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Salvage therapy with thalidomide in patients with advanced relapsed/refractory multiple myeloma

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Background and Objectives. Few therapeutic options are presently available for patients with multiple myeloma (MM) who relapse after autologous or allogeneic stem cell transplantation, or for patients who are refractory to conventional chemotherapy and not eligible for salvage high-dose therapy. Thalidomide, a glutamic acid derivative with anti-angiogenic properties, has been recently proposed as an effective therapy for patients with advanced refractory disease. The aim of this study was to evaluate the activity of thalidomide in a large series of MM patients.

Design and Methods. From October 1999 to January 2001, 65 patients (46 males/19 females) from 8 Italian institutions were treated with thalidomide. Twenty-six patients had relapsed after autologous stem cell transplantation, either single (n = 12) or double (n= 12); 38 patients had shown disease progression after ≥ 2 lines of conventional chemotherapy, 2 patients had relapsed after allotransplant, one single patient had not received previous treatment. Sixty-one (93.8%) patients were in stage III, median β2 microglobulin was 2.9 mg/L, and median bone marrow plasma cell infiltration was 50%. Thalidomide was initially administered at a dose of 100 mg/day; if well tolerated, the dose was to be increased serially by 200mg every other week to a maximum of 800 mg/day.

Results. The median administered dose of thalidomide was 400 mg/day. WHO grade > II toxic effects were constipation (52%), lethargy (34%), skin rash (11%), peripheral neuropathy (14%) and leukopenia (3%). Sixty patients are presently evaluable for response; of these, 17 (28.3%) showed ≥ 50% reduction in serum or urinary M protein concentration and 11 (18.3%) showed ≥ 25% tumor reduction, for a total response rate averaging 46.6%. After a median of 8 months' follow-up, 15/28 patients are alive and progression-free (at 2 to 16 months), 12 patients have relapsed, and 1 patient died of pulmonary edema while still in partial remission. Among pre-treatment variables that were analyzed for their potential relationship with tumor response, only the concentration of vascular endothelial growth factor (VEGF) in the conditioned media obtained upon culture of bone marrow plasma cells was statistically significant. Plasma cells from patients who responded favorably to thalidomide secreted a significantly lower amount of VEGF than plasma cells from resistant patients (126.45±165 pg/mL vs 227.11±70 pg/mL, p=0.04).

Interpretation and Conclusions. These data confirm that thalidomide is active in patients with advanced relapsed/refractory MM and represent the basis for ongoing clinical trials aimed at testing the role of this drug as front line therapy for newly diagnosed disease.

Key words: thalidomide, multiple myeloma, salvage therapy.

Multiple myeloma (MM) is a B-cell malignancy characterized by proliferation and accumulation of B-lymphocytes and plasma cells, in the bone marrow and, more rarely, in extramedullary sites.[1,2] Conventional chemotherapy, with either standard melphalan – corticosteroids or combined cytotoxic drug combinations or infusional regimens, leads to largely unsatisfactory results, since the complete remission rate

is less than 10% and median survival does not exceed 3 years.[3] Recently, widespread introduction of high-dose therapy followed by autologous[4,5] or allogeneic[6,7] stem cell support, has significantly improved patients' outcome, even though some categories of patients, namely those with chromosome 13q deletion, do not seem to benefit from these therapeutic strategies.[5] However, the relapse rate remains high in all patients even after transplantation, and this raises the issue of whether the myeloma clone can really be eradicated. In light of the above data, novel therapeutic strategies, targeting both myeloma cells and their microenvironment, are needed in an attempt to overcome chemoresistance. Recently, it has been reported that angiogenesis plays a central role in the progression of MM,[8,9] as active disease is characterized by increased bone marrow neovascularization, paralleled by increased angiogenic potential of neoplastic plasma cells, mediated by secretion of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Inhibition of angiogenesis could thus be worth exploiting in MM therapy.

Thalidomide is a glutamic acid derivative that exerts a potent antiangiogenic activity in experimental systems,[10-12] probably by inhibiting bFGF and VEGF activity.[10, 13] Furthermore, the drug has shown a broad spectrum of different effects, including modulation of T-cell activity, with induction of Th2 response and production of interleukin (IL)-2 and γ-interferon.[14] In addition, the compound acts on bone marrow stromal cells inhibiting the production of cytokines, such as tumor necrosis factor (TNF)-α,[15] IL-6 and IL-12.[16] In 1999 Singhal *et al.*[17] first reported on the efficacy of thalidomide in 84 heavily pre-treated MM patients. Other groups[18-21] subsequently confirmed these data, although in generally smaller series of patients, and using different drug dosages. We report here on the results obtained using thalidomide at the maximum tolerated dose in a larger series of patients with advanced, relapsed and refractory MM, including those with post-transplant relapses.

