RESEARCH ARTICLE

Clinical Study of Thalidomide Combined with Dexamethasone for the Treatment of Elderly Patients with Newly Diagnosed Multiple Myeloma

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Abstract

Objective: To investigate the relationship between the efficacy and safety of different doses of thalidomide (Thal) plus dexamethasone (Dex) as the initial therapy in elderly patients with newly diagnosed multiple myeloma (MM). Methods: Clinical data of 28 elderly patients with newly diagnosed MM who underwent the TD regimen as the initial therapy were analyzed retrospectively. The patients were divided into two groups according to the maximal sustained dose of Thal: lower dose (group A) and higher dose (group B). The overall response rate (ORR), progression free survival (PFS), overall survival (OS), and adverse events (AES) were compared between the two groups. Results: A total of 28 patients were followed up with a median of 18 months. The ORR was 60.1%. The median response time and PFS were 2.0 and 17.0 months, respectively. The mean sustained dose of Thal in group B was significantly higher than group A (292.9 mg v 180.4 mg, P=0.01). There was no significantly difference in ORR (57.1% v 64.3%, P=1.00) and PFS (9.63months v 17.66 months, P=0.73) between groups A and B. During the follow up, only five patients died (<40%) and, therefore, median OS values were not available. It is estimated, however, that the mean survival time in the two groups was 35.6 and 33.4 months (P>0.05), respectively. All of the patients tolerated the treatment well. The incidence of AES in patients with a grading above 3 in group B was significantly higher than in group A (P=0.033). Conclusions: The TD regimen results in a high response rate and manageable AES as the initial therapy in elderly patients with MM. TD should be considered as the front line regimen for the treatment of elderly patients with MM in areas with financial constraints. The clinical response can be achieved at a low dose Thal with minimal toxicity.

Keywords: Multiple myeloma - chemotherapy - thalidomide - dose - efficacy - toxicity

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Introduction

Multiple myeloma (MM) is a disease characterized by the malignant proliferation of clonal plasma cells, accounting for approximately 1 to 2% of all human cancer (Cohen et al., 1998). The number of geriatric patients is expected to increase over time because of the increasing life expectancy of the normal population.Patients treated with conventional chemotherapy have a median survival of3 to 4 years (San et al., 1999). Treatment consists of chemotherapy; the most common regimens are melphalan plus prednisone (MP), high-dose dexamethasone, and vincristine, doxorubicin, and dexamethasone (VAD) (Kyle and Rajkumar, 2004). The use of high-dose chemotherapy (HDT)followed by autologous transplantation of hematopoietic stem cells has improved the outcome and survival and is now considered the standard of care for symptomatic MM patients younger than 65 years (Attal et al., 1996; Child et al., 2003). Although HDT is a relatively safe procedure with a low mortality rate in experienced centers, many patients are not eligible for the procedure because of advanced age or the presence of co-morbidities(Harousseau, 2002). Moreover, the cost of autologous transplantation is about 100 000 RMB (US $16 000) in China and not totally covered by medical insurance.

In the last decade promising results have been reported in elderly patients with new therapeutic drugs such as Lenalidomide and Bortezomib (Bladé et al., 2005; Gay et al., 2010; Gay et al., 2010; Fukushima et al., 2011; Gay and Palumbo. 2011; Moreau et al., 2011). Unfortunately, Lenalidomide has not been approved by State Food and Drug Administation (SFDS) in China so far,while Bortezomib is too expensive to be received by

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most Chinese patients, whose annual income is less than $5000.

Meanwhile, thalidomide (Thal) has successfully been introduced in the target therapy of MM with high efficacy and lower cost (Yakoub-Agha et al., 2011). Furthermore, induction with Thal did not compromise the viability of stem cells collection for subsequent auto-transplantation. However, the incidence of grade 3-4 or deep vein thrombosis (DVT) was 5-fold greater among patients receiving the Thal-containing regimen (Saad et al., 2009), especially, the high dose Thal>400 mg/d. Because the increasing risks of these adverse effects may outweigh the expected therapeutic benefit of high dose Thal, it is reasonable to decrease the dose of Thal for MM patients. Since 2004, we have used Thal plus dexamethasone (Dex) as the initial therapy in elderly patients with newly diagnosed MM. In this study, we discussed the relationship between the dosage and efficacy of Thal.

