



# Induction therapy with vincristine, adriamycin, dexamethasone (VAD) and intermediate-dose melphalan (IDM) followed by autologous or allogeneic stem cell transplantation in newly diagnosed multiple myeloma

HM Lokhorst<sup>1</sup>, P Sonneveld<sup>2</sup>, JJ Cornelissen<sup>2</sup>, P Joosten<sup>3</sup>, M van Marwijk Kooy<sup>4</sup>, J Meinema<sup>1</sup>, HK Nieuwenhuis<sup>1</sup>, MHJ van Oers<sup>5</sup>, DJ Richel<sup>6</sup>, CN Segeren<sup>2</sup>, G Veth<sup>7</sup>, LF Verdonck<sup>1</sup> and PW Wijermans<sup>8</sup>

Departments of Hematology from the <sup>1</sup>University Hospital Utrecht; <sup>2</sup>University Hospital Rotterdam; <sup>3</sup>Medical Center, Leeuwarden; <sup>4</sup>Sophia Hospital, Zwolle; <sup>5</sup>Academic Medical Center, Amsterdam; <sup>6</sup>Medisch Spectrum, Twente; <sup>7</sup>St Antonius Hospital, Nieuwegein; and <sup>8</sup>Leyenburg Hospital, The Hague, The Netherlands

## Summary:

We performed a phase II study to test the efficacy and feasibility of induction therapy with vincristine, adriamycin and dexamethasone (VAD) and intermediate-dose melphalan, 70 mg/m<sup>2</sup> (IDM), to autologous or allogeneic stem cell transplantation in newly diagnosed multiple myeloma (MM). A total of 77 patients received two cycles of VAD ( $n = 62$ ) and/or two cycles of i.v. IDM 70 mg/m<sup>2</sup> ( $n = 15$ ) combined with G-CSF. PBSC were harvested after the first IDM, successfully in 87% of patients. Patients with a response to induction received myeloablative therapy with PBSCT ( $n = 50$ ) followed by IFN maintenance or allo-BMT ( $n = 11$ ). Seventy-two per cent of patients achieved a response after VAD which increased to 85% after IDM. Of patients who received PBSCT and allo-BMT, 24% and 45% achieved CR, respectively. Toxicity of induction consisted mainly of bone marrow suppression after IDM (median 8 days) with prolonged aplasia in 11% of patients after the second IDM. Only six infections WHO grade 3 occurred during induction. Treatment-related mortality of PBSCT and allo-BMT was 6% and 18%, respectively. Median time of follow-up is 44 months, and 50% of patients after PBSCT and 60% of patients after allo-BMT are still in remission. Survival rates of all patients were 82%, 75% and 63%, and for transplanted patients 86%, 79% and 68% after 12, 24 and 36 months. Well known prognostic factors, including  $\alpha$ -IFN maintenance after PBSCT, were not significant for response or survival although patients in CR after allo-BMT had a strong tendency for better outcome. VAD/IDM is an effective and safe induction therapy for autologous and allogeneic stem cell transplantation. Based on these observations a phase III trial was started in October 1995 comparing IFN maintenance with PBSCT and allo-BMT after response to induction with VAD and IDM.

**Keywords:** multiple myeloma; autologous; allogeneic stem cell transplantation

Several groups have reported encouraging results of trials with high-dose therapy and autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM).<sup>1-8</sup> Especially when applied early in the course of the disease, ASCT procedures seem to achieve more complete remissions and longer event-free and overall survival rates than conventional chemotherapy. The results of many of these trials, however, may be biased by the selective inclusion of young(er) patients with relatively good performance and better tolerance to intensive therapy. This is illustrated by a retrospective study which showed that MM patients who were potential candidates for autologous stem cell transplantation (younger age, good performance and responsive to primary induction therapy), but were treated conventionally, had similar survivals to comparable patients who did receive early high-dose therapy.<sup>9</sup> Recently, a randomized phase III trial has been published which demonstrates that autologous bone marrow transplantation improves event-free and overall survival as compared with conventional, low-intensity treatment.<sup>10</sup> The results of several prospective phase III studies with sufficient follow-up have to be awaited to define whether, and for what group of MM patients intensified chemo-(radio)therapy is beneficial.