Design and Methods

Patients

Between October 1999 and March 2001 65 patients from 8 Italian centers were enrolled in a phase II trial of thalidomide as salvage therapy for advanced, relapsed and refractory MM (Table 1). Their median age was 63 years, 75% of patients were males, and 94% were in stage III. The median time from diagnosis to thalidomide therapy was 44 months (range 0-192 months); previous therapy included autologous stem cell transplantation in 24 patients (37%), either single (12 patients) or double (12 patients), or allotransplant in 2 patients; 38 patients had been treated with conventional chemotherapy (2-9 lines, median 3 lines), while one patient was enrolled at diagnosis because poor clinical conditions had prevented the use of chemotherapy. Disease status at study entry was evaluated with respect to the last line of treatment the patient had received before thalidomide therapy; 38.5% of patients were classified as refractory, based on < 25% reduction in serum or urinary M protein; 55.4% as progressive, based on > 25% increase in tumor mass and/or appearance of new lytic bone lesions; and 4.6% of patients were classified as responsive (> 25% reduction in serum or urinary M protein but with unacceptable systemic toxicity).

Table 1. Patients' characteristics.

		%
Total number	65	100
M/F	46/19	
Median age (range)	63 yrs. (35-78)	
Ig type		
IgG	49	75.4
IgA	10	15.4
Bence Jones	5	7.7
IgD	1	1.5
Light chain		
κ	45	69
λ	20	31
Stage		
I	2	3.1
II	2	3.1
III	61	93.8
Median time from diagnosis (range)	44mo (0-192)	
Median β2 microglobulin (range)	2.9 (1.8-14)	
Median C reactive protein (range)	0.48 (0.05-43.8)	
Median lactate dehydrogenase	330 (109-909)	
Median % BMPC	50 (10-100)	
Previous therapy		
single auto transplant	12	18.5
double auto transplant	12	18.5
allo transplant	2	3.1
CHT ≤ 2 lines	18	27.7
CHT ≥ 3 lines	20	30.7
none	1	1.5
Patients' status (*)		
Responsive	3	4.6
Refractory	25	38.5
Progressive	36	55.4
de novo	1	1.5

**With respect to the last chemotherapy course, patients were classified as responsive (showing a > 25% response), refractory (< 25% response) or progressive (> 25% paraprotein increase).*

Table 2. Response to treatment.

M component reduction	*Nr. patients (%)*	*Nr. evaluable* (%)*
≥75%	5 (7.6)	5 (8.3)
≥50%	12 (18.5)	12 (20)
≥25%	11 (16.9)	11 (18.3)
Total	28 (43.1)	28 (46.6)
Median response duration (mo)	6 (2-16+)	–
No response	37 (56.9)	32 (53.3)
Stable disease	18 (27.6)	18 (30)
Median duration (mo)	4	–

**Patients who completed at least 6 weeks of treatment.*

Treatment protocol

Thalidomide was kindly provided by Grunenthal GmBH, Stolberg, Germany, as 100 mg capsules. After patients had signed the appropriate informed consent forms, treatment 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. Treatment was stopped after 9 weeks in case of disease progression, otherwise it was continued at the maximum tolerated dose. Toxicity and adverse events occurring during thalidomide therapy were evaluated according to the WHO grading system. Occurrence of grade ≥ 2 WHO toxicity prompted a thalidomide dose reduction, whereas drug administration was to be stopped in case of ≥ 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 weekly thereafter. Bone marrow aspirate was evaluated prior to treatment and subsequently in the case of response to treatment.

Assessment of tumor response

Response to thalidomide was assessed after at least 6 weeks of treatment and was based upon the criteria established by the Chronic Leukemia-Myeloma Task Force.[22] Relapse was defined as ≥ 25% increase from minimal tumor mass and /or other unequivocal signs of disease progression, including soft-tissue plasmacytomas, or appearance of new skeletal osteolytic lesions.

