Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial

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ABSTRACT

Background and Objectives

The Dutch-Belgian HOVON group performed a randomized phase 3 trial to compare single non-myeloablative intensive treatment with double, intensive treatment in previously untreated patients with multiple myeloma (MM).

Design and Methods

Three hundred and three patients with stage II/III MM were randomized after VAD induction chemotherapy to receive two cycles of non-myeloablative intermediate-dose melphalan (70 mg/m^2) (single treatment) or the same regimen followed by cyclophosphamide 120 mg/kg iv plus total body irradiation (TBI) 9 Gy and autologous stem cell transplantation (double, intensive treatment). In both treatment arms interferon αIIa was given as maintenance until relapse/progression.

Results

A significantly higher proportion of patients achieved a complete remission (CR) on protocol treatment with double, intensive therapy (32% vs 13%, $p<0.001$). Double treatment produced better outcome in terms of event-free survival (median 22 vs 21 months, 28% vs 14% at 4 years and 15% vs 7% at 6 years after randomization; logrank $p=0.013$; univariate HR 0.74, 95% CI, 0.58-0.94), progression-free survival (median 27 vs 24 months, 33% vs 16% at 4 years, and 17% vs 9% at 6 years after randomization; logrank $p=0.006$; HR=0.71, 95% CI 0.56-0.91), but not overall survival (median 50 vs 55 months, 52% vs 56% at 4 years and 39% vs 36% at 6 years after randomization; logrank $p=0.51$; HR=1.10, 95% CI 0.83-1.46). The achievement of a CR had a favorable prognostic impact on event-free survival (HR=0.60, 95% CI=0.44 -0.82, $p=0.001$) and progression-free survival (HR=0.62, 95% CI=0.45 - 0.84, $p=0.002$).

Interpretation and Conclusions

Double, intensive treatment resulted in a better CR rate, event-free survival and progression-free survival but not overall survival compared to single non-myeloablative treatment in previously untreated patients with multiple myeloma.

Key words: intermediate dose, melphalan, myeloablative treatment, HOVON 24 trial.

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The prognosis of younger patients with multiple myeloma (MM) has improved since the introduction of high-dose melphalan followed by autologous stem cell rescue in first-line treatment.[1-5] Randomized clinical trials have shown that high-dose therapy supported by autologous stem cell transplantation (SCT) has a superior outcome compared to conventional chemotherapy.[2,6,7] Other non-randomized trials have demonstrated that the achievement of complete remission (CR) is strongly correlated with longer survival.[8,9] In order to increase the proportion of patients achieving CR, the concept of repeated high-dose treatment has been applied (tandem transplantation).[10] In a French randomized trial, single therapy was compared to double high-dose therapy. There were higher rates of very good partial responses and complete responses in patients with double transplantation, and a doubling of the 7-year probability of event-free survival (EFS) and overall survival (OS) in the whole patient population although the greatest benefits were seen in patients who failed to achieve at least a very good partial response (VGPR) after the first transplant.[9]

The Dutch-Belgian HOVON group performed a randomized phase 3 trial to compare single maximum dose non-myeloablative (semi-intensive) treatment (subsequently referred to as single treatment) with the same regimen followed by myeloablative high-dose therapy in previously untreated patients with MM. In this trial, single non-myeloablative treatment consisted of intravenous melphalan 140 mg/m^2, divided into two cycles of 70 mg/m^2, which was administered without stem cell rescue in the outpatient clinic. Patients who had been randomized to double treatment were treated with additional high-dose cyclophosphamide plus total body irradiation (TBI) and autologous SCT. Maintenance treatment with interferon αIIa was given in both arms.