We present the results of a phase II trial involving 77 patients who received vincristine, adriamycin and dexamethasone (VAD) and intermediate-dose melphalan (70 mg/m<sup>2</sup>, IDM),<sup>11</sup> followed by high-dose chemo-radiotherapy and PBSCT or allo-BMT, who have been followed for a median duration of 44 months. Cyclo/TBI rather than regimens such as melphalan 200 mg/m<sup>2</sup> was chosen as the myeloablative regimen, as melphalan had been administered in induction. Based on the results of this trial, a phase III study has been initiated by the Dutch Hematology Society (HOVON) which compares VAD and IDM followed by IFN maintenance, vs VAD and IDM followed by PBSCT or allo-BMT.

## Patients

From June 1991 until July 1995, 77 previously untreated MM patients with intermediate and large tumor masses (stages 2 and 3 according to Salmon and Durie)<sup>24</sup> were included in the study. Patient characteristics are summarized in Table 1.

### Treatment

**Induction therapy:** Sixty-two patients received two courses of VAD (vincristine 0.4 mg i.v. and doxorubicin 9 mg/m<sup>2</sup> i.v., by continuous infusion every 24 h for 4 days combined with dexamethasone 40 mg orally, days 1–4, days 9–12, days 17–20) with an interval of 28 days.<sup>12</sup> Irrespective of the response to VAD, patients received two courses of IDM (70 mg/m<sup>2</sup>) with an interval of 6 weeks. The first IDM was administered between 6 and 8 weeks after the last VAD course in all patients. Recombinant human granulocyte colony-stimulating factor (G-CSF) at a dose of 5 µg/kg/day s.c. was started on day +4 after IDM and continued until recovery of neutrophils  $\geq 1.0 \times 10^9/l$ . Prophylaxis with ciprofloxacin and fluconazole or clarithromycin was started on day +4 after IDM and roxythromycin was added when the neutrophil count fell below  $0.5 \times 10^9/l$ . In 15 patients, two courses of IDM was the primary treatment.

**Peripheral stem cell harvest after IDM:** Daily monitoring of circulating CD34<sup>+</sup> cells started when the WBC count reached  $0.5 \times 10^9/l$ , which was usually between 14 and 21 days after the first IDM. All collections were performed after the first IDM. Peripheral blood stem cell collection (PBSC) was started when the WBC count reached  $1 \times 10^9/l$ , the platelet count  $\geq 40 \times 10^9/l$  and  $\geq 1\%$  CD34<sup>+</sup> cells/kg were present in the peripheral blood. Ten liters of blood were processed using a continuous flow Cobe CS.3000 machine (Cobe, Lakewood, CO, USA) or a discontinuous Hemonetics V50 machine (Hemonetics, MA, USA). A minimum of  $2.5 \times 10^6$  CD34<sup>+</sup> cells/kg was required. The total number of CFU-GM was determined prior to cryopreservation and after thawing for recovery.

**Table 1** Patient characteristics

Induction therapy	77
induction therapy IDM	15
induction therapy VAD/IDM	62
Median age, years (range)	51 (35–63)
$\geq 60$ years	7
Male/Female	40/37
Immunoglobulin	
G	54
A	18
D	1
Light chain disease	4
IIA	13
IIB	2
IIIA	55
IIIB	7
Hypercalcemia (Ca >2.70 mmol/l)	7
$\beta 2$ -microglobulin >4 mg/l	30/68

**Myeloablative therapy and stem cell transplantation:** Patients with a partial response (PR definition see below) after induction therapy who had an adequate stem cell transplant containing more than  $2.5 \times 10^6$  CD34<sup>+</sup> cells/kg proceeded to autologous stem cell transplantation. Patients with WHO performance status 3 and 4 and with severe organ dysfunction were excluded from transplantation. Patients under 56 years with an HLA-identical sibling were candidates for an allo-BMT. Patients who received an allo-BMT were matched with the PBSCT patients for the prognostic factors  $\beta 2$  microglobulin, LDH, Salmon and Durie stage, WHO performance status and response to VAD. The PBSCT group, median age 53 years (41–63), included only responsive patients, while the allo-BMT patients, median age 43 (37–51), included two refractory patients. The ablative regimen consisted of cyclophosphamide 60 mg/kg, given on 2 successive days followed by total body irradiation, 9 Gy (lung dose 8 Gy) on 1 day for ASCT patients or 12 Gy (lung dose 8.5 Gy) on 2 successive days for allo-BMT patients. Patients who received allo-BMT received a T cell-depleted graft containing  $1 \times 10^5$  T cells/kg. Patients received cyclosporin A for prevention of acute graft-versus-host disease (GVHD) until day 90.

