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CYCLOPHOSPHAMIDE (3.6 g/m²) THERAPY WITH G-CSF SUPPORT FOR RESISTANT MYELOMA

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ABSTRACT

Background. **In myeloma patients, resistance to both melphalan and doxorubicin containing regimens has been related to a very short survival of approximately 6 months. The development of effective regimens combined with a low toxicity rate is mandatory in this patient subgroup.**

Methods. **Fourteen resistant myeloma patients were treated with cyclophosphamide (a total of 3.6 g/m² was delivered in 2 doses on day 1 and 3), prednisone (2 mg/kg, days 1-4) every month for 4 cycles. G-CSF support was administered to reduce myelosuppression.**

Results. **This combination was well tolerated. The granulocyte levels fell below 0.1×10^9/L in all patients after a median of 9 days (range 8-11), followed by recovery to 0.5×10^9/L after a median of 12 days from the start of treatment (range 10-13 days). Platelets never fell below 50×10^9/L. All patients were treated on an out-patient basis and only 2 required hospitalization for major complications (pneumonia and heart failure). Response to cyclophosphamide was observed in 6/14 patients: 2 achieved complete remission, 4 showed 50% or greater reduction of M-component. Five patients are still in remission after 2, 6, 7, 9 and 10 months, 1 relapsed after 10 months. All patients except one are alive 4-16 months from the start of treatment.**

Conclusions. **This schedule may represent a new approach for resistant myeloma, the very low toxicity allowed the delivery of this intensified regimen on an out-patient basis.**

Key words: cyclophosphamide, G-CSF, resistant myeloma

Salvage treatment for patients with advanced multiple myeloma resistant to both melphalan and doxorubicin containing regimens is unsatisfactory. Resistance to these regimens has been related to a median survival of approximately 6 months.[1-3] In these patients, intermediate dose melphalan (50-70 mg/m²) and the combination of cyclophosphamide (3 g/m²) and etoposide (900 mg/m²) slightly ameliorate the outcome with a median survival time of 11 months.[4-5] Other myeloablative regimens, such as high dose melphalan (140 mg/m²) with hemopoietic stem cell support, showed encouraging results with a median survival of 17 months.[6] By contrast, other authors did not recommend myeloablative therapy for resistant or relapsing myeloma.[7] Even though the controversy is still open, the high risk of serious complications limited this approach to a small subset of patients younger than 60 years with good performance status. Unfortunately, advanced disease is usually associated with serious medical complications. The development of effective treatment overcoming drug resistance with a relatively low toxicity rate is essential.

Here, we report our experience with cyclophosphamide (3.6 g/m²) followed by G-CSF in

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14 patients resistant to both melphalan and doxorubicin. This out-patient schedule was as effective as previous intensive regimens, however toxicity and hospitalization were remarkably reduced.

Materials and Methods

Patients

Between October 1992 and January 1994, 14 patients with multiple myeloma resistant to melphalan and the combination of vincristine, doxorubicin and dexamethasone (VAD)[8] were treated. At diagnosis, 4 patients were resistant to both melphalan and VAD (primary resistance). At relapse, five patients were resistant to VAD (resistant relapse). Four initially responding patients relapsed after both melphalan and VAD treatments (relapse): median interval between the previous treatment and relapse was 15.5 months, one patient relapsed after autologous bone marrow trasplantation. Inclusion criteria were age <70, serum creatinine <3 mg/dL, normal cardiac and pulmonary functions. Patient characteristics are summarized in Table 1. The median age was 56 (range 47-65). Myeloma was of high or intermediate stage in 85%,[9] performance status was 2 or higher in 57%. Before treatment, mean hemoglobin level was 106 g/L, mean white blood cell count was 4.35×10^9/L, mean platelet count was 235×10^9/L. Either labelling index >1.5 %, or β2-microglobulin >6 mg/L, or C-reactive-protein >6 mg/L were present in 28% of patients.[10,11]

Table 1. Patient characteristics.

Median age (range)		56 (47-65)
Sex (male/female)		6/8
Ig isotype	IgG-κ	3
	IgG-λ	4
	IgA-κ	2
Bence Jones	κ	3
	λ	4
Stage at diagnosis	I A	2
(Durie & Salmon	II A	5
staging system)	III A	7
Disease status	Relapse	4
	Resistant relapse	5
	Primary resistant	4
	Relapse after ABMT*	1
Performance status	0	1
	1	5
	2	3
	3	4
	4	1
Prognostic factors	Labelling index > 1.5%	2/14
	β_2-microglobulin > 6 mg/L	1/14
	C-reactive protein > 6 mg/L	1/14
Laboratory studies	Hemoglobin < 8.5 g/dl	2/14
	Creatinine > 2 mg/dl	0/14
	Calcium > 12 mEq/L	0/14

