A Multicenter Phase II Trial of Thalidomide and Celecoxib for Patients with Relapsed and Refractory Multiple Myeloma

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Abstract Preclinical data indicates that cyclooxygenase-2 (COX-2) inhibition impairs plasma cell growth and potentially synergizes with thalidomide. We performed a trial in previously treated patients with myeloma using thalidomide up to a maximum dose of 800 mg/d with celecoxib (400 mg bid). Outcomes were compared with a prior trial of thalidomide. Sixty-six patients with median age of 67 (range, 43-85) received a median dose of thalidomide and celecoxib of 400 and 800 mg/d, respectively, with median durations of treatment of 27 and 13 weeks, respectively. The most common toxicities associated with premature discontinuation of celecoxib (n = 30 of 53, 57%) were fluid retention and deterioration of renal function. Overall response rate (RR) was 42% and with 20 months median follow-up; the actuarial median progression-free survival and overall survival were 6.8 and 21.4 months, respectively. Unlike our prior study, age >65 years was not predictive of inferior RR due to improvement in RR in older patients with the combination (37% versus 15%, P = 0.08). The RR was superior in patients who received a total dose of celecoxib exceeding 40 g in the first 8 weeks of therapy (62% versus 30%, P = 0.021). Progression-free survival and overall survival were also improved. Other predictors for inferior progression-free survival were age >65 years (P = 0.016) and elevated β_2-microglobulin (P = 0.017). This study provides evidence that the addition of high-dose celecoxib adds to the antimyeloma activity of thalidomide but this comes with unacceptable toxicity. Future studies should use newer COX-2 inhibitors with thalidomide, or their respective derivatives.

For patients with relapsed or refractory multiple myeloma, response rates (RR) of 45% to 55% have been reported with the thalidomide/dexamethasone combination which compares favorably with the 25% to 35% RR of thalidomide alone (1–3). For previously untreated patients receiving thalidomide/corticosteroid combination treatment, RRs of ~65% have been observed (1, 4). Although the thalidomide/dexamethasone combination has never been directly compared with thalidomide alone, most clinicians will now initiate thalidomide in combination with corticosteroid therapy. When we initiated this study, we were also seeking to explore a simple combination therapy that had the potential to increase RRs over that of thalidomide alone while minimizing toxicity.

Cyclooxygenase (COX) enzymes are involved in development and progression of a range of cancers with the COX-2 isoform being particularly important, metabolizing arachidonic acid to produce prostaglandin E_2, which in turn induces tumor angiogenesis (5–8), a pathologic process important for the growth of many tumors including malignant plasma cells (9). Conversely, selective inhibition of COX-2 suppresses angiogenesis, induces apoptosis, and reduces hematogenous metastases in various *in vitro* and *in vivo* tumor models (5, 8, 10–15). Recent evidence also indicates that celecoxib, a well-known COX-2 inhibitor, can exert proapoptotic effects independent of its inhibition of COX-2 (16). These preclinical findings have translated into a clinical benefit with celecoxib delaying the development of colorectal polyps in patients with familial adenomatous polyposis (17). Celecoxib has also recently been examined for the treatment of established tumors, with some early promising results in prostate and lung cancer (18–21).

In support of the postulate that hematologic malignancies are possible targets for COX-2 inhibitors, COX-2 *overexpression* has been shown in various leukemia, B-cell lymphoma, and multiple

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myeloma cell lines (15, 22–25). Moreover, with respect to primary tumor cells, Wun et al. have shown increased COX-2 expression in primary human lymphoma cells (15), whereas we[10] and others have also shown consistent overexpression of COX-2 (in the absence of COX-1 overexpression) by bone marrow plasma cells in patients with multiple myeloma (25, 26).

Celecoxib has the potential to retard plasma cell growth through various mechanisms. Interleukin-6 (IL-6) production is in part mediated by IL-1β via a prostaglandin E_2 loop. Moreover, this can be partially blocked with the nonspecific COX inhibitor, indomethacin, resulting in reduced IL-6 production (8, 27, 28). Celecoxib abrogates tumor necrosis factor/nuclear factor-κB activation, a critical regulator of apoptosis and angiogenesis (29). Another COX-2 inhibitor, R-etodolac, diminishes Wnt/β-catenin signaling, a pathway that is important in malignant plasma cell growth, induces apoptosis via a bcl-2-dependent pathway, and alters expression of adhesion molecules in chronic lymphocytic leukemia and malignant plasma cells (30–32). NS-398, a COX-2 inhibitor induces apoptosis of plasma cells via a Bcl-2-independent pathway in a dose-dependent manner. Although celecoxib has demonstrable potent inhibitory *in vitro* effects on the growth of various hemopoietic cell lines, including myeloma cell lines and primary myeloma patient cells, the predominant mechanism of action of the various COX-2 inhibitors remains unknown (15, 22–25).

There is potential for a synergistic effect with thalidomide and celecoxib. (a) Dexamethasone, which is known to act synergistically with thalidomide to induce higher RRs, inhibits the synthesis of COX-2 (8, 33, 34). (b) Thalidomide decreases levels of tumor necrosis factor-α, a strong inducer of COX-2 expression (35). (c) Thalidomide decreases production of COX-2 mRNA (36) whereas celecoxib reduces COX-2 function, both resulting in reduced prostaglandin E_2. (d) Thalidomide inhibits angiogenesis primarily through inhibition of growth factors such as vascular endothelial growth factor (37, 38), whereas celecoxib exerts its inhibitory effect on this process primarily through suppression of prostaglandin E_2 (6, 7). Animal models have also shown synergism (39). Although there have been some recent reports of a potential synergistic effect of thalidomide and COX-2 inhibitors in the treatment of various solid tumors (40, 41), to date, there have been no prospective studies of this combination.

