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Impact of age on survival after intensive therapy for multiple myeloma. A population-based study by the Nordic Myeloma Study Group.

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Running title: Impact of age on survival after auto-SCT for MM

SUMMARY

The value of intensive therapy, including autologous stem cell transplantation, in newly diagnosed myeloma patients >60 years is not clear. We evaluated the impact of age (<60 years versus 60-64 years) on survival in a prospective, population-based setting and compared survival with conventionally treated historic controls. The prospective population comprised 452 patients registered from 1998 to 2000. Of these, 414 received intensive therapy. The historic population, derived from our most recent population-based study on conventional therapy, comprised 281 patients. Of these, 243 fulfilled our eligibility criteria for intensive therapy. For patients undergoing intensive therapy we found that two factors, beta-2-microglobulin and age <60 vs. 60-64 years, had independent prognostic impact on survival. However, compared to the historic controls a survival advantage was found both for patients <60 (median 66 vs. 43 months, P<.001) and 60-64 years (median 50 vs. 27 months; P=.001). We conclude that in a population-based setting higher age adversely influences outcome after intensive therapy. Our results indicate that intensive therapy prolongs survival also at age 60-64 years but with less superiority than in younger patients.

Keywords: myeloma, transplantation, age, survival, population-based

INTRODUCTION

In the beginning of the 1980s high-dose melphalan was introduced for treatment of multiple myeloma in order to overcome resistance to standard doses of alkylating agents (McElwain & Powles, 1983). This therapy became safer when autologous stem cell rescue was introduced. Since the beginning of the 1990s there has been considerable expansion in the number of autologous transplantations for myeloma (Gratwohl *et al*, 2003). A number of studies have evaluated high-dose therapy in newly diagnosed myeloma. The results clearly indicate that high-dose therapy is superior to conventional therapy in younger patients (Attal *et al*, 1986; Barlogie *et al*, 1997; Fermand *et al*, 1998; Child *et al*, 2003). However, the upper age limit for this superiority is not clear. In spite of this, 65-70 years is a common upper age limit in many centres.

The Nordic Myeloma Study Group (NMSG) have earlier shown, in a population-based setting using historic controls for comparison, that intensive therapy prolongs survival compared to standard therapy in newly diagnosed myeloma patients younger than 60 years (Lenhoff *et al*, 2000). To address the issue whether intensive therapy is of benefit also for older patients we in 1998 initiated a population-based, prospective trial (NMSG protocol #7/98) aiming to study the effect of age on event-free survival and survival after intensive therapy in the entire population of newly diagnosed myeloma patients younger than 65 years. Survival was also compared with that of historic controls, derived from the most recent population-based NMSG study on conventional chemotherapy.

PATIENTS AND METHODS

Prospective population

Fourteen centres in Denmark, Norway and Sweden, representing a total population of 15 million inhabitants, were requested to register all newly diagnosed, symptomatic myeloma patients <65 years within their respective regions. The registration started in January 1998 in the first regions, and all regions started their registration during 1998. Registration was stopped in June 2000. A total of 452 patients were registered and constituted the prospective population (Table I). Of these 414 patients were treated according to a specified treatment protocol (NMSG #7/98, described below) and constituted the intensive therapy group. The reasons for non-entry into the treatment protocol are presented in Table I.

Historic population

The historic population was identified from a previous prospective, population-based, randomized NMSG study with inclusion of patients from 1990 until 1992. In this study the value of adding alfa-2b-interferon to standard melphalan and prednisone was investigated (Nordic Myeloma Study Group, 1996). There were 281 registered patients younger than 65 years who fulfilled the diagnostic criteria. These constitute the historic population. The records of all these patients were reviewed and updated, and 38 patients were retrospectively judged not to fulfil the eligibility criteria for intensive therapy stated in the NMSG #7/98 protocol (Table I). The remaining 243 patients constituted the control group, intended for survival comparison with the intensive therapy group. Originally 120 patients in the control group were included in the randomized study comparing melphalan and prednisone +/- interferon, the others received mainly melphalan and prednisone as up-front therapy. Twenty two patients (all of them younger than 60 years) in the control group were transplanted (9 allogeneic and 13 autologous). The majority of these transplantations (8 allogeneic and 8 autologous) were performed more than one year after registration, i.e. not as a part of the up-front therapy. In the survival analyses transplanted patients in the control group have been censored at date of transplantation.

