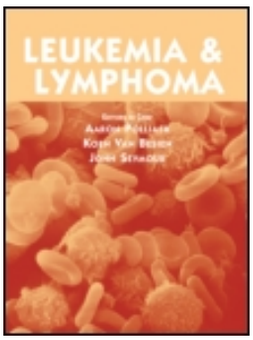

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Melphalan, prednisone, and thalidomide versus thalidomide, dexamethasone, and pegylated liposomal doxorubicin regimen in very elderly patients with multiple myeloma: a case-match study

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Abstract

The outcome of patients with multiple myeloma (MM) aged over 75 years remains poor, and the best therapeutic approach has still to be defined. We compared the response, toxicity, and outcome of 34 very elderly patients with MM receiving thalidomide, dexamethasone, and pegylated liposomal doxorubicin (ThaDD) to those of 34 patients matched for age, International Staging System (ISS), and creatinine who received melphalan, prednisone, thalidomide (MPT). ThaDD resulted in a significantly higher response: ≥PR (87.5% vs. 61.5%, $p = 0.009$) and ≥VGPR (55.5% vs. 29.5%; $p = 0.03$). No statistical differences were detected in terms of median progression-free survival (PFS) and overall survival (OS) between the two treatments. Patients treated with MPT had more neutropenia, neuropathy, and heart toxicity, whereas thromboembolism resulted more frequently in patients receiving ThaDD. Therapy discontinuation occurred in 9% and 14.5% of patients treated with ThaDD and MPT, respectively. ThaDD can be considered a therapeutic option in very elderly patients with MM since it induces a faster and deeper response than that obtained with MPT, having similar safety profile.

Keywords: *Multiple myeloma, very elderly, thalidomide, pegylated liposomal doxorubicin*

Introduction

Great progress has been made in the management of multiple myeloma (MM) during the last two decades. However, although new therapeutic approaches have significantly prolonged survival of patients younger than 60 years, no significant improvement in respect of long-term survival has been seen in older patients, particularly in those older than 70 years [1–3]. These patients represent a sizeable population, as shown by recent epidemiological data reporting an incidence of MM equal to 37% in people aged over 75 years [4]. The very elderly often are 'frail' patients because of their poor performance status and comorbidities. Therefore, this subgroup of patients with MM remains difficult to treat, since early mortality, severe side effects, and therapy interruption remain high, particularly with new drug combinations. Regimens containing high-dose dexamethasone seem to be particularly toxic for very elderly patients [5]. Actually, based on a single study that found MPT (melphalan, prednisone, thalidomide) superior to MP (melphalan, prednisone) in newly diagnosed very elderly patients with MM, MPT began to be the standard of treatment in this population [6]. However, there is much room for improvement of the results with the MPT regimen, since the complete remission rate was just 7%, and

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nearly a half of the patients were compelled to give up the therapy.

Here we report data obtained with the standard regimen MPT and with a combination containing thalidomide, dexamethasone, and pegylated liposomal doxorubicin (ThaDD), with the aim to compare response, toxicity, and outcome of the two regimens in a case-match study including very elderly patients with MM.

Patients and methods

Study design and matching criteria

Newly diagnosed very elderly (i.e. aged $\geq$75 years) patients with MM enrolled from January 2002 to May 2005 in the prospective, multicenter GIMEMA 01 (Italian Group for Adult Hematologic Diseases) [7] study were matched with those enrolled from March 2003 to May 2006 in the prospective, multicenter ThaDD study [8]. Both studies were approved by local ethical committees of participating centers, and they were conducted according to the Declaration of Helsinki.

Case-matching was performed with respect to age, Durie and Salmon staging system, International Staging System (ISS), and creatinine levels. The two groups of patients met similar eligibility criteria; in particular, patients with abnormal cardiac, respiratory, renal, and liver functions were not excluded.

The primary end-point of the study was to compare activity (rate of response at least very good partial remission [VGPR]) and efficacy (probability of progression-free survival [PFS]) of the two protocols. Secondary end-points were toxicity (rate of severe side effects), compliance (rate of reduction and discontinuation of therapy), and overall survival (OS).

