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ORIGINAL ARTICLE

**André Planting · Ate van der Gaast · Patrick Schöffski
Michele Bartkowski · Coleta Verheij · Dennis Noe
Karen Ferrante · Jaap Verweij**

A phase I and pharmacologic study of the matrix metalloproteinase inhibitor CP-471,358 in patients with advanced solid tumors

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Abstract *Background*: Matrix metalloproteinases play a role in the process of tissue invasion and metastasis by degrading the extracellular matrix. Inhibitors of matrix metalloproteinases are therefore of interest as anticancer drugs. CP-471,358 is a matrix metalloproteinase inhibitor that in vitro demonstrates strong inhibition of matrix metalloproteinases 2 and 9. The drug can be administered orally without food restriction. *Study design*: An open-label phase I study was performed in patients with advanced solid tumors to assess the safety, tolerability, maximal tolerated dose (MTD) and pharmacokinetics of CP-471,358. The CP-471,358 doses studied were 50, 100 and 200 mg three times daily (TID) continuously, 50, 100 and 200 mg TID for 21 days followed by a 1-week treatment-free interval and 75 mg and 150 mg twice daily (BID) continuously. *Results*: A total of 38 patients were treated in the study. The median number of cycles administered was two (range one to five). Myalgia and arthralgia were the most frequently observed adverse events (in 27 of 38 patients) and were observed at all dose levels and with all schedules except for the 150 mg BID continuous dosing level. In six patients National Cancer Institute (NCI) Common Toxicity Criteria (CTC) grade 3 myalgia/arthralgia was observed and this adverse event was considered to be the dose-limiting toxicity (DLT). Introduction of a 1-week treatment-free interval between cycles had no effect on the occurrence of myalgia/arthralgia. After cessation of treatment, arthralgia/myalgia was reversible in all patients. Other adverse events observed were fatigue and an increase of liver enzymes but these rarely exceeded CTC grade 2. Pharmacokinetic analysis showed that target efficacious concentrations were achieved throughout the morning dosing interval with 150 mg BID and 200 mg TID. *Conclusion*: The DLT of CP-471,358 was myalgia and arthralgia, an adverse event observed during treatment with most matrix metalloproteinase inhibitors. A drug-free interval of 1 week was unable to prevent the occurrence of these adverse effects. Clearly this represents a limitation for potential long-term use of this compound.

Keywords Phase I study · CP-471,358 · MMPI-inhibitor

A. Planting (✉) · A. van der Gaast · C. Verheij · J. Verweij
Department of Medical Oncology,
Erasmus Medical Center/University Hospital,
P.O. Box 5201, 3008 AE Rotterdam,
The Netherlands
E-mail: a.s.t.planting@erasmusmc.nl
Tel.: +31-10-4391505
Fax: +31-10-4391004

P. Schöffski
Department of Medical Oncology,
Hannover University Medical School,
Hannover, Germany

M. Bartkowski · D. Noe · K. Ferrante
Pfizer Global Research and Development,
New London, CT, USA

Introduction

Matrix metalloproteinases (MMPs) belong to a group of at least 30 structurally related zinc-dependent endopeptidases that fall into five classes related to their structure and substrate. Under normal conditions MMPs play a role in tissue remodeling, scar formation, and fracture healing. In cancer, MMPs facilitate the process of tissue invasion and metastasis by degrading the extracellular matrix and by facilitation of the process of angiogenesis [7, 9, 10]. In several solid tumors a high MMP activity in the tumor corresponds with a worse clinical outcome [1, 3, 17, 19, 21]. In preclinical and animal studies MMP inhibitors (MMPIs) have been shown to be able to inhibit tumor growth, to inhibit metastatic spread of tumor cells, and to inhibit angiogenesis [6, 11]. In clinical practice the experience with MMPIs is still limited. The most extensively studied MMPI is marimastat. In studies of marimastat, up to 30% of patients had to interrupt

or stop treatment because of musculoskeletal side effects. Marimastat is a broad spectrum MMPI of MMPs 1, 2, 3, 7, 9 and 12, and it has been postulated that this broad range of inhibitory action is responsible for the adverse effects observed with dosing [7].