Design and Methods

Patients

Patients aged 18 to 65 years with previously untreated MM, stage II or III A/B disease according to the Salmon and Durie criteria were eligible for registration.[11] Criteria for exclusion were WHO performance status >3, severe cardiac, pulmonary, neurological or organ dysfunction WHO>2, inadequate liver function (i.e. bilirubin ≥2.5 times the upper limit of normal value), prior or concomitant malignant disease except non-melanoma skin tumors or stage 0 cervical carcinoma, and prior extensive radiotherapy to the spinal cord or central nervous system which could preclude total body irradiation. In patients with myeloma–related renal failure, hemodialysis was performed during VAD treatment as needed. Treatment for hypercalcemia with pamidronate was administered when indicated. Patients received antibacterial and antifungal prophylaxis according to institutional guidelines and monthly intravenous pamidronate for the duration of the study.

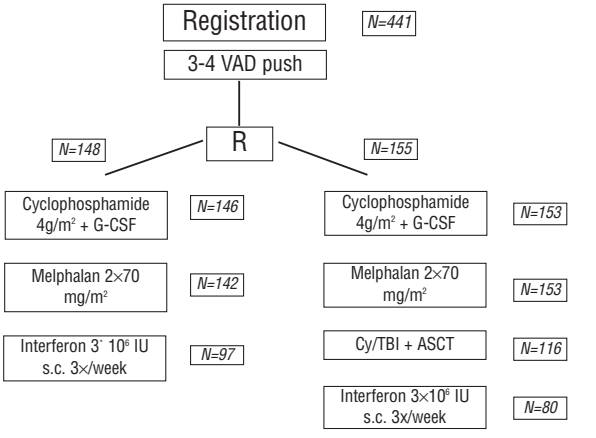

Figure 1. Flow diagram of patients included in the trial.

All patients had given written informed consent before inclusion. The study was performed according to the Helsinki agreement. The trial was approved by the protocol review committee of the Dutch National Cancer League CKTO and by the local ethics committees of all participating hospitals.

Randomization

Patients were randomly assigned to receive single or double (intensive) treatment. The randomization was performed immediately after induction chemotherapy (VAD), irrespective of the patients' response to VAD. Randomization was stratified by center. Exclusion criteria for randomization were WHO performance status 3-4, severe cardiac disease, inadequate liver function or persistent serum creatinine ≥177 umol/L. Patients under 56 years of age with an HLA-identical sibling were candidates for allogeneic SCT, in which case they were not eligible for randomization.

Treatment

Patients were treated with three or four cycles of VAD (daily vincristine 0.4 mg and doxorubicin 9 mg/m^2) administered as short time intravenous infusion for 4 consecutive days with oral dexamethasone 40 mg on days 1-4, 9-12 and 17-20 during uneven cycles and on days 1-4 during even cycles).[12] Treatment cycles were repeated at 4-weekly intervals. Following VAD, patients were randomly assigned to receive single or double treatment, irrespective of their response to VAD except in case of persisting renal failure.

The outline of randomization and treatment is presented in Figure 1. Peripheral blood stem cells were collected following high-dose cyclophosphamide (4 g/m^2) plus granulocyte colony-stimulating factor (G-CSF) as described previously.[12]

Single non-myeloablative (semi-intensive) treatment

Melphalan (140 mg/m^2) was administered in two intravenous administrations of 70 mg/m^2 at a 6-8 week interval without stem cell reinfusion.[13] Prophylactic G-CSF (filgrastim, Neupogen) was started on day +4 after melphalan at a daily dose of 300 to 480 μg subcutaneously until the neutrophil count had recovered to ≥1.0×10^9/L.

Double treatment

Patients who were randomized to the double treatment proceeded to this regimen if they had achieved at least a partial remission and if an adequate stem cell graft was available. The second, high-dose treatment was based on a myeloablative conditioning regimen consisting of cyclophosphamide 120 mg/kg iv in 2 days followed by total body irradiation (TBI) with lung shielding (9 Gy, lung dose 8 Gy). Maintenance treatment with interferon αIIa (IFN, 3×10^6 units thrice weekly) was started in both treatment groups at 60 to 90 days after melphalan (single) or cyclophosphamide/TBI (double) treatment and was continued until relapse or progression.[12]

Response evaluation

The response to treatment was monitored by means of serum immune-electropheresis and immunofixation, which were carried out after each treatment cycle and at 3-month intervals during the follow-up. Bone marrow aspirates were taken at diagnosis and after high-dose treatment or when needed to confirm complete response. Response assessments were performed according to modified criteria of the European Group for Blood and Bone Marrow Transplantation (EBMT).[14] A complete response was defined as the absence of monoclonal immunoglobulins in serum or urine by immunofixation and in addition absence of monoclonal plasma cells in the bone marrow by light chain immunophenotyping.

