of the duration of PFS was already achieved by ASCT alone; induction chemotherapy cycles contributed only 4%. Treatment duration was short with a median of 7.7 months in patients in the induction arm and a median of 4.6 months in patients in the no induction arm. For double transplant recipients (*per* protocol), median PFS was 23.7 months for patients in the induction arm compared to 23.0 months for patients in the no induction arm (*P*=0.28) (Figure 2B). In the intention-to-treat analysis, median OS for patients in the induction arm was 53.4 months compared to 55.9 months for patients in the no induction arm (HR for death 1.01, 95%CI: 0.77-1.32; *P*=0.95). *Per* protocol (double transplants), the median OS for patients in the induction arm was 68.5 months compared to 64.4 for patients in the no induction arm (*P*=0.98). A subgroup of 27 patients (6.4%) from both arms were survivors in first remission at five years. Among these 27 patients, characterized by the presence of low-risk cytogenetics (100%), 96% received MEL140, 85% received a double transplant, and 70% were not in ISS stage III. In 16 of these patients, no relapses were seen beyond five years.

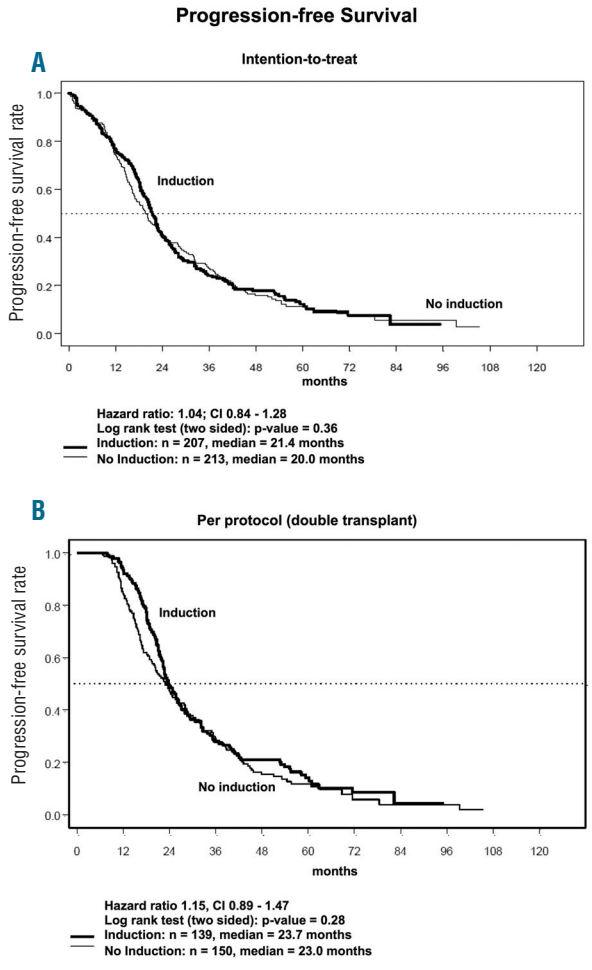

Figure 2. Long-term outcomes after randomization between induction chemotherapy cycles and no induction cycles. The curves for progression-free survival with induction chemotherapy cycles *versus* no induction cycles are shown based on intention-to-treat (A) and *per* protocol (tandem transplants) (B).

Treatment effects according to age subgroups

The discontinuation rate before the first high-dose melphalan course was higher for patients aged 65-70 years (18%) than for those aged 60-64 years (9%). The drop-out rate after the first MEL140 was similar for the younger (18%) and the older (17%) patients. More patients aged 60-64 years than aged 65-70 years completed tandem MEL140 (73% *vs.* 65%). Deaths within 100 days from the last treatment were more frequent during the induction phase in patients aged 65-70 years (6.1% *vs.* 3.1%), but were similar in both age groups following the first transplant (1.6% *vs.* 1.1%) and did not occur in either age

Table 2. Hematologic and non-hematologic toxicity during treatment steps.