Expected number of patients

The crude incidence of multiple myeloma in patients younger than 65 years was calculated to be 1.8 per 100,000 inhabitants annually, based on previous Nordic incidence studies and the official cancer statistics of Sweden. The expected number of new cases within the prospective population and in the study comprising the historic population was then estimated from this incidence figure, the known population base for each study and the study periods (Table II).

Eligibility criteria for intensive therapy

The diagnostic criteria used by the NMSG have been presented previously (Lenhoff *et al*, 2000). Only patients with symptomatic disease were registered. All patients could be treated according to the NMSG #7/98 protocol provided they were not considered ineligible for the induction therapy with VAD due to severe co-morbidity, terminal illness or refusal. Patients gave written consent to participate in the study. The study was approved by the ethical committees in Denmark, Norway and Sweden and conducted in accordance with the Helsinki declaration of 1975.

NMSG #7/98 treatment protocol.

The treatment was divided into four phases: (I) Induction therapy with three courses of VAD (vincristine 1.6 mg and doxorubicin 36 mg/m^2 as continuous intravenous infusion days 1-4, dexamethasone 40 mg daily days 1-4, 9-12, 17-20; repeated every fourth week); (II) Peripheral blood stem cell harvest of a minimum of 2 x 10^6 CD34$^+$ cells per kg body weight at regeneration after cyclophosphamide 2 g/m^2 given as a single dose intravenously and G-CSF (filgrastim) 5 µg/kg daily; (III) High-dose therapy with melphalan 200 mg/m^2 given as a single dose intravenously, followed by stem cell infusion 36-48 hours later, and G-CSF (filgrastim) 5 µg/kg daily from day four post grafting until an absolute neutrophil count of more than 1.0 x10^9/l; (IV) Maintenance therapy with interferon alfa-2b at maximum dose 3 MU/m^2 three times weekly subcutaneously, starting two months post grafting and maintained until relapse. A second course of high-dose melphalan with autologous stem cell rescue was optional. Allogeneic stem cell transplantation was accepted at the responsible

physician's discretion if the patient had a HLA identical sibling. Patients with progressive disease or with emerging contraindications to high-dose chemotherapy were taken off the treatment protocol. The responsible physician was free to choose therapy for patients leaving protocol regulated treatment and for patients with relapse or progressive disease.

Definitions

Complete response was defined by disappearance of M-protein in serum and urine in agarose gel electrophoresis and less than 5% plasma cells in bone marrow aspirate. Partial response was defined by an at least 50% reduction of the initial serum M-protein concentration and a reduction of Bence-Jones proteinuria to less than 0.2 g/24h. Minor response was defined by a 25-50% reduction of the initial serum M-protein concentration and a reduction of the Bence-Jones proteinuria by at least 50% but exceeding 0.2 g/24h. To fulfil the criteria for complete, partial or minor response the patients were not allowed to have any other signs of myeloma progression, such as persisting hypocalcaemia or progressive renal insufficiency, skeletal disease or bone marrow insufficiency due to plasma cell infiltration. Progression was defined by a confirmed increase of the serum M-protein concentration by more than 25% (but at least to 10 g/l) from the level at the time of best response, or an increase of Bence Jones proteinuria to more than 1.0 g/24h, or by other unequivocal signs of disease progression, such as hypocalcaemia, progressive skeletal disease or soft tissue plasmocytomas. Myeloma progression and death from any cause without progression were considered as events. Event-free and total survival was calculated from start of therapy.

Follow up evaluation.

Patients treated according to the NMSG #7/98 protocol were evaluated before start of phase II and phase III, and thereafter every sixth week. Patients who did not complete phase I-III treatment were evaluated every sixth week after leaving the protocol. Median follow-up of registered patients was 58 months.

Statistical analysis

The median survival for the historic population was known to be 38 months. The study was designed to, with 80 percent power, detect an improvement in median survival of 24 months for the prospective population. The recruitment target was 300 patients during two years. Forty percent of the patients were expected to be 60-64 years old. Due to a lower proportion of older patients than expected the registration period was prolonged to attain at least 120 registered patients aged 60-64 years.