CP-471,358, 3-[[4-(4-fluorophenoxy)-benzenesulfonyl]-(1-hydroxycarbamoylcyclopentyl)-amino]propionic acid, is a MMPI that can be administered orally. In vitro, CP-471,358 demonstrates potent inhibition of the human gelatinases MMP-2 and MMP-9, which can degrade type IV collagen, a component of the basement membrane, while maintaining the activity of MMP-1 responsible for collagen turnover.

Inhibition of angiogenesis by CP-471,358 has been studied in a mouse model: the angiogenic response to a β-FGF-releasing pellet implanted in the cornea. When CP-471,358 was administered by continuous infusion for 5 days, using an intraperitoneal osmotic minipump, β-FGF-induced angiogenesis was inhibited with an EC_{50} of 16 ng/ml. Corrected for differences in plasma protein binding in the two species, this corresponds to a concentration of 27 ng/ml in humans (data on file, Pfizer)

A single-dose study of CP-471,358 in healthy subjects has demonstrated that the AUC and C_{max} increase with dose (data on file, Pfizer). The apparent half-life is 2–3 h and is independent of dose. The pharmacokinetic parameters are not influenced by food intake. In this single-dose study, the adverse events were limited to asthenia, diarrhea, headache and abdominal pain, mostly of mild severity.

We report the results of the first phase I study with this MMPI using a continuous as well as an intermittent dosing regimen in patients with advanced solid tumors.

Patients and methods

Patients

Eligible patients in this study had a locally advanced or metastatic solid tumor refractory to, or progressing on, standard chemotherapy or a tumor for which no standard chemotherapy was available. Patients were required to have an evaluable or measurable lesion, age ≥18 years, ECOG performance status ≤ 2, and a life expectancy ≥12 weeks. Patients were at least 4 weeks from previous anticancer treatment. They had adequate bone marrow reserve (absolute neutrophil count $> 1.5\times10^9\ l^{-1}$ and platelets $> 100\times10^9\ l^{-1}$), adequate liver function (AST and ALT not more than 2.5 times the upper limit of normal; in case of liver metastases not more than 5 times ULN), and adequate renal function (serum creatinine ≤ 115 μmol/l or creatinine clearance ≥60 ml/min). All patients provided written informed consent.

Female patients of child-bearing potential were required to have a negative pregnancy test at enrollment; lactating women were excluded. Other reasons for non-eligibility were: patients with gastrointestinal abnormalities requiring intravenous alimentation, patients with malabsorption syndromes, patients with an active peptic ulcer or other active gastrointestinal disease that could interfere with oral medication. Additionally, patients were excluded if they had an active uncontrolled infection, symptomatic brain metastases, a second malignancy (with the exception of cervical cancer or non-melanoma skin cancer), clinically significant or unstable cardiac disease, a myocardial infarction within the previous 6 months or chronic obstructive pulmonary disease requiring hospitalization in the 12 months prior to enrollment. Prior to entry to the study, all patients had a full medical history, physical examination, CT scan of chest and abdomen of indicator lesions, and an electrocardiogram (ECG).

The first drug administration was administered on an inpatient basis for safety reasons. On admission, laboratory tests performed included hemoglobin, WBC plus differential and platelets, and serum chemistries including sodium, potassium, calcium, magnesium, phosphorus, urea, uric acid, creatinine, total protein, albumin, glucose, alkaline phosphatase, bilirubin, AST, ALT, gamma-glutamyl transpeptidase and LDH. An ECG was repeated before and after the first dose of CP-471,358. On day 15, patients were rehospitalized and laboratory tests, physical examination and ECG repeated. Thereafter, patients were evaluated every 4 weeks in the outpatient department, at which time a complete medical history, physical examination, full laboratory tests, and an ECG were performed. Toxicity was assessed weekly according to the NCI CTC (version 2.0). Response evaluation was done for the first time after the second cycle and every two cycles thereafter according to the World Health Organization criteria for response. The Medical Ethical Committee of both participating institutions approved the protocol.

Study design

The study was an open-label dose-escalation study. The starting dose of 100 mg three times daily (TID) was selected based on the pharmacokinetic data and tolerability in the single-dose phase I study in healthy subjects. Based on the adverse events observed during this study, the protocol was amended to include a twice-daily (BID) regimen and a TID regimen with dosing for 21 days out of 28 days to assess whether alternative schedules would improve drug tolerability. CP-471,358 was administered orally as 10-mg or 100-mg tablets ingested with 180–200 ml water. There were no food restrictions. Routine antiemetics were not prescribed.

