Review of thalidomide in the treatment of newly diagnosed multiple myeloma

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Abstract: The role of thalidomide has been well established in the setting of relapsed or refractory multiple myeloma (MM). More recently, studies have been focused on upfront induction therapy. In newly diagnosed MM patients, thalidomide improved the response rates and the event-free survival induced by both high-dose and conventional chemotherapy regimens. The effect on survival needs to be further investigated. The efficacy of this drug is counterbalanced by a significant rate of both acute and long-term toxicities. Thus best timing of initiation, dosing schemes and duration of therapy is still unclear. Evidence is now emerging that clinical response can be achieved also at lower doses with minimal long term toxicity.

Keywords: Multiple myeloma, thalidomide, front-line therapy

Introduction

Multiple myeloma (MM) is an incurable malignancy of terminally differentiated B-cells accounting for approximately 1 to 2% of all human cancers (Cohen et al 1998). Patients treated with conventional chemotherapy have a median survival of 3 to 4 years (San Miguel et al 1999). The use of high-dose chemotherapy (HDT) followed by autologous or allogeneic 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 with good performance status (Attal et al 1996; Child et al 2003). Response rate and survival are doubled with HDT, but relapse still occurs. 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 et al 2002). Intermittent melphalan plus prednisone (MP) therapy is considered the standard treatment for the majority of elderly patients. MP is used worldwide with response rates of about 50% and a median overall survival (OS) of 2–3 years (Alexanian et al 1969). In the last decade promising results have been reported in elderly patients with new therapeutic drugs.

The activity of thalidomide as single agent in refractory or relapsed MM has been first reported in 1999 (Singhal et al 1999); numerous phase II trials have further confirmed its activity. Response rate was significantly increased when thalidomide was combined with dexamethasone (45–75%) (Weber et al 1999; Dimopoulos et al 2001; Palumbo et al 2001;Anagnostopoulos et al 2003) and with chemotherapy (67–79%) (Moehler et al 2001; Gonzales-Porras et al 2003; Hussein et al 2003; Kropff et al 2003; Lee et al 2003; Dimopoulos et al 2004). The Food and Drug Administration has recently approved the use of thalidomide in combination with dexamethasone for the treatment of newly diagnosed MM patients. It has been shown that thalidomide acts through several mechanisms: direct pro-apoptotic effects and G1 growth arrest of multiple myeloma cells; down-regulation of binding of multiple myeloma cells to bone marrow stromal cells (BMSCs), which confers cell adhesion-mediated drug

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resistance (CAM-DR); and inhibition of multiple myeloma growth factors including IL-6, TNFα, and vascular endothelial growth factor (VEGF) (Hideshima and Anderson 2002; Hideshima et al 2002). Antiangiogenic effects are mediated via inhibition of VEGF and beta fibroblast growth factor (FGF) (Gupta et al 2001). The immunomodulatory effects of thalidomide has been evidenced by the upregulation of natural-killer cells through the release of interferon gamma and IL-2, in both preclinical studies and in MM patients (Davies et al 2001; Lentzsch et al 2003). Based on its anti-inflammatory effects thalidomide has been used in erithema nodosum leprosum and it is also being investigated for treating symptoms of prostate cancer, glioblastoma, lymphoma, arachnoiditis, Behçet's disease, and Crohn's disease. In recent trials, thalidomide has been incorporated in the front-line therapy of newly diagnosed MM patients; this will constitute the subject of this review.

Search strategy and selection criteria

PubMed was searched for references from 1999 to november 2006, in English only with the terms "thalidomide", "newly diagnosed multiple myeloma", "new drugs for myeloma", "conventional chemotherapy". Published papers, proceedings from the American Society of Hematology and the American Society of Clinical Oncology were evaluated and are cited when significant data were found.

