

A randomised, double-blind, phase II study of three different marimastat schedules administered to patients with resected Dukes C colorectal cancer

Research Article

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Summary

The aim of this study was to determine whether scheduling treatment holidays would improve tolerance of marimastat, an oral matrix metalloproteinase inhibitor known to have dose-limiting musculoskeletal side effects on continuous daily administration. The trial compared 3 different schedules of marimastat given orally, 10 mg twice daily for 48 weeks, to patients with resected Dukes stage C colorectal cancer. Twenty-nine patients were randomised to one of three treatment schedules: group 1 received marimastat daily; group 2 received 3 x 16 week cycles comprising 12 weeks of marimastat followed by 4 weeks of placebo; group 3 received 12 x 4 week cycles comprising 3 weeks of marimastat followed by 1 week of placebo. The primary end points were toxicity and safety; secondary end points were time to initiating further cancer therapy and/or death. Of 28 patients commencing treatment, 4 patients completed the study and two patients withdrew due to disease recurrence. The remaining 22 patients all withdrew due to adverse events related to the musculoskeletal system. This study suggests that alternative schedules of 1 week off in 4 or 1 month off in 4 are no better tolerated than continuous therapy. Inability to tolerate the drug leading to early withdrawal of almost 80% of patients implies that clinical trials with marimastat in the adjuvant setting are unlikely to prove successful.

I. Introduction

Marimastat is a broad spectrum inhibitor of the family of enzymes known as matrix metalloproteinases (MMPs). MMPs degrade extracellular matrix and are thought to play a key role in the process of tumour invasion. Preclinical studies have shown that in animal models, MMP inhibitors can restrict tumour growth, prevent invasion and metastasis and block neovascularisation (Egeblad and Werb, 2002; Overall and Lopez-Otin, 2002). Marimastat (BB-2516) was the first in a series of new generation MMP inhibitors entering clinical trials. From the early stages of clinical development of this group of agents, a characteristic syndrome involving musculoskeletal side effects has been observed (Hutchison et al, 1998; Drummond et al, 1999). This musculoskeletal syndrome (MSS) is characterised by muscle tendonitis and a variety of clinical signs, including stiffness, inflammation and pain particularly in the joint of hands, arms and shoulders. MSS is both dose- and time-

dependent, but reversible on stopping drug treatment (Tierney et al, 1999; Nelson et al, 2000). As with other broad spectrum MMP inhibitors, marimastat is orally bioavailable, and a daily administration schedule is standard. A number of phase II and III clinical trials evaluating marimastat in the treatment of a range of human cancers have been completed (reviewed by Coussens et al, 2002). Overall, results have proved disappointing. Two key factors probably provide most of the explanation as to why benefits anticipated from excellent preclinical data have not been realised in patients. Firstly, the high prevalence of MSS was not seen in animal models or phase I studies in normal human volunteers. This unexpected side effect had limited the ability of patients to tolerate marimastat when tested in subsequent larger trials. Secondly, most of the trials have been performed in patients with advanced, high volume malignancies. In contrast, in mouse models, MMP inhibition appears most effective in controlling early stages of cancer (Brown, 2000). To address both these

issues, a phase II trial was designed to evaluate 3 different dosing schedules of marimastat allowing for ‘drug holidays’, in the context of resected, early stage colorectal cancer.

II. Patients and methods

The study was conducted between January 1997 and January 1999 at the Queen Elizabeth Hospital, Birmingham and the Oncology Centre, Cambridge, UK. Patients eligible for treatment were ambulant, with Eastern Co-operative Oncology Group (ECOG) performance status of 0-2, having fully recovered from resection of histologically proven Dukes C colorectal cancer performed at least 2 weeks previously. Standard adjuvant radiotherapy and chemotherapy was allowed and must have been completed at least 8 weeks before trial entry. The trial had approval from research ethics committees of the local institutions and all patients entering the trial gave written informed consent

A. Treatment

Consenting patients were assigned to 1 of 3 treatment groups (Figure 1) according to a computer generated random code. Ten patients were to be assigned to each group. All patients received marimastat at a dose of 10 mg twice daily, or matching placebo twice daily. The planned treatment period was 48 weeks. Group 1 received marimastat daily for the study duration; Group 2 received 3 x 16 week cycles comprising 12 weeks of marimastat followed by 4 weeks of placebo; Group 3 received 12 x 4 week cycles comprising 3 weeks of marimastat followed by 1 week of placebo. The pharmacist and investigator were provided with sealed randomisation codes for each patient and decode envelopes were kept with the study materials stored securely in the pharmacy. The code could only be broken in emergency conditions.