Taken together, we felt there was sufficient rationale to undertake a study of the combination of thalidomide and celecoxib and selected the celecoxib dose used in prior studies of familial adenomatous polyposis (17). One objective of the study was to assess the tolerability of this combination, excluding patients with substantial renal impairment or significant bleeding risk. We did not anticipate a major pharmacologic interaction; celecoxib is metabolized mainly by cytochrome *P*450 CYP2C9, whereas thalidomide is metabolized by spontaneous hydrolysis (42, 43).

We were also interested to confirm in a prospective fashion the various prognostic markers we had previously identified with thalidomide-based therapy (44). To provide an opportunity to compare the outcomes of the two successive trials, the individual "stepwise" dose escalation remained identical. Additional objectives of the trial were to determine RR, response duration, progression-free survival, and overall survival and compare these with our prior thalidomide trial (44).

[10] Unpublished data.

Patients and Methods

Patients. Eligible patients were those with relapsed or resistant multiple myeloma following prior systemic combination chemotherapy (failure of dexamethasone monotherapy alone was not acceptable) who required further systemic therapy. Patients considered to have resistant disease were those who were refractory to front-line induction therapy that included at least two cycles of a regimen containing an alkylating agent or an anthracycline, or had an initial transient response but progressed during front-line induction therapy. Minimum age for enrollment was 18 years, with no upper age limit. Further eligibility criteria included Eastern Cooperative Oncology Group performance status 0 to 2 and written informed consent. This consent included agreement by both male and female patients to take precautions to prevent conception during the treatment program. Exclusion criteria were prior therapy with thalidomide, known hypersensitivity to celecoxib, previous life-threatening bleeding or asthma, urticaria or allergic-type reactions related to nonsteroidal anti-inflammatory drug use, previous allergic reaction to sulfonamides, concomitant use of aspirin, other nonsteroidal anti-inflammatory drug or coumadin, platelet count $<50 \times 10^9$/L, renal impairment as manifested by creatinine >1.5× upper normal limit (UNL) or creatinine clearance <50 mL/min on formal measurement, liver transaminases >2× UNL or bilirubin >1.5× UNL, females who were pregnant or lactating, concurrent serious medical or psychiatric illness which would preclude treatment administration or patient compliance with the protocol, and preexisting peripheral neuropathy exceeding grade 1 (National Cancer Institute criteria, version 2.0, 1998). The Ethics Committee of each participating institution gave approval for the study.

Treatment. Patients commenced treatment with thalidomide (Thalomid, Celgene Corp., Warren, NJ) at a dose of 200 mg/d orally, with planned dose escalation each 14 days by a further 200 mg/d, up to a total dose of 800 mg/d. Dose escalation was ceased if patients developed intolerable side effects as judged by the investigator. The dose could be reduced if necessary so that patients continued on an individual maximum tolerated dose. At the commencement of thalidomide treatment, patients also commenced celecoxib (Celebrex, Pfizer Australia Pty. Ltd., New South Wales, Australia) 400 mg oral bid. Three patients with creatinine >1.5 UNL and a further patient who had an aspartate transaminase of >2× UNL were entered into the study: they were retained in the analysis. Patients were not allowed to be receiving concomitant steroid medications. Ongoing bisphosphonates for bone disease was allowed.

If patients developed any grade ≥3 toxicity thought to be related to celecoxib, the drug was withdrawn until the toxicity fell to grade ≤1 and the patient was recommenced on celecoxib at 200 mg bid. If grade ≥3 toxicities reoccurred then the celecoxib was ceased permanently. Such patients were continued on thalidomide alone. Thalidomide ± celecoxib was continued until progressive disease or patient intolerance.

Evaluation of patients and criteria for response. At trial entry, patients had baseline history and examination findings including Eastern Cooperative Oncology Group performance status recorded. Baseline skeletal survey and bone marrow aspirate and biopsy was required with cytogenetics strongly recommended. Fluorescent *in situ* hybridization studies for otherwise occult chromosomal deletions or translocations were not done routinely. A baseline full blood count and the following biochemistry were recorded: serum creatinine, serum calcium, liver function tests, lactate dehydrogenase, C-reactive protein, CA-153 (MUC-1), and β_2-microglobulin (β_2M). Baseline serum and 24-hour urine collection were obtained for protein electrophoresis, immunoelectrophoresis, and immunofixation. Full blood count and basic

biochemistry were repeated every 2 weeks up to 24 weeks and then every 4 weeks while on treatment. Thyroid function tests were not done routinely. Toxicity assessments and serum and urine protein electrophoresis were to be done every 4 weeks. Bone marrow aspirate and biopsy were repeated three monthly until disease progression. Nerve conduction studies were done at the discretion of the investigator and skeletal survey every 4 months. If patients discontinued thalidomide ± celecoxib because of toxicity, patients were reassessed every 3 months with the date of disease progression or death from any cause being recorded.

Adverse events, apart from laboratory tests, were categorized according to their relationship to study drugs (not related, possibly, probably, or definitely related) and were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0, 1998.

Response criteria were identical to those of the previous trial (44). A complete response (CR) was defined as disappearance of serum M protein and/or Bence Jones proteinuria (determined by immunofixation) on two determinations at least 4 weeks apart plus <5% plasma cells in the bone marrow in a patient with no signs or symptoms of disease. Partial response (PR) was defined by all of the following: reduction of serum M protein level to <50% of the pretreatment value on two determinations at least 4 weeks apart; a decrease of at least 50% in urinary light chain excretion from a pretreatment value of >1.0 g/24 hours or a fall to <0.1 g/24 hours if pretreatment value was 0.5 to 1.0 g/24 hours; a decrease in the size of measurable plasmacytoma(s) of at least 50% of the sum of the products of the cross diameters of each measurable lesion; and a decrease in bone pain from moderate or severe to none or mild. Stable disease (SD) was defined as failure to meet response criteria for disease response or progression. An assessment of SD did not require confirmation on a second assessment. Progression of disease (PD) was defined as any of the following: an increase in serum M protein to >50% above the previous nadir; an increase in urinary M protein to >50% above the previous nadir and a light-chain excretion of at least 0.2 g/24 hours; appearance of a new plasmacytoma or an increase in a preexisting plasmacytoma by >50%, appearance of a new lytic bone lesion or a >50% increase in the size of any existing lesion.

