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PRE-ASSESSMENT

Thalidomide for the Treatment of Multiple Myeloma

Before CCOHTA decides to undertake a health technology assessment, a pre-assessment of the literature is performed. Pre-assessments are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided here as a quick guide to important, current assessment information on this topic. Readers are cautioned that the pre-assessments have not been externally peer reviewed.

Introduction

Multiple myeloma (MM) is a cancer of the plasma cells. Advanced MM (Durie-Salmon stages II and III)[1] is characterized by the clonal proliferation of malignant plasma cells in the bone marrow. This is associated with the presence of high concentrations of monoclonal protein (known as the M protein) in the serum or urine, osteolytic lesions, anemia, hypercalcemia and renal disease.[2-6]

MM accounts for approximately 1% of incident cancers.[7,8] It occurs largely among the elderly, as the median age of onset is 68 years.[2,3,6,9] In 2003, the estimated age-standardized incidence rate (based on the 1991 Canadian population) is six per 100,000 men and four per 100,000 women. In 2003, there was an estimated 1,800 new cases of MM diagnosed and 1,250 deaths from the disease in Canada. The ratio of deaths to new cases, at 0.68 overall, is higher in women than in men.[8] This ratio is a crude indicator of disease severity, with a value closer to 1.0 indicating a poorer prognosis.

MM is an incurable disease. The median duration of survival among patients is six months when untreated and three to six years with treatment.[2,3,10-14] Typically disseminated at presentation, MM requires systemic therapy in patients with advanced or progressive disease.[13] Many organizations, including Cancer Care Ontario,[15] the BC Cancer Agency,[16] the US National Comprehensive Cancer Network[17] and the UK Myeloma Forum (on behalf of the British Committee for Standards in Haematology),[18] have developed clinical practice guidelines for the treatment of MM.

Melphalan, either alone or with prednisolone, is the gold standard of therapy. It increases the median duration of survival to approximately three years.[4,13,15-18] More aggressive combination chemotherapy regimens, such as VAD [vincristine, doxorubicin (Adriamycin®), dexamethasone] and dexamethasone can improve biochemical response rates (defined as a ≥50% reduction in the level of M protein in the serum[16,19]), but they do not prolong survival.[4,5,13,15-18] Interferon-alfa therapy has been used as maintenance therapy, but given the cost, the adverse effects and the lack of significant improvement in survival, it is not routinely recommended.[4,16,18]

Newly diagnosed patients under the age of 60 with advanced MM, good status performance and adequate renal function are given high-dose therapy followed by autologous stem cell transplantation. This has resulted in improved response and overall survival rates.[4,5,15-20] Allogeneic stem cell transplantation may be considered in younger

patients if a histocompatible donor is available, although this procedure is associated with a high mortality rate and significant morbidity.[4,5,9,14,16-18] Even after autologous or allogeneic stem cell transplantation, the rate of relapse and progression is high.[5,14,21,22] For many patients, palliative care is the only therapeutic option.[4,9,13,15,17,18]

The development of resistance to therapy is a characteristic of MM. This has spurred research in new biologically derived treatment strategies.[22] The increased bone marrow neovascularization that is observed in MM has been correlated with disease progression.[4,11,12,14,22-24] Thus, angiogenesis-inhibiting drugs, such as thalidomide, have been proposed as a therapeutic approach in advanced MM.[12,14,24]

Thalidomide, which is a derivative of glutamic acid, is pharmacologically classified as an immunomodulator. It is a nonpolar racemic mixture with the S- and R+ isomers presumed to have differential activities.[11,22,25-27] Thalidomide was withdrawn from the Canadian market in the 1960s after it was found to be a teratogen. Subsequently, the drug was shown to have an array of biologic properties that produce anti-inflammatory, immunomodulatory and anti-angiogenic effects.[11,25,28,29] These effects provided the rationale for continued research on a spectrum of immunologically mediated and infectious disorders; and on the treatment of solid and non-solid malignancies.[28] The diseases being studied include aphthous injuries of diverse type and location, chronic cutaneous erythematous lupus, ankylosating spondylitis, rheumatoid arthritis, Crohn's disease, graft-versus-host disease, some AIDS-associated disorders and diverse types of tumours. Trials in MM have shown promising results, producing favourable responses in patients for whom most available therapies had failed.

Thalidomide may be acting against MM in several ways. First, thalidomide may have a direct anti-tumour effect on myeloma or bone marrow stromal cells through free radical-mediated oxidative deoxyribonucleic acid (DNA) damage and effects on cell surface adhesion molecules. It may also induce G_1 growth arrest or apoptosis and alter drug resistance. Second, thalidomide may be acting in the bone marrow microenvironment by reducing the secretion and bioactivity of stimulatory cytokines, such as interleukin (IL)-6, IL-1β, IL-10, vascular endothelial growth factor (VEGF) and tumour necrosis factor (TNF)-α, triggered by myeloma cell to bone marrow stromal cell binding. Third, thalidomide has potent anti-angiogenic properties, probably because of its ability to block the action of VEGF and basic fibroblast growth factor (bFGF). It may play a role in tumour cell growth and survival; and in bone marrow angiogenesis. Finally, thalidomide may be active against MM via its immunomodulatory effects. It may inhibit the production of TNF-α, stimulate cytotoxic T cell proliferation and increase the secretion of interferon-γ (IFN-γ) and interleukin-2 (IL-2). It may also increase T helper cell type 2 (Th2) cytokine production, inhibit T helper cell type 1 (Th1) production and stimulate natural killer cell responses.[5,10,14,22,23,25,29-36]