**ABMT: autologous bone marrow transplantation*

Chemotherapy

A peripheral venous catheter was inserted and intravenous infusion was performed with normal saline at a rate of 200 mL/h, 8 h/day from day 1 to 3. Chemotherapy consisted of cyclophosphamide 1.8 g/m^2 in 500 mL dextrose 5% i.v. over 3 h on day 1 and 3 (total dose 3.6 g/m^2), and prednisone 2 mg/kg i.v. from day 1 to 4. Cyclophosphamide infusion was devided into 2 doses to avoid hemorragic cystitis. Methyl-ethane-sulfonic acid (MESNA) 600 mg/m^2 in 100 mL dextrose 5% was administered i.v. 2 and 5 h after cyclophosphamide. G-CSF was begun on day 5 at a dose of 5 μg/kg s.c. for 8-10 days. A fluid intake of at least 2 L/day was recommended. Ciprofloxacin 500 mg p.o. twice daily and fluconazole 400 mg p.o. once daily were prescribed as antimicrobial and antimycotic prophylaxis. No patient was hospitalized to receive chemotherapy. All responding patients received recombinant α2b-interferon (3 M.U. s.c. 3 times a week) plus dexamethasone 40 mg p.o. (each morning for 4 days, every month) as maintenance therapy until relapse.

Toxicity evaluation

Physical examination, blood cell count and serum chemistry were performed every day for the first two weeks after chemotherapy and then weekly. Toxicity was recorded and graded according to WHO criteria.

Response and survival analysis

Complete response was defined as disappearance of myeloma protein by standard serum electrophoresis and decrease in bone marrow plasmacytosis to less than 1%; objective response as 50% reduction of myeloma protein or decline of Bence Jones proteinuria >75%. Partial response was defined as myeloma protein reduction >25% but <50%; no response or stable disease as M component decline >0% but <25%; relapse as an increase >50% from the lowest level of serum M component, or an increase in the size or number of lytic bone lesions. Survival was evaluated from the start of therapy, remission from a 50% reduction of myeloma protein to the earliest sign of relapse.

Results

Toxicity

Cyclophosphamide was very well tolerated during the 3 day period of infusion. Drugs were always administered on an out-patient basis, nausea and vomiting were well controlled with ondansetron. The infusion of MESNA was limited to few hours after cyclophosphamide and gross hematuria was never observed. Subsequently, granulocyte levels fell below 0.1×10^9/L in all patients after a median of 9 days (range 8-11), followed by recovery to 0.5×10^9/L after a median of 12 days (range 10-13). Severe granulocytopenia lasted a median of 3 days (range 1-4) (Figure 1a). Platelets never fell to less than 50×10^9/L. In 8 patients, platelets fell below 100×10^9/L (Figure 1b). Hemoglobin levels were almost unaffected, red blood cell support was required in only one patient. Regimen-related toxicities are described in Table 2. As a result of the short myelosuppression, only two patients developed unexplained fever without signs of overt infection, one patient contracted bacterial pneumonia requiring broad spectrum intravenous antibiotics. Two patients suffered from herpes-zooster eruption, treated with acyclovir. Four patients experienced microscopic hematuria between day 1 and 10. One patient experienced heart failure secondary to fluid overload and responsive to diuretics, 1 patient

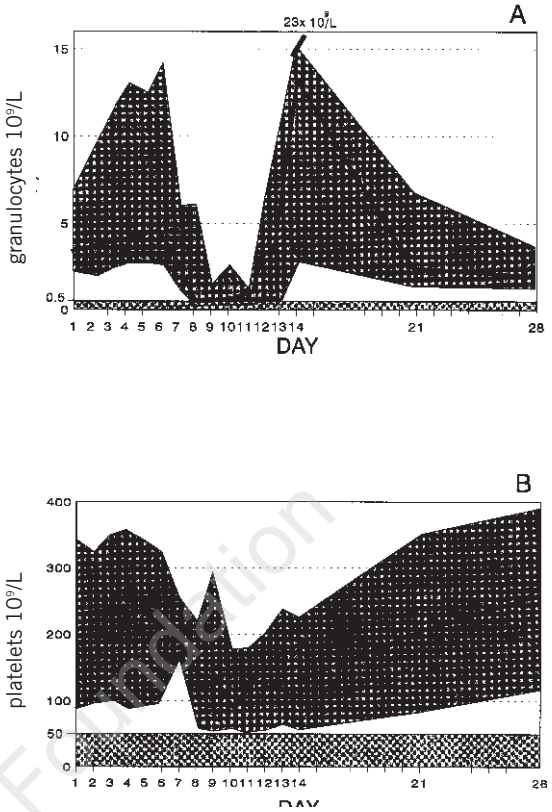

Figure 1. Changes in blood counts after cyclophosphamide. A) Median (——) and range (gray area) of granulocytes on days 1-14, 21, 28 during 56 courses of cyclophospamide; B) Median (——) and range (gray area) of platelets.

supraventricular tachycardia. G-CSF was well tolerated except for bone pain in 4 patients and was never discontinued. Only 2 patients

Table 2. Toxicity of cyclophosphamide.