Comparison with previous thalidomide trial. This trial followed on from a previously reported 75-patient phase II trial of thalidomide for patients with relapsed or refractory myeloma (MMTHAL99/031; ref. 44). The dose escalation strategy of thalidomide in the prior trial was identical, and IFN-α was added at week 12 in selected patients in the prior trial (n = 19). For MMTHAL99/031, patients entered the trial between September 26, 1999 and June 20, 2001, with a close-out date of January 2, 2002 chosen for time to event analyses.

In an attempt to obtain a similar group of patients for an exploratory comparison of the results from the two trials, we retrospectively examined patient data from that trial including only patients that met the same additional exclusion criteria incorporated into the current trial; platelets < 50×10^9/L and renal impairment as manifested by creatinine >1.5× UNL or creatinine clearance of <50 mL/min on formal measurement. Fifty-eight of the original 75 patients met such criteria. Seventeen of the 58 patients received IFN-α on trial MMTHAL99/031 commencing after week 12.

Statistical methods. The predetermined sample size was based on showing a significant ($P < 0.05$) RR (CR + PR) of ≥50%, equivalent to a 60% improvement in the prior RR of 29% observed in our prior thalidomide trial, with a 90% power to detect this difference. This derived an initial sample size of 39 patients. However, after 20 patients were accrued, an interim analysis of toxicity showed that 30% of patients had discontinued celecoxib by 3 months, primarily due to the development of significant peripheral edema (see below). In an attempt to better assess the potential contribution of celecoxib in addition to thalidomide, the planned sample size was increased to 66 patients.

A close-out date of March 1, 2004 was chosen for all time to event analyses, with the vital status of each patient taken to be the vital status on the close-out date.

RRs were calculated as percentages of all patients and 95% exact confidence intervals (95% CI) were estimated using the probabilities of the binomial distribution. Time to response and duration of response were estimated using Kaplan-Meier analysis, with censoring of times at the close-out date for those patients still on treatment without having responded or not having relapsed in the case of response duration. The two-sided Fisher exact test or the Cochran-Armitage test for trend was used to compare the RRs between prognostic factor subgroups.

Prognostic factors prospectively stipulated for analyses were age at commencement of treatment (≤65 versus >65 years), β_2M level (≤3 versus >3 to <6 versus ≥6 mg/L), lactate dehydrogenase level (within reference range, above normal), hemoglobin level (≥110 versus <110 g/L), C-reactive protein level (<6 versus 6 – 10 versus >10 mg/L), serum creatinine level (≤0.13 versus >0.13 mmol/L), serum calcium level (≤2.6 versus >2.6 mmol/L), plasma cells in bone marrow (≤50% versus >50%), response to last prior chemotherapy (no versus yes), and CA-153 (within reference range versus above normal).

All patients who commenced treatment were included in the analyses of progression-free survival and overall survival. Progression-free survival time was measured from the date of commencing protocol treatment to the date of first progression or death from any cause without prior progression. Overall survival was measured from the date of commencing protocol treatment to the date of death from any cause. The Kaplan-Meier method was used to estimate overall survival and progression-free survival, with censoring of survival times at the close-out date for those patients not experiencing the relevant event. The Brookmeyer-Crowley method was used to estimate 95% CIs for median survival times; 95% CIs for the percentages surviving at particular times were calculated using the logit transformation. Differences or trends between groups were tested using the Mantel-Cox log-rank test. Multivariate analyses of prognostic factors for progression-free survival and overall survival were carried out using Cox proportional hazards regression and the stepwise backward procedure to identify independent prognostic factors, with P values based on the likelihood ratio test. Removal and entry levels of significance were 0.05 and 0.01, respectively. Patients with unknown values of any prognostic factor in the model were excluded from the multivariate analyses. Chromosome 13 deletion was not included in the analyses because it was undetermined for a large number of patients.

As some patients were still on therapy at the close-out date, the Kaplan-Meier method was used to estimate median total dose and duration of thalidomide treatment, with the Mantel-Cox log-rank test used to make comparisons between the current and previous trial. The Wilcoxon rank sum test was used to compare the individual maximum tolerated dose and average dose per day between the current and previous trial. The worst grades of adverse events, which were categorized as probably or definitely related to study drugs, have been reported as toxicities.

Results

Patient characteristics. Sixty-six patients were accrued across seven Australian centres between August 24, 2001 and October 15, 2003, with a close-out date of March 1, 2004 chosen for time-to-event analyses. The median age was 67 years (range, 43-85). Table 1 summarizes the baseline characteristics of the patients. The median duration of follow-up from commencement of treatment to the close-out date was 20 months (range, 4-30 months). Fifteen (23%) patients remained on treatment at the close-out date.

Treatment received and toxicity: Thalidomide. There were no deaths related to thalidomide or celecoxib. The median average dose per day of thalidomide was 329 mg (range, 85-727 mg).

Table 1. Baseline patient characteristics

Characteristics	*n* (%)
Gender	
Male	39 (59)
No. prior chemotherapy regimens	
1	17 (26)
2	22 (33)
3	20 (30)
4-8	7 (11)
Stage (Durie salmon)	
I	5 (8)
II	46 (69)
III	15 (23)
Plasma cells in bone marrow aspirate (%)	
≤50	51 (77)
>50	13 (20)
Dry specimen	1 (2)
Not done	1 (2)
Disease state on commencing thalidomide	
Relapsed	52 (79)
Refractory or transient response to prior treatment	14 (21)
ECOG performance status	
0	24 (36)
1	24 (36)
2	14 (21)
Unknown	4 (7)
Hemoglobin, <100 g/L	23 (35)
Platelets, 50-150 $\times 10^9$/L	18 (28)
Neutrophils, <1.0 $\times 10^9$/L	11 (17)
β_2-Microglobulin (mg/L)	
≤3	26 (39)
>3 to <6	23 (35)
≥6	16 (24)
Not done	1 (2)
LDH	
<UNL	54 (82)
>UNL	10 (15)
Not done	2 (3)
CA153	
≤UNL	41 (62)
>UNL to 2× UNL	11 (17)
≥2× UNL	3 (5)
Not done	11 (17)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