The proportion of patients with a given characteristic was compared by chi-square test for variables with frequency scale, and Wilcoxon rank-sum test for remaining variables. Event-free and total survival was calculated according to the Kaplan-Meier method, and survival comparisons between groups made by the log-rank test. The Cox proportional hazard regression model was used to estimate the prognostic importance of different variables. Bone marrow plasma cells, blood haemoglobin, serum creatinine, blood platelets, white blood cell count, serum albumin, serum lactate dehydrogenase, serum C-reactive protein, serum albumin and serum beta-2-microglobulin at diagnosis were all included as continuous variables. The following variables were dichotomised; age (<60 years versus 60-64 years), sex (male versus female), WHO performance status (grade 0-1 versus 2-4), M protein class (IgG versus other; IgA versus other; light chains only versus other), osteolytic bone lesions (no versus limited or advanced), serum calcium (within versus above upper reference limit). In the multivariate analyses a forward stepwise variable selection was used. All analyses were performed on an intention-to-treat basis.

RESULTS

Intensive therapy group

Baseline characteristics for the intensive therapy and control group and differences between the groups are presented in Table III.

Completion of assigned therapy in the intensive therapy group and the reasons for not undergoing transplantation are given in Table IV.

The response rate after each phase, calculated on an intention-to-treat basis, is presented in Fig 1. There were no statistical significant differences in response rate between patients younger than 60 years and patients 60-64 years at any stage of the treatment.

The event-free survival for the patients in the intensive-therapy group is shown in Fig 2. For patients <60 years the event-free survival at four years was 37% (95% confidence interval (CI) 31-43%), and the median event free survival was 36 months. The corresponding figures for patients 60-64 years old were 19% (95% CI 11-24%) and 24 months, respectively. In a multivariate Cox analysis of the entire intensive-therapy group, three variables were found to be significantly associated with event-free survival; serum beta-2-microglobulin, age <60 or 60-64 years and platelet count at diagnosis. When excluding non-responders the median event-free survival was 39 months for the younger patient group and 29 months for the older (P=.01). For those who actually underwent transplantation the median event-free survival was 40 and 29 months, respectively (P=.007).

The survival is shown in Fig 3. In the intensive therapy group, survival at four years for patients <60 years was 67% (95% CI 61-73%) and the median survival 67 months, while the corresponding figures for patients 60-64 years were 50% (95% CI 41-60%) and 48 months respectively (P=.004). In a multivariate Cox analysis of the entire intensive-therapy group, two variables were found to be significantly associated with survival; serum beta-2-microglobulin and age <60 or 60-64 years at diagnosis.

108 of the 294 (37%) included patients younger than 60 years have died. 100 died from reasons related to the myeloma disease (defined as all deaths occurring after progression or in patients not being in first, at least minor, response at time of death). Eight patients (2.7%) died while being in first response at time of death. One patient died from infection within 100 days after autologous transplantation resulting in 0,4% transplant-related mortality at 100 days. Four auto-transplanted patients died more than 100 days after transplantation because of cerebral haemorrhage, pneumonia, diffuse large B-cell lymphoma and from unknown cause. One allo-transplanted patient died from chronic graft versus host disease. Two patients who never were transplanted died from pneumonia and cervix cancer while being in response.

Of the 120 included patients 60-64 years 59 (50%) have died, 56 from reasons related to the myeloma disease. Three patients (2.5%) died while being in first, at least minor, response at time of death. One patient died from infection within 100 days after autologous transplantation, resulting in a 1% transplant-related mortality at 100 days. One auto-transplanted patient died more than 100 days after transplantation from thrombo-embolic disease. One patient who never was transplanted died from lung cancer.

For patients who progressed the median survival after progression was 20 months for patients <60 years and 15 months for patients 60-64 years (P=.05). When restricting this analysis only to patients who relapsed after prior (at least minor) response, the median survival after relapse was 23 and 18 months, respectively (P=.20). For patients who actually were transplanted and who relapsed thereafter the median survival after relapse was 23 and 16 months, respectively (P=.18).

The median age of the whole intensive therapy group was 56 years. Patients younger than 56 years (N=205) had a median event-free and overall survival of 37 and 67 months, respectively. The corresponding figures for patients aged 56-59 years (N=89) was 31 and 64 months, respectively. There were no significant differences in event-free survival (P=.11) and survival (P=.64) between these two age groups. Patients aged 60-64 years (N=120) had inferior event-free (24 months; P=.002) and overall

(48 months; P=.004) survival compared to patients younger than 56 years, while the outcome compared to patients 56-59 years was significant for survival (P=.04) but not for event-free survival (P=.07).