Initially, three patients were to be enrolled per cohort. The decision to escalate the dose was based on the safety findings of all patients in the cohort and enrollment in the next cohort began only after the 28-day safety and tolerance data of the last patient entered in the preceding cohort were known. Once DLT was observed in one patient in a cohort, three additional

patients were to be enrolled at that dose level. DLT was defined as any CTC grade 3 or 4 toxicity. If an additional patient experienced grade 3 or 4 toxicity then that dose level was considered above the MTD and the previous dose level was considered the MTD. An intermediate dose level could have been added after discussion between the investigators and the sponsor. Based on the estimation of the number of tablets feasible for ingestion in 1 day, the maximal daily dose planned for exploration was 3000 mg.

Patients were hospitalized for 5 days during the first cycle for safety monitoring and pharmacokinetic sampling. On the first day, CP-471,358 was administered as a single dose (either one-third the total daily dose for patients on a TID regimen or one-half for patients on the BID regimen). From the second day onward, the dosing was continued as a TID or BID regimen as scheduled. Patients were rehospitalized on day 15 for 24 h for pharmacokinetic sampling. Treatment for 28 days was considered as one treatment cycle.

Pharmacokinetic sampling

For pharmacokinetic analyses, 1.5-ml blood samples were collected and centrifuged at 3000 rpm for 10–15 min at 5°C; the plasma was stored at −20°C. Blood samples were obtained before dosing and at 1, 2, 3, 4, 6, 8, 16 and 24 h after dosing on days 1, 2 and 15 of cycle 1, and before dosing and at 2, 8 and 16 h after dosing on days 3, 4 and 5 of cycle 1. Urine was sampled for 24 h on days 1, 2 and 15 of cycle 1 and stored at 4°C. A 10-ml urine sample was collected and frozen at −70°C for shipment.

Plasma and urine samples were assayed for CP-471,358 at Pfizer Global Research and Development (Groton, Ct.). CP-471,358 and internal standard (Pfizer compound CP-524,144) were extracted from acidified plasma or urine by liquid–liquid extraction with MTBE. The organic extract was evaporated to dryness using N_2, reconstituted and analyzed by reverse-phase LC/MS/MS. The working range of the assay for plasma was 1–200 ng/ml; the working range for urine was 10–5000 ng/ml. Individual patient pharmacokinetic parameter values were estimated from each patient's concentration–time data using standard noncompartmental approaches. Renal clearance was calculated as the amount of CP-471,358 excreted in the urine over the dosing interval on day 15 divided by the area under the plasma concentration–time curve for the corresponding dosing interval.

Results

Patients

Enrolled in the study were 39 patients, and of these 38 were treated. One patient was never treated due to rapid elevation of liver enzymes. A summary of patient characteristics is provided in Table 1. The median number of cycles administered per patient was two (range one to five). Dose levels and schedules studied are presented in Table 2.

Toxicity

The most frequently reported adverse events in this study were myalgia, typically observed in the shoulder girdle, and arthralgia. Arthralgia was reported for large joints such as knees and elbows but also occasionally occurred in the hands associated with swelling and stiffness of distal interphalangeal joints. These symptoms were not well controlled by acetaminophen, tramadol or nonsteroidal antiinflammatory agents.

Myalgia/arthralgia was reported at all dose levels except for the 150 mg BID continuous dosing level. Details are provided in Table 2. Six patients, mainly

Table 1 Patient characteristics

No. of patients treated	38
Male/female	26/12
Age (years)	
Median	55
Range	25–75
Performance Status (ECOG)	
0	11
1	22
2	5
Prior chemotherapy	32
Prior surgery	34
Prior radiation therapy	14
Tumor types	
Colorectal cancer	10
Soft tissue sarcoma	6
Adenocarcinoma unknown primary	5
Non-small-cell lung cancer	4
Renal cancer	4
Esophageal cancer	2
Mesothelioma	2
Breast cancer	1
Ovarian cancer	1
Gastric cancer	1
Melanoma	1
Cervical cancer	1

Table 2 Dose-limiting toxicity myalgia and arthralgia; CTC grade, worst toxicity reported per patient