The median total dose of thalidomide received up to the close-out-date was 64 g, with a median duration of thalidomide treatment of 27 weeks. The median individual maximum tolerated dose was 400 mg/d (range, 200-800 mg/d) with doses of 200 to 300, 400 to 500, 600, and 800 mg/d received by 22%, 43%, 18%, and 18% of patients, respectively. We compared the doses of thalidomide in this trial with that received by the 58 patients with similar eligibility criteria in the prior thalidomide trial. This comparison is detailed in Table 2. Patients in the current study received a lower average dose per day (398 versus 329 mg, $P = 0.018$) and a lower median individual maximum tolerated dose per day (600 versus 400 mg, $P = 0.01$).

There were no unexpected thalidomide-related side effects and the side effects seen were generally manageable (Table 3). The most common toxicities (grade >1) included constipation (50%), fatigue (45%), sensory (32%), and motor neuropathy (15%). Three patients (5%) had nonfatal thromboembolism. Fifty-one patients had discontinued thalidomide by the close-out date, 45% due to progressive disease, and 20% due to toxicity, with neurotoxicity being the primary reason in six (60%). Of these 51 patients, 29 (57%) had already stopped celecoxib treatment because of toxicity (25), intercurrent illness (2), need for concomitant drugs (1), and other (1).

Celecoxib. The median average dose per day of celecoxib was 738 mg (range, 153-800 mg) with a median total dose of celecoxib received up to the close-out date of 50 g and a median duration of celecoxib treatment of 13 weeks. Fifty-three (80%) patients came off celecoxib by the close-out date with a median duration of treatment in that group of 11 weeks (range, 1-72 weeks). Reasons for discontinuation of celecoxib at any time during the study were toxicity in 30 (57%; see below), progressive disease (19%) intercurrent illness (7.5%), need for concomitant drugs (4%), death (2%), and "other" reasons (11%).

The celecoxib related side effects are detailed in Table 3. Celecoxib-related fluid retention (grade >1) was more problematic, manifested either as peripheral edema (30%) or shortness of breath as a result of pulmonary congestion (18%). Five patients (8%) developed a progressive rise in creatinine (grade ≥1) while receiving the celecoxib/thalidomide combination, in the absence of progressive myeloma renal disease. Upper gastrointestinal toxicity manifested as epigastric/esophageal discomfort or hematemesis/melena occurred in 11% and 3% of patients, respectively. Notably, no patients suffered demonstrable myocardial or cerebral ischemic events.

Of the 30 patients who ceased celecoxib for toxicity, the reasons were peripheral edema (8), worsening renal function (7), rash (5), pulmonary edema (5), upper gastrointestinal toxicity (2), nonfatal venous thromboembolism requiring anticoagulation (1), thrombocytopenia (1), and worsening neuropathy (1). Of these, seven also came off thalidomide due to toxicity (two at the same time and five at a later date). One patient discontinued thalidomide because of toxicity but remained on celecoxib.

With respect to dose modifications of celecoxib, 27 of 66 (41%) patients either had a dose reduction in celecoxib or stopped and restarted on the same or a lower dose. Of these, 12 subsequently had to cease celecoxib because of toxicity. Although 39 patients (59%) did not have "dose reduction" of celecoxib, 18 (46%) of these discontinued celecoxib because of toxicity without interim dose reductions. Thus, 45 patients (68%) either required interim cessation, and/or dose reduction, or immediate discontinuation of celecoxib because of toxicity.

Efficacy. The overall RR to the protocol treatment based on intention-to-treat analysis was 42% (95% CI, 30-55%) with two CR (3%) and 26 PR (39%). Thirty-two patients (48%) achieved SD as their best response and three patients (5%) progressed. The remaining three were not assessable for response because they were removed from study before

Table 2. Summary of thalidomide treatment received

	Thalidomide/celecoxib	Thalidomide*	P
n	66	58	
Duration on treatment† (wk)			
Median (95% CI)	27 (18-41)	24 (16-42)	0.8‡
Total thalidomide dose† (g)			
Median (95% CI)	64 (39-105)	66 (50-180)	0.18‡
Average daily thalidomide dose† (mg)			
Median (range)	329 (85-727)	398 (82-767)	0.018§
Maximum daily thalidomide dose (mg/d)†			
Median	400	600	0.01§
Range	200-800	200-1,000	
200	11 (17%)	8 (14%)	
300	3 (5%)	1 (2%)	
400	27 (41%)	16 (28%)	
500	1 (2%)	1 (2%)	
600	12 (18%)	5 (9%)	
800	12 (18%)	25 (43%)	
900	0 (0%)	1 (2%)	
1,000	0 (0%)	1 (2%)	

*Prior thalidomide trial (44).
†Up to close-out date.
‡Log-rank test.
§Wilcoxon rank sum test.

completing 2 weeks of therapy. The median time to first response was 2.5 months (95% CI, 2.1-2.8 months) with all responses occurring within 13 months of commencing treatment.

Among the 28 patients who achieved a CR/PR, 13 (46%) had relapsed (9) or died (4) by the close-out date. The median duration of response was 13.7 months (95% CI, 7.3 to >28 months) and the 12-month actuarial duration of response was 56.9% (95% CI, 34.6-76.7%). Median progression-free survival and overall survival for all 66 patients was 6.8 months (95% CI, 4.6-12.6 months) and 21.4 months (95% CI, 14.3 to >30 months), respectively. The estimated 1-year progression-free survival and overall survival was 37% (95% CI, 26-50%) and 65% (95% CI, 52-76%), respectively.