Treatment regimens

Patients enrolled in the GIMEMA 01 study received oral melphalan 4 mg/m^2 on days 1–7, oral prednisone 40 mg/m^2 on days 1–7 for six cycles every 4 weeks, and thalidomide 100 mg/day continuously until relapse or intolerable toxicity (MPT). Patients were given no antithrombotic prophylaxis until December 2003, when enoxaparin 40 mg/day subcutaneously was delivered during the first four cycles of therapy. Prophylaxis of infections was not initially mandatory but was recommended during severe neutropenia.

Patients enrolled in the ThaDD protocol received pegylated liposomal doxorubicin 40 mg/m^2 on day 1, dexamethasone 40 mg on days 1–4 and 9–12 for six cycles every 4 weeks, and thalidomide 100 mg/day until relapse or intolerable toxicity. Patients received fixed-dose (i.e. 1.25 mg) warfarin as antithrombotic prophylaxis. Ciprofloxacin 250 mg twice a day was administered as antibiotic prophylaxis.

In both protocols, zoledronic acid, erythropoietin, and granulocyte colony-stimulating factor (G-CSF) was administered at the discretion of the attending physician.

Study procedure

During induction therapy, patients underwent serum and/or urine electrophoresis every 2 weeks, and bone marrow biopsy and skeletal X-rays after the first 6 months of treatment. Subsequently, patients were followed with history, physical examination, and laboratory tests every 2 months, bone marrow biopsy every 6 months, and skeletal X-rays every year.

Response to treatment was defined as per the International Myeloma Working Group Uniform Response Criteria [9], excluding the stringent complete remission category, since free light chain assessments were not available in all patients. Progressive disease was defined as an increase of 25% or greater of monoclonal protein and/or plasma cells, progression of bone disease, development of new or increases in soft tissue plasmocytoma, or hypercalcemia.

Assessment of toxicity, graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2, was performed with medical interview, physical examination, and laboratory tests.

The dose of thalidomide was reduced by 50% or discontinued on the occurrence of any non-hematological grade 2 or grade 3–4 adverse event, respectively. The dose of pegylated liposomal doxorubicin or melphalan as well as the dose of dexamethasone or prednisone was reduced by 25–50% for any grade 2 toxicity and discontinued for any grade 3–4 non-hematological toxicity.

Statistical methods

Paired comparisons of baseline characteristics were performed using the χ^2 test for categorical variables and the Mann–Whitney test for continuous variables.

Outcome was analyzed on an intent-to-treat basis and response was provided by number of patients and rate. Time to progression (TTP) was calculated from the time of enrollment to progression, relapse, death from myeloma, or the date the patient was last known to be in remission. PFS was calculated from the time of enrollment to progression, relapse, or the date the patient was last known to be in remission. OS was calculated from the time of enrollment to the date of death from any cause or the date the patient was last known to be alive. All curves were plotted according to the Kaplan–Meier method and

compared by log-rank test. For statistical analysis, the Statistical Package for the Social Sciences version 17 (SPSS, Chicago, IL, USA) was used.

Results

Patient characteristics

Among the 59 and 37 very elderly patients with MM receiving MPT and ThaDD, respectively, 34 patients of the two groups were matched in terms of the abovementioned criteria.

The characteristics of the two groups of patients are shown in Table I. Briefly, median age was nearly the same in the groups as well as the proportion of patients aged 80 years or older. Moreover, patients were very similar as regards Eastern Cooperative Oncology Group (ECOG) performance status and comorbidities, particularly diabetes and cardiac disease. Moreover, B Durie and Salmon stage and the other known prognostic variables matched, while cytogenetic data were insufficient to be included in the matching variables.

Comparison of activity

Partial response (PR) was observed in 11 patients (32%) in the ThaDD group and in 11 patients in the MPT group. The number of patients obtaining very good partial remission (VGPR) was 12 (35%) and two (6%), respectively. Complete remission (CR) was achieved by seven patients (20.5%) treated with ThaDD and eight patients (23.5%) receiving MPT. Only one patient (3%) progressed under the ThaDD protocol, whereas a progression was documented in three patients (9%) who underwent MPT. A significantly higher proportion of patients achieved at least a PR and VGPR with the ThaDD regimen compared with MPT (87.5% vs. 61.5%; $p = 0.009$ and 55.5% vs. 29.5%; $p = 0.031$, respectively) as shown in Table II.