Role of thalidomide in the treatment of smoldering or indolent MM

Smoldering/indolent myeloma constitutes approximately 15% of all newly diagnosed cases of MM (Dimopoulos et al 1993, 2000). Patients are generally asymptomatic; however the rate of progression is approximately 25% per year, with a median time to progression of approximately 3 years. Standard treatment options for smoldering/indolent MM are limited to observation or investigational therapy within a clinical trial (Kyle and Greipp 1980; Hjorth et al 1993). Patients with risk factors for progression to symptomatic disease, such as increase number or proliferative rate of circulating plasma cells, elevated bone marrow plasma cell labeling index, IgA isotype, serum M component greater than 3 g/dL or urinary M protein greater than 50 mg/d and abnormal magnetic resonance imaging of the spine may be candidates to start therapy to delay or prevent progression. Two phase II trials have evaluated single-agent thalidomide in patients with asymptomatic MM (Rajkumar et al 2001, 2003; Weber et al 2003). In both studies thalidomide was started at 200 mg dose/daily with dose escalations to a maximum of 600 mg and 800 mg respectively; the median maximum tolerated dose was 400 mg in both studies. In the study conducted at the Mayo Clinic 31 patients were treated and 29 were evaluated. Partial responses (PR) (≥50% reduction in serum and urine M-component) were noted in 10 (34%) patients, with the inclusion of minor responses the response rate was 66%. In this study thalidomide was continued in responding patients at a maximum dose of 200 mg, with several patients maintaining responses at lower doses of 50–100 mg/d. Overall survival (OS) at 2 years was 96% (Rajkumar et al 2003).

Another study conducted at the MD Anderson Cancer Center (MDACC) evaluated 28 patients, and the overall response rate was 36%. After a median follow-up of 25 months, relapse had occurred in 3 patients (Weber et al 2003). While the time to progression may be prolonged for those patients with responsive disease, premature and long-term therapy in asymptomatic patients may increase neurological toxicities and contribute to later drug resistance. Randomized phase III trials are needed to define the role of thalidomide in the treatment of newly diagnosed smoldering myeloma. Trials involving the use of thalidomide, pamidronate and zolendronate are ongoing in the United States and in many other countries. More data on the durability of response are needed before recommending this strategy for standard clinical practice.

Role of thalidomide as part of HDT in the treatment of symptomatic newly diagnosed MM

Thalidomide has shown synergistic activity with dexamethasone in relapsed MM patients (Alexanian et al 2003), the combination of these 2 drugs has been recently investigated as induction therapy.

Phase II clinical trials have shown the activity of this combination for induction therapy in newly diagnosed MM patients (Rajkumar et al 2003; Weber et al 2003; Cavo et al 2004; Abdelkefi et al 2005; Wang et al 2005). Thalidomide was administered at doses ranging from 100 mg/d to 800 mg/d, the median maximum tolerated dose was 200 mg in all these studies and the median duration of treatment was 3 to 4 months. Response-rates up to 73% were observed also in patients with high tumor mass (Wang et al 2005), with manageable toxicities, mostly skin rash, deep vein thrombosis (DVT), neuropathy and constipation. The results of a randomized phase III trial of thalidomide and