**Definition of remission:** Complete remission (CR) was defined as complete disappearance of myeloma proteins, as determined by immunofixation of serum and/or concentrated urine (10 $\times$ ) and a normal bone marrow with less than 5% plasma cells in a representative biopsy. In addition monoclonal plasma cells had to be absent after immunophenotyping of cytocentrifuged bone marrow cells. Absence of monoclonality was defined as a normal kappa:lambda ratio within the malignant heavy chain.

Partial remission (PR) was defined as a minimal reduction by 50% of the myeloma proteins in serum and/or urine and improvement of clinical symptoms of myeloma such as anemia and/or bone pain.

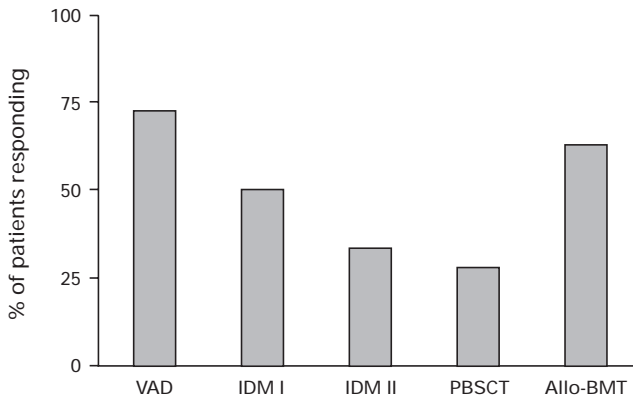
Ongoing response at each treatment step was defined as an additional decrease of tumor load as measured by 50% decrease of the myeloma proteins or by the induction of CR.

**Statistical analysis:** Curves for overall and progression-free survival were plotted according to the method of Kaplan–Meier and were compared by the log-rank test.<sup>13,14</sup> Prognostic factors for response, overall and event-free survival were determined by Cox regression analysis.  $\chi^2$  test or Fisher's exact test was used to determine the significance of differences in categorical variables.

## Results

### Response to induction

The response after VAD in 62 patients was 72% (PR 70%, CR 2%), which increased to 85% (PR 75%, CR 10%) after IDM. In 15 patients who received only IDM as induction, the response was 80% including one patient with CR. In the whole group of patients, the response was 85% (PR 75%, CR 10%) after induction therapy. Fifty percent of responding patients and 58% of non-responding patients after VAD



**Figure 1** Efficacy of the different treatment phases of induction therapy and PBSCT to induce response or ongoing tumor reduction. Ongoing tumor reduction defined as (additional) 50% decrease of the myeloma proteins or by the induction of CR.

showed an ongoing tumor reduction after the first IDM. Thirty-three percent of patients showed an ongoing tumor reduction from the first to the second IDM (Figure 1). Five patients were in CR after IDM1 and additionally, three patients in PR after IDM1 achieved CR after IDM2.

#### Stem cell collection after IDM

In 54 of 60 patients eligible for stem cell collection, (performance status 0–2, absence of symptomatic progressive disease) sufficient peripheral blood cells were harvested (threshold  $\geq 2.5 \times 10^6/l$ ) in two (1–5) leukapheresis procedures. The median CD34<sup>+</sup> yield was  $4.2 \times 10^6/kg$  ( $2.5–11.5 \times 10^6/kg$ ). In four patients insufficient peripheral CD34<sup>+</sup> cells were present during monitoring. In two other patients insufficient CD34<sup>+</sup> cells ( $< 2.5 \times 10^6/kg$ ) were collected. Additional bone marrow harvest was successful in one patient, and was unsuccessful in another patient; two patients refused bone marrow collection. In 17 patients PBSC harvest was not performed due to unresponsive or progressive disease ( $n = 6$ ) or a planned allo-BMT ( $n = 11$ ).

