

Salvage therapy with thalidomide in multiple myeloma patients relapsing after autologous peripheral blood stem cell transplantation

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Background and Objectives. The introduction of high-dose therapy with stem cell support has significantly improved the outcome of patients with multiple myeloma (MM) in terms of increased complete remission (CR) rate and extended survival, both disease-free and overall. Few options, however, are presently available for patients who relapse after single or double autologous stem cell transplantation (SCT). Thalidomide, a glutamic acid derivative with anti-angiogenetic properties, has been recently proposed as salvage treatment for such patients. The present study was aimed at evaluating thalidomide as single agent therapy for patients who had previously received autologous peripheral blood stem cell transplantation.

Design and Methods. From October 1999 to August 2000, 11 patients (7 males/4 females) who had relapsed after single (n=4) or double (n=7) autologous peripheral blood SCT were enrolled in the trial. Thalidomide, always employed as a single agent, was initially administered at a dose of 100 mg/day; if well tolerated, the dose was increased serially by 200 mg every other week to a maximum of 800 mg/day.

Results. The median administered dose was 600 mg/day. WHO grade > II toxic effects were constipation, lethargy, and leukopenia. Four patients (36%) showed > 50% reduction in serum M protein concentration and 4 showed > 25% reduction, for a total response rate averaging 72%. After a median follow-up of 5 months, 3 out of 8 responding patients are alive and progression-free and 5 patients have relapsed.

Interpretation and Conclusions. These data confirm that thalidomide is active in poor-prognosis MM patients such as those relapsing after autologous SCT, and could thus deserve further testing in combination therapy.

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Key Words: thalidomide, multiple myeloma, autologous stem cell transplantation

Multiple myeloma (MM) is a fatal B-cell malignancy characterized by the proliferation and accumulation of neoplastic B-lymphocytes and plasma cells producing monoclonal immunoglobulins.¹ Virtually, no significant improvement in prognosis has been made with conventional chemotherapy since the introduction of melphalan and steroids in the early 1960s. Recently, it has been demonstrated that more intensive chemotherapy with single or double transplantation of autologous hematopoietic progenitor cells is superior to conventional chemotherapy as it produces longer disease-free and overall survival.² However, the relapse rate after autologous, and even allogeneic transplantation is unfortunately high,^{3,4} a finding which raises the issue of whether the myeloma clone can be eradicated. Therapeutic options for MM patients who relapse after autologous stem cell transplantation (SCT) are limited. Superiority of salvage autologous bone marrow transplantation (BMT) over standard therapy has been reported, with a response rate averaging 30-40% and a 3-year event-free survival of approximately 20-25%.^{5,6} On the other hand, allogeneic transplantation performed under this unfavorable condition was associated with a high therapy-related mortality.⁵

Thalidomide is a glutamic acid derivative that has demonstrated activity in advanced relapsed/refractory MM patients. In particular, in a large series of patients with progressive disease, 69% of whom had previously received high-dose therapy, a 32% response rate was observed;⁷ these favorable results have been confirmed more recently in smaller series of patients.⁸⁻¹¹

We report here a single center experience with the use of thalidomide as salvage therapy for patients relapsing after single or double autologous peripheral blood SCT (PBSCT).

Design and Methods

Patients

Between October 1999 and August 2000, 11 consecutive patients (7 males, 4 females, median age 55 years) with stage III MM relapsing after single (n= 4) or dou-

Table 1. Clinical characteristics of the patients at study entry.

Pt	Sex/Age	MM isotype	Time since diagnosis (months)	No. of transplants	Time since transplant (months)	Chemotherapy after post-transplant relapse	Disease status pre-thalidomide	M component (mg/dl)	% BMPC
1	F/60	IgG/ κ	25	2	11	MP	refractory	1730	90
2	F/56	IgG/ λ	59	1	28	VAD+MP	relapsed	5290	50
3	M/55	IgG/ κ	33	2	12	MP	refractory	3260	70
4	M/42	IgG/ κ	82	2	47	VID+MP	refractory	6280	50
5	F/60	IgG/ κ	59	1	42	CTX 1-3, HDDEX, MP	refractory	3370	90
6	M/57	IgA/ κ	51	2	16	VAD	relapsed	4280	80
7	M/54	IgG/ λ	36	2	6	none	relapsed	2510	50
8	M/53	IgG/ κ	48	1	41	MP, CTX 1-3, VID	refractory	4350	50
9	M/57	IgG/ κ	32	2	10	none	relapsed	3870	30
10	F/55	IgG/ κ	72	1	66	CTX 1-3, HDDEX	relapsed	3990	20
11	M/50	IgG/ κ	53	2	2	none	relapsed	2070	not evaluable

MP = melphalan 10 mg/m² + prednisone 80 mg/m², days 1 to 4; VAD = perfusion of vincristine + doxorubicin + dexamethasone, VID = vincristine + idarubicin + dexamethasone. CTX 1-3 = cyclophosphamide 1.2 g/m²/day, days 1 and 3 + dexamethasone 40 mg/day, on days 1 to 4, HDDEX = dexamethasone 40 mg/day, days 1 to 4.