Statistical analysis

The first analysis of the randomization was performed in November 2001, as previously described.[12] Here we report the long-term results. The primary end-point of the trial was event-free survival (EFS) from randomization, and the study was designed to detect, with a statistical power of 80% and a two-sided significance level α=0.05, a 15% increase in 2-year EFS from 40% to 55% in the double treatment arm. Secondary end-points were CR rate, progression-free survival (PFS) and overall survival (OS). EFS was calculated from the date of randomization until not at least a PR after high-dose melphalan, progression/relapse after previous response or death without progression, whichever came first. Data on patients who had no events were censored at the time of last contact. In patients who did not achieve at least a PR after high-dose melphalan, treatment was considered to have failed at day 1 after randomization. PFS was determined from randomization until progression/relapse or death, whichever came first. OS was measured from the date of randomization until death; patients still alive at the time of last contact were then censored. For the current analysis, the data were used as available of November 7, 2006. The characteristics of the patients in the two treatment arms were compared using Pearson's χ^2 test or Fisher's exact test whichever was appropriate, in the case of discrete variables, or the Wilcoxon rank-sum test in case of continuous variables. The CR rate was compared between the two arms using logistic regression analysis[15] and an odds ratio (OR) with a 95% confidence interval (CI) was calculated. EFS, PFS and OS were estimated by the Kaplan-Meier method.[16] Kaplan-Meier curves were generated to illustrate differences between the two treatment arms and compared using the log-rank test.[17] Cox regression analysis was used to evaluate the impact of treatment arm when other prognostic factors were also included.[18] Hazard ratios and 95% CI were constructed. The following baseline characteristics were included in the regression analyses: age, stage according to Salmon and Durie (II vs. III), Ig isotype (IgA vs other), hemoglobin, β2-microglobulin (natural logarithm) and lactate dehydrogenase(LDH)/upper normal limit (UNL) (natural logarithm). In the multivariate analyses, missing baseline characteristics were imputed using a single-imputation method, i.e. conditional mean imputation based on the other available variables.[19] The impact of reaching a CR on EFS, PFS and OS from randomization was evaluated with Cox regression, using CR as a time-dependent co-variate. The analyses were performed according to the intention-to-treat principle, i.e. patients who were eligible for randomization were analyzed according to the treatment arm they were assigned to. All reported *p*-values are two-sided and a significance level α=0.05 was used.

Results

Patients' characteristics and treatment received

Overall, 453 patients were registered from 46 hematology centers in the Netherlands and Belgium over a period from November 1995 to March 2000; of these patients, 12 were not eligible for inclusion in this study. Sixty-three patients with an HLA identical sibling donor proceeded to allogeneic transplantation and were not, therefore, randomized; their results have been reported elsewhere.[20] Another 75 patients were not randomized because of early death (n=16), poor performance status (n=17), renal failure (n=8), patients' refusal (n=7), non-eligibility (n=8) or other (n=19). A total of 303/441 patients (69%) were randomized and were included in this analysis: 148 for single and 155 for double intensive therapy. The characteristics of the randomized patients are listed in Table 1. The myeloma subtypes, level of β-2-microglobulin, Salmon and Durie stage and age were not different between the two treatment arms. The actual treatment given is summarized in Figure 1. In treatment

Table 1. Patients' characteristics.

