Primary treatment with pulsed melphalan, dexamethasone and thalidomide for elderly symptomatic patients with multiple myeloma

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Fifty patients with multiple myeloma ≥75 years of age received primary treatment with melphalan (M) 8 mg/m^2 on days 1-4, dexamethasone (D) 12 mg/m^2 on days 1-4 and 17-20 and thalidomide (T) 300 mg at bedtime on days 1-4 and 17-20. This regimen was repeated every 5 weeks for three courses. Patients without evidence of disease progression received nine additional courses of MDT, but without DT on days 17-20, every 5 weeks. Sixty-two percent of patients achieved a partial response and 10% a complete response. The median time to response was 2 months. The median time to progression for all patients was 21.2 months. Deep venous thrombosis and peripheral neuropathy each occurred in 9% of patients.

Key words: multiple myeloma, elderly, thalidomide

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High-dose therapy supported by autologous stem cell transplantation may improve the survival of patients with multiple myeloma (MM) and is usually applied to patients up to 70 years of age.[1-3] Older patients are not usually candidates for high-dose therapy. Standard therapy has improved such patients' outcome but their median survival is usually less than 2 years.[4-6] Thus, such patients are candidates for trials which include novel agents. Thalidomide is usually administered orally continuously once daily and has shown activity in 30% of patients with heavily pretreated MM.[7] Moreover, when thalidomide-containing combinations are administered as primary treatment of MM, they induce objective responses in 60-80% of patients.[8] Thalidomide can cause side effects whose incidence and severity may be related to the maximum dose and duration of thalidomide treatment. Furthermore, this drug may be poorly tolerated by older patients.[9] We have previously shown that intermittent administration of thalidomide combined with cyclophosphamide and dexamethasone pulses is effective and well tolerated in previously treated patients with MM.[10] In our current study we evaluated the efficacy and the tolerability of the intermittent administration of melphalan, dexamethasone and thalidomide (MDT) as primary treatment for patients with MM ≥75 years of age.

Design and Methods

This study included patients with previously untreated MM who were ≥75 years old and who had an indication for treatment. Patients were included regardless of performance status, renal function and presence of comorbid conditions. Patients who presented with a deep vein thrombosis (DVT) were treated with low molecular weight heparin (LMWH) and were included in the study. All patients provided informed consent according to institutional guidelines. All patients were staged according to the International Staging System (ISS) which consists of the following stages: stage I, serum β2 microglobulin <3.5 mg/L plus serum albumin ≥3.5g/dL; stage II, neither stage I nor III; stage III, serum β2 microglobulin ≥5.5mg/L.[11] DVT and peripheral neuropathy were assessed clinically before initiation of treatment and before each course of MDT. A clinical suspicion of DVT was confirmed by venous ultrasound. Treatment consisted of melphalan 8 mg/m^2 p.o. on days 1-4, dexamethasone 12 mg/m^2 p.o. on days 1-4 and 14-18 and thalidomide 300 mg p.o. on days 1-4 and 14-18. This regimen was repeated every 5 weeks for three courses. Subsequently, patients without evidence of progressive disease were scheduled to receive nine additional courses of MDT but without dexamethasone and thalidomide on days 14-18. These courses were repeated every 5 weeks. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria. All patients who received MDT for at least one day were eligible for assessment of response. Patients who discontinued treatment before a response could be assessed were considered to have had no response to treatment (intent-to-treat analysis). Response was evaluated according to the EBMT criteria.[12] The time to response was defined as the interval between the start of therapy and the first documentation of a partial response. The time to progression was defined as the time from the start of therapy to disease progression. Overall survival was calculated from the start of therapy to death from any cause or the last follow-up visit.

Results and Discussion

Between February 2003 and October 2004, 50 previously untreated patients ≥75 years of age with symptomatic MM were treated with MDT. The final analysis of the study was performed in October 2005. Patients and disease features are shown in Table 1. In three patients clinically evident DVT of the lower limbs was detected before the initiation of MDT. These patients were treated with LMWH in addition to entering the MDT trial. The DVT resolved and the patients continued anticoagulation while receiving treatment with MDT. On an intent-to-treat basis 36 patients (72%) achieved an objective response to treatment: 62% of patients achieved a partial response and 10% of patients achieved a complete response with negative immunofixation. The median time to 50% reduction of monoclonal protein was 2 months (range: 0.5 to 14 months). Several variables such as gender, age, myeloma heavy and light chain type, hemoglobin, platelet count, serum lactate dehydrogenase (LDH), performance status, bone marrow plasmacytosis, and ISS were evaluated for their possible correlation with response to MDT. None of these variables was associated with higher or lower likelihood of response. Seventeen patients (34%) received the planned 12 courses of MDT, six patients (12%) received nine courses, five patients (10%) received six or seven courses, eight patients (16%) received four or five courses, eight patients (16%) received two or three courses and six patients (12%) received only one course. Among the 33 patients who received less than 12 courses, the reasons for this deviation were progressive disease during treatment (9 patients), unrelated death or development of second primary malignancy (6 patients), physicians' decision and/or protocol violation (5 patients) and side effects or complications that were attributed to the treatment (11 patients). These included fatigue and asthenia in four patients, severe infections in three patients, uncontrollable diabetes, severe somnolence, severe tremor, gait imbalance and Budd-Chiari syndrome in one patient each.

The median time to progression for all patients is 21.2 months (Figure 1). Multiple variables were evaluated for their possible correlation with the probability of progression but none showed a statistically significant correlation. For patients who achieved an objective response, the median time to progression was 25 months. The median overall survival was 28.2 months. The 3-month and 6-month death rate was 4% and 14%, respectively. Seventeen patients have died including five patients whose cause of death was not directly related to myeloma or to the treatment: cerebral bleeding in two patients, non-pathologic hip fracture in two patients and brain tumor in one patient. The only variable associated with overall survival was serum LDH, the median survival being 11 months when LDH was elevated and 31 months when it was normal (p=0.02).