#### Toxicity of induction

**During VAD:** There were five WHO infections grade 2 and 2 WHO infections grade 3 during VAD. Neurotoxicity grade 1–2 was observed in seven patients. There were no deaths during VAD treatment. One patient died shortly after the second VAD course due to progressive disease.

**During IDM** All patients received standard anti-emetics, usually ondansetron before infusion of IDM which prevented nausea and vomiting almost completely in the majority of patients. Eight patients experienced grade 3 nausea and vomiting. No mucositis WHO grade  $\geq 2$  was observed. The major toxicity observed after IDM was myelosuppression, starting approximately 1 week after IDM, which lasted for a median of 8 days (0–16, Table 2). Prolonged myelosuppression defined as granulocytopenia ( $\leq 0.5 \times 10^9/l$ ) and/or thrombocytopenia ( $\leq 20 \times 10^9/l$ ) more than 21 days occurred in one patient (33 days) after the first IDM and in eight patients after the second IDM. Severe thrombocytopenia ( $\leq 50 \times 10^9$ ) occurred in two patients. Five patients were hospitalized due to infections WHO grade 3 after the first IDM, and two patients with WHO infections grade 3 after the second IDM course (4.7% of 149 IDM courses). There were no treatment-related deaths as a result of IDM treatment. In Table 2, IDM toxicity and the number of transfusions during bone marrow hypoplasia are summarized.

#### Response to stem cell transplantation

Sixteen patients (22%) did not proceed to stem cell transplantation for the following reasons: stem cell harvest failure ( $n = 3$ ); performance status WHO  $\geq 3$  ( $n = 1$ ); progressive and/or unresponsive disease ( $n = 12$ ). Forty-nine patients underwent PBSCT, one patient autologous BMT and 11 patients allo-BMT. PBSCT induced an ongoing tumor reduction in 28% of patients. Twelve patients (24%) were in CR after PBSCT, and in 10 patients the serum M-protein became less than 1 g/l.

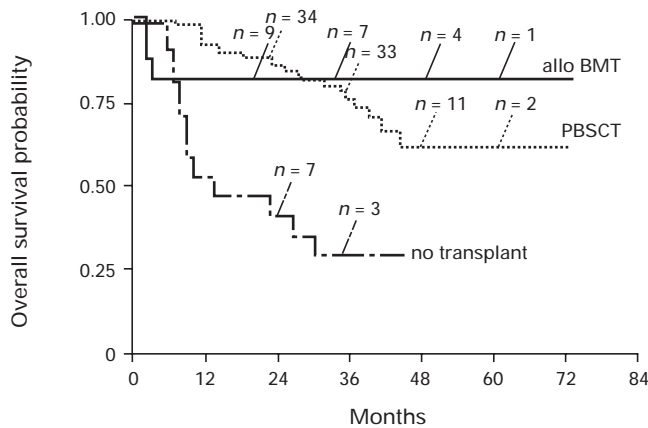
Treatment with allo-BMT induced an ongoing tumor reduction in 7/11 (63%) of patients. Five patients (45%) were in CR after allo-BMT. Four patients received systemic corticosteroids for acute GVHD grade II; four patients had acute GVHD grade I localized to the skin. Three patients had no acute GVHD. None of the patients suffered from chronic GVHD.

#### Hematologic recovery after PBSCT

Hematologic recovery after PBSCT could be adequately recorded in 40 patients. Granulocytes reached  $0.5 \times 10^9/l$  after a median of 14 days (9–28) and the platelets reached  $30 \times 10^9/l$  after a median of 15 days (9–31). Hemoglobin recovery was similarly rapid.

**Table 2** Toxicity of IDM

	Neutrophils $\leq 0.5 \times 10^9/l$		Platelets $< 20 \times 10^9/l$		Platelet transfusion median (n)		WHO infections grade 2 and 3 (n)	
	IDM1	IDM2	IDM1	IDM2	IDM1	IDM2	IDM1	IDM2
Days median (n)	8 (0–28)	8 (0–33)	6 (0–16)	6 (0–42)	2 (0–9)	3 (0–17)	5	3
>14 days, patients (n)	10	8	2	11				
>21 days, patients (n)	1	7	0	8				



