The VAD-DCEP sequence is an effective pre-transplant therapy in untreated multiple myeloma

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A B S T R A C T

Background and Objectives. Standard treatment for patients with multiple myeloma is debulking chemotherapy with non-alkylating agents followed by a regimen to mobilize peripheral blood stem cells (PBSC) and the transplantation of the mobilized, autologous PBSC. The aim of this study was to evaluate the efficacy of a new regimen and compare it with that of a previous regimen.

Design and Methods. In a large cohort of 106 patients (group I) we administered a new pre-transplant program which includes 2 courses of pulsed-VAD (vincristine, adriamycin, dexamethasone) followed by 2 courses of DCEP (dexamethasone, cyclophosphamide, etoposide and cis-platinum). We compared the efficacy of this new VAD-DCEP sequence, in terms of mobilizing capacity, toxicity and anti-myeloma activity in comparison with that of the previous VAD-high-dose cyclophosphamide program (group II, 40 patients).

Results. In group I 81/106 (76.4%) patients yielded $\geq 4\times10^6$/kg CD34$^+$ cells, as did 30/40 (75%) in group II but with a significantly higher toxicity in this latter group. In detail, 9 patients in group I (8.5%) had WHO grade III neutropenia versus 35 in group II (87.5%), 5 patients of group I (4.7%) had grade III thrombocytopenia versus 12 patients in group II (30%), and 8 patients in group I (7.5%) experienced an infections fever versus 9 patients in group II (22.5%). Therefore, nearly all patients in group II had to be admitted to hospital (39/40, 97.5%). There was a higher percentage of responses (CR+VGPR+PR) in group I than in group II: 73% versus 50% (p=0.02).

Interpretation and Conclusions. the VAD-DCEP sequence has an adequate mobilizing capacity, without significant toxicity, and a good anti-myeloma activity, and therefore represents a safe and effective therapeutic approach for multiple myeloma patients at the onset of their disease.

Key words: DCEP, HDCTX, high-dose therapy, CD34$^+$ cells, mobilization.

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High dose therapy with autologous stem cell transplantation is the standard treatment for multiple myeloma patients.[1-4] These programs generally include a debulking phase with non-alkylating agents (vincristine, adriamycin, dexamethasone (VAD or VAD-like regimens) followed by a regimen to mobilize peripheral blood stem cells (PBSC) prior to high dose melphalan with autologous stem cell support. High-dose cyclophosphamide (HDCTX) is considered the standard mobilizing therapy, even though it is burdened by several toxic effects which often require the patient's admission to hospital.[5] Alternative mobilizing regimens have shown a greater mobilizing capacity than HDCTX, but often at the price of greater toxicity.[6-9] Nevertheless, we previously reported that a regimen of dexamethasone, cyclophosphamide, etoposide and cis-platinum (DCEP) is better tolerated and mobilizes better than HDCTX.[10,11] Other studies have demonstrated that this regimen also has good anti-myeloma activity in patients with refractory multiple myeloma.[12-14]

On the basis of these observations, we designed a new pre-transplant sequence which includes two courses of pulsed-VAD followed by two courses of DCEP. The aim was to achieve a better pre-transplant response, knowing that patients with a good response before transplant have the best benefit from that procedure. This paper reports the results of the VAD-DCEP regimen and offers a comparison with the results of the standard VAD-HDCTX program in terms of mobilizing efficacy, anti-myeloma activity and toxicity.

Design and Methods

From 1996 to 2002, 146 consecutive untreated multiple myeloma patients (M 80, F 66) with a median age of 54 years were enrolled in two successive high dose programs including autologous stem cell transplantation. From 1996 to 1999, 40 patients received debulking and mobilizing therapy with 3 cycles of pulsed-VAD followed by one cycle of HDCTX (group II), prior to a single autotransplant primed with high-dose melphalan. From 2000 to 2002 we applied a new debulking and mobilizing regimen, including two pulses of VAD followed by two courses of DCEP chemotherapy in 106 patients (group I). Peripheral blood stem cells were collected after each DCEP cycle. Inclusion criteria in both protocols were: Durie and Salmon multiple myeloma in stage II, III, or stage I in progression and no severe cardiac, pulmonary, hepatic dysfunction. The age limit was 65 years in group I and 60 years in group II. Written informed consent was obtained from all patients prior to the start of treatment.

Table 1. Clinical characteristics at onset in the 146 patients with multiple myeloma.