dexamethasone (TD) versus dexamethasone alone has been recently published (Rajkumar et al 2006). Response rates were higher in the thalidomide arm (63% *v* 41%, p = 0.0017), but a higher incidence of adverse events was observed. The authors recommend initial single-agent high-dose dexamethasone, with the addition of thalidomide later in lower risk patients, as an alternate approach, with the combined therapy reserved for those patients with advanced disease and high risk features at presentation. A recent retrospective analysis compared TD to VAD as induction therapy before high-dose therapy and autologous stem cell transplantation (Cavo et al 2005). TD resulted in both a significantly higher response rate (76% *v* 52%, respectively) and a greater reduction in monoclonal proteins. Furthermore thalidomide did not compromize the ability to harvest autologous peripheral blood stem cells (PBSC) in this study and others. A retrospective study addressed specifically this issue; the total number of CD34 cells collected was not affected by previous duration or dose of thalidomide, or duration between thalidomide cessation and mobilization (Ghobrial et al 2003), while in another study the median number of CD34 was affected by the time from thalidomide discontinuation (Abdelkefi et al 2005). Long-term outcome after TD is not possible to ascertain in these studies, since the studies were intended to examine the TD regimen as a pretransplant induction therapy. Ongoing, larger multicenter studies will provide more information on progression-free survival and overall survival post-TD. The combination of TD with the proteasome inhibitor bortezomib (V) had induced remission in 55% of patients with myeloma resistant to standard therapies (Zangari et al 2005). The VTD combination has been evaluated as induction treatment for previously untreated MM patients at the MDACC; bortezomib was given at 3 different doses, 1.3 mg/m^2 (15 patients), 1.5 mg/m^2 (11), and $\geq$1.6 mg/m^2 (10), with thalidomide at a maximum dose of 200 mg and pulsed oral dexamethasone (20 mg/m^2 days 1–4, 9–12 and 17–20), leading to an overall response rate of 78% and a manageable toxicity profile (Wang et al 2005). The combination of thalidomide with chemotherapy has also been widely evaluated. Two small studies have evaluated the association of thalidomide at doses ranging from 200 mg to 400 mg with different chemotherapeutic agents, leading to similar results in terms of overall response rates (up to 81%) (Zervas et al 2004; Schutt et al 2005). In both studies stem cell collection could be performed successfully. Another phase II trial evaluated the AD-TD combination in 45 newly diagnosed patients (Hassoun et al 2005). In this study doxorubicin and dexamethasone were given for 2 or 3 months followed by TD for 2 months. The overall response rate was 84% with minimal treatment related morbidity. A large trial, the HOVON-50/GMM-HD3, is being conducted to evaluate whether thalidomide as part of induction therapy before and as maintenance after intensive treatment improves response rate, event-free (EF) and overall survival (OS). The standard treatment arm comprized 3 cycles of VAD, mobilization with CAD+G-CSF (cyclophosphamide; adriamycin; dexamethasone; G-CSF until end of harvest), HDT with 1 or 2 cycles of melphalan 200 mg/m^2, followed by autologous peripheral blood SCT (PBSCT), and maintenance with interferon-alpha (9 MU per week). In the experimental arm, TAD (thalidomide, 200 mg for HOVON/400 mg for GMMG; adriamycin; dexamethasone 40 mg) was used for induction treatment. Mobilization and HDT were identical to the standard arm. Experimental maintenance was thalidomide (50 mg per day). Preliminary results are available for a first group of 406 patients (of 1050 included) that are evaluable for the comparison of VAD *v* TAD and response after 1st HDT. TAD induced a significant higher response rate (80% *v* 63%, p = 0.001), but this effect was completely offset by HDT (overall response rate 91% *v* 88%, p = 0.4). No data are currently available on EFS and OS (Goldschmidt et al 2005). The Southwest Oncology Group (SWOG) embarked on a trial (SWOG 0204) of TD induction, modest-dose cyclophosphamide for PBSC mobilization, melphalan (MEL)-based tandem autotransplant and subsequent prednisone-thalidomide maintenance. Preliminary data on this study suggest that TD for induction starting at 50 mg of thalidomide and incrementing by 50 mg weekly to a target dose of 400 mg is well tolerated and allows for all patients to receive autotransplant in a timely fashion with no increase in toxicity. Longer follow-up will eventually provide information on survival (Hussein et al 2005). The combination of thalidomide and dexamethasone has been also evaluated as consolidation treatment in a small study at the MDACC. Twenty-one patients with stable PR after HDT received the TD (thalidomide 100 mg to a maximum dose of 300 mg) for a median of 3 months and patients with a marked reduction of MM markers were maintained on thalidomide alone until disease progression. This combination further reduced tumor mass markedly in 57% of patients with stable, residual disease after myeloablative therapy. The authors conclude that such an effect may produce longer disease-free survival and/or preserve tumor sensitivity to later retreatment with previously effective drugs (Alexanian et al 2002). Small studies have evaluated the feasibility of