Median time to PR was 28 days (14–112 days) in the ThaDD regimen and 42 days (28–220 days) in the MPT protocol ($p = 0.031$).

Table I. Baseline characteristics of the two groups of patients.

Characteristic	ThaDD ($n = 34$)	MPT ($n = 34$)	p-Value
Age (median, range)	77 (75–88)	76 (75–89)	0.684
Age ≥80 years (%)	5 (15)	6 (18)	
ECOG performance status >1 (%)	11 (32)	9 (26.5)	0.791
Immunophenotype (%)			
IgG	16 (47)	20 (59)	0.537
IgA	12 (35)	8 (23.5)	
BJ	6 (18)	6 (17.5)	
D–S stage (%)			
II	8 (23.5)	13 (38)	0.409
III	26 (76)	21 (62)	
A	25 (73.5)	27 (79)	0.776
B	9 (26.5)	7 (21)	
ISS stage (%)			
I	8 (23.5)	10 (29)	0.582
II–III	26 (76.5)	24 (71)	
Creatinine (median, range) (mg/dL)	1.1 (0.7–2.7)	0.8 (0.7–2.6)	0.385
β_2-Microglobulin (median, range) (mg/L)	4.3 (0.6–23)	4.2 (0.4–25)	0.956
β_2-Microglobulin level >3.5 mg/L (%)	21 (62)	23 (68)	0.800

ThaDD, thalidomide, dexamethasone, pegylated liposomal doxorubicin; MPT, melphalan, prednisone, thalidomide; ECOG, Eastern Cooperative Oncology Group; D–S, Durie and Salmon; ISS, International Staging System.

Comparison of efficacy

After a median follow-up of 40 months in surviving patients in both studies, PFS was similar in the two groups of patients, as illustrated in Figure 1. Median PFS was 35 months in the ThaDD group and 31 months in the MPT group ($p = 0.559$). However, the PFS curves separated after 36 months, so the 5-year PFS was 36% vs. 19% in the ThaDD and MPT groups, respectively.

Median OS was not reached (60% at 5 years) in patients who received the ThaDD regimen, while it was 45 months (34% at 5 years) in those who received MPT ($p = 0.091$; Figure 2).

Comparison of toxicity and compliance

Early death occurred in one patient (3%) treated with MPT and in two patients (6%) who underwent the ThaDD regimen. Fifteen patients (44%) receiving MPT and 12 (35%) receiving ThaDD experienced grade 3–4 adverse events ($p = 0.132$). Major adverse events in the two groups are shown in Table III.

The significantly higher rate of adverse events in the MPT group included neutropenia (26.5% vs.

Table II. Response according to the two treatments.

Maximal response	ThaDD, n (%)	MPT, n (%)	p-Value
CR	7 (20.5)	8 (23.5)	0.800
≥VGPR	19 (55.5)	10 (29.5)	0.031
≥PR	30 (87.5)	21 (61.5)	0.009
Progression	1 (3)	3 (9)	0.132

ThaDD, thalidomide, dexamethasone, pegylated liposomal doxorubicin; MPT, melphalan, prednisone, thalidomide; CR, complete remission; VGPR, very good partial remission; PR, partial remission.