In 1998, thalidomide (Thalomid®), which is manufactured by Celgene Corporation, was approved by the U.S. Food and Drug Administration (FDA) for the acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL), an inflammatory condition associated with leprosy; and as maintenance therapy for the prevention and suppression of cutaneous manifestation recurrences.[37] Because of the risk of teratogenicity, thalidomide is approved for marketing under a unique and comprehensive patient, physician, and pharmacist education and distribution program called the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®).[26,37] In March 2002, Celgene announced that it will conduct an additional clinical trial in early stage MM patients before submitting an application to the FDA.[38]

Pharmion Corporation has acquired the marketing and development rights to Thalomid® in Europe and Australia from Celgene. On August 19, 2003, thalidomide (Pharmion Corporation) was recommended for approval by the Australian Drug Evaluation Committee for the treatment of both relapsed and refractory MM and cutaneous manifestations of ENL.[39] Australia will be the only country in which thalidomide is approved as a therapy for relapsed and refractory MM. Pharmion filed a Marketing Authorization Application for thalidomide as a treatment for both relapsed and refractory MM and ENL in Europe during the first quarter of 2002.[40,41]

As of October 2003, there is no official information regarding the regulatory status of thalidomide in Canada. Thalidomide is available through Health Canada's Special Access Programme. In 2002, 3,074 authorizations were granted by the Special Access Programme, mostly for patients with MM (Mr. Ian MacKay**,** Unit Head, Special Access Unit, Clinical Trials and Special Access Programme, Senior Medical Advisor Bureau, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada, Ottawa, ON: personal communication, 2003 Feb 26).

Two new classes of thalidomide analogues are being developed. The immunomodulatory drugs (IMiDs™; Celgene) and the selective cytokine inhibitory drugs (SelCIDs™; Celgene) are composed of small molecules. These orally available compounds have a better safety profile and are many times more potent than thalidomide.[2,42] One IMiD, CC-5013 (Revimid™, Celgene), received fast track designation from the FDA for the treatment of relapsed or refractory MM[42] and for the treatment of myelodysplastic syndromes.[43] CC-4047 (Actimid™, Celgene), the next IMiD, is being tested in a phase I-II clinical trial in refractory MM. A third IMiD is in preclinical evaluation.[42]

Thalidomide for the Treatment of Multiple Myeloma

Research Questions

Thalidomide is the first drug in three decades to show activity in patients with MM.[2,12,30,44] The advantages of thalidomide include its oral route of administration (Thalidomid® is available as capsules of 50 mg, 100 mg and 200 mg strengths) and its lack of myelosuppression.[3,5,24,36] Potential teratogenicity and peripheral neuropathy, however, limit its use.

- What is the evidence regarding benefits from the use of thalidomide for the treatment of MM?
- What are the potential harms associated with thalidomide?

Assessment Process

A literature search strategy for PubMed (1966-5 Sep 2003), The Cochrane Library (2003 Issue 2), web sites, clinical practice guidelines and clinical trials registries (according to the Canadian Coordinating Office for Health Technology Assessment's HTA checklist) was performed by an information specialist in consultation with the lead researcher.

Summary of Findings

Tables 1 to 5 summarize the guidelines and selected prospective and retrospective studies from 1999 to date.

Table 1: Thalidomide for the treatment of MM

Type of Report	Citation	Main Findings
Guideline	Cavenagh *et al.,* 2003[45]	"Thalidomide has significant activity both as a single agent and in combination with other therapies in patients with de novo and advanced myeloma. However, several major questions remain unanswered. Indeed, the optimal dose is still uncertain, as is its role in maintenance therapy following high-dose melphalan. The potential benefit of combining thalidomide with dexamethasone as induction therapy for newly diagnosed patients with myeloma is being investigated and results are awaited with considerable interest. Similarly, the combination of thalidomide with chemotherapy is still of uncertain benefit. All these questions need to be addressed in prospective randomized clinical trials before recommandations about the precise role of thalidomide can be given." "Despite the difficulties and uncertainties, the use of thalidomide is a major advance in the clinical management of myeloma."
Retrospective study in cohort of patients treated at Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; and enrolled in five clinical trials	Zangari *et al.,* 2003[46] (earlier publications reported incidence of deep venous thrombosis in three of five clinical trials[47-49])	"Zangari *et al.* have analyzed risk factors associated with development of deep venous thrombosis in a cohort of 535 patients treated with thalidomide with cytotoxic chemotherapy or without cytotoxic chemotherapy (thalidomide and dexamethasone only). A total of 82 patients (15.3%) developed deep venous thrombosis; 4 cases (0.7%) of pulmonary embolism were observed, but none were fatal. On multivariate analysis, the combination of thalidomide with chemotherapy including doxorubicin was associated with the highest odds ratio (OR) for deep venous thrombosis (4.3; P≤0.001); in addition, newly diagnosed disease (OR, 2.5; P=0.001) and chromosome 11 abnormality (OR, 1.8; P=0.048) were also independent predictors for DVT." "However, the development of deep venous thrombosis did not adversely affect survival when examined as a time-dependent variable and adjusted for standard risk features (hazard ratio, 0.8; P=0.162)."
Case-series study (most common primary diagnoses were multiple myeloma and renal cell carcinoma)	Bennett *et al.,* 2002[50]	"Sixty-seven case reports of thalidomide-associated thrombotic events in thalidomide-treated patients were identified from MedWatch reports, the FDA's spontaneous reporting program, for the period between October 1998 and June 2001. After case matching to exclude duplicate reports, data were obtained on 29 additional in thalidomide-treated patients participating in phase 2 and 3 clinical trials who experiences thrombotic events." "Of the 96 patients, 48 developed deep venous thrombosis, 25 developed pulmonary embolism, and 23 developed both deep venous thrombosis and pulmonary embolism. Twelve patients died of complications related to pulmonary embolism." "The findings suggest that, when thalidomide and chemotherapy or corticosteroids are coadministered, as many as 1 in 2 to 1 in 5 treated patients developed thromboembolic complications." "Although thalidomide is likely to be a therapeutic advance in the treatment of cancer, physicians should be vigilant about the potential occurrence of thromboembolic complications, especially among patients who are being treated with other forms of chemotherapy."