Materials and Methods

Patients

Twenty-eight elderly patients with newly diagnosed MM who underwent the TD regimen as the initial therapy in our hospital from October 2004 to August 2008 were included. All of the patients met the WHO diagnostic criteria (International Myeloma Working Group., 2003). Clinical staging was performed according to the Durie-Salman (DS) and International Staging System (ISS) criteria. The patients included 19 males and 9 females with a median age of 69 (60-81) years old. For DS staging, one case was stage I, eight were stage II, eighteen were stage III A, and 1 was stage III B. For ISS staging, six were stage I, thirteen were stage II, and 9 were stage III. M protein typing was done: IgG type in 17 cases, IgA in 7 cases, IgD in 1 case, and the light chain type in 3 cases.

Methods

The patients were divided into two groups according to the maximal sustained dose of Thal: the lower dose (thal 100-200 mg/d, group A, 14 patients) and the higher dose (Thal 225-400 mg/d, group B, 14 patients). The baseline age, D-S stage, β2-MG (β2 microglobulin), C-reactive protein (CRP), serum calcium levels, hemoglobin (Hb), and plasma cells ratio in bone marrow during the disease were comparable between groups. The clinical data are in Table 1. All of the patients underwent blood, urine, liver, and kidney function, electrolytes, immunoglobulins, serum protein electrophoresis, quantitative urine light chain, β2 microglobulin, CRP, and blood glucose tests before the beginning of the next treatment course. ECG was examined regularly and the blood test was reexamined. X-rays for the involved bone, ultrasound, bone marrow cytology, M protein identification were carried out when necessary. The efficacy assessment was performed according to uniform response criteria for MM (Durie et al., 2006). The definition of response is no less than partial response(PR). Disease progression-free survival (PFS) refers to the time from the beginning of treatment to the time of disease progression or death. The follow-up time was from the beginning of TD treatment to death or August 2008. Adverse events (AES) were asked in detail and recorded, such as drowsiness, constipation, rash, numbness, swelling, and assistant examination. Adverse reactions were determined as a common naming standard for AES made by the U.S. National Cancer Institute.

Treatment regimen

All patients used the TD regimen as the initial treatment. The starting dose of Thal was 50 mg per night and it was increased 50-100 mg per week to the maximal dose of 400 mg or reduced to the previous dose until it could not be tolerated. Then, the dose was maintained. 20-40 mg/d of Dex was given orally after a meal in the divided dose. In the odd-number course, Dex was given orally at day 1-4, day 9-12, and day 17-20. In the even-number course, Dex was given at day 1-4. Every course included 4 weeks. If Dex-related adverse reactions occurred, such as hypertension, high blood glucose, or serious infection, Dex given at day 17-20 in the odd-number course should be stopped and symptomatic treatment, such as antihypertension and antidiabetic drugs, should be given. Bisphosphonates, a gastric mucosal protective agent, and a stool softening drug were used as adjuvant therapy during the course of disease. Other regimens were used when the disease progressed.

Statistical analysis

SPSS13.0 statistical package was used for statistical processing. The survival rate was calculated and the survival curve was drawn using the Kaplan-Meier method. The measurement data of group A and B were compared using the t test, and the count data were compared using the Fisher exact probabilities test.

Results

Efficacy evaluation

The follow up lasted 1 to 47 months with a median follow-up time of 18 months. The ORR was 60.7% (17/28 patients), of which 1 case achieved CR, three achieved a very good partial response (VGPR), thirteen achieved PR, eight in a stable disease (SD), and 3 in a progressive disease (PD). The median response time was 2 months and the mean PFS was 17.04months. And the mean PFS were no significant difference in both groups (9.63months v 17.66months, P=0.73) (Figure 1). The ORR in groups A and B were 57.1% (8/14 cases) and 64.3% (9/14 cases)

Table 1. Baseline Clinical Data of Patients in Both Groups

Group	Median age (year)	Maintenance dose of Thal (mg)	D-S stage (n) I	II	III	CRP (mg/L)	Albumin(g/L)	Serum calcium (mmol/L)	β2- MG (mg/L)	Bone marrow plasma cells proportion	Hb (g/L)
GroupA	70	180.36±10.54	1	4	9	25.57±13.74	33.36 ±2.35	2.24±0.45	6.86±2.36	0.29±0.06	87.14±8.40
Group B	68	292.86±27.66	0	4	10	21.62±9.35	34.62±1.62	2.37±0.05	4.46±1.01	0.35±0.05	86.38±5.89
P		0.01		0.78		0.81	0.93	0.2	0.37	0.84	0.94