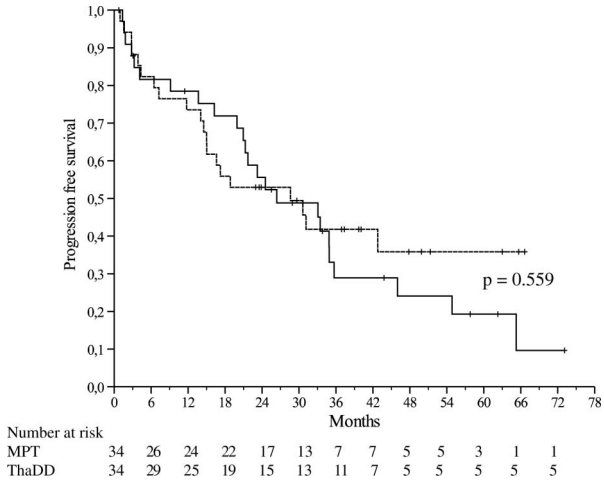

Figure 1. Progression-free survival in patients treated with ThaDD regimen (dashed, finalupper line) and MPT regimen (solid line). Median PFS was 35 months (95% CI: 14–45.5) in the ThaDD group and 31 months (95% CI: 13–39) in the MPT group ($p = 0.559$).

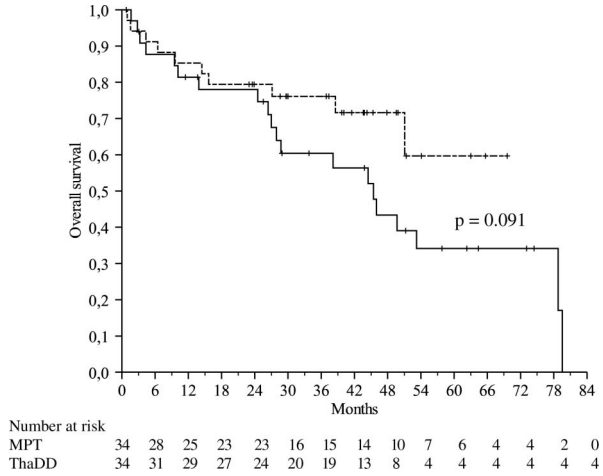

Figure 2. Overall survival in patients treated with ThaDD regimen (dashed line) and MPT regimen (solid line). Median OS was not reached (95% CI: 48–NR) in the ThaDD group and 45 months (95% CI: 34–56) in the MPT group ($p = 0.091$).

Table III. Major hematologic and non-hematologic toxicities.

Grade 3–4 toxicity	ThaDD (%)	MPT (%)	*p*-Value
Neutropenia	6	26.5	0.021
Thrombocytopenia	14.5	6	0.231
Infection	12	6	0.393
Neuropathy	9	29.5	0.031
Cardiac toxicity	6	17.5	0.132
Edema*	32.5	12	0.041
DVT	17.5	12	0.493

ThaDD, thalidomide, dexamethasone, pegylated liposomal doxorubicin; MPT, melphalan, prednisone, thalidomide; DVT, deep venous thrombosis.
*Any grade.

6%; $p = 0.021$), neuropathy (29.5% vs. 9%; $p = 0.031$), and heart toxicity (17.5% vs. 6%; $p = 0.132$). Rates of infections were similar in the two protocols, while deep venous thrombosis (DVT) were higher in the ThaDD group, without statistical significance (Table III). Treatment discontinuation rate due to toxicity was 9% in the ThaDD regimen and 14.5% in the MPT regimen ($p = 0.452$). Nevertheless, thalidomide reduction and discontinuation because of toxicity were significantly higher with the MPT regimen (32.5% vs. 6%; $p = 0.005$ and 50% vs. 17.5%; $p = 0.004$). The main reasons for discontinuation were cardiac toxicity in the MPT group and DVT in the ThaDD group.

Discussion

More than one-third of patients with newly diagnosed MM are 75 years old or more. In contrast to younger patients, the outcome of this subgroup of patients has been slightly if at all improved in the last 10 years, despite the introduction of new drugs [1–3]. Indeed, these patients are often excluded from effective therapy in the belief that compliance to therapy of very elderly patients is suboptimal because of old age, comorbidities, and/or poor performance status [10]. This issue is probably the major reason for lack of outcome improvement in this subgroup of patients.