Patients were instructed to take the study drug twice a day at 12 hourly intervals, with water and with or after meals and to return supplies at each study visit for a drug accountability and compliance check, before further supplies were dispensed.

B. Patient evaluation

Patients were assessed prior to commencing treatment and then at 4 weekly intervals during the planned study period of 48 weeks. Physical examination, performance status, weight, blood count, renal and liver function tests, carcinoembryonic antigen and plasma marimastat levels were evaluated at baseline and at every study visit. Toxicity, compliance and concomitant medications were recorded at every visit. Toxicity was assessed using the National Cancer Institute common toxicity criteria (NCI CTC). For the purposes of this study, grading of musculoskeletal toxicity was modified slightly from the NCI CTC, as described in Table 1. Study drug was discontinued in the event of any grade II or higher musculoskeletal toxicity and any other grade III or higher toxicity thought to be related to marimastat. If symptoms resolved within 3 weeks, treatment was

reinitiated, otherwise the patient was withdrawn. Similar omission of treatment was allowed if symptoms recurred a second time, but on the third occasion, the patient was withdrawn from the study.

Table 1: Grading of musculoskeletal toxicity, amended from NCI CTC

Grade	Symptoms and signs
0	None
1	Aches and pains with no restriction of movement
2	Pain, causing restriction of activity
3	Pain and the presence of nodules or clinically inflamed joints or tendons
4	Pain and the presence of contracture

A second treatment interruption for toxicity was allowed, but further toxicity necessitating treatment cessation led to the patient being withdrawn. After halting study drug, patients were followed 3 monthly for survival and/or time to initiation of next anti-cancer treatment.

C. Statistical methods

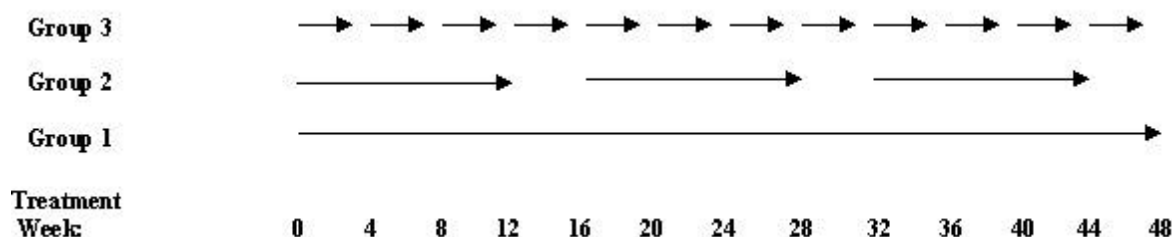
No statistical sample size calculation was performed for this study. However, 10 patients per group was regarded as a minimum number of patients to meet the study objectives. The times to treatment interruption and times to musculoskeletal events were presented as Kaplan-Meier plots and compared between groups using the log-rank test.

III. Results

Twenty-nine (17 male, 11 female, median age 64 years, range 39 -76 years) patients entered the study, all of whom had received prior adjuvant chemotherapy and 5 had prior radiotherapy. Nine patients were randomised to Group 1 (continuous daily treatment), 9 to Group 2 (12 weeks on, 4 weeks off marimastat) and 11 to Group 3 (3 weeks on, 1 week off marimastat). One patient in Group 3 did not receive study treatment and withdrew after screening due to disease recurrence.

Four patients (3 male, 1 female) completed the 48 week study period. Two patients (1 in Group 1 and 1 in Group 3) chose to continue to take study treatment beyond 48 weeks. Twenty-four patients failed to complete the study. Two withdrew due to disease recurrence and the remaining 22 withdrew because of adverse events (Table 2). Of these, 20 withdrew because of one or more events classed under the musculoskeletal body system and two withdrew because of events that were musculoskeletal in nature, although classed under other body systems.

Figure 1: Schematic to describe the three treatment schedules



The median duration of study treatment for those commencing therapy, excluding drug holidays, was 115 days for Group 1, 85 days for Group 2 and 106 days for Group 3. The proportion of patients with an interruption to treatment within the first 12 weeks of the study was 4/9 (44%) for Group 1, 5/9 (56%) for Group 2 and 6/10 (60%) in Group 3. The respective proportions with treatment interruptions within the first 20 weeks were 6/9 (67%), 7/9 (78%) and 7/10 (70%). The median time to the first treatment interruption was 88 days for Group 1, 84 days for Group 2 and 66.5 days for Group 3. Eight patients in each group experienced musculoskeletal events requiring treatment modification.

The most commonly recorded adverse events were musculoskeletal in nature, as would be expected for this particular drug, and were reported for all but one patient on study.