Table 2. Clinical Efficacy and Time Events of Patients in Both Groups

Group	Follow up time (month)	TD median treatment time (month)	Evaluation of efficacy (n) ≥VGPR	PR	SD	PD	Estimated mean survival time (month)
Group A	17.3	5	2	6	5	1	35.6
Group B	19.4	4	2	7	3	2	33.4
P				1.0*			>0.05

*Comparison of efficacy ≥PR between the two groups

Table 3. The Main Adverse Events of Patients in Both Groups

Group	constipation (n)		Fatigue, weakness (n)		Rash (n)	Edema (n)	Peripheral neuropathy (n)		Lethargy (n)		Dizziness (n)		Infection (n)		arrhythmia (n) (grade 1-2)	hematologic toxicity (n)	Total cases above grade 3
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 1-2	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4			
Group A	9	0	8	1	4	3	3	0	3	0	2	0	1	0	0	2	1
Group B	9	1	6	2	5	5	4	1	4	1	2	1	2	1	2	4	7
P*	1		1		1.00a	0.68a	0.68		0.68		1		0.6		0.50a	0.65a	0.033b

*Comparison of adverse reactions between the two groups, a no grade 3-4 events, b above grade 3 of the two groups

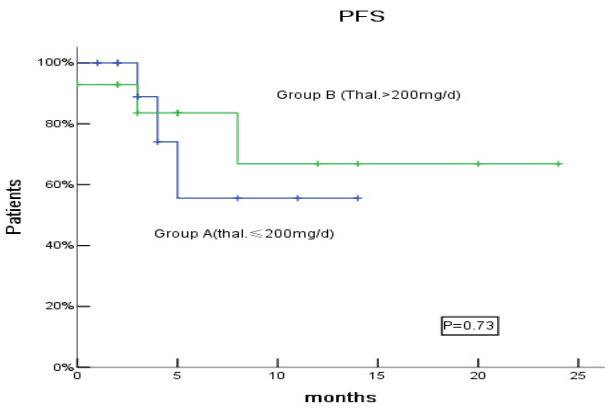

Figure 1. Progression Free Survival (PFS) after Different Doses of Thal. Plus Dex

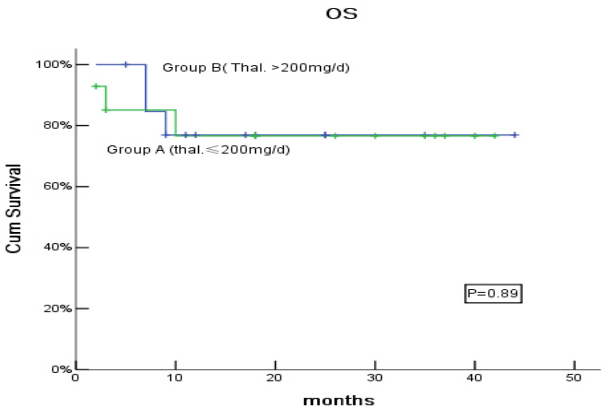

Figure 2. Overall Survival (OS) after Different Doses of Thal. Plus Dex

without a significant difference between the two groups (P=1.00), respectively. The specific efficacy of the two groups is shown in Table 2.

Survival analysis

Because of the short follow-up and no more than half of patients died in both groups, the median survival time could not be calculated. It is estimated that the mean survival time in the two groups were 35.6 and 33.4 months (P=0.89), respectively (Figure 2).

Adverse reactions

Many adverse reactions were observed, such as constipation, fatigue, weakness, rash, peripheral edema, peripheral neuropathy, somnolence, dizziness, infection, hematologic toxicity, arrhythmia, and most were between Grades 1 to 2. AES are shown in Table 3. There were 7 AES (above grade 3) in group B and 1 in group A (P=0.033) with a significant difference between the two groups. The hematological toxicity was mild for all patients and no bone marrow suppression effect was seen. In addition, no patient had deep venous thrombosis.

Discussion

Multiple myeloma is a hematological cancer that often occurs in elderly patients and its incidence increases with age. Since the 1960s, an MP (Melphalan plus prednisone or dexamethasone) regimen had been the classical treatment for MM patients who were old or ineligible for autologous stem cell transplantation for its advantages, such as convenient administration, no venous catheter, and lower cost (Alexanian et al., 1969). However, Mel had high toxicity on normal bone marrow stem cells and the toxicity was cumulative, which can impact the quality of hematopoietic stem cells. The application of MP in elderly patients causes serious adverse reactions, mainly presenting as bone marrow suppression, severe infection, and sepsis. Therefore, searching for more effective and lower toxicity chemotherapy has been a clinical challenge. Successful application of target drugs represented by Thal in the treatment of MM creates a new era for MM treatment. Thal monotherapy or combination chemotherapy almost covers the treatment of all types of MM and the various stages of MM treatment. However, the appropriate optimal dose of Thal remains uncertain.