	Induction phase		Mobilization		1. MEL 140		2. MEL 140	
	Induction	No induction	Induction	No induction	Induction	No induction	Induction	No induction
Hematologic (%)								
Anemia	84	64	89	95	100	100	100	100
Leukopenia	59	26	86	88	100	100	100	100
Neutropenia	47	15	77	82	100	100	100	100
Grade III/IV	22	5	63	75	100	100	100	100
Thrombocytopenia	27	16	77	84	100	100	100	100
Grade III/IV	5	2	40	44	100	100	100	100
Non-hematologic (%)								
Nausea	32	10	45	45	70	72	71	72
Grade III/IV	2	0	1	4	7	14	5	9
Vomiting	15	1	18	23	36	46	39	43
Diarrhea	11	2	13	18	41	42	31	34
Constipation	15	5	7	9	10	9	12	8
Mucositis	17	3	23	28	51	51	46	49
Grade III/IV	4	0	2	6	11	16	5	7
Infection	33	14	31	40	49	58	56	49
Grade III/IV	17	4	17	30	35	44	38	34
Dyspnea	11	6	5	11	13	10	10	6
Creatinine	18	22	17	23	25	19	16	16

MEL140: melphalan 140 mg/m².

Table 3. Responses with consecutive treatment steps according to EBMT criteria.

	Induction phase		Mobilization		1. MEl140		2. MEL140	
	Induction	No induction	Induction	No induction	Induction	No induction	Induction	No induction
*ORR (%)	48	30	58	46	78	79	87	87
†CR (%)	0	1	2	2	6	9	17	12
‡PR (%)	48	29	56	44	72	70	70	75
§MR (%)	19	14	20	19	13	12	7	8
¶NC (%)	25	52	20	32	6	8	5	5
¶PD (%)	7	4	2	3	3	2	2	0

*EBMT: European Society for Blood and Marrow Transplantation; MEL140: melphalan 140 mg/m². *ORR: overall response rate (CR+PR); †CR: complete response; ‡PR: partial response; §MR: minimal response; ¶NC: no change; ¶PD: progressive disease.*

group after the second transplant. On the intention-to-treat basis, median PFS in younger *versus* older patients (19.5 and 22.1 months; *P*=0.23) and median OS (56.3 and 53.1 months; *P*=0.58) were similar (Figure 3A).

Cytogenetic risk and outcome

Of the 210 evaluated patients, 108 patients (51%) fulfilled the IMWG[32,33] low-risk cytogenetics criteria: absence of translocation (4;14), deletion 17p13, amplification of 1q21.2) (Table 1). High-risk cytogenetics [presence of translocation (4;14) and/or deletion 17p13] were found in 21%, intermediate-risk cytogenetics [presence of amplification of 1q21.2, absence of translocation (4;14) and deletion (17p13)] were present in 28% of cases. A highly significant difference between low-risk and high-risk cytogenetics was seen for PFS (median 23.5 *vs.* 14.9 months; *P*<0.0001) and OS (median 74.7 *vs.* 32.9 months; *P*<0.0001) (Figure 3B). The patients with low-risk cytogenetics who completed double transplantation (78%) had an excellent outcome (median PFS 26.7 months and median OS 87.4 months). Patients still alive in sustained first remission beyond five years were considered to be in the low-risk cytogenetics group.

Discussion

Our trial abandoned induction chemotherapy cycles before ASCT in one arm of the study in order to test the relationship between induction chemotherapy and ASCT, and did not use consolidation or maintenance therapy. This must be considered when comparing the outcome of our trial to others which applied the common strategy of incorporating all available drugs into treatment phases before and after ASCT with the aim of achieving a maximum duration of PFS after first-line treatment in MM patients. Unexpectedly, we found that a large part of the anti-tumor effect (96%) was achieved with high-dose chemotherapy and ASCT alone, and that the 4 cycles of anthracycline-based induction chemotherapy only made a small contribution. By 3-4 months of anthracycline-based induction therapy, the PFS was improved by only two months. Based on the HR of the comparison between the two arms, such induction chemotherapy cycles achieved only 4% of the PFS. Anthracycline-based induction chemotherapy was the standard approach when our trial started but has since been replaced by induction regimens incorporating novel agents. In this respect, both arms of