Schedule	*n*	Grade 1	Grade 2	Grade 3	Grade 4
50 mg TID 21/28 days	4	1	2	0	0
50 mg TID continuous	7	4	0	1	0
75 mg BID continuous	3	1	0	0	0
100 mg BID continuous	1	1	0	0	0
100 mg TID 21/28 days	6	4	1	1	0
100 mg TID continuous	7	1	1	2	0
150 mg BID continuous	3	0	0	0	0
200 mg TID 21/28 days	3	1	1	1	0
200 mg TID continuous	4	3	0	1	0

Table 3 All causality nonmusculoskeletal toxicities; CTC grade, worst toxicity reported per patient

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	8	1	1	0
Vomiting	5	1	0	0
Anorexia	7	0	0	0
Constipation	5	2	1	0
Diarrhea	4	2	2	0
Headache	4	2	0	0
Skin rash	3	2	0	0
Asthenia	18	6	1	0
SGOT/SGPT	1	1	0	0
Bilirubin[a]	0	0	2	1

[a]Two patients with increase in bilirubin had a marginally elevated bilirubin at start of therapy but were accepted onto the study after approval of the sponsor

treated with the TID regimens, reported CTC grade 3 myalgia/arthralgia. Myalgia/arthralgia grade 3 was reported during the first and second cycle by one patient each. In other patients grade 3 myalgia/arthralgia did not develop until the third or fourth cycle. Introduction of a "drug holiday week" every 28 days did not reduce the incidence of this adverse event. Other adverse events (all causality) observed were asthenia, elevation of liver enzymes and nausea and diarrhea. Details are given in Table 3. In total, 8 of the 38 patients were withdrawn from the study as a result of adverse events, 6 because of arthralgia/myalgia. In all patients, the symptoms resolved after discontinuing CP-471,358 treatment. Three patients with an elevated bilirubin concentration due to liver metastases were enrolled in the study, after discussion between investigators and sponsor, to allow for study of the pharmacokinetics in this setting (one patient on 50 mg TID and two patients on 200 mg TID). The patients were withdrawn after one cycle because of further increase in bilirubin concentration in one patient and rapidly progressive disease in the other two.

Pharmacokinetic analysis

Single-dose (day-1) pharmacokinetic parameter values were estimated in 33 patients. The mean parameter values are listed in Table 4. AUC_{0-inf} and C_{max} increased with dose in an approximately dose-proportional manner. The terminal half-life of CP-471,358 averaged 1.85 h across dose cohorts; it did not vary with dose over the dosing range studied.

Multiple-dose (day-15) pharmacokinetic parameter values were estimated in 26 patients receiving CP-471,358 TID and in six patients receiving CP-471,358 BID. The parameter values are listed in Table 5 (note: because CP-471,358 was administered at 8 a.m. and 4 p.m. on the BID schedule, the a.m. dosing interval was 8 h, not 12 h, as is usual for BID schedules). One of the patients receiving CP-471,358 100 mg TID, had a pharmacokinetic specimen drawn on day 22 rather then day 15. All measures of multiple dose exposure increased with dose in an approximately dose-proportional manner. On the TID dosing schedule, there was slight accumulation, despite the short half-life, as indicated by a mean accumulation ratio (R) greater than 1 ($P < 0.01$ by t-test for 100-mg and 200-mg doses). There was no accumulation on the BID dosing schedule.

The time-course of the plasma concentration of CP-471,358 following the a.m. dose on day 15 is shown in Fig. 1 (BID dosing) and in Fig. 2 (TID dosing). For BID dosing, the geometric mean concentration exceeded the target efficacious concentration of 27 ng/ml for 6 h following the 75-mg dose and throughout the a.m. dosing interval following the 150-mg dose. For TID dosing, the target efficacious concentration was exceeded for 6 h following the 50-mg and 100-mg doses and throughout the a.m. dosing interval following the 200-mg dose. The renal clearance of CP-471,358 averaged 140 ml/min across dose cohorts; it did not vary

Table 4 Day 1 (single dose) CP-471,358 pharmacokinetic parameters

Dosing group	AUC_{0-inf} (h ng/ml)	C_{max} (ng/ml)	$T_{1/2}$ (h)
50 mg TID ($n=9$)			
Mean	746	272	1.73
SD	266	101	0.57
100 mg TID ($n=12$)			
Mean	1270	421	1.98
SD	1000	216	0.58
200 mg TID ($n=7$)			
Mean	4000	1150	1.91
SD	1730	1070	0.49
75 mg BID ($n=3$)			
Mean	1150	585	1.57
SD	180	237	0.38
150 mg BID ($n=2$)			
Mean	3470	1480	1.85
SD	710	177	0.07