We compared the RRs, duration of response, progression-free survival, and overall survival in this trial to that observed by the 58 patients with similar eligibility criteria in the prior MMTHAL99/031 thalidomide trial (44). This comparison is

Table 3. Summary of frequently reported nonhemopoietic treatment-related adverse events by maximum National Center Institute grade for all patients (*N* = 66)

Adverse event	Total, *N* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Nausea	18 (27)	11 (17)	7 (11)	—	—
Constipation	51 (77)	18 (27)	22 (33)	11 (17)	—
Rash/desquamation	20 (30)	7 (11)	9 (14)	4 (6)	—
Headache	10 (15)	5 (8)	4 (6)	1 (2)	—
Fatigue	55 (83)	25 (38)	25 (38)	4 (6)	1 (2)
Depressed level of consciousness	34 (52)	12 (18)	19 (29)	3 (5)	—
Motor neuropathy	23 (35)	13 (20)	8 (12)	2 (3)	—
Sensory neuropathy	46 (70)	25 (38)	14 (21)	7 (11)	—
Mouth dryness	19 (29)	13 (20)	4 (6)	2 (3)	—
Peripheral edema	31 (47)	11 (17)	16 (24)	4 (6)	—
Pulmonary edema	16 (24)	4 (6)	7 (11)	4 (6)	1 (2)
Renal Impairment	5 (8)	2 (3)	2 (3)	1 (2)	—
Upper gastrointestinal toxicity	7 (11)	2 (3)	3 (5)	2 (3)	—
Bleeding	2 (3)	2 (3)	—	—	—
Thrombosis	3 (5)	—	1 (2)	2 (3)	—

Table 4. Comparison of outcomes of patients on current thalidomide/celecoxib trial to previous thalidomide trial

	Thalidomide/celecoxib (95% CI)	Thalidomide* (95% CI)	*P*
n	66	58	
Response (%)			
CR/PR	42 (30-55)	29 (18-43)	0.14 †
CR/PR (age ≤65)	48 (30-67)	42 (25-61)	0.80 †
CR/PR (age >65)	37 (21-55)	15 (4-34)	0.08 †
SD	48 (36-61)	53 (40-67)	0.59 †
PD	5	12	
NE	5	5	
Time to response (mo)	2.5 (2.1-2.8)	3.6 (1.9-5.6)	0.21 ‡
Duration of response (mo)	13.7 (7.3 to >28.2)	13.6 (9.1 to >36.4)	0.88 ‡
Median PFS (mo)	6.8 (4.6-12.6)	6.3 (3.7-10.3)	0.26 ‡
% 12-mo PFS	37 (26-50)	28 (17-41)	
Median OS (mo)	21.4 (14.3 to >30)	19.8 (12.6 to >26.3)	0.96 ‡
% 12-mo OS	65 (52-76)	67 (53-78)	

Abbreviations: PFS, progression-free survival; OS, overall survival.
*Prior thalidomide trial (44).
†Fisher's exact test.
‡Log-rank test.

detailed in Table 4 and Figs. 1 and 2. With respect to RR, response duration, progression-free survival, and overall survival for the entire cohort, there was no significant difference between the two trials.

In an unplanned retrospective analysis, we compared the RR (CR/PR) in patients >65 years in the prior thalidomide trial (adjusted for the modified eligibility criteria) with the current thalidomide/celecoxib trial and showed a trend in favor of the thalidomide/celecoxib combination; 15% (4 of 27) versus 37% (13 of 35; $P = 0.08$, Fisher's exact test). Of note, the vast majority of the responses in the prior study occurred in the first 3 months, a period where patients had not yet commenced IFN-α.

We also did an analysis where we compared this study to the 41 patients in the prior MMTHAL99/031 thalidomide trial who had not received IFN. The RR (CR/PR) of those patients in the prior trial who received thalidomide alone was inferior (17%, 7 of 41; 95% CI, 7-32%) to that observed in the current trial [42%, $P = 0.01$, Fisher's exact test]. The median progression-free survival and predicted 12-month progression-free survival were also inferior at 4.6 months (95% CI, 2.8-6.9 months) and 21% (95% CI, 10-37%), respectively ($P = 0.049$,

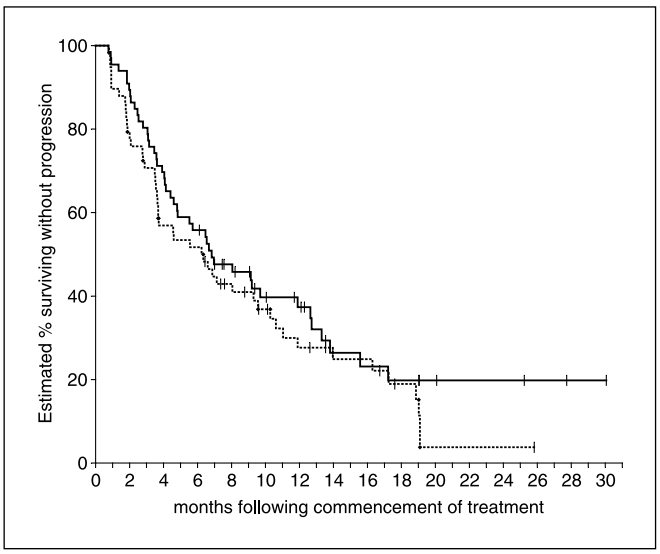

Fig. 1. Kaplan-Meier curve of progression-free survival for those on the current trial (*solid line*) and the prior thalidomide trial (*dotted line*). Patients with censored progression-free survival times are shown with tick marks. Median progression-free survival was 6.8 months (95% CI, 4.6-12.6) versus 6.3 months (95% CI, 3.7-10.3). $P = 0.26$.