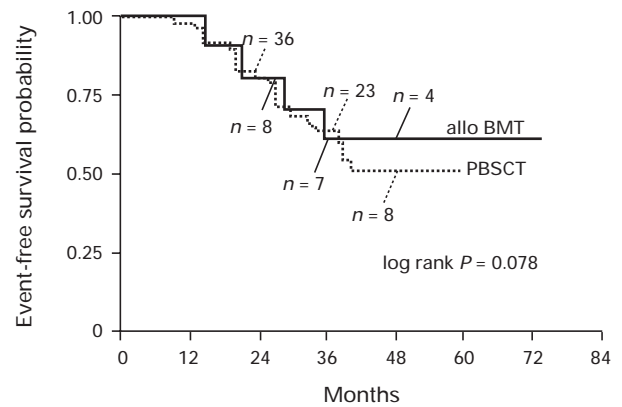
**Figure 2** Overall survival from the start of treatment. The distribution of prognostic parameters ( $\beta$ 2M, LDH, stage, performance) in the three groups was not statistically different.

### IFN maintenance therapy

Patients with a WHO performance status 0–2 and a normal blood cell count 3 months after PBSCT were eligible for interferon- $\alpha$  (IFN) maintenance therapy,  $3 \times 10^6$  units subcutaneously, three times weekly. Fourteen patients refused IFN treatment and 18 patients (40%) stopped IFN after a median of 2 months<sup>1–6</sup> due to side-effects: 12 patients had a fatigue syndrome, four patients had bone marrow insufficiency, one patient had interstitial pneumonitis, one patient had ischemic retinitis. In the remaining 14 patients (30% of eligible patients) IFN was administered for a median of 30 months (4–42+). Seven patients stopped IFN due to progression of MM. Median EFS after PBSCT in the patients that continued on  $\alpha$ -IFN was 35 months, and median OS was 40 months, which is not statistically different from the responding patients who did not receive  $\alpha$ -IFN maintenance.

### Duration of survival and progression-free survival

*The median time of follow-up was 44 months:* The overall and event-free survival of all patients and of patients after PBSCT and allo-BMT is shown in Figures 2 and 3. The median event-free survival for patients who received PBSCT was 40 months from start of therapy and 34 months after PBSCT. Twenty patients relapsed after PBSCT (13 from PR and seven from CR). The median EFS after allo-BMT has not been reached yet, but was not statistically different from PBSCT (Figure 3). Four patients in PR after allo-BMT relapsed. Two of these patients received donor leukocyte infusions (DLI) in escalated doses. All patients in CR after allo-BMT are still in remission after a median of 41 months of follow-up. The median overall survival (OS) has not been reached (Figure 2). Overall 30 patients died, 14 after PBSCT, including two patients in remission due to interstitial pneumonitis. Two patients died after allo-BMT, one from interstitial pneumonitis and one from a rapidly progressive Epstein–Barr-virus-associated lymphoma. The survival rates of all patients were 81%, 75% and 65% after 12, 24 and 36 months, respectively. For patients who received PBSCT and allo-BMT the survival rates were 90%



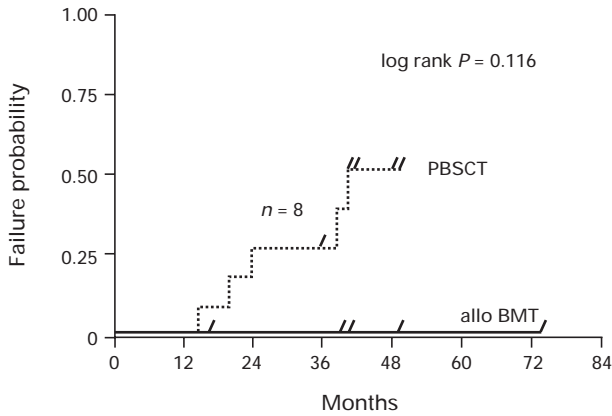
**Figure 3** Event-free survival from the start of treatment. Only patients with a response to induction with VAD and IDM were eligible for PBSCT. Four responding patients were not autotransplanted due to stem cell harvest failure ( $n = 3$ ) and WHO performance 3 ( $n = 1$ ). Patients that received PBSCT matched with the allo-BMT patients for prognostic factors  $\beta$ 2M, LDH, Salmon and Durie stage, performance status and response to VAD, median age of the PBSCT group was 54 (41–63) years and included only responding patients; median age of allo-BMT patients was 43 (35–51) years and included two refractory patients.

and 82%, 82% and 82%, 71% and 82% at 12, 24 and 36 months, respectively. The survival curves are currently not statistically different between PBSCT and allo-BMT (Figure 2). Thirty-nine patients were alive more than 3 years after start of treatment and 24 patients more than 3 years after stem cell transplantation. The median survival of patients who were not transplanted was 10 months (3–40+) (Figure 2).