Swelling of hands coded as peripheral oedema is also a recognised toxicity of marimastat and occurred in eight (29%) patients (**Table 3**). The types of musculoskeletal events experienced by patients were similar in all groups, namely pain and stiffness in the muscles and joints of the shoulders, arms, elbows and fingers. The severity of events and the numbers of joints affected tended to shift from mild to moderate and in some cases, to severe, with continued treatment. Two patients developed nodules and/or contractures in the palmar aponeurosis. Patients were allowed access to any analgesics in this study. In twenty-two patients, nonsteroidal analgesics were initiated and 3 patients received paracetamol-based products, primarily in an attempt to control pain associated with the MSS. The benefit of such intervention was unclear. Three patients, one of whom completed the full 48 week study, did not receive any analgesia. The severity of the events reversed after stopping treatment. No other side effects occurred. There were no statistically significant differences between groups with respect to the sequencing or time to development of musculoskeletal events.

Over the first 12 weeks, mean marimastat concentrations were 28.7 ng/ml for Group 1 (N=8), 47.1 ng/ml for Group 2 (N=6) and 23.5 ng/ml for Group 3 (N=8). These levels are comparable with ranges recorded in other marimastat trials (Bramhall et al, 2002) and are at the lower end of the target range of 40 – 200 ng/ml thought to be associated with biological activity (Miller et al, 2002). The high rate of treatment discontinuation in this study makes interpretation of plasma marimastat concentrations measured at later time points difficult to interpret.

All patients had baseline CEA values within the normal range. As for pharmacokinetic analysis, the high patient attrition rate in this study precludes any meaningful conclusions being drawn from subsequent data points.

At the time of final audit of the data, median follow-up was 2 years 9 months. At this time, 21 patients were disease free and 2 patients were known to have died.

IV. Discussion

The aim of this study was to determine whether prospectively planned treatment “holidays” would provide a better tolerated treatment schedule for patients receiving

Table 2: Summary of patients on treatment

	Group 1	Group 2	Group 3	Total
No. entered study	9	9	11	29
No. receiving study treatment	9	9	10	28
No. completed study	1	1	2	4
No. not completing study:	8	8	9	25
- disease recurrence	0	1	2	3
- adverse event	8	7	7	22

Group 1: continuous daily treatment

Group 2: 12 weeks on, 4 weeks off treatment

Group 3: 3 weeks on, 1 week off treatment

Table 3: Occurrence of treatment- related events involving predicted toxicities: musculoskeletal events and peripheral oedema.

	Group 1 N=9	Group 2 N=9	Group 3 N=10
Musculoskeletal events:			
- mild	10 (8)	8 (8)	11 (8)
- moderate	14 (9)	12 (9)	12 (7)
- severe	6 (5)	5 (5)	5 (4)
Peripheral oedema:			
- mild/moderate	4 (4)	1 (1)	3 (3)
- severe	1 (1)	1 (1)	2 (2)

The number of patients experiencing toxicity is shown in brackets

Group 1: continuous daily treatment

Group 2: 12 weeks on, 4 weeks off treatment

Group 3: 3 weeks on, 1 week off treatment

marimastat, compared with standard continuous daily dosing in the adjuvant setting. Musculoskeletal side effects of marimastat tend to develop in the second and third months of treatment. Although the number of patients with grade III/IV musculoskeletal toxicity was a little lower (not statistically significant) in the group of patients receiving a 3 week on, 1 week off treatment schedule, the time to onset and incidence of treatment interruption due to musculoskeletal side effects were not improved. Thus, it appears that the simple strategy of altered treatment scheduling does not ameliorate the problem of dose-limiting MSS. The mechanism of MSS is not fully understood, although several hypotheses have been proposed (Drummond et al, 1999). A rat model predictive of MSS was recently described (Renkiewicz et al, 2003). It is hoped that such models will yield a better understanding of the underlying pathology and significantly improve the chances of identifying more selective, less toxic MMP inhibitors in the future.

The small size of this pilot study prevents any conclusions from being drawn regarding the clinical utility of marimastat as an adjuvant therapy for colorectal cancer. The chosen dose for this study of 10 mg twice daily was recommended after initial marimastat trials in cancer patients determined that higher doses up to 50 mg twice daily were too poorly tolerated (Nemunaitis et al, 1998; Primrose et al, 1999). The most promising trial outcome to date was recorded in a study evaluating the 10 mg twice

daily marimastat schedule in patients with advanced gastric cancer (Bramhall et al, 2002). In this placebo-controlled study of 369 patients, marimastat offered a modest median and 2 year survival benefit. One explanation for possible tumour site specificity may be that high drug concentrations are preferentially achieved in the stomach wall (Bramhall et al, 2002).