maintenance therapy with thalidomide and suggested that such a treatment may improve survival (Brinker et al 2006; Sahebi et al 2006). The UK Myeloma Forum group examined the long-term tolerance of single agent thalidomide as maintenance therapy after HDT. Thalidomide was evaluated at 5 doses (50 mg, 100 mg, 200 mg, 250 mg, 300 mg) starting 3 months post HDT. There was an improvement in progression free survival (PFS) for those who managed to tolerate thalidomide for at least 6 and preferably 12 months. Only 8% of patients sustained a dose of 300 mg. Side effects, particularly peripheral neuropathy, led to discontinuation in 2 thirds of patients at a median follow up of 23.5 months. The best outcome was seen in patients who achieved a CR only after the initiation of thalidomide (Feyler et al 2005). Two large studies have provided data on survival with thalidomide as part of upfront treatment in multiple myeloma patients undergoing HDT. One has been recently published by Barlogie and colleagues (2006) from the University of Arkansas. This was a large randomized trial conducted on 668 patients between October 1998 and February 2004. At enrollment, patients were randomly assigned either to a control group (no thalidomide) or to experimental group (thalidomide). The thalidomide doses were 400 mg daily during induction chemotherapy (withheld on day 5 of cycle 3 of chemotherapy for the PBSC collection), 100 mg daily between transplantations, 200 mg daily with consolidation therapy, 100 mg daily during the first year of maintenance therapy, and then 50 mg on alternating days until relapse or occurrence of adverse events. In the experimental group a higher rate of complete response (CR) (62% *v* 43%, $p < 0.001$) and a superior 5-year EFS (56% *v* 44%, $p = 0.001$) were observed. The 5-year OS was approximately 65% in both groups ($p = 0.90$), with a median survival after relapse of 1.1 year in the thalidomide group and 2.7 years in the control group ($p = 0.001$). Barlogie and colleagues (2005) are currently evaluating in the Total Therapy 3 protocol the incorporation of bortezomib in thalidomide-chemotherapy based regimen for induction, consolidation and maintenance treatment. The other study has been conducted by The Intergroupe Francophone du Myelome (IFM). In this study patients withouth progressive disease 2 months after the second transplant were randomized to receive: no manteinance (Arm A), maintenance treatment with pamidronate (Arm B) or with thalidomide and pamidronate (Arm C). Thalidomide has improved the 3-year EFS (36% *v* 37% *v* 52%, $p < 0.009$), especially for those patients without chromosome 13 deletion and beta2microglobulin >2.5 mg/dl. The 4-year OS was better for Arm C compared to arm B (87% v 74%, $p < 0.003$) (Attal et al 2006). Table 1 summarizes the prominent findings of the above studies.

Thalidomide as part of conventional treatment for the elderly MM patients or for patients not candidates to HDT

For elderly MM patients conventional chemotherapy has remained the treatment of choice since 1960. The TD combination has been proven effective in a small study inducing an overall response rate of 48% with a median time to disease progression of 18 months (Dingli et al 2005). The combination of thalidomide with conventional dose chemotherapy can further improve response as shown with the ThaDD combination. The ThaDD regimen consisted of Thalidomide 100 mg/day, pegylated liposomal doxorubicin 40 mg/m^2 on day 1 and dexamethasone 40 mg days 1–4, 9–12; the overall response rate was 89%, with a 2-yr EFS and OS of 65% and 70% respectively (Offidani et al 2006). The combination of thalidomide, cyclophosphamide and pulsed dexamethasone (CTD) was effective in refractory/relapsed patients (Garcia-Sanz et al 2002; Dimopoulos et al 2004). The Medical Research Council (MRC) Myeloma IX trial is currently comparing in the non intensive pathway the melphalan-prednisone (MP) regimen to an attenuate version of the CTD. The CTD combination (oral cyclophosphamide 500 mg, days 1, 8 and 15, thalidomide at a maximum dose of 200 mg and oral dexamethasone 40 mg, days 1–4 and 15–18) was found to be very effective in a group of 15 patients (Williams et al 2004). Higher rates of complete response approaching the rates observed with HDT plus stem cell transplantation have recently been found in trials of thalidomide combined with standard treatment with melphalan and steroids (Palumbo et al 2005, Dimopoulos et al 2006; Palumbo et al 2006). In the study of Dimopoulos and colleagues (2006), thalidomide at the fixed dose of 300 mg (days 1–4 and 14–18) was associated with oral melphalan (8 mg/m^2, days 1–4) and pulsed dexamethasone (12 mg/m^2, days 1–4 and 14–18), for 3 courses, and followed by additional 9 courses where the 3 drugs where given at the same doses on days 1–4 only. The overall response rate was 72%, with a median time to progression of 21.2 months and a median OS of 28.2 months (Dimopoulos et al 2006). A prospective, multicenter randomized trial of oral MP with or without thalidomide for the treatment of patients with newly diagnosed MM age > 65 years was initiated. Patients were randomly assigned to receive oral MP (Melphalan 4 mg/m^2, days 1–7; prednisone 40 mg/m^2 days 1–7) with or

Table 1 Thalidomide in upfront therapy in SMM/indolent MM and symptomatic MM patients candidates for high dose chemotherapy (HDT)