### Prognostic factors

The prognostic parameters  $\beta$ 2M, LDH, Salmon and Durie stage and performance status in the three treatment groups (no transplant, PBSCT, allo-BMT) were comparable. Median age of patients that received allo-BMT was 43 years (35–51). Median age of the PBSCT patients and of non-transplanted patients was 53 (41–63) and 54 (43–61) years, respectively.

The only factor that was associated with a reduced survival rate was disease refractory to induction therapy ( $P < 0.00001$ ). As refractoriness to induction therapy was an exclusion criterion for further intensive treatment with PBSCT this factor cannot be evaluated for the outcome of autologous stem cell transplantation. Two of nine allo-BMT patients were refractory to induction treatment and responded to allo-BMT (1PR/1CR). The event-free survival for patients in CR after allo-BMT may be prolonged as none of the five patients in CR relapsed, as opposed to seven of 12 patients in CR after PBSCT (Figure 4). None of the other prognostic factors tested was associated with response to induction, progression-free and overall survival (Table 3). Also, achievement of response (PR, CR) after IDM1 or IDM2 and IFN maintenance (evaluable only in 14 patients) did not affect EFS and OS.



**Figure 4** Relapse of patients in CR after PBSCT and allo-BMT.

**Table 3** Single prognostic factors for response to VAD and progression-free and overall survival

	Patients n = 77	NR	P	Overall survival log rank P	Event-free survival log rank P
$\beta$ 2M (mg/l)					
>4	30	3	0.68	0.77	0.64
<4	38	5			
LDH					
>30 U/l	13	2	0.62	0.56	0.48
<30 U/l	57	6			
IgG subtype					
IgG	54	10	0.25	0.99	0.39
non-IgG	23	2			
Stage Salmon and Durie					
II	15	1	0.29	0.11	0.78
III	62	11			
VAD response					
NR	16	7		0.08	0.78
PR, CR	42				
Post-transplantation status					
PR	48			0.76	0.51
CR	17				
Transplantation					
PBSCT	50			0.49	0.95
Allo-BMT	11				
No transplant	16			<0.00001	
$\alpha$ -IFN post PBSCT	14			NS	NS

**Discussion**

In a previous feasibility study, we reported the effectiveness and safety of intermediate-dose melphalan (IDM) 70 mg/m<sup>2</sup>, as induction therapy for autologous stem cell transplantation. The objective of this approach was to maintain the anti-myeloma activity of high-dose melphalan, 140 mg/m<sup>2</sup> (HDM) while reducing toxicity. In this study, two courses of IDM followed by G-CSF resulted in a high response rate (85% including 18% CR) and rapid tumor reduction in previously untreated MM, associated with minor toxicity. Moreover, PBSC collection in the repopulation phase after the first IDM for subsequent autotransplantation was successful in the majority of patients (85%). The potential advantage of this approach was that PBSC harvest was performed after substantial tumor reduction