Cytokine secretion

Ten milliliters of heparinized bone marrow was obtained at study entry. Mononuclear cells were collected after sedimentation on Ficoll Hypaque (Lymphoprep, Nycomed Pharma, Oslo, Norway) and subsequently resuspended in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS), 1% glutamine and 1% penicillin + streptomycin. After 2 hours of adherence in 25cm^2 plastic flasks, non-adherent cells, mainly plasma cells and B lymphocytes, were collected and resuspended in RPMI 1640 medium without FCS. Next, 10×10^6 cells were seeded in 25 cm^2 plastic flasks and placed in a humidified incubator at 37°C in an atmosphere of 5% CO_2. After 36-48 hours of incubation, culture medium (= plasma cell conditioned medium) was centrifuged at 12,000 rpm for 10', filtered through a 0.22 μm membrane and frozen at -80°C until analysis. bFGF and VEGF secretion was evaluated by ELISA testing (R&D Systems) according to the manufacturer's directions.

Statistical analysis

Kaplan-Meier analysis[23] was used to estimate disease-free and overall survival, which were calculated from the beginning of treatment with thalidomide. Fisher's exact test was used to evaluate the association between baseline characteristics and response achievement. Student's t test was used to compare VEGF and bFGF secreted by plasma cells of patients sensitive or resistant to thalidomide. *p* values were always two-tailed and were considered statistically significant when less than 0.05

Results

Response

Out of 65 patients, 60 were considered evaluable for response, as they completed at least 6 weeks of treatment (Table 2). Reduction in serum or urinary M protein concentration was ≥ 75% in 5 patients (8.3%), between 50% and 74% in 12 patients (20%) and below 50% but higher than 25% in 11 patients (18.3%); thus, the overall response rate was 46.6%. Maximal response was achieved at a median of 8 weeks of treatment (range 5-13 weeks). Thirty-two patients did not show response to treatment; of these, 18 had either < 25% decrease in serum or urinary M component or no signs of disease progression, for a median of 4 months (range 3-10 months). Post-treatment bone marrow evaluation was performed in 15 out of 28 responsive cases, 12 of them showed a reduction in bone marrow plasma cell infiltration consistent with M protein decrease. None of the baseline values that have been described to possess a prognostic significance after thalidomide treatment[25] was associated with a favorable response in the present series of patients (Table 3).

Table 3. Relationship between patients' baseline characteristics and response to thalidomide therapy.

	Sensitive N = 28		*Resistant N = 37*		*p*
	Total	*%*	*Total*	*%*	
Hb < 10 g/dL	13	46	17	46	Ns
C reactive protein > 3 mg/L	2	7	5	13	Ns
β^2 microglobulin > 3 mg/L	12	43	16	43	Ns
LDH > 400 U/L	9	32	11	30	Ns
BMPC > 30%	20	71	27	73	Ns
IgG type	21	75	24	65	Ns
κ light chain	22	79	27	73	Ns
Previous transplant	13	46	13	35	Ns
Refractory disease*	11	39	14	38	Ns

**With respect to the last chemotherapy course.*

Table 4. Adverse events and treatment interruction.

	Grade > 2 Toxicity (%)	*Treatment interruption (%)*	*Treatment resumed*
Constipation	34 (52.3)	3 (4.6)	–
Lethargy	22 (33.8)	–	1
Neurological toxicity	9 (13.8)	2 (3.0)	–
Skin rash	7 (10.7)	3 (4.6)	1
Renal toxicity	3 (4.6)	1 (1.5)	
Edema	2 (3.0)	–	–
Leukopenia	2 (3.0)	1 (1.5)	1
DVT	1 (1.5)	1 (1.5)	–
Other	3 (4.6)	–	–
None	2 (3.0)	–	–

Toxicity

Distribution of the maximum tolerated dose of thalidomide is reported in Figure 1. Only 2 patients could tolerate the full planned drug dose, while in the majority of the cases occurrence of WHO grade ≥ 2 toxic effects prevented further dose escalation or prompted dose reduction. As reported in Table 4, constipation and lethargy were the most frequent adverse events encountered during thalidomide therapy. Neurologic toxicity, mainly dizziness, tingling and numbness, was observed in 9 patients; this was mainly a late-onset toxic effect as none of the patients showed neurologic toxicity during the initial period of treatment. Seven patients showed disappearance of the symptoms upon dose reduction, but in 2 patients thalidomide treatment had to be stopped with no improvement in one of them. Seven patients experienced a skin rash, in 3 cases treatment was interrupted and in 2 of them