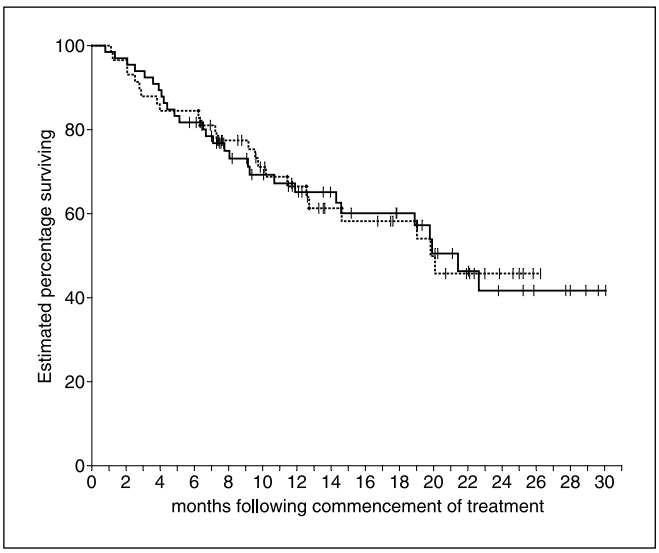

Fig. 2. Kaplan-Meier curve of overall survival for those on the current trial (*solid line*) and the prior thalidomide trial (*dotted line*). Patients with censored overall survival times are shown with tick marks. Median overall survival was 21.4 months (95% CI, 14.3 to >30 months) versus 19.8 months (95% CI, 12.6 to >26 months. $P = 0.96$.

log-rank test). The overall survival of 19 months (95% CI, 9.2 to >25.2 months) and predicted 12-month overall survival of 56% (95% CI, 40-71%) were not different (P = 0.386). However, we recognize that by only analyzing those patients in the prior trial who did not receive IFN, we are potentially excluding a better prognosis subgroup (i.e., those with a good PS and good enough hematopoietic variables to receive IFN).

To further assess for any antimyeloma effect of celecoxib, we wanted to examine outcome according to actual amount of celecoxib received. We recognized that by examining only the total dose of celecoxib patients received over the entire study period, we would bias the results in favor of those patients who remained progression free and, by protocol definition, remained on celecoxib/thalidomide longer (thus receiving a higher total dose of celecoxib). Therefore, we examined the outcome of patients depending on the total dose of celecoxib received by week 8 of treatment. This time was chosen as our prior trial showed that the majority of responses had occurred by this time and coincided with a time point for disease assessment. At this 8-week time point, the planned maximum dose of celecoxib to be received was 44.8 g (equivalent to 800 mg/d). To account for transient drug interruptions, we divided the patients into those who received >40 or <40 g total dose in the first 8 weeks (23 of 26 received 44.8 g). For patients receiving <40 g, the RR was 30% (12 of 40) compared with a RR of 62% (16 of 26) for patients who received a higher total dose of celecoxib of 40 to 44.8 g (P = 0.021, Fisher's exact test). Moreover, those who received the higher dose had a superior median progression-free survival (12.7 versus 4.6 months) and predicted 12-month progression-free survival [51% (95% CI, 31-70%) versus 28% (95% CI, 16-45%); P = 0.039, log-rank test; Fig. 3]. With respect to overall survival, those who received the higher dose had a superior outcome with the median overall survival not yet reached compared with 18.9 months in those receiving <40 g celecoxib. The predicted 12-month overall survival

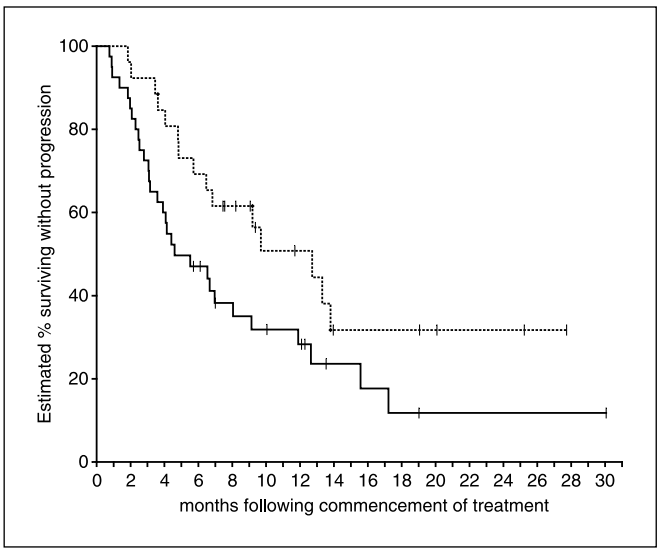

Fig. 3. Kaplan-Meier curve of progression-free survival for those who received <40 g celecoxib in the first 8 weeks of treatment (*solid line*) and those who received ≥40 g (*dotted line*). Patients with censored progression-free survival times are shown with tick marks. Median progression-free survival was 4.6 months (95% CI, 3.2-9.1) versus 12.7 months (95% CI, 5.7-›27.7. P = 0.039.

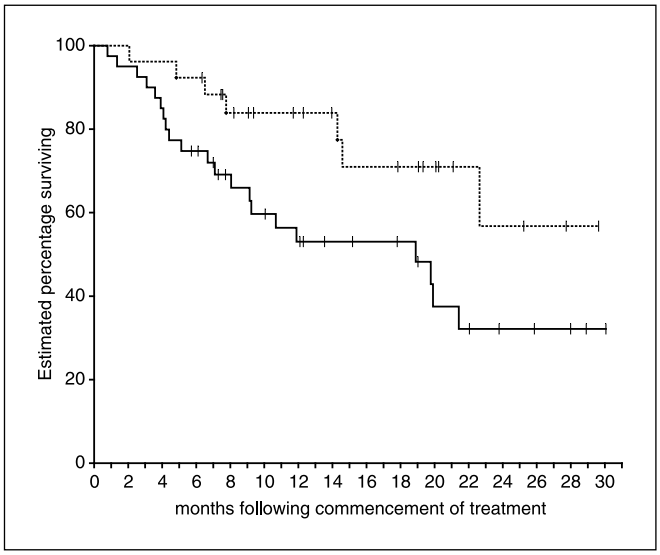

Fig. 4. Kaplan-Meier curve of overall survival for those who received <40 g celecoxib in the first 8 weeks of treatment (*solid line*) and those who received ≥40 g (*dotted line*). Patients with censored overall survival times are shown with tick marks. Median overall survival was 18.9 months (95% CI, 8.1 to ›30.1) versus ›29.6 months (95% CI, 14.6 to ›29.6. P = 0.035.

was 84% (95% CI, 64-94%) versus 53% (95% CI, 37-69%; P = 0.035, log-rank test; Fig. 4).