Survival comparison between the intensive therapy and the control group

Survival for patients younger than 60 years in the intensive-therapy group and the control group is shown in Fig. 3. The survival was longer for the intensive therapy group than for the control group (risk ratio (RR) 0.50; 95%CI 0.38-0.67; P<.001). Survival at 4 years was 67% (95%CI 72-83%) in the intensive-therapy group and 44% (95%CI 36-53%) in the control group, with a median survival of 67 and 43 months, respectively.

Survival for patients 60-64 years in the intensive-therapy group and the control group are also shown in Fig. 3. The survival was longer for the intensive therapy group than for the control group (RR 0.65; 95%CI 0.42-0.92; P=.02). Survival at 4 years was 50% (95%CI 41-60%) in the intensive-therapy group and 39% (95% CI 30-49%) in the control group, with a median survival of 48 and 28 months, respectively.

Survival comparison between the prospective and the historic population

Survival for patients younger than 60 years in the prospective and historic populations is shown in Fig 4. In this comparison, comprising all known patients and approximately 80% of the calculated number of new cases, there was a survival advantage for the prospective population (RR 0.49; 95%CI 0.38-0.64; P<.001). Survival at four years was 66% (95%CI 61-72%) in the prospective population and 43% (95%CI 35-51%) in the historic population, and the median survival was 66 and 43 months, respectively.

For patients 60-64 years old the prospective and historic population comprised approximately 70% of the calculated number of new cases. Survival for the two populations is shown in Fig 4. For patients 60-64 years old there was also a survival advantage for the prospective population (RR 0.58; 95%CI 0.42-0.80; P=.001). Survival at four years was 51% (95%CI 42-61%) in the prospective population and

35% (95%CI 26-44%) in the historic population, and the median survival was 50 and 27 months, respectively.

DISCUSSION

We have studied the impact of age on outcome after intensive therapy in newly diagnosed multiple myeloma. Age is a prognostic factor for survival in patients receiving standard chemotherapy (Myeloma Trialists´ Collaborative Group, 1998; Hjorth *et al*, 1992; Finnish Leukaemia Group, 1999; Turesson *et al*, 1999). The published results on high-dose therapy may have generated a preference for this treatment modality also in elderly. The issue of age limits is important as the median age at diagnosis in an unselected material is around 70 years and the incidence increases progressively with age (Hjorth *et al*, 1992; Wislöff *et al*, 1991). Consequently, it is important to try to define the upper age limit for the entire myeloma population where high-dose therapy is superior to the less toxic and less expensive conventional therapy (Gulbrandsen *et al*, 2001).

We found in a previous population-based study that in patients younger than 60 years high-dose therapy improves survival compared to conventionally treated historic controls (Lenhoff *et al*, 2000), and that age was not a prognostic factor. Here we increased the upper age limit to 65 years. In order to avoid selection bias as far as possible we used a population-based technique where participating centres were asked to register all symptomatic myeloma patients under the age of 65, whether they were included in the treatment protocol or not. The conventionally treated historic controls were derived from a previous NMSG study where the same technique was used. We also calculated the expected number of new cases in each group in order to estimate if our patient material was representative or not. The vast majority of the prospectively registered patients were included in the treatment protocol, and according to our calculations 68-83% of the expected number of patients in the different groups was registered. We therefore believe that our study gives a realistic estimation of the impact of age on survival after high-dose therapy on the whole myeloma population aged <65 years.

In the intensive therapy group we found that patients 60-64 years old had an inferior outcome regarding event-free survival and survival compared to patients <60 years.