	DCEP (Group I)	*HD-CTX (Group II)*	*p*
N. of patients	106	40	–
Male/Female	54/52	26/14	0.140
Median age (range)	54 (35-65)	49 (32-60)	0.002
Component type			
IgG	59 (56%)	27 (67%)	
IgA	20 (19%)	9 (23%)	0.296
Light chain	24 (22%)	3 (7.5%)	
Non-secretory	3 (2.5%)	1 (2.5%)	
Biclonal	1 (0.5%)	0	
Stage			
I	20 (19%)	13 (32%)	
II	20 (19%)	7 (18%)	0.219
III	66 (62%)	20 (50%)	

Study design

Group I patients received 2 courses of pulsed-VAD (vincristine 2 mg i.v. on day 1, doxorubicin 50 mg/m^2 on day 1, dexamethasone 40mg/die i.v. days 1-4, 14-17), followed by 2 courses of DCEP plus G-CSF. PBSC were collected after each cycle in order to obtain a sufficient number of CD34$^+$ cells for two transplants. The DCEP schedule was as follows: dexamethasone 40 mg/die for 4 days, and a 4-day continuous infusion of cyclophosphamide 400 mg/m^2/die, etoposide 40 mg/m^2/die and cisplatin 10 mg/m^2/die. G-CSF, at a dose of 5 μg/kg, was started 48 hours after the end of chemotherapy until PBSC leukaphereses were concluded. Group II patients received 3 pulses of VAD followed by HDCTX and G-CSF. HDCTX was administered at 4 g/m^2 in two fractions over 24 hours. The G-CSF was given at the same dosage and schedule as used in group I.

In both groups the first collection started when there were at least 20 peripheral blood CD34$^+$ cells/μL with a collection target of CD34$^+$ cells ≥ 4×10^6/kg in each procedure. The mobilizing capacity of HDCTX was compared with that of the first cycle of DCEP.

Evaluation of response

Patients were assessed for response after PBSC collection, before transplantation. Responses were defined as follows: complete response (CR): absence of M component in serum and urine by immunofixation and <5% plasma cells in the bone marrow aspirate; very good partial response (VGPR): 90% decrease of serum and urine paraprotein level; partial response (PR): at least a 50% decrease of serum paraprotein level and a 90% decrease of Bence Jones protein; stable disease (SD): less than a 25% decrease of serum paraprotein level and Bence Jones protein; no response (NR): no variation or increase of serum or urine paraprotein level.

Statistical analysis

Continuous variables are summarized as the median and range, and categorical variables as frequencies and percentages. Treatment groups were compared by means of the Mann-Whitney U test and Fisher's exact test for continuous and categorical variables, respectively. The role of treatment protocol in determining a good response to treatment was assessed by means of a logistic model; the estimated odds ratio (OR) and 95% confidence interval (95%CI) were controlled for age, gender, stage, plasmacytosis and treatment center. Stata 8 software (StataCorp, College Station, TX, USA) was used for all computations. A 2-sided *p* value < 0.05 was considered statistically significant.

Results

The clinical characteristics of the 146 multiple myeloma patients registered at onset are detailed in Table 1. Patients in the two groups had similar characteristics without significant differences except for median age which was higher in group I.

The characteristics of the PBSC mobilization following VAD-DCEP protocol are reported in Table 2. In detail, 81 patients (76.4%) of group I and 30 patients

Table 2. Characteristics of PBSC collections in the two groups.

	DCEP (Group I)	*HD-CTX (Group II)*	*p*
N. of patients	106	40	–
N. of patients yielding $CD34^+$ cells ≤ 2×10^6/kg	6 (5.6%)	5 (12.5%)	0.17 (NS)
N. of patients yielding $CD34^+$ cells ≥ 4×10^6/kg	81 (76.4%)	30 (75%)	0.8 (NS)
Median N. of $CD34^+$ cells $\times10^6$/kg (range)	5.29 (0-25.7)	7.06 (0-19.8)	0.2 (NS)

Table 3. Toxicity of the two mobilizing regimens.