In an attempt to assess whether different doses *below* the 40 g threshold affected outcome, we used a further cut point of 20 g. (Note: doses of 200, 400, and 800 mg/d equate to total doses over an 8-week period of 11.2, 22.4, and 44.8 g, respectively). The RR for <20, 20 to 40, and ≥40 g groups were 33% (8 of 24), 25% (4 of 16), and 62% (16 of 26), respectively (P = 0.047, Cochran-Armitage test for trend). There was no statistical difference between the two lower dose groups.

With regard to thalidomide, there was no significant difference in outcome with respect to RR, progression-free survival, and overall survival for those patients who received more or less than a total of 20 g in the first 8 weeks (equivalent to ~400 mg/d).

Prognostic factors. An analysis of potential prognostic factors was done for response, progression-free survival (Table 5), and overall survival (Table 6). No single factor was found to be predictive of a higher likelihood of response by univariate analysis. Of note, the RR was not statistically different for patients ages ≤65 years (15 of 31, 48%) versus those ages >65 years (13 of 35, 37%; P = 0.46, Fisher's exact test).

Prognostic factors predictive for inferior progression-free survival in univariate analyses were age >65 years (P = 0.016) and elevated serum β_2M (P = 0.017; Table 4). In contrast to results from our prior study, elevated lactate dehydrogenase was not significant (P = 0.554). Neither β_2M nor age reached statistical significance on multivariate analysis.

Prognostic factors predictive for inferior overall survival in univariate analyses were bone marrow plasma cells > 50% (P = 0.005), elevated serum β_2M (P = 0.013), hemoglobin <110 g/L (P = 0.024), and serum creatinine >0.13 mmol/L (P = 0.048; Table 6). There was a trend for age >65 years predicting an inferior overall survival (P = 0.06). On multivariate analysis, bone marrow plasma cells >50% was significant (P = 0.005).

Table 5. Univariate analyses of progression-free survival by prognostic factors ($P < 0.1$)

	No. patients	Estimated median PFS (mo)	Estimated % PFS at 1 y	Relative hazard rate (95% CI)	*P* (log-rank)
All patients	66	6.8	37		
Age group					
≤65	31	9.7	50	1.00 (reference)	0.016
>65	35	4.8	26	2.07 (1.13-3.81)	
β_2M (ND* = 1), mg/L					
≤3	26	9.2	37	1.00 (reference)	0.017†
>3 to <6	23	6.5	50	1.28 (0.62-2.62)	
≥6	16	3.8	26	2.45 (1.19-5.03)	
Celecoxib dose‡ (g)					
≥40	26	12.7	51	1.00 (reference)	0.039
<40	40	4.6	28	1.91 (1.02-3.56)	
Haemoglobin (g/L)					
≥110	30	12.7	54	1.00 (reference)	0.052
<110	36	4.1	24	1.81 (0.99-3.32)	
Plasma cells (ND* = 2), %					
≤50	51	8.1	41	1.00 (reference)	0.073
>50	13	6.7	29	1.83 (0.94-3.58)	

Abbreviation: PFS, progression-free survival.
*ND, not done (number of patients not assessed).
† Trend.
‡ Total celecoxib dose in first 8 wks.

Discussion

This prospective trial confirms the activity of thalidomide in patients with relapsed or refractory multiple myeloma with a RR for the entire cohort of 42%, a rate similar to that observed with the thalidomide/dexamethasone combination when used in the relapsed or refractory setting (2, 3). However, the toxicity of celecoxib in this trial was substantial. The 47% incidence of peripheral edema was unexpected and substantially higher than the observed 2.1% incidence in patients with arthritis (45) indicating a possible synergistic effect with thalidomide, which itself is known to cause fluid retention in ~5% of patients (44). As patients with myeloma are also at risk of renal disease, the addition of celecoxib was also a potential concern. Although we did observe deterioration in renal function in 8% of patients, it was reversible on cessation of the celecoxib while continuing the thalidomide (data not shown).

There is no preclinical data on the optimum concentration of celecoxib required to achieve clinically relevant COX-2 inhibition in malignant plasma cells. Thus, the dose of celecoxib selected in this trial was based on prior studies showing an antitumor effect in colonic polyposis (17). It is quite likely that the dose of 400 mg bid, which is two to four times higher than that needed to achieve anti-inflammatory effects, is likely to have contributed to the higher than expected incidence of side effects. Our results would support that dose is also important for an antimyeloma effect. A total dose of celecoxib of ≥40 g in the first 8 weeks (equivalent to ~800 mg/d) was associated with a better RR (62% versus 30%), progression-free survival, and overall survival than lower doses.

Given the recent controversy surrounding COX-2 inhibitors, it is noteworthy that we did not observe any myocardial or cerebral ischemic events; however, most patients received celecoxib for a relatively short duration. With respect to the issue of "class effect" of the COX-2 inhibitors (noting the recent worldwide withdrawal of Vioxx) the potential value of rofecoxib may not be the same as celecoxib as *in vitro* data indicates that its antitumor effects may be less than that of celecoxib (23, 46).

This study also confirms our previous observation of the importance of age and serum β_2M as critical prognostic indicators for progression-free survival in patients with relapsed or refractory myeloma receiving thalidomide-based therapy (44). As predictors for overall survival, the importance of an elevated serum β_2M was confirmed and advanced age approached statistical significance. The additional prognostic markers of extent of bone marrow plasma cell infiltrate and anemia were shown. Of interest, elevated serum CA153 (MUC-1) which has previously been described as an adverse prognostic marker in myeloma (47, 48), was elevated in 25% of the patients tested, but again, as we found in a prior study, we were unable to show it as a predictor of response, progression-free survival, or overall survival (49). Nonetheless, these patients had relapsed disease; thus, the potential value of CA153 as a prognostic marker needs to be further assessed prospectively in patients with newly diagnosed disease.