In principal, this could be due to higher vulnerability to intensive therapy and/or more resistant disease and/or higher co-morbidity. The early death rate (i.e. deaths occurring during the induction therapy with VAD) was higher in the older group (5% versus 1.7% in the younger group). Also, a somewhat larger fraction of the older patients (11% versus 7% in the younger group) never underwent transplantation due to contraindications to high-dose melphalan that emerged during the induction therapy. In contrast, the actual transplant-related mortality was very low indicating that high-dose melphalan with autologous stem cell support can be performed in older patients as safe as in younger provided they have an acceptable performance status. After the early period there was no difference in the non-progression death rate. The older group had a significantly higher serum beta-2-microglobulin level at diagnosis and consequently more patients with higher stage according to ISS; however the impact of age on event-free survival and survival persisted in the multivariate analyses. We do not have information on the chromosomal aberrations in all patients, and an imbalance in prognostic unfavourable aberrations between the age groups cannot be ruled out. There was no significant difference in the response rate between the two age groups. In spite of this, the event-free survival was significantly shorter in the older age group, also when restricting the analysis to those who achieved at least minor response or to those who actually underwent transplantation. There was a non-significant trend towards inferior survival after progression in patients 60-64 years, a trend that persisted in a similar order of magnitude also for patients relapsing after prior response and for patients relapsing after transplantation. It is obvious that no single factor can explain the difference in outcome between the age groups; our data indicate that both higher vulnerability to intensive therapy and more aggressive disease resulting in inferior disease control contribute to the difference found.

Our finding that age above 60 years is an adverse prognostic factor for patients undergoing intensive therapy is in contrast to other published results (Siegel *et al*, 1999; Sirohi *et al*, 2000; Reece *et al*, 2003). However, in contrast to our study these were all retrospective comparisons on a selected group of patients who actually

underwent autologous transplantation and survival was calculated from time of transplantation and not from initiation of therapy.

The main question is whether high-dose therapy is superior to conventional therapy also for older patients. In the IFM-90 study the survival advantage for high-dose therapy was restricted to patients 60 years and younger (Attal *et al*, 1996). In the MRC VII trial no data are presented concerning the impact of age on outcome after high-dose therapy (Child *et al*, 2003). Palumbo *et al* (2004) randomized 194 patients aged 50-70 years between receiving two courses of melphalan 100 mg/m^2 and conventional melphalan and prednisone. In this study, with similar treatment intensity in the two arms as in our study, a significantly better event-free survival and survival was found for patients receiving intensive therapy, also when restricting the analysis to older patients. Fermand *et al* (2005) randomized 190 patients aged 55-65 years between high-dose or conventional therapy. In contrast to our study and in the study by Palumbo *et al*, the treatment schedule for the conventional arm comprised more agents than conventional melphalan and prednisone. With approximately ten years of follow-up there was a trend to better event-free survival but no survival advantage for the transplanted group.

In this study we compared the outcome with that of historic controls derived from a population-based study on conventional therapy (melphalan and prednisone +/- interferon) performed by the NMSG eight years earlier. We found a significant difference in survival in favour of the intensive therapy group also for patients 60-64 years old. When comparing survival for all known newly diagnosed patients during the two time periods, there was a significant survival benefit for the prospective group. These comparisons with historic controls must be interpreted with great caution. It cannot be ruled out that the introduction of new therapies other than high-dose therapy since the late 1990s and improvements in supportive care may have an impact on the improved survival seen during the later time period. On the other hand, survival for patients <60 years in the present study (median 67 months) was not significantly different to that of our previous trial (Lenhoff *et al*, 2000) from 1994-

1997 (median 63 months) and before that time the continuous improvement in supportive care and other therapeutic interventions had no substantial influence on overall survival in myeloma (Hjorth *et al*, 1999). It is therefore likely that the improvement in survival between the prospective and the historic populations mainly is due to the introduction of up-front intensive therapy.

In conclusion, in this population-based study we found that older age is an independent adverse prognostic factor for outcome after intensive therapy. Our results indicate that intensive therapy prolongs survival compared to conventional chemotherapy with melphalan and prednisone also in patients 60-64 years old, but with less superiority than in patients younger than 60 years.

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Table I. Number of patients in the prospective and historic populations and reasons for non-inclusion into the intensive therapy group and control group.

Population:	Prospective		Historic	
Age:	<60y	60-64y	<60y	60-64y
Total number registered, fulfilling diagnostic criteria	317	135	166	115
Not receiving intensive therapy from physician-related reasons	4	3	-	-
Treatment according to other intensive-therapy protocol than NMSG #7/98	1	0	-	-
Not eligible for intensive therapy due to				
- severe co-morbidity	13	5	13	10
- bad performance status	1	1	5	5
- patients´ choice	4	6	2	3
Total number included in the intensive therapy group / control group	294 (93%)	120 (89%)	146 (88%)	97 (84%)

Table II. Expected number of patients in the prospective population and the historic population, proportion of patients registered, and proportion of patients included in the intensive-therapy group or control group.