which might reduce myeloma cell contamination of the graft. The present study confirms and extends our previous data on repeated IDM alone or combined with VAD as an effective and well tolerated therapy for newly diagnosed MM. There were no treatment-related deaths and 85% of all patients responded. Seventy-eight percent of patients proceeded to myeloablative therapy followed by stem cell rescue after a median time interval of 6 months from start of treatment. These results compare favorably with response rates to stem cell transplantation with other induction schemes: response to VBAP/VMCP used by Attal *et al*<sup>10</sup> is usually between 60–75%, response to VAD and EDAP, used by Barlogie *et al*<sup>15</sup> prior to double transplantation, was 69%. Response to HDM used as induction for a second HDM,<sup>16</sup> was 71.5% including 25% CR. The median survival of patients undergoing transplantation was 41 months and the median duration of remission was 28 months. However, only 36% of this group of 97 patients (44 advanced MM and 53 newly diagnosed MM) proceeded to autologous transplantation due to the (stem cell) toxicity of the HDM including poor hematologic recovery, poor clinical status and fungal infections. This is in strong contrast to VAD/IDM which was administered almost completely in the out-patient clinic with acceptable toxicity and comparable efficacy. Additional tumor reduction was seen with each treatment step resulting in a CR rate of 24% in patients who received PBSCT and of 45% after allo-BMT. With a median follow-up of 44 months, 65% of all patients were alive at 3 years after the start of treatment. For patients who received PBSCT and allo-BMT, median EFS and OS have not been reached yet. Treatment-related mortality (TRM) of PBSCT was 4%. TRM after allo-BMT was 18% which is quite different from other studies reporting a TRM of 40% or more.<sup>17,18</sup> The outcome of these studies, however, was probably strongly negatively influenced by the inclusion of a large proportion of heavily pretreated and refractory patients. We have now treated a larger group of patients (n = 43) with allo-BMT after VAD/IDM and the preliminary results seem to confirm that a short period of induction is a major prognostic factor for allo-BMT in MM (manuscript in preparation). In our study tumor reduction was most efficacious if VAD and IDM were repeatedly given. PBSCT induced a further reduction in only 28% of the patients. This suggests (and is the conclusion of the French group Myeloma-autografte Paris, Creteil and Caen) that the value of high-dose therapy early in the course of the disease in responsive patients may be limited. The French group found that high-dose therapy with PBSCT had a similar effect on overall survival of young patients with aggressive MM when performed either early as front-line therapy, or late as rescue treatment.<sup>19</sup> Achievement of CR is the ultimate goal for cure in MM. As patients in CR after PBSCT show a high relapse rate and there is no plateau in EFS and overall survival curves, it is unlikely that cure can be achieved by stem cell transplantation alone. It is also unclear whether achievement of CR after PBSCT is associated with longer survival. In our study, patients in CR or PR after PBSCT had similar overall and progression-free survival rates. Although double transplants<sup>15</sup> are reported to result in high CR rates, EFS and overall survival rates may not be different from those seen in patients

treated less intensively, as is illustrated by preliminary results of a French randomized phase III trial comparing single vs double transplants.<sup>20</sup>

EFS and overall survival of allo-BMT patients were not significantly different from those seen in patients who underwent PBSCT, probably because of the small number of patients. Ongoing tumor reduction achieved by allo-BMT as compared to PBSCT, however, can be more effective and CRs after allo-BMT may be more durable: none of five patients in CR after allo-BMT relapsed, as compared to seven of 12 evaluable patients in CR after PBSCT. The beneficial graft-versus-myeloma (GVM) effect, recently proven by the induction of response after donor leukocyte infusions (DLI) in patients with relapse after allo-BMT<sup>21,22</sup> may be responsible for better outcome and even for cure in a subset of patients undergoing allo-BMT. This is in agreement with our findings that allo-BMT, as determined with patient-specific Vh primers, induces more 'molecular' remissions than high-dose chemo-radiotherapy alone (manuscript in preparation).

In our study, none of the well known prognostic factors tested had any statistical significance for response or survival. Also,  $\alpha$ -IFN maintenance therapy, evaluable in only 30% of eligible patients, had no influence on EFS and OS after PBSCT. The absence of prognostic significance in this study could be due to the small number of patients. However, it may be that these factors are more important for the outcome of patients who were treated conventionally. Recently it became clear that specific chromosomal abnormalities (any translocation, partial or complete deletions of chromosome 13 and 11q abnormalities) are very strong and independent prognostic factors in patients receiving intensified therapy.<sup>23</sup>

In conclusion, VAD/IDM induction followed by stem cell transplantation is a feasible and effective approach for newly diagnosed MM patients. Outcomes of the phase III study started by the HOVON group and of other randomized phase III studies, however, have to be awaited to define more precisely whether intensive treatment improves the prognosis of MM. Since a much larger cohort of patients will undergo allo-BMT in our study and they can be compared to patients with the same characteristics undergoing PBSCT, the clinical significance of the graft-versus-myeloma effect can also be established.