Table 2: Single-agent thalidomide in patients with relapsed or refractory MM

Citation	Design Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Singhal *et al.*, 1999[12] Barlogie *et al.*, 2001[30]	Uncontrolled, prospective trial Single-centre Median follow-up of surviving patients: 22 months	N=169 THAL 200 to 800 mg/day	30	Discontinuations due to intolerance or toxicity: 17 Toxicities ≥grade 2: 58 Central nervous system (mainly sedation and somnolence, confusion, depression, tremor): 25 Gastrointestinal tract (mainly constipation, infrequently nausea or vomiting): 16 Peripheral nerves (sensory neuropathy): 9 Deep venous thrombosis: <2 Cytopenia: <2
Alexanian and Weber, 2000[51]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=45 THAL 100 to 800 mg/day	24	Discontinuations due to intolerance or toxicity: 4 Constipation: 66 Fatigue: 60 Dry skin, pruritus or rash: 35 Unsteadiness: 28 Numbness, tingling or tremor: 25 Dry mouth: 24 Mild neutropenia: <20 Ankle edema: <20 Deep venous thrombosis: 7
Durie and Stepan, 2000[52]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=36 THAL 50 to 400 mg/day	25	Discontinuations due to intolerance or toxicity: 25 Sedation, dizziness, tremor, incoordination or confusion: 14 Increased serum creatinine (including one death due to renal failure): 8 Transient mild rash: 6 Mild peripheral neuropathy: 6 Constipation: 3 Palmar erythema: 3 Extra medullary relapse: 3
Hideshima *et al.*, 2000[53]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=44 THAL 100 to 800 mg/day	27	No data
Juliusson *et al.*, 2000[54]	Uncontrolled, retrospective trial Multicentre Follow-up: no data	N=23 THAL 200 to 800 mg/day	43	Discontinuations due to intolerance or toxicity: 9 Drowsiness: 100 Sedation, vertigo and mood changes: 17 Skin problems: 17 Pneumonia: 17 Leg edemas: 13 Moderate peripheral neuropathy: 4 Asymptomatic sinus bradycardia: 4 Advanced hypothyrosis: 4

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*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Kneller *et al.*, 2000[55]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=17 THAL 200 to 800 mg/day	59	Discontinuations due to intolerance or toxicity: 6 Somnolence: 65 Severe tiredness: 29 Constipation: 29 Spells of dizziness: 6 Bradycardia: 6
Pini *et al.*, 2000[56]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=5 THAL 100 to 200 mg/day	60	Discontinuations due to intolerance or toxicity: no data Toxicities were grade 1 or 2, including: Constipation: 40
Rajkumar *et al.*, 2000[57] Kumar *et al.*, 2003[58]	Uncontrolled, prospective trial Single-centre Median follow-up of entire study population: 18.7 months Median follow-up of surviving patients: 28.5 months (range 3.7 to 20.3)	N=32 THAL 200 to 800 mg/day	31	Discontinuations due to intolerance or toxicity: no data Toxicities ≥grade 3: Neutropenia: grade 3: 25 grade 4: 6 Neuropathy: 16 Sedation: 13 Neuromotor effects: 6 Constipation: 6 Sinus bradycardia: 6 Febrile neutropenia: 6 Dyspnea: 3 Fatigue: 3 Aspartate transaminase: 3 Cerebral ischemia: 3 Thrombosis: 3 Rash: 3 Vertigo: 3
Yakoub-Agha *et al.*, 2000[59] Yakoub-Agha *et al.*, 2002[60]	Uncontrolled, retrospective trial Multicentre Median follow-up of study population: 338 days (range 247 to 629)	N=83 THAL 50 to 800 mg/day	48	Discontinuations due to intolerance or toxicity: 16 176 adverse events recorded in 72 patients during first 90 days of treatment: Somnolence: 56 events Constipation: 45 events Edema: 15 events Depression or mood changes: 14 events Peripheral neuropathy: 10 events Xerostomia: 9 events Nausea or vomiting: 8 events Others: 19 events

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Citation	Design Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Hus *et al.*, 2001[61]	Uncontrolled, prospective trial Multicentre Follow-up: no data	N=53 THAL 200 to 400 mg/day	36	Discontinuations due to intolerance or toxicity: 9 Somnolence: grade 1: 79 Weakness or fatigue: grade 1: 66 grade 2: 6 Constipation: 58 Leukopenia: grade 1: 17 grade 2: 4 grade 3: 6 Tingling or numbness: grade 1: 19 grade 2: 4 Peripheral neuropathy: grade 1: 19 grade 2 4 Fever: grade 1: 8 grade 2: 2 Vertigo: 9 Skin rash: grade 1: 6 grade 2: 2 Sinus bradycardia: grade 1: 4 grade 2: 2 Mood changes or depression: grade 1: 2 grade 2 : 4 Deep venous thrombosis: 4
Tosi *et al.*, 2001[62] Tosi *et al.*, 2002[63]	Uncontrolled, prospective trial Multicentre Median follow-up of study population: 8 months (range 2 to 16)	N=65 THAL 100 to 800 mg/day	26	Discontinuations due to intolerance or toxicity: 12 Toxicities >grade 2: Constipation: 52 Lethargy: 34 Neurological toxicity: 14 Skin rash: 11 Renal toxicity: 5 Edema: 3 Leukopenia: 3 Deep venous thrombosis: 2 Others: 5
Neben *et al.*, 2001[64] Neben *et al.*, 2001[65] Neben *et al.*, 2002[66]	Uncontrolled, prospective trial Single-centre Median follow-up of study population: 17 months (range 1 to 30)	N=83 THAL 100 to 400 mg/day	20	Discontinuations due to intolerance or toxicity: 14 Somnolence: grade 1 to 2: 51 Constipation: grade 1 to 2: 48 Dryness of mouth: grade 1 to 2: 42 Tingling or numbness: grade 1 to 2: 36 grade 3: 6 Fatigue or weakness: grade 1 to 2: 36 Tremor: grade 1 to 2: 33 Infection: grade 1 to 2: 24 grade 3: 6 grade 4: 2