	grade (WHO)			
Toxicity	*1*	*2*	*3*	*4*
Hemoglobin	5/14	1/14	1/14	–
Granulocytes	–	–	–	14/14
Platelets	6/14	2/14	–	–
Hemorrhage	–	–	–	–
Fever	–	2/14	–	–
Infection	2/14	1/14	–	–
Renal/bladder	4/14	–	–	–
Diarrial	–	–	–	–
Nausea/vomiting	–	1/14	–	–
Cutaneous	2/14	–	–	–
Cardiac	1/14	–	1/14	–

Table 3. Response and long-term outcome.

patients	response (months)	response duration (months)	survival*	performance status pre-therapy	performance status post-therapy	before treatment PLC% (g/dl)	before treatment M-Comp (g/24h)	before treatment Bence Jones (g/dL)	after treatment PLC % (g/24h)	after treatment M-Comp	after treatment Bence Jones
1	NR	–	12	3	2	31	–	3.1	21	–	1.0
2	OR	9+	13+	1	0	8	4.7	–	2	2.0	–
3	OR	10	15+	1	1	12	–	1.0	1	–	0.0
4	NR	–	12+	1	0	22	3.1	8.9	20	3.2	5.3
5	CR	7+	9+	3	1	9	1.6	–	1	0.0	–
6	OR	6+	7+	4	1	35	–	3.6	1	–	0.0
7	CR	2+	5+	0	0	40	1.9	2.5	1	0.0	0.0
8	NR	–	4+	2	1	10	–	4.5	6	–	4.6
9	NR	–	5+	2	1	12	4.4	–	15	4.8	–
10	NR	–	14+	3	4	64	2.7	–	58	2.6	–
11	PR	–	4+	1	1	20	6.0	–	14	3.4	–
12	OR	10+	12+	3	1	30	4.5	–	8	1.8	–
13	PR	–	4+	2	1	27	4.2	–	12	2.9	–
14	NR	–	16+	1	0	24	–	2.0	8	–	1.8

**from the beginning of therapy, CR: complete response, OR: objective response; PR: partial response NR: no response, PLC: bone marrow plasma cell, M–Comp: monoclonal myeloma protein, Bence Jones: Bence Jones proteinuria*

required hospitalization for major complications (pneumonia and heart failure).

Response and survival

All 14 patients were assessed for response to therapy: 2 achieved complete remission, 4 a reduction of myeloma protein >50%, 2 a reduction >25% and 6 did not respond (Table 3). Among responders, serum protein halving time occurred at 1, 1, 2, 2, 3, 4 months. Performance was highly impaired in 8 patients primarily because of bone pain. After chemotherapy, performance improved significantly in 6 patients who discontinued analgesic treatment and were able to perform their normal daily activities. Five patients are still in remission after 2, 6, 7, 9, 10 months, 1 relapsed after 10 months. After a median follow-up of 10.5 months, all patients except one are still alive.

Discussion

Patients with advanced multiple myeloma who are resistant to melphalan and doxorubicin have a very poor prognosis, with a median survival of 6 months.[2,3] Our cyclophosphamide regimen resulted in a response rate of 42%, a life expectancy of approximately one year and a low toxicity rate.

In these patients, intravenous melphalan and cyclophosphamide have been extensively used. Intermediate dose melphalan (50-70 mg/m^2) induced response in only 30% of patients resistant to VAD, the median duration of response was 3 months, prolonged myelosuppression and an early mortality of 10-20% were observed.[4] The combination of cyclophosphamide (3 g/m^2) and etoposide (900 mg/m^2) achieved good clinical results: response was 40% and median survival 11 months. Toxicity was lower in comparison to other intensive therapies: median time for agranulocytosis was 3 weeks and early mortality 4%. This treatment required frequent hospitalization, 95% of patients developed overt infection or unexplained fever requiring intravenous antibiotics and 12% had severe mucositis demanding parenteral nutrition.[5] Autologous bone marrow transplantation and peripheral blood stem cell support drastically reduced myelosuppression (always shorter than 2 weeks), response was higher (70%), and the estimated rate of 1 year overall survival showed an excellent 85%.[12] Unfortunately, this procedure is limited to young patients with good performance status. Our regimen seems as effective as other more toxic treatments: it induced response in 42% of patients, all patients except one are alive after a median follow up of 10.5 months. Granulocyte recovery required only 12 days, platelets were never affected, infections distressed only 20% of patients, hospitalization for chemotherapy-induced complications was required in 2 patients and early mortality was never observed.

G-CSF was included in the attempt to shorten the duration of granulocytopenia and allowed a very low incidence of infections. The duration of myelosuppression induced by cyclophosphamide at the dose of 3.6 g/m^2 followed by G-CSF was similar to that induced by cyclophosphamide at lower doses (2.4 g/m^2).[13-15] Thus, G-CSF allowed an intensification of dose of 30% without any increase in hematological toxicity. At present, the major limiting factor seems related to the cardiac compliance, a careful evaluation of the cardiovascular function is therefore mandatory in all patients. Unexpectedly, a relative high incidence of Herpes-Zooster infections was noticed suggesting the need of acyclovir profilaxis for elderly and/or heavily pretreated patients.

In conclusion, our regimen provided a practical salvage regimen for many patients with advanced myeloma, because toxicity and hospitalization were remarkably reduced.

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