Trial	Regimen	Thalidomide dose (mg/day)	Duration	Timing	No. of patients	Response (EBMT criteria)	Survival
Phase II (Weber et al 2003)	T	200–600	Until PD	I/M	28	PR 36%	–
	TD (1)	100–400	3 months	I	48	PR + CR 72%	–
Phase II (Rajkumar et al 2003)	T	200–800	Until PD	I/M	29	PR + MR 66%	–
Phase II (Rajkumar et al 2002)	TD (2)	200–800	4 cycles	I	50	PR + CR 64%	–
Phase II (Wang et al 2005)	TD (1)	100–300	2 cycles	I	26	PR + CR 73%	–
Phase II (Abdelkefi et al 2005)	TD (1)*	200	3 months	I	60	PR + CR 74%	–
Phase II (Cavo et al 2005)	TD (2)	100–200	4 months	I	100	PR + CR 76%	–
Phase III (Rajkumar et al 2006)	TD *v* D (3)	200	4 cycles	I	207	PR + CR 63% *v* 41%	–
Phase II (Wang et al 2005)	VTD (4)	100–200	2 cycles	I	36	PR + CR 78%	–
Phase II (Zervas et al 2004)	T-VAD doxil (5)	200	4 cycles	I	39	PR + CR 74%	22mos EFS 55% OS 74%
Phase II (Schutt et al 2005)	T-VED (6)	200–400	Until PD	I/M	31	PR + CR 80%	3y EFS 26% 3y OS 62%
Phase II (Hassoun et al 2005)	AD-TD (7)	100–200	2 cycles	I	45	PR + CR 84%	-
Phase III (Goldschmidt et al 2005)	T with HDT *v* HDT (8)	200–400	Until PD	I/M	604	PR + CR 91% *v* 88%	-
Phase III (Hussein et al 2005)	T with HDT (9)	100–400	Until PD	I/M	130	PR + CR 80%	-
Phase III (Barlogie et al 2006)	T with HDT *v* HDT (10)	400, 100, 200, 50	Until PD	I/T/C/M	668	CR 62% *v* 43%	5y EFS % 56 *v* 44; similar OS
Phase II (Alexanian et al 2002)	TD (1)	100–300	Until PD	C	21	Further response 57%	Median remission 22 months
Phase II (Sahebi et al 2006)	T	50–400	Until PD	M	29	PR + CR 68%	2y PFS 49% 2y OS 83%
Phase II (Brinker et al 2006)	T	200	Until PD	M	20	–	Median OS 65 months
Phase II (Feyler et al 2005)	T	50, 100,200,250,300	Until PD	M	100	–	Median PFS 35 months
Phase III (Attal et al 2005)	TP *v* P *v* No maintenance	–	Until PD	M	593	–	PFS % 56 *v* 37 *v* 34 similar OS

Abbreviations: T, Thalidomide; D, Dexamethasone; P, pamidronate; PD, progressive disease; I, induction; T, transplant; C, consolidation; M, manteinance; EBMT, European Group for Blood and Marrow Transplantation; MR, minimal response; PR, partial response; CR, complete response; EFS, event free survival; PFS, progression free survival; OS, overall survival; TD(1), 20mg/m^2 d 1–4, 9–12 and 17–20; TD (1)*, D 20mg/m^2 d 1–4, 9–12 and 17–20(odd cycles) d 1–4 (even cycles); TD(2), D 40 mg d 1–4, 9–12 and 17–20 (odd cycles) d 1–4 (even cycles); TD (3), D 40 mg d 1–4, 9–12 and 17–20; VTD(4), D 20 mg/m^2 days 1–4, 9–12, and 17–20, *v* 1.3 mg/m^2 (15 patients), 1.5 mg/m^2 (11), and ≥1.6 mg/m^2 (10); T-VAD doxil (5), Vincristine 2 mg i.v. day 1, Liposomal doxorubicin 40 mg/m^2 i.v. day 1, D 40 mg days 1–4; T-VED (6), Vincristine 1.5 mg i.v. day 1, Epirubicin 30 mg/m^2 i.v. days 1–2, D 20 mg/m^2 days 1–5; AD-TD (7), Doxorubicin 9 mg/m^2 i.v. d 1–4, D 40 mg d 1–4, 9–12 and 17–20; after 3 AD cycles, T 100–200 mg d 1–28, D40 mg d 1–4, 9–12 and 17–20, (8) HOVON -50/GMMG-HD3. (9) SWOG 0204. (10) Total Therapy 2.