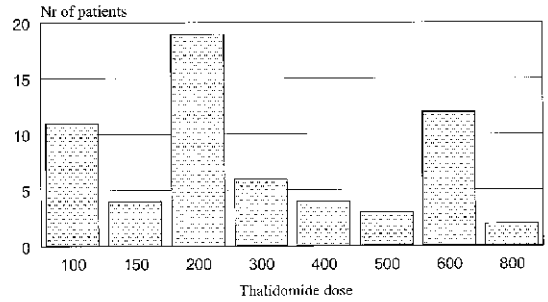

Figure 1. Distribution of the maximum tolerated dose of thalidomide.

it was not resumed. Three patients showed an increase in serum creatinine levels; in one patient interruption of thalidomide administration was immediately followed by an increase in serum or urinary M component, so that this effect should probably be more correctly attributed to disease progression. In the remaining two patients creatinine increased during the course of an infectious episode. Deep venous thrombosis (DVT) was recorded in one case (1.5%).

In the majority of the cases toxic effects were grade < 3 according to the WHO grading system, so that dose reduction was performed. In 11 patients (16.9%), treatment was interrupted due to occurrence of grade ≥ 3 toxicity; 3 patients were subsequently re-treated at a lower dose with no recurrence of side effects.

Cytokine secretion

bFGF and VEGF secretion by bone marrow plasma cells was evaluated by ELISA testing (Figure 2) in 24 patients at study onset. While bFGF secretion in plasma cell conditioned media did not differ in thalidomide sensitive and resistant cases, VEGF secretion was significantly lower in sensitive cases (126.45±165 pg/mL vs 227.11±70 pg/mL, p=0.04).

Patients' status and survival

The median duration of response was 8 months (range 2-16+ months) (Figure 3). After a median follow-up of 9 months, 15 responding patients are alive and progression-free, 12 patients showed disease progression, 7 of whom are alive while 5 have died. In 4 out of 12 relapsed cases, disease progression did not occur as an increase in serum or urinary M component, but with the appearance of new skeletal lesions (2 cases) or occurrence of plasma-cell pleural effusion (2 cases). This discrepancy

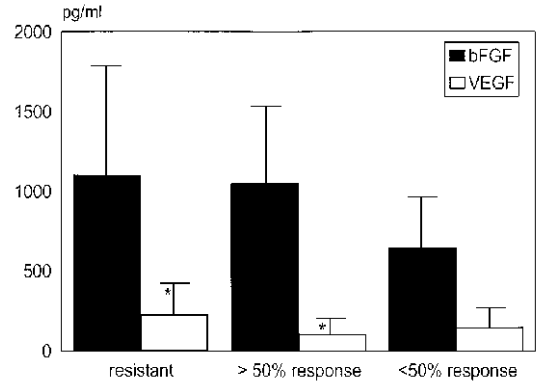

Figure 2. VEGF and bFGF secretion by bone marrow plasma cells as evaluated by ELISA testing of cell supernatant. At diagnosis, plasma cells isolated from bone marrow of patients who subsequently showed a > 50% paraprotein response, secreted a significantly ($p = 0.04$) lower amount of VEGF than plasma cells harvested from patients who were resistant to thalidomide.

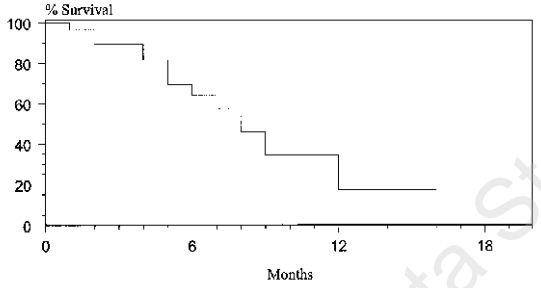

Figure 3. Event-free survival of responsive patients.

has already been reported by other groups[20] and probably parallels the lack of response in soft-tissue plasmacytomas that has also been described.[24] One patient died of pulmonary edema while still in partial remission. At variance to what has been reported elsewhere[25] event-free survival and overall survival were not different in patients showing higher β_2 microglobulin and C-reactive protein levels as well as >30% bone marrow plasmacytosis.