Population:	Prospective		Historic	
	<60y	60-64y	<60y	60-64y
Expected	380	200	220	150
Registered	317	135	166	115
Proportion registered of expected	83%	68%	75%	77%
Included	294	120	146	97
Proportion included of expected	77%	60%	66%	65%

Table III. Patient characteristics at time of diagnosis

		Intensive-Therapy Group		Control Group	
Characteristic	Category	<60y	60-64y	<60y	60-64y
Age, median		52	62	52	62
Male/female ratio		1,62	1,31	1,50	1,11
M-protein class	IgG	57%	62%	60%	66%
	IgA	21%	21%	13%	16%
	IgD	1%	1%	0%	0%
	Light chains only	21%	16%	27%	18%
WHO performance status	0-1	51%	47%	45%	43%
	2-4	49%	53%	55%	57%
	(Missing data)	(14%)	(10%)	-	-
Advanced osteolytic lesions		50%	52%	45%	32%
Serum creatinine	> 200 umol/l	16%	13%	8%	10%
Blood haemoglobin	< 100 g/l	37%	45%	32%	33%
Serum calcium	> upper ref.	31%	34%	33%	29%
Bone marrow plasma cells	>25%	56%	63%	55%	64%
Serum albumin	<35 g/l	45%	55%	38%	42%
	(Missing data)	(8%)	(10%)	(6%)	(2%)
Serum beta-2-microglobulin	<3,5 mg/l	51%	36%	36%	27%
	3,5-5,5 mg/l	27%	29%	23%	32%
	>5,5 mg/l	22%	35%	41%	41%
	(Missing data)	(23%)	(22%)	(15%)	(9%)
Stage (Durie and Salmon)	I	6%	4%	5%	9%
	II	26%	22%	41%	36%
	III	68%	74%	54%	55%
Stage (International Staging System; ISS)	I	33%	21%	26%	15%
	II	44%	43%	33%	44%
	III	23%	36%	41%	41%
	(Missing data)	(27%)	(24%)	(15%)	(10%)

Statistical significant differences between group with age <60 years and group with age 60-64 years in the intensive-therapy group: serum beta-2-microglobulin, serum albumin, stage (ISS).

Statistical significant differences between intensive-therapy group and control group for patients with age <60 years: serum beta-2-microglobulin, stage (Durie and Salmon), stage (ISS).

Statistical significant differences between intensive-therapy group and control group for patients with age 60-64 years: stage (Durie and Salmon), osteolytic lesions.

Table IV. Intensive therapy group. Completion of assigned therapy and reasons for not undergoing transplantation.

Age group:	<60y	60-64y
Number of patients included	294	120
Death during induction therapy	5 (2%)	6 (5%)
Progressive disease during induction therapy	7 (2%)	3 (2%)
Emerging contraindications to transplantation due to	21 (7%)	13 (11%)
- heart or lung disease	3	1
- persisting renal insufficiency	6	0
- psychiatric illness	2	0
- uncontrolled infection	1	5
- bad performance status	2	4
- unsuccessful stem cell harvest	4	2
- patients´ choice	3	1
Number of patients actually transplanted	261 (89%)	98 (82%)
- single autologous transplantation	209 (71%)	82 (69%)
- double autologous transplantation	46 (16%)	16 (13%)
- allogeneic transplantation	6 (2%)	0 (0%)