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Citation	Design Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
				Dizziness: grade 1 to 2: 24 Rash: grade 1 to 2: 14 Mood changes: grade 1 to 2: 12 Deep venous thrombosis: grade 3: 4 Syncope: grade 3: 2 Worsening of congestive heart failure: grade 3: 2 Myocardial infarction: grade 4: 1 Hearing disturbances: grade 3: 1 Leukocytopenia: grade 3 : 1
Boulin *et al.*, 2002[67]	Uncontrolled, retrospective trial Single-centre Follow-up: no data	N=21 THAL 150 to 700 mg/day (mean dosage)	19	Discontinuations due to intolerance or toxicity: 19 Somnolence: 100 Constipation: 100 Polyneuropathy: 24
Ciepluch *et al.*, 2002[68]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=13 THAL 200 to 400 mg/day, patients also received pamidronate 90 mg IV, 3h continuous infusion, at regular 28-day intervals	54 (≥25% reduction of serum M protein level)	Discontinuations due to intolerance or toxicity: 23 Constipation: 38 Somnolence: 30 Dizziness: 30 Neutropenia: 23 Thrombocytopenia: 23 Polyneuropathy: 15 Tremors: 7 Dry skin: 7 Confusion syndrome: 7
Dmoszyńska *et al.*, 2002[69]	Uncontrolled, retrospective trial Single-centre Follow-up: no data	N=30 THAL 200 to 500 mg/day	33	No data
Johnston and Abdalla, 2002[70]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=8 THAL 50 to 400 mg/day	38	Discontinuations due to intolerance or toxicity: no data Toxicities were mild, mainly somnolence. No evidence of neuropathy

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Citation	Design Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Leleu *et al.*, 2002[71]	Uncontrolled, prospective trial Single-centre Median follow-up of surviving patients: 483 days (range 230 to 529)	N=16 THAL 50 to 400 mg/day. Patients who progressed at 50 mg/ day received salvage therapy: increased THAL dose alone or with another drug, usually dexamethasone	44	Discontinuations due to intolerance or toxicity: no data Toxicity ≥grade 2 at 200 to 400 mg/day: Neurological: 13 Digestive: 13 Toxicity at 50 mg/day: Mild nausea: 6
Kakimoto *et al.*, 2002[72]	Uncontrolled, prospective trial Single-centre Mean follow-up of study population: 44 weeks (range 6 to 26)	N=26 THAL 200 to 400 mg/day	31	Discontinuations due to intolerance or toxicity: 12 Most toxicities were grade 1: Somnolence: 73 Peripheral neuropathy: 50 Constipation: 42 Skin rash: grade 1: 31 grade 2: 4 Neutropenia: grade 2: 4 grade 3: 8 grade 4: 23 Dry mouth: 27 Headache: 7 Finger tremor: 12 Low-grade fever: 12 Mild muscle weakness: grade 2: 8 Mild elevation of transaminase: 4 Dyspnea: 4 Lymphocytopenia: 4 Depression: 4 Mild myalgia with elevation of serum creatinine phosphokinase (CPK): 4

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†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Corso *et al.*, 2003[73]	Uncontrolled, prospective trial Single-centre Mean follow-up of study population: 3 months	N=17 THAL 100 to 200 mg/day	35	Discontinuation due to intolerance or toxicity: 0 Adverse events always mild: no data
Huang *et al.*, 2003[74]	Uncontrolled, prospective trial Single-centre Mean follow-up of study population: 13 months (range 2 to 34)	N=50 THAL 100 to 800 mg/day	20	Discontinuations due to intolerance or toxicity: no data Major toxicities, generally grade 2: Fatigue, dizziness and somnolence: 75 Constipation: 63 Transient leukopenia: 44 Skin eruptions: 44 Digital numbness: 44
Mileshkin *et al.*, 2003[75]	Uncontrolled, prospective trial Multicentre Median follow-up of study population: 18 months (range 6 to 26)	N=75 THAL 200 to 1,000 mg/day	23	Discontinuations due to intolerance or toxicity: 16 Frequently reported toxicities (>10%): Constipation: grade 1: 17, grade 2: 44, grade 3: 13 Fatigue: grade 1: 28, grade 2: 39, grade 3: 8 Sensory neuropathy: grade 1: 16, grade 2: 21, grade 3: 3 Motor neuropathy: grade 1: 17, grade 2: 8, grade 3: 4 Depressed level of consciousness: grade 1: 12, grade 2: 7, grade 3: 3 Rash or desquamation: grade 1: 7, grade 2: 8, grade 3: 3 Nausea: grade 1: 8, grade 2: 8 Mouth dryness: grade 1: 8, grade 2: 5 Headache: grade 1: 5, grade 2: 7 Dizziness: grade 1: 7, grade 2: 5 Nonfatal thromboembolism: 4 Febrile neutropenia: 3 Sinus bradycardia: grade 3: 1