Side effects after treatment with MDT are shown in Table 2. Four episodes of neutropenic fever were noted, one of which was fatal. Thirty non-neutropenic infectious episodes were noted. Most of these were upper respiratory tract infections, although two patients developed non-neutropenic septicemia. As far as concerns thrombosis, three patients presented with DVT and one patient was already on coumadin because of atrial fibrillation. Four patients developed clinically evident DVT after treatment. This represents 9% of 46 evaluable patients (Table 2). Furthermore, if the six patients who received only one course of treatment are excluded from the denominator the incidence of DVT after MDT was 10%. The four patients who developed DVT after MDT were treated with LMWH and were able to continue the MDT regimen. Clinically evident peripheral neuropathy developed after treatment in four patients. This side effect was grade 1 in three patients and grade 2 in one patient. If the six patients who received only one course of treatment are excluded, the incidence of peripheral neuropathy was 9% (Table 2). This incidence increased to 11% among the 36 patients who received four or more courses of MDT. The incidence and severity of neuropathy did not increase

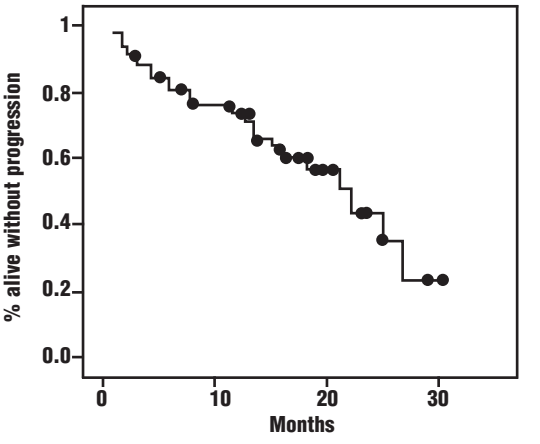

Figure 1. Time to progression after MDT.

Table 1. Patients and disease characteristics.

Patient (n.)	*50*
Male/Female (n.)	29/21
Median age (years)	77
range	75-85
Myeloma type (%)	
IgG	56
IgA	36
Light chain only	4
IgD	2
Non secretory	2
Performance status (%)	
0,1	44
2,3,4	56
Hemoglobin<10 g/dL (%)	50
Calcium>11.5 mg/dL (%)	18
LDH>250 IU (%)	16
Creatinine>2 mg% (%)	26
BM plasma cells> 40% (%)	70
International Staging System (%)	
1	10
2	32
3	58

Table 2. Toxicity after MDT.

	Percent with grade	
	1,2	3,4
Neutropenia	27	22
Thrombocytopenia	18	10
Somnolence	47	4
Constipation	51	0
Tremor	22	2
Ataxia	0	2
Xerostomia	20	0
Headache	22	0
Skin	11	0
Deep vein thrombosis	0	9
Peripheral neuropathy	9	0

with prolonged administration of MDT. Dysregulation of blood glucose was noted in six patients and one patient experienced diarrhea after each course of MDT.

Our study is one of few designed specifically for myeloma patients aged ≥75 years old. Patients were included regardless of perfrormance status, renal function and presence of comorbid conditions. We observed that our pulsed MDT regimen was associated with a high response rate. Responses occurred regardless of the presence of adverse features such as advanced ISS and high levels of serum LDH. Furthermore the median time to progression for all patients was 21.2 months. The high activity of our regimen is in accordance with the results of an ongoing study reported by Palumbo *et al*. who randomized patients to primary treatment with melphalan and prednisone (MP) with or without thalidomide (MPT).[13] An analysis of 177 patients with a median age of 72 years (range 56-85 years) indicated that patients treated with MPT had a higher response rate (77.1 % versus 46.7%) and a longer event-free survival (25.2 months versus 13.7 months) than patients treated with MP. In our study, the median time to 50% reduction of monoclonal protein was 2 months. This fast rate of monoclonal protein reduction is likely due to thalidomide. Rapid control of myeloma may be of particular importance in elderly patients with MM because such patients tend to have a high early mortality rate.[3,4] Another ongoing study is focusing on previously untreated patients with MM 65 to 75 years old and is randomizing patients to receive standard MP, MP with thalidomide or two courses of intermediate dose intravenous melphalan (100 mg/m^2). So far the MPT arm has produced at least a partial response in 84% of patients versus 34% in the MP arm.[14] Compared to the studies of Palumbo *et al*. and Facon *et al*. the more intensive corticosteroid schedule that we used does not seem to be associated with any major benefit. Furthermore, the higher doses of corticosteroids were also potentially associated with more adverse effects such as diabetes. Our pulsed MDT regimen was relatively well tolerated. Twenty to 50% of our patients developed complications that usually occur with thalidomide. However these were mild and manageable. The most problematic adverse effects of thalidomide are DVT and peripheral neuropathy. DVT occurred in 9% of our patients. This complication has been reported in 19% and in 12% of elderly patients with myeloma who were receiving MP with continuous thalidomide.[13,14] As far as peripheral neuropathy is concerned we documented this complication in 9% of our patients. This incidence appeared lower than the 32% and 36% incidence of neuropathy reported in the other studies.[13,14]

We conclude that the pulsed MDT regimen was active and relatively well tolerated. It provided an opportunity for disease control in most of our elderly patients for whom treatment options are limited. However the definitive conclusion regarding the role of thalidomide in this age group will come from the French IFM 01-01 trial which is randomizing patients >75 years of age to MP + thalidomide or to MP + placebo.

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