	Single	*Double*	*Total*
Total (#)	148	155	303
Sex			
Male	85	98	183
Female	63	57	120
Median age (yr, range)	55 (37-65)	56 (32-65)	56 (32-65)
≤55	76	69	145
56-60	43	53	96
61-65	29	33	62
WHO PF status			
0	63	54	117
1	58	128	
≥2	27	31	58
Salmon & Durie stage			
2A	38	36	74
2B	0	2	2
3A	101	107	208
3B	9	10	19
Hemoglobin (mmol/L)			
Median (range)	6.8 (3.9-9.8)	7.0 (3.4-10)	6.9 (3.4-10.0)
≤6.2	53	43	96
>6.2	95	112	207
Serum calcium (mmol/L)			
Median (range)	2.4 (1.1-4.0)	2.4 (1.7-3.7)	2.4 (1.1-4.0)
≤2.65	122	137	259
>2.65	24	16	40
Serum β-2-microglobulin (mg/L)			
Median (range	2.9 (0.4-58.0)	3.0 (0.1-14.1)	3.0 (0.1-58.0)
≤3.0	64	72	136
>3.0	55	70	125
M-protein			
IgA	41	39	80
IgG	84	93	177
IgD	4	3	7
Light chain disease	14	14	28
Non/oligosecretory	5	6	11
Serum lactodehydrogenase			
LDH /ULN, median (range)	0.7 (0.1-11.9)	0.7 (0.2-2.1)	0.7 (0.1-11.9)
Normal	114	122	236
Elevated	24	19	43

ULN: upper limit of normal value.

arm A (single treatment) 25 patients received only one administration of melphalan, 117 received both melphalan administrations and 97 patients started on IFN maintenance. In arm B (double), 25 patients received only one dose of melphalan, 128 received two doses, 116 patients completed the second, high-dose treatment with autologous SCT and 80 started with IFN maintenance. The second intermediate-melphalan dose cycle was not administered in 50 patients, most frequently due to toxicity (34%) or resistance/progression after the first dose (n=18), while the exact reason was unknown in 17 patients (34%). One patient had to be rescued with autologous SCT after melphalan because of incomplete hematologic recovery. IFN maintenance was stopped prematurely because of toxicity in 33 of 97 (34%) patients randomized to single treatment and in 53 of 80 (66%) of patients who received the double treatment. The duration of IFN maintenance treatment was not different between the treatment groups, being a median of 7 months in the double treatment arm vs 12 months in the single treatment arm (logrank p=0.52).

Table 2. Response according to randomization arm.

	Single	*Double*	*Total*
Patients [N.]	148	155	303
CR on protocol treatment (p<0.001)			
No	129 (87%)	106 (68%)	235 (78%)
Yes	19 (13%)	49 (32%)	68 (22%)
Cumulative CR rate following subsequent treatments*			
VAD	1 (1%)	6 (4%)	7 (2%)
HDM	14 (9%)	27 (17%)	41 (14%)
ASCT	–	40 (26%)	54 (18%)
IFN	19 (13%)	49 (32%)	68 (22%)
In follow-up	26 (18%)	52 (34%)	78 (26%)

*VAD: vincristine, doxorubicin and dexamethasone; HDM: high-dose melphalan; ASCT: autologous stem cell transplantation; IFN: interferon-α..*The table indicates the number and percentage of patients who achieved a CR after the different treatment phases. For example, from the 7 patients with CR after VAD and 41 patients with CR after high-dose melphalan, it can be concluded that HDM resulted in a CR in 41 - 7 = 34 patients.*