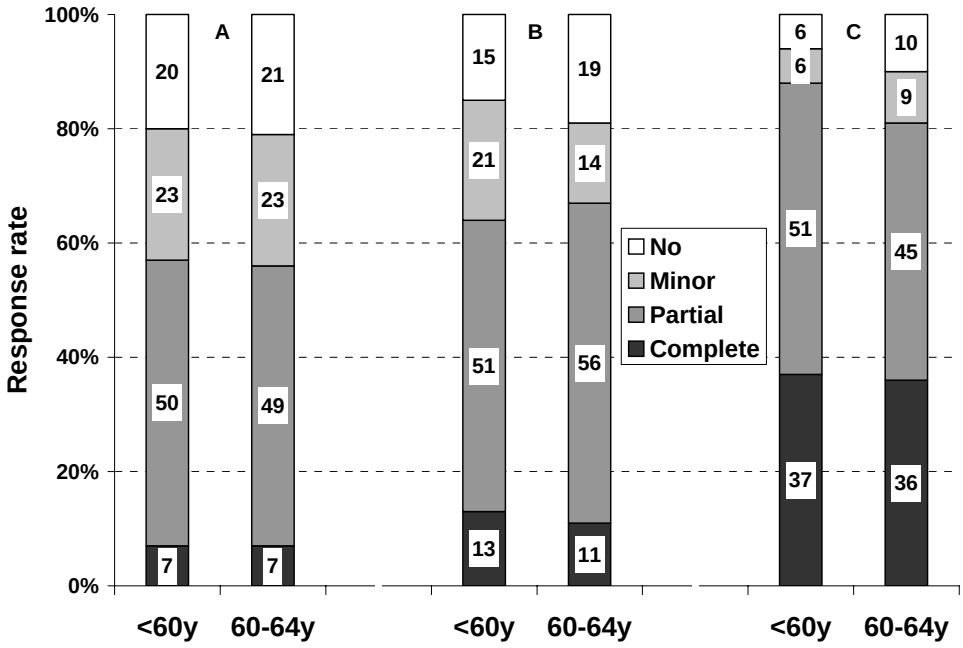

Fig 1. The best degree of response, calculated on an intention-to-treat basis, after each treatment phase for patients in the intensive therapy group (<60 and 60-64 years). Columns A show response rate after induction with VAD, B after mobilization and stem cell harvest and C after high-dose melphalan with autologous stem cell support.

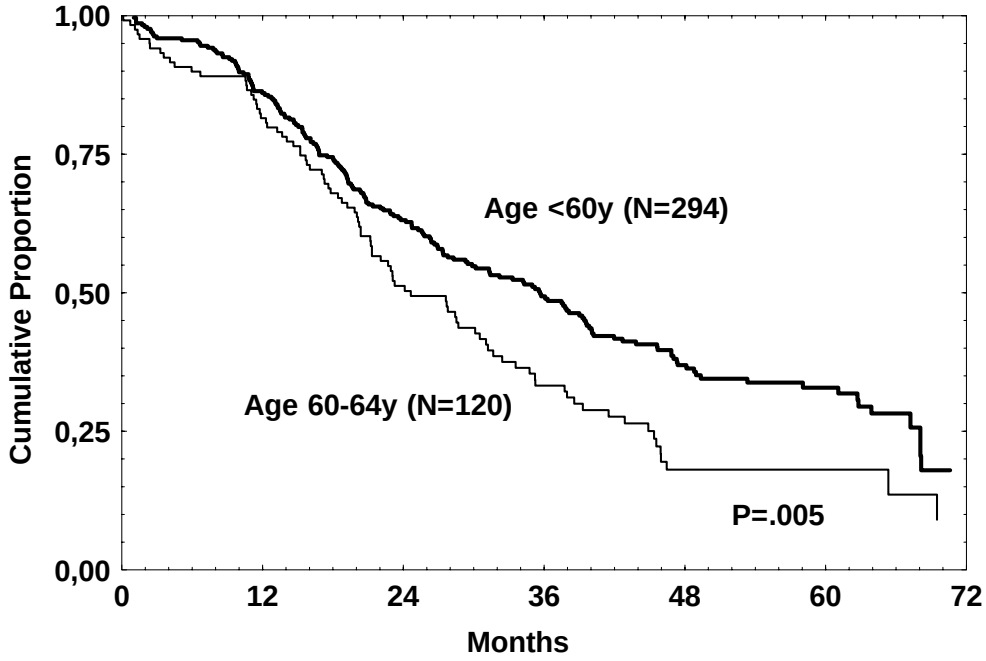

Fig 2. Event-free survival for patients in the Intensive therapy group aged <60 years and 60-64 years.