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†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Patriarca *et al.*, 2003[76]	Uncontrolled, retrospective trial Single-centre Follow-up: no data	N=10 THAL 100 to 400 mg/day	38	Discontinuations due to intolerance or toxicity: no data Peripheral neuropathy: grade 2: 10 Myalgia: 10
Wechalekar *et al.*, 2003[77]	Uncontrolled, retrospective trial Single-centre Follow-up: no data	N=30 THAL 100 to 200 mg/day	30	Discontinuations due to intolerance or toxicity: 17 All toxicities were grade 1 to 2: Fatigue 54 Sleepiness: 48 Constipation: 43 Neuropathy: 24 Dizziness: 10 Rash: 8 Skin dryness: 8 Blurring vision: 2 Chin numbness: 2 Cracked feet: 2 Oral vesicular eruptions: 2

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†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Table 3: Single-agent thalidomide in patients with previously untreated asymptomatic MM

Citation	Design, Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Rajkumar *et al.*, 2001[78] Rajkumar *et al.*, 2003[79]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=31 THAL 50 to 800 mg/day	32	Discontinuations due to intolerance or toxicity: no data Constipation: grade 1 to 2: 87 Peripheral neuropathy: grade 1 to 2: 87 grade 3 to 4: 3 Sedation: grade 1 to 2: 74 grade 3 to 4: 6 Fatigue or weakness: grade 1 to 2: 65 grade 3 to 4: Skin rash: grade 1 to 2: 55 Tremor: grade 1 to 2: 35 Sinus bradycardia: grade 1 to 2: 23 grade 3 to 4: 3 Edema: grade 1 to 2: 16 grade 3 to 4: 3 Ataxia: grade 1 to 2: 16 Hearing loss: grade 3 to 4: 3 Deep venous thrombosis: grade 3 to 4: 3
Weber *et al.*, 2003[80]	Case-control study Single-centre Follow-up: no data	N=28 THAL 100 to 600 mg/day	36 (≥75% reduction of serum M protein level)	Discontinuations due to intolerance or toxicity: no data Most toxicities were grades 1 to 2: Constipation: 68 Numbness or tingling: 68 Rash or dry skin: 61 Unsteadiness: 43 Fatigue: 39 Tremor: 36 Edema: 25 Infection: grade 3: 14 Thrombotic or embolic event: grade 3: 4

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*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]
†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Table 4: Combination therapy with thalidomide in patients with relapsed or refractory MM

Citation	Design, Follow-up	Number of Patients Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Dimopoulos *et al.*, 2001[81]	Uncontrolled, prospective trial Multicentre Follow-up: no data	N=44 THAL 200 to 400 mg/day DEXA 20 mg/m^2/day orally, days 1 to 4, 9 to 12, 17 to 20 in month 1, days 1 to 4 in subsequent months	55	Discontinuations due to intolerance or toxicity: 7 Most toxicities were grades 1 to 2: Constipation: 75 Somnolence or fatigue: 57 Xerostomia: 34 Mood changes: 33 Tremor: 30 Peripheral neuropathy: grade 1 to 2: 16 grade 3 to 4: 8 Skin rash: 21 Headache: 21 Edema: 17 Leukopenia: 9 Deep venous thrombosis: 7
Palumbo *et al.*, 2001[82]	Uncontrolled, prospective trial Single-centre Median follow-up of study population: 8 months (range 3 to 16)	N=77 THAL 50 to 100 mg/day DEXA 40 mg/m^2/day orally, days 1 to 4 every month	42	Discontinuations due to intolerance or toxicity: 10 Most toxicities were grade 1: Tingling and numbess: grade 1: 14 grade 2: 3 Constipation: 12 Weakness and fatigue: 8 Sedation: 6 Changes in work habit: 4 Mood changes and depression: 4 Tremor: 3 Dizziness: 3 Hypothyroidism: 3 Erysipelas: grade 3: 3 Renal toxicity (including one case of acute renal failure requiring dialysis): 3

CIS=cisplatin; CLAR=clarithromycin; CTX=cyclophosphamide; DEXA=dexamethasone; DOXO=doxorubicin (Adriamycin); ETO=etoposide; IFN=interferon; PRED=prednisone; THAL=thalidomide; VIN=vincristine.
*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]
†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design, Follow-up	Number of Patients Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Ahmad *et al.*, 2002[83]	Uncontrolled, retrospective trial Single-centre Follow-up: no data	N=4 THAL 50 to 400 mg/day VIN 0.4 to 0.5 mg/day IV continuous infusion for 4 days monthly DOXO 9 to 10 mg/m^2/day IV continuous infusion for 4 days monthly DEXA 40 mg/day orally days 1 to 4, 9 to 12 and 17 to 20 monthly	100	One patient (25%) discontinued THAL due to congestive heart failure; plans to restart once cardiac status stabilizes. Somnolence and constipation were common: no data Mild to moderately severe peripheral neuropathy: 25 Congestive heart failure: 25 Central nervous system progression: 25
Boulin *et al.*, 2002[67]	Uncontrolled, retrospective trial Single-centre Follow-up: no data	Patients refractory to THAL monotherapy N=4 THAL 150 to 700 mg/day (mean dosage) DEXA 40 mg/m^2/day IV, days 1 to 4 monthly N=4 THAL same as above DEXA same as above CTX 400 mg/m^2/day IV continuous infusion for 4 days monthly ETO 40 mg/m^2/day IV continuous infusion for 4 days monthly	50	No specific data See Table 2, same citation

CIS=cisplatin; CLAR=clarithromycin; CTX=cyclophosphamide; DEXA=dexamethasone; DOXO=doxorubicin (Adriamycin); ETO=etoposide; IFN=interferon; PRED=prednisone; THAL=thalidomide; VIN=vincristine