Several phase III trials demonstrated that MPT assured a better outcome than that with MP in elderly patients with MM not eligible for transplant, although toxicity was higher [6,7,11–13]. One study showed similar results also in very elderly patients with MM [6]. Therefore, MPT became the standard treatment for elderly and very elderly patients with MM. However, compliance to the MPT regimen cannot be considered satisfactory, since more than one-third of patients withdrew from therapy because of toxicity. Particularly, in the Intergroupe Francophone du Myélome (IFM) 01/01 trial [6], more than one-third of very elderly patients discontinued therapy because of adverse events, and this might explain the low rate of CR (7%) compared with that obtained with MPT in the present study (23%), in which fewer than 15% of patients discontinued therapy due to side effects. Despite the fact that in the present study the performance of MPT in terms of quality response and compliance is the best among those published in the literature, the ThaDD regimen has been found to be significantly better in terms of at least VGPR rate (55% vs. 29%), and similarly regarding compliance to therapy since only 9% (vs. 14%) of patients discontinued treatment because of toxicity.

Considering that no substantial difference in terms of activity between doxorubicin and melphalan can

be hypothesized, and that the thalidomide dose was the same in the MPT and ThaDD regimens, it is likely that a higher dose of steroid such as dexamethasone administered with ThaDD played a key role in the better high-quality response obtained with this regimen.

Several studies demonstrated that regimens including high-dose dexamethasone increased the response rate both before [5,14] and after the new-drugs era [15–18]. Nevertheless, this better response does not translate into a better outcome in any of these trials at the present follow-up, since the toxicity of combinations containing high-dose dexamethasone counterbalanced their efficacy, particularly in very elderly patients [15]. However, it is important to remark that the dose of dexamethasone used in the abovementioned trials was a classical schedule of 40 mg on days 1–4, 9–12, 17–20 for a total of 480 mg every 4 weeks [5,16–18], higher than the intermediate dose included in the ThaDD regimen (i.e. a total of 320 mg every 4 weeks). The thalidomide dose was still higher (i.e. $\geq$200 mg) [15–17] in comparison with that administered in the ThaDD regimen (i.e. 100 mg/day). Moreover, in most of these trials, adequate antibiotic and antithrombotic prophylaxis was not mandatory, leading to an impressive treatment discontinuation and early mortality due to thromboembolic and cardiac complications as well as infectious events, particularly in very elderly patients [15–18]. These differences might explain the better compliance and the lower toxicity of ThaDD in comparison with those of the abovementioned regimens.

However, the most important difference among the abovementioned regimens and our own is that the former are two-drug regimens whereas the latter is a three-drug regimen. Incidence and severity of complications depend on a complex interaction among patient characteristics (age, performance status, comorbidities, etc.), disease features (size, activity, immunosuppression, cytokine production, etc.), and mechanism of action of the therapy (immunosuppression, thrombogenicity, organ damage, etc.). It is well known that most treatment-related complications leading to therapy interruption or early death occur in the first courses of therapy, namely when the disease is active and bulky [8,19–22]. Therefore, the main risk factors of complications are those related to disease, and consequently the time at risk of complications depends mostly on time to disease control. Three-drug regimens, such as MPT and ThaDD, clearly allow frequent, rapid, and deep responses compared to those that can be obtained with two-drug protocols, and this is the reason why they are better tolerated. In conclusion, disease control, rather than dose or type of steroid, should be considered as the most powerful factor affecting tolerability and compliance to therapy.

Moreover, pegylated liposomal doxorubicin, minimizing the classical toxicity of chemotherapeutic agents, is well tolerated, at least better than melphalan. Therefore, the safety profile of MPT, in which a low-dose steroid such as prednisone was administered, was not so different from that of ThaDD, but the activity of this latter regimen was significantly superior. Thus, although the difference was not statistically significant because of the low number of patients, the PFS and OS curves seemed to separate after 3 years of follow-up in favor of patients who had undergone ThaDD, suggesting again that better activity translates into a better efficacy.

In conclusion, this study demonstrated that in very elderly patients with MM, ThaDD, namely an intermediate dose of dexamethasone in a three-drug association with low-dose thalidomide and pegylated liposomal doxorubicin, with adequate antibiotic and antithrombotic prophylaxis, is safe and well tolerated as are regimens containing a low-dose steroid such as MPT. However, ThaDD induces a quicker and deeper response than MPT that seems to translate into a better long-term survival. Therefore, ThaDD might be considered a suitable therapeutic option for very elderly patients with MM, particularly in those with aggressive disease.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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