without thalidomide (100 mg per day continuously until any sign of relapse or progressive disease). Higher response rates (76% *v* 47.6%) and longer 2 year EFS (54% *v* 27%) were observed in the experimental arm, but longer follow-up is needed to assess effect on OS (Palumbo et al 2006). In another trial patients were randomized to TD (thalidomide 200 mg/day, dexamethasone 40 mg, days 1–4 and 15–18 on odd cycles and days 1–4 on even cycles) or MP (melphalan 2.5 mg/kg day 1–4 and P 2 mg/kg days 1–4, q 4–6 weeks). The interim analysis showed a higher response rate and a significantly shorter time to response in the TD group (Ludwig et al 2005).

In May 2000, the IFM initiated a new trial, IFM 99–06, for patients aged 65–75 years, comparing MP (12 courses at 6 weeks intervals) to MP T (MP plus thalidomide at the maximum tolerated dose, 400 mg/day, but stopped at the end of MP) and a MEL100-based treatment (intermediate-dose MEL). The PFS time was significantly longer in the MP T group than in the MP group (hazard ratio estimate, RR = 2.4, 95% CI = 1.8–3.3, P < 0.0001), but no significant difference was noted between MP and MEL100 groups (RR = 1.2, P = 0.12). In the secondary PFS comparison, there was a clear advantage in favor of MP T *v* MEL 100 (RR = 2.0, 95% CI = 1.4–2.8, P = 0.0001). The PFS advantage in favor of MP T group translated to a significant benefit in terms of OS. The OS time was significantly longer in MP T group than in MP group (RR = 1.9, 95% CI = 1.3–2.9, P = 0.0009), but not significantly different between MP and MEL100 groups (RR = 1.2, P = 0.38). In the secondary OS comparison, superiority of MP T on MEL100 was evidenced (RR = 1.7, P = 0.022). The authors suggest that MP T should be considered the reference treatment for newly diagnosed MM patients ineligible for high-dose therapy (Facon et al 2005). The combination of bortezomib with thalidomide and/or conventional chemotherapy regimens has shown promising results in phase II trials on relapsed patients (Palumbo et al 2005; Terpos et al 2005; Berenson et al 2006). The Spanish Myeloma Group has recently published data from a phase I/II trial in which patients ineligible for HDT were treated with standard MP and bortezomib; the overall response rate was 89%, with 32% CR (Mateos et al 2006). Data from the multicenter international randomized trial VISTA, that has completed the accrual of patients, are not available yet. Table 2 summarizes the prominent findings of the above studies.

Toxicity profile

An important matter in the studies that have evaluated thalidomide as front-line therapy for newly diagnosed MM

Table 2 Thalidomide in upfront therapy symptomatic MM patients not candidates for high dose chemotherapy (HDT)

Trial	Regimen	Thalidomide dose (mg/day)	Duration	No.of patients	Response (EBMT criteria)	Survival
Phase II (Dingli et al 2005)	TD (1)	200	Until PD	21	PR + MR 48%	Median PFS 18 months
Phase II (Dimopoulos et al 2006)	TDM (2)	300	3 cycles*	50	PR + CR 72%	Median time to progression 21.2 months
Phase II (Palumbo et al 2005)	MPT (3)	100	6 cycles#	41	PR + CR 73%	Median EFS 30 months
Phase III (Palumbo et al 2006)	MPT *v* MP (3)	100	6 cycles#	255	PR + CR 76% *v* 47.6%	2*y* EFS 54% *v* 27%
Phase II (Offidani et al 2005)	ThaDD (4)	100	–	41	PR + CR 89%	2*y* EFS 65% 2*y* OS 70%
Phase II (Williams et al 2004)	CTD (5)	200	2–6 cycles	15	PR + CR = 100%	–
Phase III (Ludwig et al 2005)	TD *v* MP for induction (6) T + IFN *v* IFN for maintenance	200–400	Until PD	146	PR + CR 57% *v* 50%	–
Phase III (Facon et al 2005)	MP *v* MPT *v* MEL100	50–400	1 year	436	–	Median PFS 17 *v* 28 *v* 19