*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

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Citation	Design, Follow-up	Number of Patients Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Coleman *et al.,* 2002[84]	Uncontrolled, prospective trial Multicentre Follow-up: no data	N=55 (including 6 patients treated for Waldenström's macroglobulinemia and 9 with previously untreated disease) Data from 50 patients available for analysis THAL 50 to 200 mg/day DEXA 40 mg/day orally once weekly or every two weeks CLAR 250 to 500 mg orally twice daily	74	Discontinuations due to intolerance or toxicity: 16 Sudden deaths (three patients with cardiac and pulmonary disease at baseline): 6 Gastrointestinal (constipation, abdominal discomfort, metallic taste): grade 1: 24; grade 2: 8 *Clostridium difficile* infections: grade 3: 4 Neurotoxicity (tremor, drowsiness, paresthesias): grade 1: 22; grade 2: 30; grade 3: 16; grade 4 to 5: 2 Endocrine (cushingoid facies, hypertension, glucose intolerance, hyperactivity): grade 1: 18; grade 2: 6; grade 3: 4 Cardiovascular: Deep venous thrombosis: grade 3: 4 Pulmonary emboli: grade 4 to 5: 4 Cerebrovascular accident: grade 4 to 5: 2 Other (skin, hematologic, edema, pulmonary): grade 1: 12; grade 2: 18; grade 3: 2; grade 4 to 5: 6
García-Sanz *et al.,* 2002[85]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=22 THAL 200 to 800 mg/day DEXA 40 mg/day orally for 4 days every three weeks CTX 50 mg/day orally	41	Discontinuations due to intolerance or toxicity: 9 One sudden death and one death due to septicemia: Most frequent toxicities were grade 2: Somnolence: 32 Infections: 27 Constipation: 23 Neutropenia: grade 2 to 3: 18 Dizziness: 13 Meralgia paresthetica: 5

CIS=cisplatin; CLAR=clarithromycin; CTX=cyclophosphamide; DEXA=dexamethasone; DOXO=doxorubicin (Adriamycin); ETO=etoposide; IFN=interferon; PRED=prednisone; THAL=thalidomide; VIN=vincristine

*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design, Follow-up	Number of Patients Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity (%)
Abdalla and Mahmoud, 2003[86]	Uncontrolled, retrospective trial Single-centre Mean follow-up of study population: 98 weeks (range 75 to 141)	N=4 THAL 50 to 200 mg/day DEXA 20 mg/m^2/day orally once a week, starting after maximum response to THAL obtained	100, all showed further drop of paraprotein level when DEXA added to therapy (data not reported)	Neuropathy: grade 1: 25 grade 2: 25 grade 3: 25 Deep venous thrombosis: 25
Anagnostopoulos *et al.*, 2003[87]	Uncontrolled, retrospective trial Single-centre Follow-up: no data	47 THAL 100 to 600 mg/day DEXA 20 mg/m^2/day orally on days 1 to 5, repeated every 15 days	47 (≥75% reduction of serum M protein level)	Discontinuations due to intolerance or toxicity: no data Constipation: grade 1 to 2: 51 Paresthesias: grade 1 to 2: 39 Skin dryness or rash: grade 1 to 2: 23 grade 3: 4 Fatigue or somnolence: grade 1 to 2: 21 Numbness or tingling of feet: grade 3: 8 Deep venous thrombosis (including one case of non-fatal pulmonary embolism): grade 3: 8 Ileus: grade 3: 2
Huang *et al.*, 2003[74]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=25 THAL 100 to 800 mg/day DEXA 4 mg/day orally every other day	24	Discontinuations due to intolerance or toxicity: no data Treatment-related mortality (one case of idiopathic interstitial lung disease with death due to respiratory failure and one case of sudden cardiac death): 8 Unusual toxicities: Vascular thrombosis (artery and vein): 8 Acute acalculous cholecystitis: 8 Other toxicities: no data

CIS=cisplatin; CLAR=clarithromycin; CTX=cyclophosphamide; DEXA=dexamethasone; DOXO=doxorubicin (Adriamycin); ETO=etoposide; IFN=interferon; PRED=prednisone; THAL=thalidomide; VIN=vincristine

*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design, Follow-up	Number of Patients Regimen (Range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Kropff *et al.*, 2003[88]	Uncontrolled, prospective trial Multicentre Follow-up: no data	N=60 THAL 100 to 400 mg/day DEXA 20 mg/m^2/day orally days 1 to 4, 9 to 12, 17 to 20 every month; could be reduced to days 1 to 4 only, after first month CTX (hyperfractionated): 300 mg/m^2 IV over 3 h every 12 h for 6 doses, days 1 to 3 (total dose 1.8 mg/m^2) every month	68	Discontinuations due to intolerance or toxicity: 8 Treatment-related mortality: 3 Neutropenia: grade 3: 19; grade 4: 67 Neuropathy (mainly tingling, numbness and tremor): grade 1: 13; grade 2: 40; grade 3: 16 Constipation: grade 1: 19; grade 2: 14; grade 3: 13 Thrombocytopenia: grade 3: 13; grade 4: 17 Infections: grade 3: 17; grade 4: 9 Deep venous thrombosis: grade 3: 7; grade 4: 2 Liver (serum aspartate transaminase and serum alanine transaminase): grade 3: 9 Hyperglycemia: grade 3: 3; grade 4: 5 Myelodysplasia or secondary acute myeloid leukemia: 7 Mood changes: 7 Renal failure: grade 3: 3; grade 4: 3 Atrial arrhythmia: grade 3: 3; grade 4: 2 Edema: grade 3: 5 Cerebrovascular events: grade 3: 5 Bradycardia: grade 3: 3 Sedation: 3 Hypothyroidism: grade 2: 2

CIS=cisplatin; CLAR=clarithromycin; CTX=cyclophosphamide; DEXA=dexamethasone; DOXO=doxorubicin (Adriamycin); ETO=etoposide; IFN=interferon; PRED=prednisone; THAL=thalidomide; VIN=vincristine