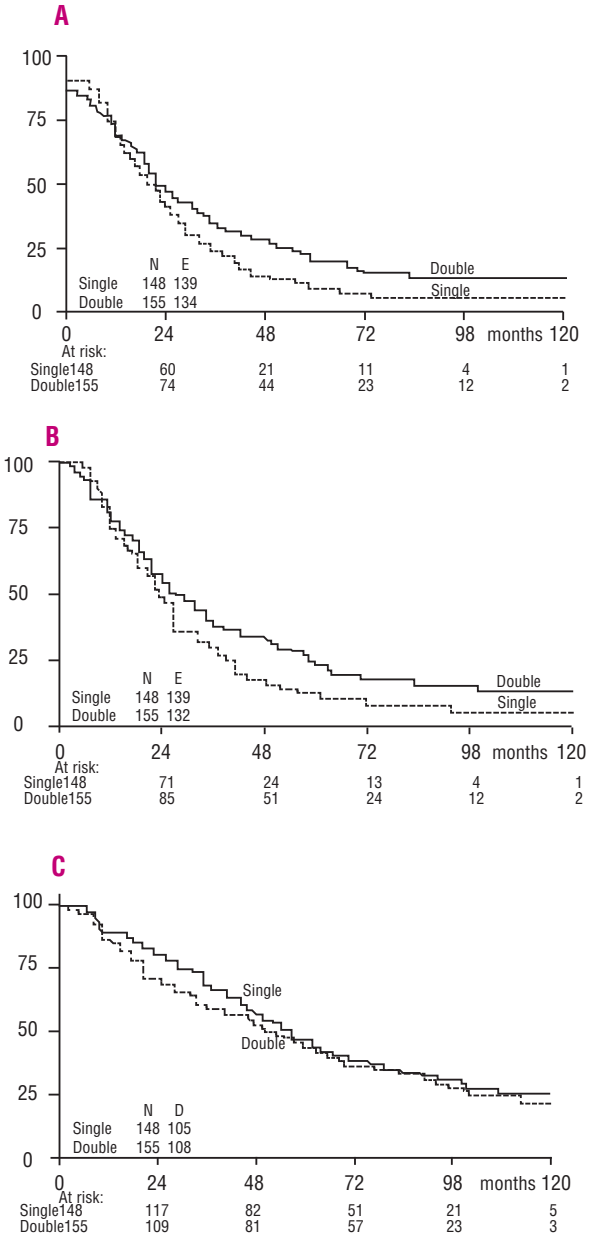

Figure 2. Kaplan-Meier survival curves. (A) event-free survival, (B) progression-free survival and (C) Overall survival.

Response

The response data are presented in Table 2. An objective response (PR or CR) after melphalan was achieved in 267/303 (88%) patients. An evaluation at the end of chemotherapy and before the start of maintenance showed that the complete response rate was significantly higher in patients given double treatment than in those given single treatment (26% *vs* 9%, $p<0.001$). During maintenance, the CR rate increased to 32% in the double treatment group and 13% in the single treatment group ($p<0.001$). Prognostic factors associated with a higher CR rate were Salmon and Durie stage 3, a higher hemoglobin and lower serum β2-microglobulin level.

Table 3. Multivariate analysis by Cox regression.

Event-free survival

Co-variate	HR	95% CI	*p* value
Treatment arm	0.73	0.57-0.93	0.01
Age	1.03	1.01-1.05	0.008
Salmon and Durie stage 3	1.22	0.92 -1.62	0.17
IgA (vs. other isotype)	1.42	1.08 -1.87	0.01
Hemoglobin	0.86	0.76-0.96	0.01
Log(β2-microglobulin)	1.17	0.94 -1.46	0.17
Log(LDH/ULN)	1.22	0.97 -1.52	0.09

Progression-free survival

Co-variate	HR	95% CI	*p* value
Treatment arm	0.69	0.54-0.88	0.003
Age	1.03	1.01-1.05	0.005
Salmon and Durie stage 3	1.26	0.95 -1.67	0.12
IgA (vs. other isotype)	1.67	1.27 -2.20	<0.001
Hemoglobin	0.82	0.73 -0.92	<0.001
Log(β2-microglobulin)	1.17	0.93 -1.49	0.18
Log(LDH/ULN)	1.25	1.01 -1.56	0.04

Overall survival

Co-variate	HR	95% CI	*p* value
Treatment arm	1.06	0.81 -1.40	0.66
Age	1.04	1.02-1.07	< 0.001
Salmon and Durie stage 3	1.41	1.00 - 1.97	0.05
IgA (vs. other isotype)	1.61	1.19 -2.19	0.002
Hemoglobin	0.76	0.67 -0.87	<0.001
Log(β2-microglobulin)	1.19	0.92 -1.54	0.18
Log(LDH/ULN)	1.36	1.06 -1.75	0.02