Abbreviations: T, Thalidomide; D, Dexamethasone; P, prednisone; IFN, interferon α2b; PD, progressive disease; EBMT, European Group for Blood and Marrow Transplantation; MR, minimal response; PR, partial response; CR, complete response; EFS, event free survival; PFS, progression free survival; OS, overall survival; TD (1), D 40 mg d 1–4, 9–12 and 17–20 (odd cycles) d 1–4 (even cycles); TDM (2), D 12 mg/m^2 d 1–4, 17–20, Thalidomide 300 mg d 1–4, 17–20, oral melphalan 8 mg/m^2 d 1–4* Patients without evidence of PD received 9 additional cycles of MTD d 1–4; MP (3), Oral melphalan 4 mg/m^2 d 1–7, Prednisone 40 mg/mq d 1–7; #Patients without evidence of PD in the MPT arm continued T until PD; ThaDD (4), Thalidomide 100 mg/day, pegylated liposomal doxorubicin (40 mg/m^2 on day 1), dexamethasone (40 mg days 1–4, 9–12); 28-day cycle; CTD (5) , Oral cyclophosphamide 500 mg, d 1, 8 and 15, thalidomide at a dose of 100 to 200 mg daily , and oral D 40 mg on d 1–4 and 15–18. TD *v* MP (6), TD: Thalidomide 200 to 400 mg/day, D 40 mg days 1–4 and 15–18 (odd cycles) and days 1–4 (even cycles); MP: M 0.25 mg/kg d 1–4, P 2 mg/kg d 1–4.

patients concerns its dose- and the duration-related toxicity. Single agent thalidomide has been used in SMM/indolent MM at doses ranging from 200 mg to 800 mg, with frequent, mild, short term, reversible side effects, that were generally manageable with appropriate dose reduction. The most common adverse events included skin rash, sedation, constipation, peripheral neuropathy and fatigue (Rajkumar et al 2001, 2003; Weber et al 2003). In symptomatic myeloma patients thalidomide has been associated with chemotherapy, leading to an increased incidence of serious adverse events. Deep-vein thrombosis and peripheral neuropathy were the major adverse effects of thalidomide therapy in all these studies, leading to thalidomide discontinuation and/or dose reduction (Table 3). Thalidomide given in combination with chemotherapy including dexamethasone is associated with an increased risk of thrombosis (Zangari et al 2002, 2004). Mechanisms that lead to an increased risk of DVT for MM patients who receive primary therapy with TD or doxorubicin based regimens are still poorly defined and probably multifactorial. No relation between age and DVT and response has been detected (Rajkumar et al 2006). This complication occurred most commonly during induction treatment, when the burden of tumor is high, reaching incidence up to 34% without prophylactic anticoagulation (Barlogie et al 2006). After observing a high incidence of DVT in the initial phases of these studies, prophylactic anticoagulation was added and the DVT incidence was reduced in most of those studies (Abdelkefi et al 2005; Cavo et al 2005; Barlogie et al 2006; Dimopoulos et al 2006). The optimal prophylaxis for DVT after thalidomide has not been clearly established. It is now recommended that DVT prophylaxis, with prophylactic doses of LMWH, or full-dose anticoagulation with oral warfarin, or aspirin at doses from 81 mg to 325 mg per day, should be used in all patients starting therapy with thalidomide plus dexamethasone and or chemotherapy. Full-intensity warfarin and prophylactic doses of low molecular weight heparin (LMWH) have been advocated by some as preferable to aspirin, largely due to the inefficacy of aspirin as DVT prophylaxis in other settings (Clagett et al 1988).