*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design, Follow-up	Number of Patients Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity (%)
Lee *et al.*, 2003[89]	Uncontrolled, prospective trial Single-centre Follow-up: 3 months after second cycle	N=236 2 cycles (repeated at a 4 to 6 week interval) of: THAL 400 mg/day DEXA 40 mg/day orally for 4 days CIS 10 mg/m^2/day IV continuous infusion for 4 days DOXO 10 mg/m^2/day IV continuous infusion for 4 days CTX: 400 mg/m^2/day IV continuous infusion for 4 days ETO: 40 mg/m^2/day IV continuous infusion for 4 days	32 (≥75% reduction of serum M protein level)	Discontinuations due to intolerance or toxicity: no data Treatment-related mortality: 4 Hematologic toxicities ≥grade 2: Neutropenia: 65 Thrombocytopenia: 11 associated with 22 episodes of hemorrhage Non-hematologic toxicities ≥grade 3: Gastrointestinal: Nausea and vomiting: 6 Stomatitis or pharyngitis: 4 Colitis: 3 Esophagitis or gastritis: 2 Diarrhea: 2 Hepatobiliary: Hypoalbuminemia: 2 Hyperbilirubinemia: 1 Cardiovascular: Thromboembolism: 15 Supraventricular arrhythmia: 2 Sinus bradycardia: 1 Hypotension: 1 Congestive heart failure: 1 Pulmonary: Dyspnea: 1 Pulmonary edema: 1 Neurologic: Sensory neuropathy: 4 Ataxia: 2 Syncope: 2 Seizure: 1 Infectious: Documented infection: 4 Neutropenic fever: 9 Metabolic: Hypophosphatemia: 4 Hypocalcemia: 3 Hypokalemia: 2 Hypomagnesemia: 1 Hyponatremia: 1 Decrease in bicarbonate: 1 Erythema or rash 1

CIS=cisplatin; CLAR=clarithromycin; CTX=cyclophosphamide; DEXA=dexamethasone; DOXO=doxorubicin (Adriamycin); ETO=etoposide; IFN=interferon; PRED=prednisone; THAL=thalidomide; VIN=vincristine

*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Citation	Design, Follow-up	Number of Patients Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity (%)
Mileshkin *et al.*, 2003[75]	Uncontrolled, prospective trial Multicentre Follow-up: no specific data for this phase of trial	Patients with stable or responsive disease after 12 weeks of THAL monotherapy N=19 THAL 200 to 1,000 mg/day IFN 1.5 to 3.0 X 10^6 U subcutaneous injection thrice weekly	47 (addition of IFN improved response in 4 patients, with conversion from stable disease to partial response; 5 maintained partial response)	Discontinuations due to intolerance or toxicity: 53 Toxicities ≥grade 3: Neutropenia: grade 3: 26 grade 4: 5 Fatigue: grade 3: 11 Seizures: grade 3 : 11 Constipation: grade 3: 5 Cerebrovascular schemia: grade 3: 5 Inner ear or hearing: grade 3: 5 Anemia: grade 4: 5
Minnema *et al.*, 2003[90]	Cross-sectional study Single-centre Follow-up: no data	N=6 THAL 100 to 200 mg/day DEXA 40 mg/day orally for 4 days DOXO 9 mg/m^2/day IV short infusion for 4 days N=12 THAL same as above DEXA (pulsed): 20 mg/day N=2 THAL same as above PRED 10 to 20 mg/day	65	Discontinuations due to intolerance or toxicity: no data Deep venous thrombosis: 35 Other toxicities: no data

CIS=cisplatin; CLAR=clarithromycin; CTX=cyclophosphamide; DEXA=dexamethasone; DOXO=doxorubicin (Adriamycin); ETO=etoposide; IFN=interferon; PRED=prednisone; THAL=thalidomide; VIN=vincristine

*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Table 5: Combination therapy with thalidomide in patients with previously untreated symptomatic MM

Citation	Design, Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Rajkumar *et al.*, 2002[91]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=50 THAL 200 mg/day (except in first 7 patients in whom dose escalation up to 800 mg/day was permitted as tolerated) DEXA 40 mg/day orally, days 1 to 4, 9 to 12, 17 to 20, odd cycles days 1 to 4, even cycles repeated monthly	64	Dose escalation discontinued after first 7 patients, because of unexpected grade 3 or 4 skin toxicity in one case of toxic epidermal necrolysis and in one case of generalized erythroderma; and grade 2 exfoliation in another patient. Constipation: grade 1 to 2: 72; grade 3 to 4: 8 Neuropathy: grade 1 to 2: 58; grade 3 to 4: 2 Fatigue: grade 1 to 2: 50 Sedation: grade 1 to 2: 46; grade 3 to 4: 2 Rash: grade 1 to 2: 38; grade 3 to 4: 6 Tremor: grade 1 to 2: 30 Edema: grade 1 to 2: 28; grade 3 to 4: 2 Dyspnea: grade 3 to 4: 4 Depression: grade 3 to 4: 2 Arrhythmia: grade 3 to 4: 2 Inner ear: grade 3 to 4: 2 Syncope: grade 3 to 4: 2
Ghobrial *et al.*, 2003[92]	Case-control study Single-centre Follow-up: no data	N=24 THAL 100 to 600 mg/day DEXA 40 mg/m^2/day orally, days 1 to 4, 9 to 12, 17 to 20, each month, alternating with days 1 to 4	71 (plateau and response at BMT)‡	No data.

[i]DEXA=dexamethasone; THAL=thalidomide

*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]

†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

‡Plateau and response undefined. BMT=bone marrow transplantation. Authors concluded: "Although this is a small retrospective study and needs to be verified in larger cohorts, our data demonstrate that thalidomide, used for a limited time and discontinued approximately 3 to 4 weeks before attempted mobilization, does not substantially affect peripheal stem cell mobilization or engraftment, but delays early platelet engraftment of 20,000/μl."