Event-free survival

The median EFS from randomization was 21 months with single treatment vs 22 months with double treatment. Actuarial probabilities at 4 and 6 years were 28% and 15% in the double treatment versus 14% and 7% in the single treatment arm (logrank $p=0.014$) (Figure 2). The univariate hazard ratio (HR) for treatment arm was 0.74 (95% CI, 0.58-0.94). Similar results were obtained when adjusted for baseline characteristics (Table 3). Significant negative prognostic factors for EFS in the Cox regression analysis were higher age, IgA isotype and lower hemoglobin concentration.

Progression-free survival

The median PFS from randomization was 24 months with single treatment (16% at 4 years and 9% at 6 years) versus 27 months (33% at 4 years and 17% at 6 years) with double treatment (logrank $p=0.006$; HR=0.71, 95% CI 0.56-0.91). The effect of treatment arm remained statistically significant when adjusted for baseline covariates (Table 3). Significant negative prognostic factors for PFS in the Cox regression analysis were higher age, IgA isotype, lower hemoglobin and higher LDH/ULN values.

Overall survival

As of November 7, 2006, 213 of 303 patients (70%) had died: 105 in the single treatment group and 108 in

the double treatment group. The median follow-up from randomization of the 90 patients still alive was 92 months (range, 17-129). The median survival was 55 months in the single treatment group and 50 months in the double treatment group. Actuarial probabilities at 4 and 6 years were 52% and 39%, respectively, in the double treatment group versus 56% and 36%, respectively, in the single treatment arm (logrank p=0.81; HR=1.03, 95% CI 0.79-1.35). A similar result was obtained when the analysis was performed with adjustment for baseline covariates (Table 3).

Negative prognostic factors for PFS were also predictive for worse overall survival. Of note, 45 (30%) patients who relapsed after single treatment were salvaged by high-dose therapy with stem cell support, as compared with only six (4%) patients treated with double treatment. The Kaplan-Meier survival curves are depicted in Figure 2. It should be noted that with 213 deaths among 303 patients, the study had 83% power to detect only a HR of 0.67, which is equivalent to an improvement in (median) OS of 50%. The power to detect a smaller, but clinically still relevant, improvement in OS was, therefore, limited.

Prognostic value of CR

Univariate Cox regression analysis indicated that obtaining a CR during treatment had a favorable prognostic impact on EFS (HR=0.60, 95% CI=0.44-0.82, p=0.001) and PFS (HR=0.62, 95% CI=0.45-0.84, p=0.002) but not on OS (HR=0.81, 95% CI=0.57-1.13, p=0.21). These results remained very similar when treatment arm was also included and are, therefore, not shown.

Causes of death

At the time of analysis, 105/148 (71%) patients in the single treatment group had died as compared to 108/155 (70%) in the double treatment. Active myeloma was the primary cause of death in 82/105 in the single treatment arm (78%), and in 86/108 in the double, intensive arm (80%). Treatment-related mortality was 6/148 (4%) in the single treatment arm and 16/155 (10%) in the double, intensive arm

Discussion

The introduction of high-dose therapy supported by autologous SCT has significantly improved the prognosis of patients with active MM.[1,2,4,6,7,12,13,21-28] Several randomized trials have investigated whether high-dose therapy is superior to conventional chemotherapy.[2,6,28-31] The Nordic Study Group found that high-dose therapy had a superior impact on survival compared with treatment in historic controls[27] and in two prospective trials.[2,6] In contrast, the Spanish Pethema study demonstrated a higher CR rate, but no impact of high-dose therapy on PFS and OS compared with conventional chemotherapy.[29] A study from the Groupe Myelome-Autogreffe showed an effect on EFS but not OS, while the US Intergroup Trial S9321 failed to demonstrate an effect of high-dose therapy on response rates or survival.[28,31] Most treatment protocols use high-dose treatment as part of the initial therapy, although others have shown that the effect of salvage transplantation may be equal to transplantation upfront.[7]