Prospective, randomized studies are needed to determine the best prophylactic anticoagulation. Neuropathy is the most common cause of thalidomide discontinuation or dose reduction in newly diagnosed patients; it has been shown to be the major treatment-limiting toxicity affecting 50% to 80% of relapsed patients, the severity and reversibility of which have been related to both dose and duration of drug administration (Kumar et al 2003). In the study conducted by Barlogie et al (2006) peripheral neuropathy with a grade of more than 2 was observed in 27% of patients and was more common among patients at least 65 years old than among younger patients (29% *v* 20%, $P = 0.02$). Forty-one percent of patients who were at least 65 years old and who were receiving thalidomide had peripheral neuropathy, as compared with 17 percent of younger patients in the control group ($P < 0.001$). Peripheral neuropathy improved to less than grade 2 within three to four months after a dose reduction or cessation of thalidomide in nearly

Table 3 DVT and pheripheral neuropathy in newly diagnosed patients treated with thalidomide

Trial	DVT (%)	DVT prophilaxis (Y/N)	Peripheral neuropathy (%)
Phase II (Rajkumar et al 2002)	12	N	2 (grade 3–4)
Phase III (Rajkumar et al 2006)	17	N	7 (grade 3–4)
Phase II (Wang et al 2005)	7	Y	4 (grade 3–4)
Phase II (Abdelkefi et al 2005)	3	Y (after the first 13 patients)	5 (grade 3–4)
Phase II (Cavo et al 2005)	15	Y (after the first 19 patients)	4 (grade 3–4)
Phase II (Zervas et al 2004)	10	N	2.5 (grade 3–4)
Phase II (Schutt et al 2005)	26	N	26 (grade not known)
Phase II (Hassoun et al 2005)	11	Y	–
Phase III (Barlogie et al 2006)	30	Y (after the first 162 patients)	27 (≥ grade 2)
Phase III (Goldschmidt et al 2005)	8	Y	–
Phase II (Dimopoulos et al 2006)	9	N	9 (grade 2)
Phase III (Palumbo et al 2006)	12	Y (after the first 65 patients)	8 (grade 3–4)
Phase II (Offidani et al 2005)	12	Y	0
Phase II (Wang et al 2005)	5	Y	8 (grade 3)
Phase III (Ludwig et al 2005)	20	N	19 (grade 2–3)
Phase II (Alexanian et al 2002)	0	N	14
Phase II (Sahebi et al 2006)	0	N	7
Phase II (Brinker et al 2006)	0	N	4
Phase II (Dingli et al 2005)	0	N	5

90%. Lower incidence was observed in other studies both in old (grade 3–4 neuropathy was present in up to 10%), (Wang et al 2005; Dimopoulos et al 2004, 2006), and young patients (Abdelkefi et al 2005; Cavo et al 2005), where thalidomide was used either at lower doses (100 mg) or for a shorter period of time, suggesting that intermittent schemes of combined thalidomide can be used without loosing efficiency.

Thalidomide increased also the risk of grade 3–4 infections in most of these studies, thus anti-infective prophylaxis has been suggested to reduce this risk (Schutt et al 2005; Dimopoulos et al 2006; Offidani et al 2006). Other toxicities were observed less commonly or were milder, such as bradicardia, constipation and skin rash.

Conclusion

Thalidomide treatment may be an effective and relatively well-tolerated alternative front-line therapy for multiple myeloma. As an initial treatment to prepare patients for autologous stem-cell transplantation, thalidomide in combination with dexamethasone resulted in higher response rates than the combination of vincristine, doxorubicin, and dexamethasone or dexamethasone alone. However the results of the study of Barlogie and colleagues (2006) indicate that a complete response may not be a valid surrogate for overall survival in clinical trials. The higher rate of failure to respond to salvage therapy in the thalidomide group needs to be investigated further, with particular attention to the salvage potential of new drugs in patients who had received thalidomide as initial treatment. It will also be important to assess whether relapses of aggressive myeloma, such as those reported by Barlogie and colleagues (2005), also occur when thalidomide is reserved for maintenance therapy or combined initially with chemotherapy at conventional doses. The optimal timing for thalidomide administration is not well established. There may be significant advantages of receiving thalidomide for maintenance therapy after transplantation: resistance may be avoided; the risk of thromboembolism can be reduced, since this risk is highest during induction therapy; and the incidence of neurotoxic effects should be reduced with the later introduction of thalidomide at lower doses (50 to 100 mg) during maintenance therapy. Recent studies show that lenalidomide, may be safer and more effective than thalidomide. Similarly high activity has been observed with bortezomib in several phase II trials. Future trials should compare these active induction regimens to determine the optimum initial therapy for MM.

Acknowledgments

FC is recipient of Research Fellowship from the Fondazione Internazionale di Ricerca in Medicina Sperimentale, Torino, Italy.

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