	DCEP (Group I) n=106	*HD-CTX (Group II) n=40*	*p*
Pts. needing hospitalization after CHT	12 (11.3%)	39 (97.5%)	0.000
Pts. with neutrophils < 1,000/μL	9 (8.5%)	35 (87.5%)	0.000
Pts. with platelets < 50,000/μL	5 (4.7%)	12 (30%)	0.000
Pts. with infectious complications	8 (7.5%)	9 (22.5%)	0.019

(75%) of group II yielded ≥4×10^6/kg $CD34^+$ stem cells. The percentage of patients in whom mobilization was poor (<2.0×10^6/kg $CD34^+$ cells) was lower in group I than in group II (5.6% versus 12.5%), even though the difference was not statistically significant. The toxicity of the two mobilizing regimens is reported in Table 3. No patient in group I required transfusions and cisplatin-related nausea was always tolerated and easily controlled. All types of toxicity were statistically significantly worse in group II.

Table 4 shows the response to pre-transplant chemotherapy in the two groups. The percentage of responses (CR+VGPR+PR) was higher among patients receiving the VAD-DCEP sequence (73%) than in those treated with the VAD-HDCTX program (50%) (adjusted OR=2.80 (95%CI 1.04-7.54), p=0.018). The percentage of good responders (CR+VGPR) was also higher in group I (42 patients, 39.6%) than in group II (11 patients, 27.5%), although in this case the difference was not statistically significant. Of note, we did not observe differences between group I and II in terms of responses after the induction phase with 2 or 3 cycles of pulsed-VAD. This suggests that the difference in responses observed between the two groups could be attributed mainly to the DCEP regimen.

Table 4. Response at the end of the two pre-transplant chemotherapy regimens.

	DCEP (Group I)	*HD-CTX (Group II)*	*p*
CR	8 (7.5%)	0	
VGPR	34 (32.5%)	11 (27.5%)	
PR	35 (33%)	9 (22.5%)	
Responders	77 (73%)	20 (50%)	0.0011
SD	9 (8.5%)	7 (17.5%)	
NR	20 (18.5%)	13 (32.5%)	
Non responders	29 (27%)	20 (50%)	0.041

Discussion

Autologous stem cell transplantation has improved response and survival of multiple myeloma patients.[1,16,18] The initial treatment usually includes a debulking therapy with VAD or VAD-like regimens followed by chemotherapy plus G-CSF to mobilize peripheral blood progenitor cells. The aim of the initial phase of therapy is to reduce the tumor burden, without damaging bone marrow stem cells, and to mobilize an adequate number of progenitor cells for autologous transplantation. We previously reported on the safety and mobilizing capacity of DCEP with G-CSF for the treatment of multiple myeloma patients.[10] This regimen showed better mobilizing capacity than did HDCTX.[11] The aim of this study was to evaluate the anti-myeloma activity of the VAD-DCEP sequence with respect to the VAD-HDCTX sequence knowing that the sensitivity to the initial therapy preludes to a better response to transplantation and to a longer-progression-free survival.[4,15,17,19]

Much effort has been made to improve the pre-transplant response using more intensive regimens.[20-23] The improvement of response, however, has been often burdened by increased toxicity. The VAD-DCEP sequence resulted in a statistically significant increase of the percentage of responses (CR+VGPR+PR; 73% vs 50%) (p=0.02) with respect to the percentage induced by the VAD-HDCTX sequence but without additional toxicity. The DCEP combination seems able to further improve the response obtained after standard VAD. Of note, patients in group I were significantly older (p=0.002) than those of group II. Even when considering only the good responders (CR+VGPR), we found a higher per-

centage in group I (42 patients, 39.6%) than in group II (11 patients, 27.5%), although in this case the difference was not statistically significant. We also confirmed that DCEP is a good and safe mobilizing regimen in a larger cohort of patients. However, the mobilizing capacity of HDCTX and DCEP was not statistically different even though the percentage of poor mobilizers was much lower in group I.

In conclusion, the combination of pulsed-VAD with the non-cross-resistant DCEP combination is an effective and safe pre-transplant sequence which rapidly produces high rates of response and, at the same time, has a good mobilizing capacity. Integrating the DCEP combination with novel biological agents, such as thalidomide and immunomodulatory drugs, might further improve the percentage of responses before transplantation.

AC was primarily responsible for the conception and design of the study and together with PZ and SM for the interpretation of the data and writing the manuscript; LB, RC, EPA, DF, SF, MF, GF, LI, AL, AD, CV, LB, DP, GU, GP, MS, LU, AV, were responsible for the collection of the data and for the management of the patients, CK performed the statistical analysis, EM and ML critically revised the paper.

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