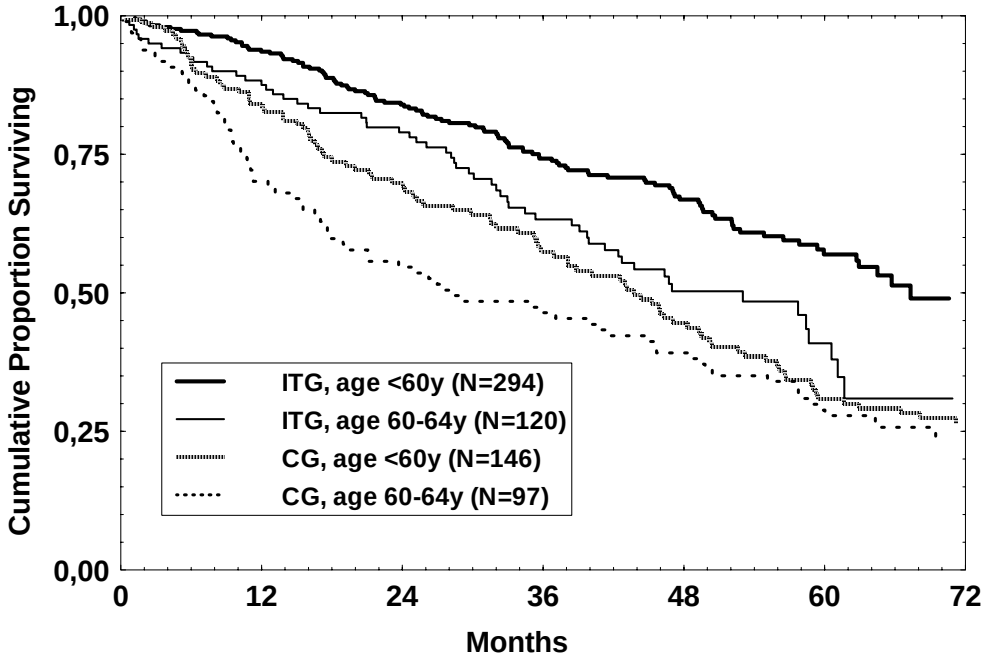

Fig 3. Survival for patients aged <60 and 60-64 years in the intensive therapy group (ITG) and historic control group (CG). Log-rank tests: P=.004 (ITG<60y vs. ITG60-64y), P<.001 (ITG<60y vs. CG<60y), P=.02 (ITG60-64y vs. CG60-64y).

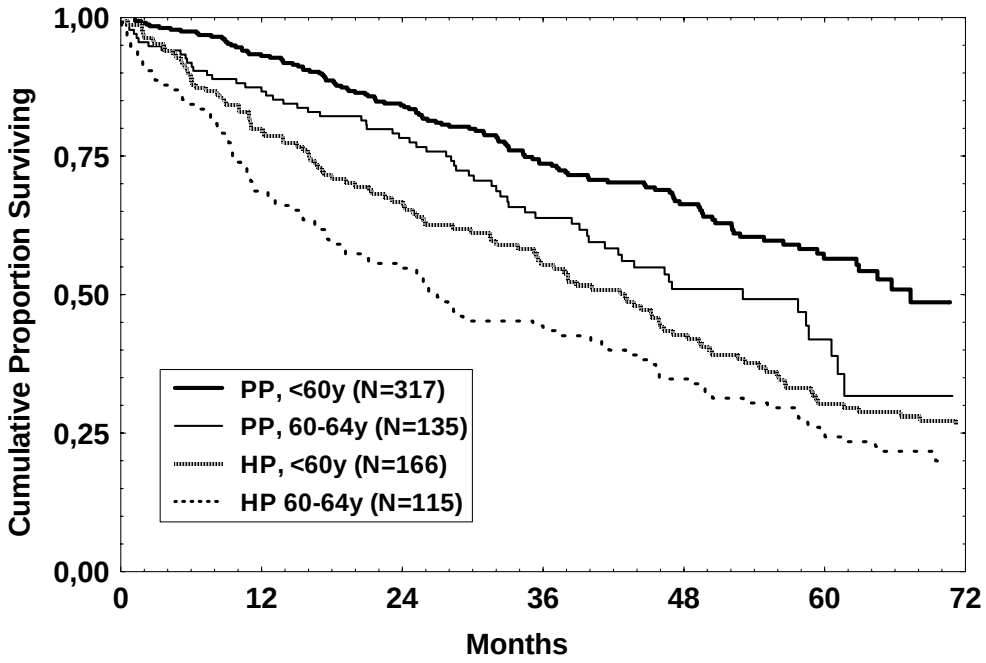

Fig 4. Survival for patients aged <60 and 60-64 years in the prospective population (PP) and historic population (HP). Log-rank tests: P=.006 (PP<60y vs. PP60-64y), P<.001 (PP<60y vs. HP<60y), P=.001 (PP60-64y vs. HP60-64y).