The overall picture from these trials is that high-dose therapy improves the response rate as well as EFS or PFS but that the effect on survival differs. Even with high-dose treatment upfront, the majority of patients will ultimately relapse and a further intensification may, therefore, be considered in order to improve the quality of the initial response. The concept of repeated intensive treatment was pioneered in the total therapy 1 and 2 programs.[8,32] The French IFM group showed, in a randomized trial, that double high-dose treatment followed by autologous SCT improves the PFS in patients who do not achieve a very good partial response or complete response with one intensive treatment.[9] In addition, the Bologna study also showed superior CR, EFS and OS rates although a final analysis has not yet been published.[33] In another trial from the IFM group in high-risk patients, repeated high-dose melphalan was not found to have a significant effect on OS.[34]

With our trial we wanted to compare intermediate-dose melphalan as non-myeloablative semi-intensive treatment (single treatment) with the same regimen followed by high-dose therapy and autologous stem cell transplantation (double treatment). Intermediate-dose melphalan was designed as two non-myeloablative, intravenous doses of melphalan of 70 mg/m^2 each. This dose is lower than that reported by others[35] and is based on our previous phase II trial,[36] in an attempt to achieve intensive therapy without restricting the availability of autologous stem cells. Concerning this trial, we previously reported that with a short follow-up (median 33 months) no difference was observed between these two treatments in myeloma.[12] However, with longer follow-up (median almost 8 years) a small but significant difference was observed for PFS, but not OS. The difference became evident late (>4 years) after treatment. Also, the number of complete responses was higher following double treatment and improved even further during maintenance treatment. Patients who achieved a CR had a better probability of EFS and PFS. The results of this study illustrate that the benefit of repeated (intensive) treatment during front-line therapy is restricted to a better CR rate and PFS. No significant effect on OS was achieved with this approach. This may also confirm that the use of TBI as a myeloablative preparative regimen for autologous SCT in myeloma is not very effective and should be omitted. Moreau *et al.* demonstrated that the efficacy of TBI used after high-dose melphalan in tandem transplantation may be limited.[37] The French IFM group has proposed that tandem transplantation is the pre-

ferred treatment in (high-risk) patients who fail to achieve at least a very good PR or a CR with a single autologous transplant.[9,34,37] This approach is based on the finding that the achievement of CR is an important favorable prognostic factor for durable responses.[38] However, it remains to be determined whether repeated high-dose treatment is the best approach for accomplishing CR. Finally, the lack of efficacy of interferon and the poor patient compliance in this and other trials underlines that this compound has become obsolete in the treatment of myeloma.[39]

The introduction of novel agents such as thalidomide and bortezomib has demonstrated that higher CR rates are possible in relapsed patients and in front-line treatment with remission induction chemotherapy.[40-43] Combinations of these drugs with high-dose treatment may provide a new opportunity to improve the treatment results in MM.[26,32,40,44] In view of the lack of improvement of OS following double intensive treatment, these new agents must be introduced in front-line therapy, and consequently the role of double intensive treatment needs to be re-evaluated. It remains to be established, however, what the long-term outcome will become in patients who receive these agents as part of their front-line therapy, since it has been shown that rescue treatment may be less effective in patients who are continuously exposed to thalidomide.[45] Thalidomide and bortezomib are currently being investigated as part of induction therapy prior to high-dose therapy and maintenance in two HOVON trials and several international studies.

Authors' Contributions

PS, HML: principal investigator, substantial contribution to design, analysis and interpretation of the data, drafting or revising the article for intellectual content, final approval of manuscript; BvdH, CMS, EV, AJC, GEGV, JJC, MRS, MHJvO, PWW, PHMW: substantial contribution to design, analysis and interpretation of the data, drafting or revising the article for intellectual content, final approval of manuscript

Conflict of Interest

The authors reported no potential conflicts of interest.

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