Discussion

Thalidomide has been demonstrated to be highly effective in patients with advanced, relapsed/refractory MM. The efficacy of the drug is equal, if not superior, to that shown by any other conventional or high dose therapy regimen[26,27] when used in the same category of patients. Furthermore, even though very few patients can generally tolerate 800 mg/day, side effects reported at lower doses are mild; specifically, according to our study, only 8 patients had to stop the therapy definitely, and it should be taken into account that in these heavily pretreated patients tolerance to conventional cytotoxic chemotherapy is poor due to reduced marrow reserve and multi organ toxicity. Our findings, together with those reported by other groups,[17-21] contribute to establishing that thalidomide is a useful weapon in the therapeutic scenario of MM.

Several issues concerning thalidomide therapy in MM, however, still need to be elucidated. First, it has not been clarified yet whether the activity of this compound is related to the administered dose, so what the optimal drug dosage should be is still a matter of debate. Barlogie *et al.*,[25] updating the results of the Arkansas trial, demonstrated that the cumulative dose at three months represents a predictor of response; conversely, other groups[28] have shown that responses can be achieved at doses as low as 200 mg/day and even at 50 mg/day.[29] Our present data indicate that refractory and sensitive patients did in fact receive the same median drug dose (300mg/day). Secondly, the mechanism of action of thalidomide in MM, as well as in other hematologic malignancies, is presently unknown. After wide testing in relapsed/refractory patients, trials are presently ongoing, using thalidomide as first-line therapy in MM. Rajkumar *et al.*[30] has shown a 38% response rate in untreated patients with smoldering MM; this is comparable to the rate obtained in pretreated patients. These results support the concept that thalidomide exerts its antineoplastic activity through pathways that are different from those followed by conventional cytotoxic chemotherapy. Whether bone marrow angiogenesis is really perturbed by thalidomide, however, is still under investigation. Early observations by Singhal *et al.*[17] showed no difference in bone marrow microvessel density (MVD) comparing bone marrow biopsies of sensitive and resistant patients. Conversely, Cheng *et al.*[31] demonstrated that an increased pre-treatment MVD could predict response to therapy. VEGF secretion by MM cell lines is not influenced by *in vitro* treatment with thalidomide according to Rajkumar *et al.*,[32] while Weber *et al.* demonstrated that VEGF serum levels were higher in responding patients,[33] and our results show that the activity of thalidomide is superior in patients whose plasma cells secrete lower amounts of VEGF. Given these contrasting findings, although inhibition of bone marrow

angiogenesis has been claimed to be the major mechanism of thalidomide action in MM, other mechanisms are presumably involved. Thalidomide is able to induce apoptosis of bone marrow plasma cells upon *in vivo* treatment[34] and to possess immunomodulatory activity, by stimulating T-cell proliferation and increasing NK-cell-mediated cytotoxicity.[35] Cytokine production, both by T-cells (IL- 2 and γ-interferon) and by stromal cells (TNF-α), can also be influenced by thalidomide and could thus potentially play an important role in determining the activity of this compound. The hypothesis that the effects of thalidomide represent the results of co-operation of multiple pathways could be supported by the relatively rapid response (1-2 months) that can be achieved in sensitive patients.

Finally, clinical results that have been obtained so far prompt a wider and prolonged use of thalidomide in MM patients, and this raises the issue of long-term toxicity: it should not be overlooked that the incidence of neurologic toxicity increases after long-term thalidomide therapy.[25] These problems may be solved in the near future with the use of novel thalidomide derivatives that possess an efficacy comparable to that shown by the parent drug coupled with less toxicity: results of wider testing of these compounds are thus awaited.

Contributions and Acknowledgments

PT, EZ, CC, FP, PM, FDR, FL, MG, MC designed the trial, analyzed the results and drafted the paper; SR, FB, AL, LM and DC co-operated in patients' follow-up and in data interpretation; AV and RR performed all the laboratory studies on angiogenesis; ST, MB and MC gave the final approval of the version to be submitted.

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Disclosures

Conflict of interest: none.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor S. Vincent Rajkumar, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Rajkumar and the Editors. Manuscript received November 5, 2001; accepted February 8, 2002.

What is already known on this topic

Recent studies have shown that thalidomide is effective in 20-25% of patients with relapsed, refractory multiple myeloma.

What this study adds

This study confirms the effectiveness of thalidomide in relapsed/refractory myeloma. In addition the study shows that the amount of vascular endothelial growth factor secreted by plasma cells may be a predictor of response to thalidomide therapy.

Potential implications for clinical practice

The activity of thalidomide in advanced myeloma has been confirmed and represents an important advance in the treatment of this disease.

S. Vincent Rajkumar, Associate Editor