Citation	Design, Follow-up	Number of Patients, Regimen (range)	Main Findings (based on entire study population)	
			Response* (%)	Toxicity† (%)
Weber *et al.*, 2003[80]	Uncontrolled, prospective trial Single-centre Follow-up: no data	N=40 THAL 100 to 400 mg/day DEXA 20 mg/m^2/day orally, days 1 to 4, 9 to 12, 17 to 20, repeated monthly	72 (≥75% reduction of serum M protein level)	Treatment-related mortality: 8 Most toxicities were grades 1 to 2: Constipation: 55 Fatigue: 55 Rash or dry skin: 55 Numbness or tingling: 50 Edema: 35 Tremor: 30 Thrombotic or embolic event: grade 3: 15 Unsteadiness: 13 Infection: grade 3: 13

[i]DEXA=dexamethasone; THAL=thalidomide
*Efficacy criteria: response defined as reduction in level of M protein≥50% in serum.[16,19]
†Toxicity graded according to World Health Organization (WHO) criteria: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

Conclusion

Thalidomide has produced biochemical responses in patients for whom most available therapies have failed. The daily dose may vary between 50 and 800 mg, with a median tolerated dose of 400 mg.[11,14,36] Major toxicities of thalidomide include constipation, sedation, skin rash, fatigue and peripheral neuropathy. These may limit its use. Close monitoring is recommended, as thromboembolic complications and toxic epidermal necrolysis have been reported, especially among patients who are being treated with thalidomide plus high-dose dexamethasone or anthracyclines.[3,23,46-50,93-100]

Prospective clinical trials are needed to determine the optimal dose and schedule of thalidomide and its role in combination with glucocorticoids, chemotherapeutic agents and stem cell transplantation, in both untreated and relapsed or refractory MM, and to understand its mechanisms of action.[5,9,11,14,30,36]

Although the literature on thalidomide is extensive, there is a lack of high quality evidence regarding its impact on the quality of life in individuals with MM. Clinical investigations in progress or recently completed will help define the role of thalidomide in the management of both untreated and relapsed or refractory MM (Tables 6, 7).

Table 6: Ongoing or recently completed phase II clinical trials of thalidomide in MM

Clinical Trial Register	Project Status	Project Title
National Cancer Institute	Not specified	Phase II pilot study of vincristine, doxorubicin, dexamethasone and low-dose thalidomide in patients with newly diagnosed stage I, II or III multiple myeloma.
National Cancer Institute	Not specified	Phase II randomized study of bevacizumab with or without thalidomide in patients with relapsed or refractory multiple myeloma.
National Cancer Institute	Not specified	Phase II study of oblimersen, thalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma.
National Cancer Institute	Not specified	Phase II study of sequential high dose melphalan, busulfan, and cyclophosphamide followed by peripheral blood stem cell rescue, interferon alfa, pamidronate and thalidomide in patients with multiple myeloma.
National Cancer Institute	Not specified	Phase II study of thalidomide and dexamethasone induction followed by tandem melphalan and peripheral blood stem cell transplantation followed by prednisone and thalidomide maintenance in patients with multiple myeloma.
National Research Register	Completed	The effect of thalidomide on bone turnover in patients with relapsed multiple myeloma treated consecutively at the Royal Hallamshire Hospital.
National Research Register	Completed	A study in the safety and efficacy of oral melphalan, prednisolone and thalidomide in the treatment of multiple myeloma.
National Research Register	Completed	A study of the safety and efficacy of thalidomide combined with vincristine, Adriamycin and dexamethasone (T-VAD) in the treatment of younger patients with multiple myeloma.
National Research Register	Completed	A phase II study of thalidomide for relapsed or refractory multiple myeloma (UKMF study).
National Research Register	Ongoing	A study of the safety, efficacy and mechanism of action of thalidomide in the treatment of multiple myeloma.
National Research Register	Ongoing	An analysis of potential underlying factors contributing to thrombogenicity in myeloma patients treated with thalidomide (safety study).
National Research Register	Ongoing	Thalidomide after high-dose therapy in myeloma.
National Research Register	Ongoing	Thalidomide maintenance following high dose therapy in multiple myeloma: a phase II study.

Table 7: Ongoing or recently completed phase III clinical trials of thalidomide in MM

Clinical Trial Register	Project Status	Project Title
ClinicalTrials.gov	Ongoing	A multicenter parallel-group, placebo controlled, randomized, double-blind study of combination thalidomide plus glucocorticoid therapy versus glucocorticoid therapy alone as induction therapy for previously untreated subjects with multiple myeloma.
Lombardi Cancer Center – Clinical Services	Ongoing	Cyclophosphamide and thalidomide in relapsed or refractory multiple myeloma.
National Cancer Institute	Not specified	Phase III randomized study of dexamethasone with or without thalidomide in patients with newly diagnosed multiple myeloma (protocol E1A00). (This is a Canadian clinical trial.)
National Cancer Institute	Not specified	Phase III randomized study of thalidomide and prednisone as maintenance therapy after autologous stem cell transplantation in patients with multiple myeloma (protocol CAN-NCIC-MY10). (This is a Canadian clinical trial.)
National Cancer Institute	Not specified	Phase III randomized study of doxorubicin, dexamethasone, and high-dose melphalan with or without thalidomide in patients with multiple myeloma.
National Cancer Institute	Not specified	Combination chemotherapy with or without thalidomide in treating patients with multiple myeloma.
National Cancer Institute National Institutes of Health	Not specified	A trial comparing two post-autologous stem cell transplant strategies for multiple myeloma patients: matched sibling non-myeloablative allogeneic stem cell transplantation versus dexamethasone and thalidomide therapy. (This is a phase II-III clinical trial.)

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