Although the exact mechanism and optimal dose of Thal are unknown, it is still widely used in the treatment of MM. It was mainly used for refractory MM at first, and the daily maintenance dose was between 100 to 1,000 mg. The larger dose (400-800 mg/d) can lead to a relatively high response rate. Its single-agent response rate (≥PR) was between 15% and 48% and combination with Dex, or other target therapies could further improve its efficiency (Kastritis et al., 2007). Considering the strong anti-refractory effect of Thal, Rajkumar reported the administration of TD in newly diagnosed MM as a initial therapy in the United States in 2002 (Rajkumar et al., 2002). In the study, the maintenance dose of Thal was 200–800 mg/d and the ORR was 64% after 4 cycles. From 2003 to 2006, four phase II clinical trials and one phase III clinical trial were reported. All of these trials

used TD as the initial treatment for newly diagnosed MM and the Thal maintenance dose tends to decrease. The largest maintenance dose was 100-400 mg/d and the maintenance therapy lasted for 2 to 4 months. The ORR was 63-76% (Cavallo et al., 2007), which was higher than the traditional MP regimen. Therefore, the FDA approved TD as a first-line induction therapy in MM patients prior to transplantation (Rajkumar et al., 2006). Rajkumar (Rajkumar et al., 2008) reported a clinical multicenter, randomized, double-blind placebo-controlled trial on MM treatment in 2008. The treatment group underwent the TD regimen. 50 mg of Thal was given on the first day of the first treatment course and 100 mg of Thal was given at day 15. In the second course, 200 mg/d was used as the maintenance dose. In the control group, only Dex plus placebo was given. The ORR in the treatment group and control group were 63% and 46%, respectively (P<0.01). Hulin et al. (2007) used MPT as induction therapy for elderly MM patients (age ≥ 75 years old) and its maintenance was 100 mg/d. The OS and PFS in the treatment group were longer than the MP regimen in the control group, suggesting that the efficacy of Thal was close among 100-400 mg/d and the lower dose led to milder side effects (Cavallo et al., 2003). Our results also showed that ORR of all the patients was 60.7% and no difference in short-term ORR, PFS, and long-term OS was not found between groups A and B (P>0.05), which was similar to results reported by others.

The AES of Thal in turn limit its application. The main AES include drowsiness, constipation, rash, fatigue, cardiovascular toxicity, peripheral neuropathy, and venous thrombosis. Peripheral neuropathy and venous thrombosis are multiple and serious adverse reactions in Europe and America MM patients receiving Thal treatment. The occurrence of neuropathy was dose dependent, occurring in 50% to 80% of patients. In MM patients receiving the initial treatment, the incidence of venous thrombosis was 3% when only Thal was used, the incidence of venous thrombosis was 12%-26% when combined with Dex, and the incidence of venous thrombosis was 6% to 34% when combined with other cytotoxic drugs (Palumbo et al., 2008). Our results also showed that Thal can cause many minor adverse reactions and most patients can tolerate well during the time of Thal reduction and symptomatic treatment. The incidence of peripheral neuropathy in our study was lower than the foreign study, which may be related to the use of high doses of Thal in the early years. In recent years, the maximal maintenance dose of Thal tended to decline. It is noteworthy that no thrombotic complications occurred in this study, while the incidence of venous thrombosis in foreign patients was significantly higher than Chinese patients, despite a lower maintenance dose of Thal and the prophylactic anticoagulant therapy being given, which may be related to different races. In addition, eight cases had AES (above grade 3) in the whole group, of which 7 were in group B and 1 in group A (P=0.033), suggesting that a higher dose of Thal can cause serious AES.

In conclusion, a TD regimen has a significant anti-myeloma effect. Thal can cause many minor adverse reactions and most patients can tolerate it after appropriate management. Therefore, we believe that the TD regimen has high efficacy and acceptable side effects as the initial therapy for elderly MM patients in poverty area. Moreover, some patients can receive treatment in the outpatient service due to its convenient administration. Thus, the TD protocol is accepted for use as first-line induction regimens for the initial treatment of elderly patients with MM.Given the efficacy and toxicity, we believe that low doses of Thal (100-200 mg/d) were superior to the higher dose. This study is retrospective and had a small number of cases. Therefore, more evidence is needed to confirm its advantages by prospective clinical trials.

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