In an attempt to explore the effect of celecoxib on outcome, we compared the current study results with those of our previous thalidomide trial (excluding patients with thrombocytopenia or substantial renal impairment). We recognize that

the results of such comparisons should be treated with caution, as they are not based upon a randomized two-arm trial and any differences detected may be due to factors that are unknown and therefore not allowed for in the analysis; thus, conclusions can only be suggestive and not definitive. Nonetheless, we did make some interesting observations that warrant discussion. When comparing the two cohorts, we showed a numerical improvement in RR for the thalidomide/celecoxib combination (42% versus 29%) but this did not reach statistical significance (P = 0.14). However, it is worth highlighting that the study sample size was designed to detect a 50% RR and thus was insufficiently powered to detect a true difference of the magnitude observed. Of interest, older patients seemed to benefit from the addition of celecoxib with a superior RR of 37% versus 15% (P = 0.08) which nullified the effect of older age for predicting an inferior RR which we had observed in our prior study. When we excluded the 17 patients in the prior study who had received IFN (from week 12 if they had adequate blood counts and performance status) and compared the results with the current trial, we observed a statistically significant superior RR and progression-free survival for the thalidomide-celecoxib combination. Bearing in mind the inherent flaws of doing selected comparisons with noncontemporaneous studies, we believe our results are interesting and warrant further exploration of the addition of COX-2 inhibitors, or derivatives, with thalidomide (or its related compounds).

In this study, we did not show an improved progression-free survival or overall survival compared with thalidomide alone despite indicators of improvement in RR. Possible explanations may be that any celecoxib effect was only short lived or alternatively, as a substantial proportion of patients had to discontinue (57%) and/or dose modify celecoxib (68%) because of toxicities, any long-term benefits could not be shown. Indeed, the median duration of celecoxib treatment was only 13 weeks. It is also possible that the celecoxib may have had a "thalidomide-sparing" effect as the progression-free survival of our two studies are very similar despite a lower average dose of thalidomide delivered in the recent study. It is also of interest that trials of thalidomide/dexamethasone have not been subject to long-term follow-up for progression-free survival or overall survival comparing the combination with thalidomide alone and it is conceivable that dexamethasone's contribution to a thalidomide combination may also be short term.

Over the 5-year period during which our two sequential trials were done, there has been a trend in the use of lower doses of thalidomide than those originally proposed by Barlogie et al. (50). Indeed, this was reflected in this trial where investigators were less "tolerant" of thalidomide side effects and consequently were less aggressive in pursuing the 800 mg dose as specified in the trial design. Neben et al. and Barlogie et al. have shown that daily doses of <400 mg within the first 3 months achieve inferior outcomes, whereas our data would indicate that doses above this are probably not required (51, 52). Thus, future studies could examine lower doses of thalidomide or thalidomide derivatives in an attempt to reduce toxicity.

Table 6. Univariate analyses of overall survival by prognostic factors (P < 0.1)

	No. patients	Estimated median survival (mo)	Estimated % surviving at 1 y	Relative hazard rate (95% CI)	P (log-rank)
All patients	66	21.4	65		
Age group					
≤65	31	22.6	80	1.00 (reference)	0.06
>65	35	14.6	51	2.07 (0.95-4.51)	
β_2M (ND* = 1), mg/L					
≤3	26	22.6	76	1.00 (reference)	0.013†
>3 to <6‡	23	>30.1	71	1.19 (0.45-3.18)	
≥6	16	7.4	38	3.05 (1.25-7.49)	
Hemoglobin (g/L)					
≥110‡	30	>29.6	83	1.00 (reference)	0.024
<110	36	14.3	52	2.59 (1.10-6.11)	
Celecoxib dose§ (g)					
≥40‡	26	>29.6	53	1.00 (reference)	0.035
<40	40	18.9	84	2.44 (1.04-5.75)	
Serum creatinine (mmol/L)					
≤0.13	58	22.6	67	1.00 (reference)	0.048
>0.13	8	10.6	50	2.43 (0.98-6.06)	
Plasma cells (ND* = 2), %					
≤50	51	22.6	74	1.00 (reference)	0.005
>50	13	8.1	37	2.94 (1.34-6.44)	

*ND, not done (number of patients not assessed).
†Trend.
‡Percentage surviving does not drop to 50%; thus, no estimate of median survival is possible.
§Total celecoxib dose in first 8 wks.

How can we further explore the potential value of the thalidomide/celecoxib combination? In this study, we have shown that although there is promising data with respect to the antimyeloma effect of COX-2 inhibition, the toxicity profile will limit the investigation of the thalidomide/celecoxib combination in progressive or nonprogressive myeloma. Although lower doses of celecoxib may be better tolerated, our results of a dose-response effect of celecoxib and previous *in vitro* data would indicate that the effect of COX-2 inhibition is dose dependent (16, 25). Thus, another approach would be to investigate the use of other COX-2 inhibitors with different toxicity profiles or to use celecoxib derivatives. Indeed, it has recently been recognized that the proapoptotic effects of celecoxib may, at least in part, be mediated through mechanisms other than COX-2 inhibition (15, 16, 23, 25, 29, 30). Our data would suggest that this observation could be exploited by combining novel celecoxib derivatives such as OSU03012 (53) and etodolac (32) with thalidomide or its related compounds.

In summary, this trial provides evidence that the addition of high-dose celecoxib adds to the antimyeloma activity of thalidomide but this comes with unacceptable toxicity. Celecoxib derivates or other COX-2 inhibitors, with better toxicity profiles, should be investigated with thalidomide, or related compounds, for the treatment of myeloma.

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Clinical Cancer Research

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