ble (n=7) autologous PBSCT gave their informed consent to be enrolled into a pilot clinical trial aimed at evaluating the efficacy and toxicity of thalidomide as salvage single agent therapy (Table 1). Autologous PBSCT was performed after VAD remission induction chemotherapy² administered for 4 courses followed by collection of PBSC upon priming with cyclophosphamide 7 g/m² combined with G-CSF, 5 μ g/kg daily. Preparative regimens to autologous SCT were melphalan 200 mg/m² (first transplant) or a combination of busulfan 12 mg/kg and melphalan 120 mg/m² (second transplant). Double autologous PBSCT was performed as front-line therapy in 3 patients; the other four patients received a second transplant as salvage therapy for relapse occurring after their first transplant. In 8 patients, conventional chemotherapy with melphalan and steroids, anthracycline-containing regimens, intermediate-dose cyclophosphamide or high-dose steroids was administered upon relapse after transplant; 5 of these patients were refractory, while 3 patients showed a transient response. The median times to thalidomide therapy from diagnosis and from post-transplant relapse were 51 and 16 months, respectively.

Thalidomide therapy

Thalidomide was purchased from Penn Pharmaceuticals Ltd. (Tredegar, Gwent, UK) as 100 mg capsules. Therapy was started at 100 mg once daily for one week and was subsequently increased by 200 mg every other week, to a maximum of 800 mg/day in two divided doses. Treatment was stopped after 8 weeks in case of no response, otherwise it was continued at the maximum tolerated dose. No other antimyeloma therapy was added to thalidomide. If grade \geq 2 WHO toxicity developed, the dose of thalidomide was reduced; drug administration was to be stopped in case of grade \geq 3 WHO toxicity.

Clinical and laboratory evaluation

Physical examination, quality of life assessment, blood cell counts, serum electrolytes, serum levels of immunoglobulins, and Bence-Jones proteinuria were evaluated before treatment and every other week thereafter. Bone marrow trephine biopsy was performed prior to treatment and microvessel density was evaluated by staining with the following monoclonal antibodies: anti CD34, anti CD31 and anti factor VIII related antigen, as described elsewhere.^{7,13}

Toxicity and adverse events occurring during thalidomide therapy were evaluated according to the WHO grading system.

Assessment of tumor response

Response to thalidomide was assessed according to the criteria established by the Chronic Leukemia-Myeloma Task Force.¹⁴ Relapse was defined as \geq 25% increase from minimal tumor mass and/or other unequivocal signs of disease progression, including soft-tissue plasmacytomas.

Results

Response evaluation

Four patients (#1, 3, 6 and 8) showed more than 50% reduction in serum M component concentration, while in four more patients (#5, 7, 9 and 10) a decrease $>$ 25% was observed; the total response rate was thus 72%. Three patients were refractory. Figure 1 shows the kinetics of serum M component reduction in MM patients responsive to thalidomide. Maximal M component decrease was observed at a median of two months after the start of therapy.

Post-treatment bone marrow evaluation in responsive patients showed a hypocellular picture, while microvessel density was not significantly modified after thalidomide treatment.

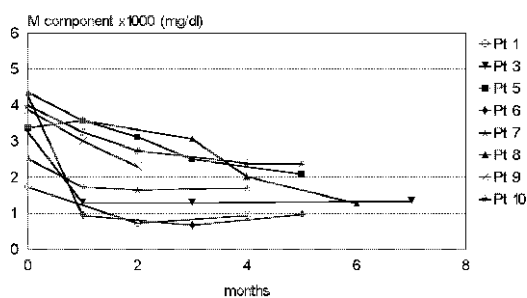


Figure 1. Kinetic course of serum M component upon thalidomide therapy in responsive patients.

Toxicity

The median administered dose of thalidomide was 600 mg/day; 2 patients tolerated the full planned dosage, the other patients required a dose reduction because of leukopenia (1 case), lethargy \pm constipation (5 cases) leg edema (2 cases) or skin rash (1 case). After dose reduction, thalidomide was well tolerated, and did not adversely affect the patients' quality of life.

Clinical follow-up

The clinical outcome of the thalidomide-treated patients is reported in Table 2. The median response duration was 5 months. With a median follow-up of 5 months, 5 out of 8 responding patients relapsed after a median of 4 months, while 3 patients have maintained their best response. Interestingly, in 2 of the patients who have relapsed, the M component remained stable, but a progressively worsening pleural plasmacytosis developed. This finding is similar to that reported by Juliusson *et al.*¹⁵ who observed an extramedullary MM localization occurring during serological response to thalidomide.