## References

- Jagannath S, Barlogie B, Dicke KA *et al*. Autologous bone marrow transplantation in multiple myeloma: identification of prognostic factors. *Blood* 1990; **76**: 1860–1866.
- Tricot G, Jagannath S, Vesole D *et al*. Peripheral blood stem cell transplant for multiple myeloma: identification of favourable variables for rapid engraftment in 225 patients. *Blood* 1995; **85**: 588–597.
- Ferland J-P, Chevret S, Revaud P *et al*. High-dose chemoradiotherapy and autologous blood stem cell transplantation in multiple myeloma: results of a phase II trial involving 63 patients. *Blood* 1993; **82**: 2005–2009.
- Cunningham D, Paz-Ares L, Milan S *et al*. High-dose melphalan and autologous bone marrow transplantation as consolidation in previously untreated myeloma. *J Clin Oncol* 1994; **12**: 759–763.
- Harousseau J-L, Attal M, Divine M *et al*. Autologous stem cell transplantation after first remission induction treatment in multiple myeloma: a report of the French Registry on Autologous Transplantation in Multiple Myeloma. *Blood* 1995; **85**: 3077–3085.
- Alexanian R, Dimopoulos M, Smith T *et al*. Limited value of myeloablative therapy for late multiple myeloma. *Blood* 1994; **83**: 512–516.
- Marit G, Faberes C, Pico JL *et al*. Autologous peripheral-blood progenitor-cell support following high-dose chemotherapy or chemoradiotherapy in patients with high-risk multiple myeloma. *J Clin Oncol* 1996; **14**: 1306–1313.
- Bjorkstrand B, Ljungman P, Bird JM *et al*. Autologous stem cell transplantation in multiple myeloma: results of the European Group for Bone Marrow Transplantation. *Stem Cells* 1995; **13**: 140S–146S.
- Bladé J, San Miguel JF, Fontanillas M *et al*. Survival of multiple myeloma patients who are potential candidates for early high-dose therapy intensification/autotransplantation and who were conventionally treated. *J Clin Oncol* 1996; **14**: 2167–2173.
- Attal M, Harousseau J-L, Stoppa A-M *et al*. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *New Engl J Med* 1996; **335**: 91–97.
- Lokhorst HM, Sonneveld P, Wijermans PW *et al*. Intermediate-dose melphalan (IDM) combined with G-CSF (filgrastim) is an effective and safe induction therapy for autologous stem cell transplantation in multiple myeloma. *Br J Haematol* 1996; **92**: 44–48.
- Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. *New Engl J Med* 1984; **310**: 1353–1356.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–481.
- Cox DR. Regression models and life-tables. *JR Stat Soc* 1972; **34**: 187–220.
- Barlogie B, Jagannath S, Vesole DH *et al*. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 1997; **89**: 789–793.
- Harousseau J-L, Milpied N, Laporte J-P *et al*. Double-intensive therapy in high-risk multiple myeloma. *Blood* 1992; **79**: 2827–2833.
- Bjorkstrand B, Ljungman P, Svensson H *et al*. Allogeneic bone marrow transplantation vs autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European group for Blood and Marrow Transplantation. *Blood* 1996; **88**: 4711–4718.
- Bensinger WI, Buckner CD, Anasetti C *et al*. Allogeneic bone marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood* 1996; **88**: 2787–2793.
- Ferland J-P, Ravaut P, Chevret S *et al*. Early vs late high-dose therapy (HDT) and autologous peripheral blood stem cell (PBSC) transplantation in multiple myeloma (MM): results of a prospective randomized trial. *Blood* 1996; **88**: 685a.
- Attal M, Payen C, Facon F *et al*. Single vs double transplant in myeloma: a randomized trial of the Inter Group Français du Myelome. *Blood* 1997; **90**: 418a.
- Tricot G, Vesole DH, Jagannath S *et al*. Graft-versus-myeloma effect: proof of principle. *Blood* 1996; **87**: 1196–1198.
- Lokhorst HM, Schattenberg A, Cornelissen JJ *et al*. Donor leukocyte infusions are effective in relapsed multiple myeloma. *Blood* 1997; **90**: 4206–4211.
- Tricot G, Sawyer J, Jagannath S *et al*. Unique role of cytogenetics in the prognosis of patients with myeloma receiving high-dose therapy and autotransplants. *J Clin Oncol* 1997; **15**: 2659–2666.
- Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. *Cancer* 1975; **36**: 42–52.