The mean plasma concentrations of marimastat in the gastric cancer patients were typical and similar to those recorded in the current study, as was the extent of MSS recorded. In line with pre-set dose interruptions and reductions, 43% of marimastat-treated gastric cancer patients remained on the twice daily schedule at 3 months falling to 11% by 6 months. Even so, the overall quality of life over the first 3 months measured by the EORTC-QLQC30 questionnaire was not statistically different between the placebo and marimastat arms. Only 10% of advanced gastric cancer patients on marimastat withdrew due to adverse events. This, compared with the 80% withdrawal rate seen in the current adjuvant study, illustrates the poor tolerance of non-selective drugs by essentially well people.

The practical, ethical, and financial implications of undertaking large, properly powered randomised trials of novel, rationally designed cytostatics in the early stages of cancer are formidable. However, important lessons from the development of the MMP inhibitors suggest that, unless these challenges are met head on, there will remain a sense that the clinical cancer community has failed to truly evaluate the potential of these agents as effective anti-cancer therapy.

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References

- Bramhall SR, Hallissey MT, Whiting J, Scholefield J, Tierney G, Stuart RC, Hawkins RE, McCulloch P, Maughan T, Brown PD, Baillet M, Fielding JWL (2002). Marimastat as maintenance therapy for patients with advanced gastric cancer: a randomised trial. **Br J Cancer** 86: 1864-1870.
- Brown PD (2000). Ongoing trials with matrix metalloproteinase inhibitors. **Expert Opin Investig Drugs** 9: 2167 - 2177.
- Coussens LM, Fingleton B, Matrisian LM (2002). Matrix metalloproteinase inhibitors and cancer; trials and tribulations. **Science** 295: 2387-2392.
- Drummond AH, Beckett P, Brown PD, Bone EA, Davidson AH, Galloway WA, Gearing AJ, Huxley P, Laber D, McCourt M, Whittaker M, Wood LM, Wright A (1999). Preclinical and clinical studies of MMP inhibitors in cancer. **Ann NY Ac Sci** 878: 228-35.
- Egeblad M, Werb Z (2002). New functions for the matrix metalloproteinases in cancer progression. **Nat Rev Cancer** 2: 163-174.
- Hutchison JW, Tierney GM, Parsons SL, Davis TR (1998). Dupuytren's disease and frozen shoulder induced by treatment with a matrix metalloproteinase inhibitor. **J Bone Joint Surg Br** 80; 907-908.
- Miller KD, Gradishar W, Schuchter L, Sparano JA, Cobleigh M, Robert N, Rasmussen H, Sledge GW (2002). A randomized phase II trial of adjuvant marimastat in patients with early breast cancer. **Ann Oncol** 13: 1220-1224.
- Nelson AR, Fingleton B, Rothenberg ML, Matrisian LM (2000). Matrix metalloproteinases; biologic activity and clinical implications. **J Clin Oncol** 18; 1135-1149.
- Nemunaitis J, Poole C, Primrose J, Rosemurgy A, Malfetano J, Brown P, Berrington A, Cornish A, Lynch K, Rasmussen H, Kerr D, Cox D, Millar A (1998). Combined analysis of studies of the effects of the matrix metalloproteinase inhibitor marimastat on serum tumor markers in advanced cancer: selection of a biologically active and tolerable dose for longer-term studies. **Clin Cancer Res** 55: 3263-3266.
- Overall CM, Lopez-Otin C (2002). Strategies for MMP inhibition in cancer: innovations for the post-trial era. **Nat Rev Cancer** 9: 652-672.
- Renkiewicz R, Qiu L, Lesch C, Sun X, Devalaraja R, Cody T, Kaldjian E, Welgus H, Baragi V (2003). Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rats. **Arthritis & Rheum** 48: 1742-1749.
- Primrose JN, Bleiberg H, Daniel F, Van Belle S, Mansi JL, Seymour M, Johnson PW, Neoptolemos JP, Baillet M, Barker K, Berrington A, Brown PD, Millar AW, Lynch KP (1999). Marimastat in recurrent colorectal cancer: exploratory evaluation of biological activity by measurement of carcinoembryonic antigen. **Br J Cancer** 79: 509-514.
- Tierney G, Steele R, Griffin N, Stuart R, Kasem H, Lynch KP, Lury JT, Brown PD, Millar AW, Parsons S (1999). A pilot study of the efficacy and effects of the matrix metalloproteinase inhibitor marimastat in gastric cancer. **Eur J Cancer** 35: 563-568.