our trial may be regarded as a 'baseline' from which the achievements of novel agent-based induction therapy can be evaluated. The current use of bortezomib-based induction regimens,[13,11,15,34-36] were found to increase the PFS over the typical anthracycline-based regimen VAD[13,15] by approximately six months. Despite this improvement, the estimated impact of such induction therapy on the overall PFS appears to be limited when we consider our 'baseline' results and those from other trials demonstrating a high efficacy of post-transplant treatments with novel agents.[10,12,14] Our study is the first prospective randomized trial to characterize the 'real' toxicity and efficacy of MEL140 with ASCT in older MM patients. The results highlight an independent role for ASCT in older patients. MEL140 was well-tolerated. The rate of severe mucositis was approximately 10%, TRM approximately 1%. It should be emphasized that following the treatment pause after the first MEL140, the non-hematologic toxicity of the second MEL140 appeared to be a little lower compared to the first MEL140 and the TRM was 0%. Importantly, the long-term outcome identified a subgroup of patients who did not relapse after MEL140 even over a number of years. This may indicate some curative potential with age-adjusted high-dose melphalan. For more than 200 patients aged 65-70 years, the outcome was at least as good compared to the younger patients in this study, demonstrating that an age cut off at 65 years for MEL140 was not relevant. The long-term outcome for the tandem MEL140 component in conjunction with the large number of patients treated may serve as a point of reference for future trials. Geriatric assessment and comorbidity scores will be helpful to encourage autologous transplantation in many MM older patients.[37,38] The low rate of second primary malignancies following tandem MEL140 in comparison to that in the published literature[39] is noteworthy and could be related to the limited first-line treatment in the study population.

Due to the significant efforts of a central laboratory, we can present up-to-date cytogenetic data for around 200 patients. Many publications define high-risk *versus* stan-