Discussion

Thalidomide is a glutamic acid derivative with sedative properties. After discovery of its teratogenic potential in the early sixties, its use was abandoned. Later on, the drug was employed in different settings, including cutaneous lepromatosis,¹⁶ AIDS-related aphthous ulcers¹⁷ and wasting syndrome,¹⁸ cutaneous lesions of systemic lupus erythematosus¹⁹ and cutaneous and pulmonary sarcoidosis.²⁰ Interest in the drug has been renewed by demonstration of its activity in controlling chronic graft-versus-host disease;^{21,22} further studies conducted in a smaller number of patients have confirmed these data,²³ even though poor tolerance renders the drug difficult to administer to patients submitted to allogeneic BMT. Thalidomide seems to possess a wide variety of different effects, including modulation of cellular immunity, inhibition of production of cytokines such as tumor necrosis factor- α , interleukin-6 and interleukin-12,²⁴⁻²⁶ and inhibition of angiogenesis.²⁷

Table 2. Response evaluation and toxicity.

Pt	Max. tolerated dose (mg)	WHO>2 toxicity	M comp. decrease (%)	Response duration (mos)	Survival duration (mos)	Status
1	600	leukopenia	51	4	5	dead, pleural plasmacytosis
2	800	none	-	-	3	dead, infection
3	800	none	61	7	7+	alive, disease progression
4	400	lethargy	-	-	7	dead, disease progression
5	600	lethargy	40	5	11+	alive, disease progression
6	600	constipation	85	9+	9+	alive, well
7	600	constipation + lethargy	34	2	2	dead, pleural plasmacytosis
8	300	skin rash	64	7+	7+	alive, well
9	200	leg edema	41	4	5+	alive, well
10	300	constipation + lethargy	41	5+	5+	alive, well
11	150	leg edema	-	-	3+	alive, well

Some of these effects could be responsible for the activity of thalidomide in MM as they could potentially interfere with MM cell growth and disease progression. Interleukin-6 is known to be the major growth factor for MM cells,²⁸ so that inhibition of interleukin-6 production could represent one of the most important determinants of thalidomide-mediated cell growth inhibition even *in vivo*, as postulated by Hideshima *et al.*¹⁰ Also the anti-angiogenic potential of thalidomide could be important in defining the activity of the drug. In fact, angiogenesis plays a central role in tumor progression in several malignancies;²⁹ in particular, active MM is characterized by enhanced bone marrow neovascularization and increased angiogenic potential of neoplastic plasma cells,³⁰ a finding that supports the use of thalidomide in this setting.

A recent study by Singhal *et al.*⁷ demonstrated that thalidomide is active in heavily pre-treated MM patients; further studies performed in a smaller number of patients substantially confirmed the data.^{8-11,15} Our group has evaluated the drug in a small series of patients who had previously received autologous stem cell transplantation, and we have obtained an overall response rate exceeding 70%. It could be argued, however, that the response duration has been short, though in line with data reported elsewhere.^{8-11,15} As far as this last issue is concerned, it should be underlined that patients who entered our protocol had already received intensive cytotoxic therapy, and the majority of them had also been treated with one or more courses of conventional chemotherapy upon relapse after transplant. Thus, our data deserve consideration as they have been obtained in patients for whom virtually no alternative therapeutic options were available, as further conventional

chemotherapy or sub-myeloablative treatment either were not applicable or could have led to unacceptable toxicity. Thalidomide, on the other hand, was extremely well tolerated, with lethargy and constipation being the most pronounced side effects. No therapy-related deaths were observed. Tolerance could be further improved using lower drug doses, which could be potentially as effective as high ones.³¹ Even though a larger number of patients needs to be treated before definite conclusions can be drawn, the results reported here encourage a wider use of thalidomide in MM patients relapsing after high-dose (sub)myeloablative therapy. Furthermore, in order to enhance the activity of thalidomide, the potential efficacy of drug combinations should be exploited. The association of high dose dexamethasone with thalidomide seems to be highly effective in refractory/relapsed MM³² and even in patients who had been previously shown resistant to dexamethasone.³³ As demonstrated by Hideshima *et al.*,¹⁰ thalidomide and its analogs were able to increase dexamethasone-induced cytotoxicity and apoptosis in MM cells; in addition the drug did not show cross resistance with other antineoplastic agents, thus rendering it suitable for a variety of drug combinations, that could be potentially tested *in vivo*.

Contributions and Acknowledgments

PT and MC designed the trial; PT, SR, EZ, TG and DC cooperated in patient follow-up and data interpretation, SAP evaluated all bone marrow biopsies with specifically designed staining techniques, ST, MB and MC gave their final approval of the version to be submitted.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Boccadoro, who acted as an Associate Editor. The final decision to accept this paper was taken jointly by Prof. Boccadoro and the Editors. Manuscript received December 11, 2000; accepted February 26, 2001.

Potential implications for clinical practice

Thalidomide is effective and safe in MM patients relapsing after autologous stem cell transplantation. The drug could be proposed in combination therapy with conventional antineoplastic agents, even in untreated patients.

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