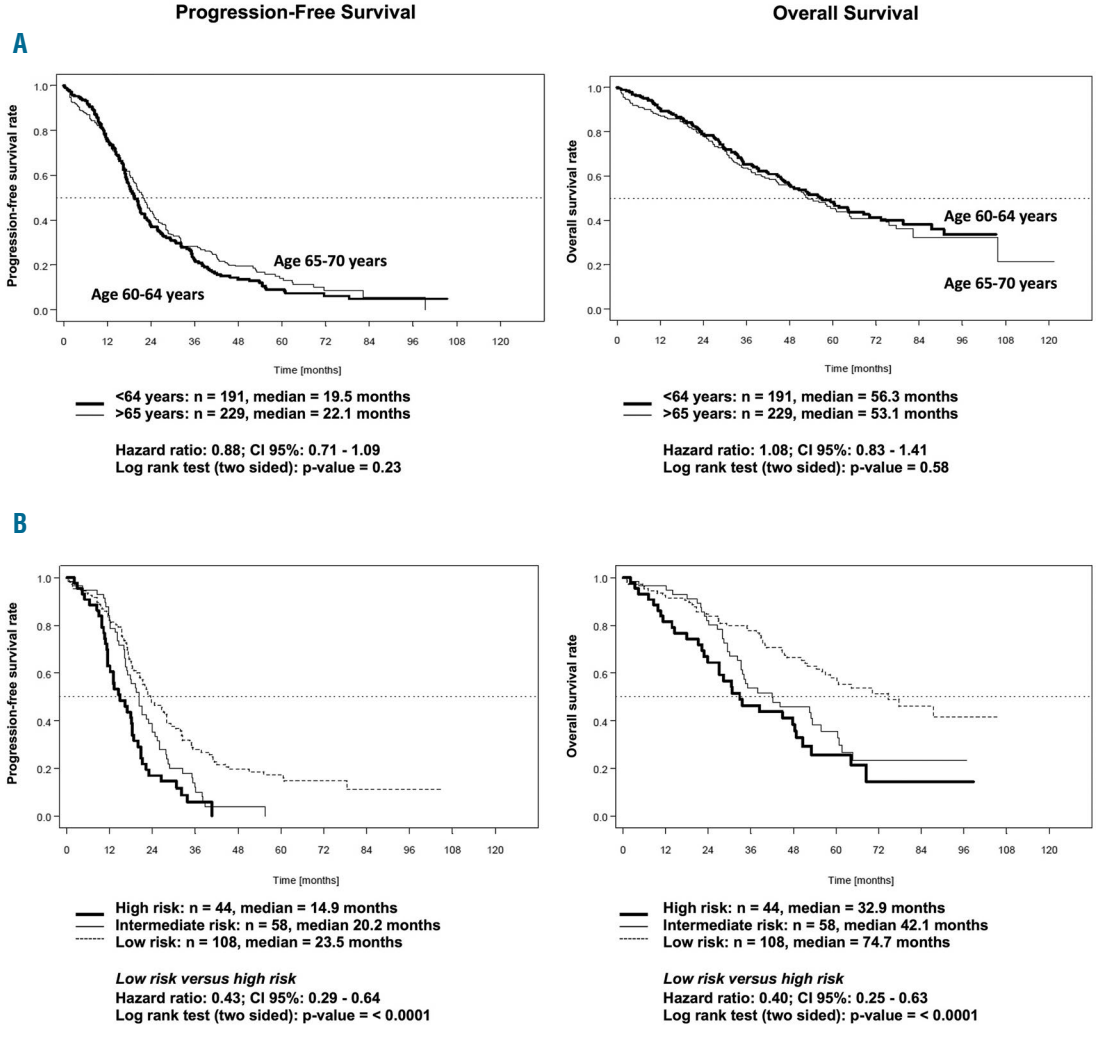

Figure 3. Outcome for age and cytogenetic risk groups. The curves for progression-free survival and overall survival are shown for (A) the age groups 60-64 years and 65-70 years, and (B) for high-risk, intermediate-risk and low-risk cytogenetics.

dard-risk groups but very few reports indicate a low-risk group as defined by the IMWG.[33,34] This requires investigation of 1q21 gains together with analysis of translocation (4;14) and deletion 17p. We found that 50% of the MM patients of this age group who had a low-risk cytogenetic profile showed excellent survival rates with front-line age-adjusted high-dose melphalan. Importantly, the patients with low-risk cytogenetics included those with sustained unmaintained first remission, and some of these could be considered 'cured'. Recently, treatment with novel agents plus ASCT has been found to be more effective than novel agents plus conventional chemotherapy in patients up to 65 years of age.[14,16,17] Similar randomized clinical trials are also needed in the older patient population and treatment should be based on tandem MEL140.

Another important aspect to consider is that the concept of age-adjusted high-dose melphalan includes double transplantation, which compensates the dose reduction of single melphalan. The tandem MEL100 regimen divided the standard MEL200 dose in two parts and enabled older patients to proceed to ASCT with reduced toxicity.[5,26,40] A tandem application of MEL200 in older patients, however, was found to decrease steeply with higher age due to the well-known risks associated with these patients.[22] In contrast, in our trial, a rapid improvement in performance status post transplant allowed the second MEL140 course to be given after two months in approximately 80% of patients. Therefore, as far as feasibility is concerned, tandem MEL140 (cumulative melphalan dose 280 mg/m^2) represents an alternative to single MEL200 (200 mg/m^2) in the older patient population. Such a comparison should be investigated in a prospective randomized trial for patients aged 60-70 years.

In fact, our trial shows that the treatment arm consisting of stem-cell mobilization chemotherapy followed by tandem MEL140 with ASCT, despite its short treatment time of 4-5 months, is extremely effective, with a PFS of 20-23 months. Current non-transplant regimens used in this age group, such as VMP[41] or MPT[42] or MPR[43] or Rd,[44] provide similar PFS rates (median 22, 20, 14 and 21 months, respectively) but are associated with the development of neuropathy or thrombosis and thromboembolism and require a prolonged treatment time that often does exceed one year. On the other hand, our trial demonstrates that age-adjusted high-dose therapy is not necessarily 'aggressive', nor is this 'aggressiveness' observed in all patients. Older fit patients may, therefore, benefit from an age-adjusted transplant program that would allow longer unmaintained remissions following transplantation during which patients can enjoy freedom-from-therapy. When lenalidomide is continued as maintenance therapy in the MPRR[43] or continues Rd[44] regimens, the PFS can be extended. Similarly, lenalidomide maintenance can also be used after MEL140.[10,12,14,40] The preference for MEL140 or MEL200 in subgroups of older patients is beyond the scope of the present paper as this has been discussed extensively in previous publications. The known arguments center around the specific features of MEL200 (higher toxicity, potentially higher efficacy, single transplantation, upper age limit around 70 years) *versus* MEL140 (lower toxicity, potentially lower efficacy, tandem transplantation possible, upper age limit around 75 years). Obviously, any valid recommendation can only be made on the basis of the availability of results from prospective randomized trials in specific age groups which, however, are completely lacking. Therefore, for the moment, MEL140 and MEL200 represent complementary rather than competing options for older patients. In conclusion, short-term tandem MEL140 with ASCT can lead to long-lasting unmaintained remission, and should be considered an independent component of myeloma therapy. A sustained first remission is associated with low-risk cytogenetics present in approximately 50% of patients.

Funding

Novartis provided financial support for conducting the study, but was not involved in data collection, data analysis or writing the manuscript. Molecular cytogenetic analysis was supported by the Deutsche José Carreras Leukämie-Stiftung.

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