Table 5 Day-15 pharmacokinetic parameters of CP-471,358 following the morning dose (R AUC_{0-8} day 15/AUC_{0-8} day 1, CL_R renal clearance rate)

Dosing group	$AUC_{0-8\,h}$ (h ng/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	R	CL_R (ml/min)
50 mg TID ($n=8$)					
Mean	874	297	17	1.22	147
SD	400	170	14	0.36	60
100 mg TID ($n=12$)					
Mean	1520	575	45	1.38	131
SD	1220	592	74	0.59	60
200 mg TID ($n=6$)					
Mean	4740	1290	179	1.46	166
SD	3050	976	135	0.40	79
75 mg BID ($n=3$)					
Mean	1060	402	16	0.95	154
SD	190	139	7	0.05	56
150 mg BID ($n=3$)					
Mean	2970	1100	129	0.72	87
SD	1930	939	165	0.63	52

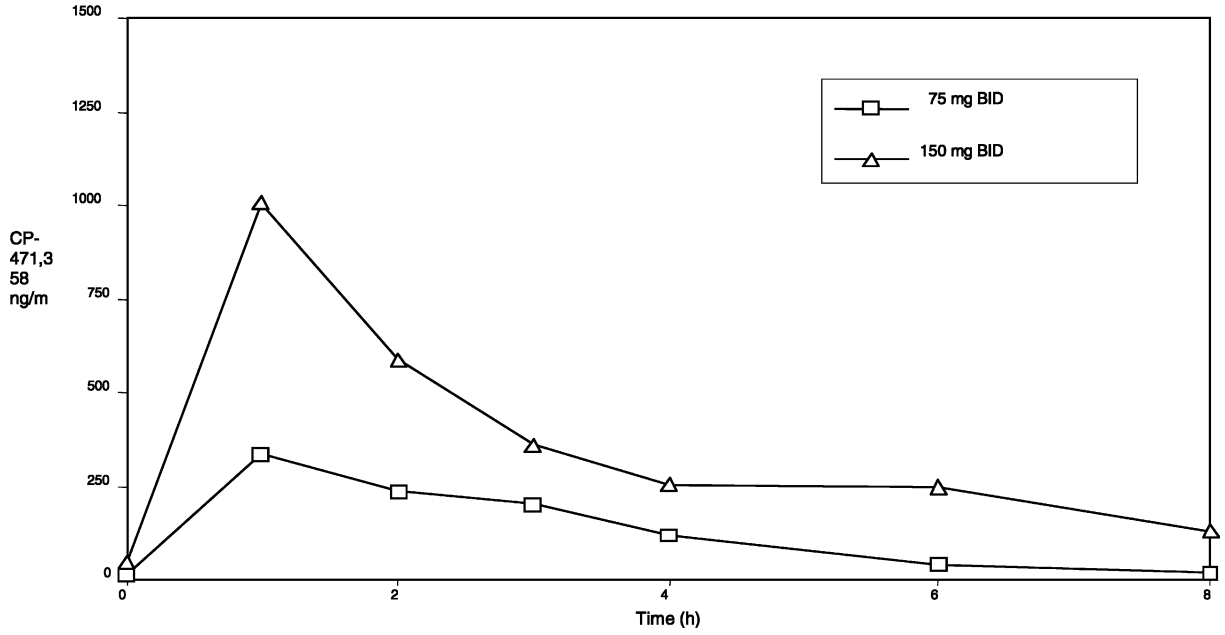


Fig. 1 Day-15 geometric mean concentration–time plots for CP-471,358 administered BID (at 8 a.m. and 4 p.m.). The plots are for the a.m. dose (75 mg $n=3$; 150 mg $n=3$)

with dose over the dosing range studied. The plasma protein binding of CP-471,358 was high (91.5% protein bound in healthy volunteer plasma) so the maximum glomerular clearance was small, much smaller than the measured urinary clearance, implying that much of the renal elimination of CP-471,358 is due to tubular secretion.

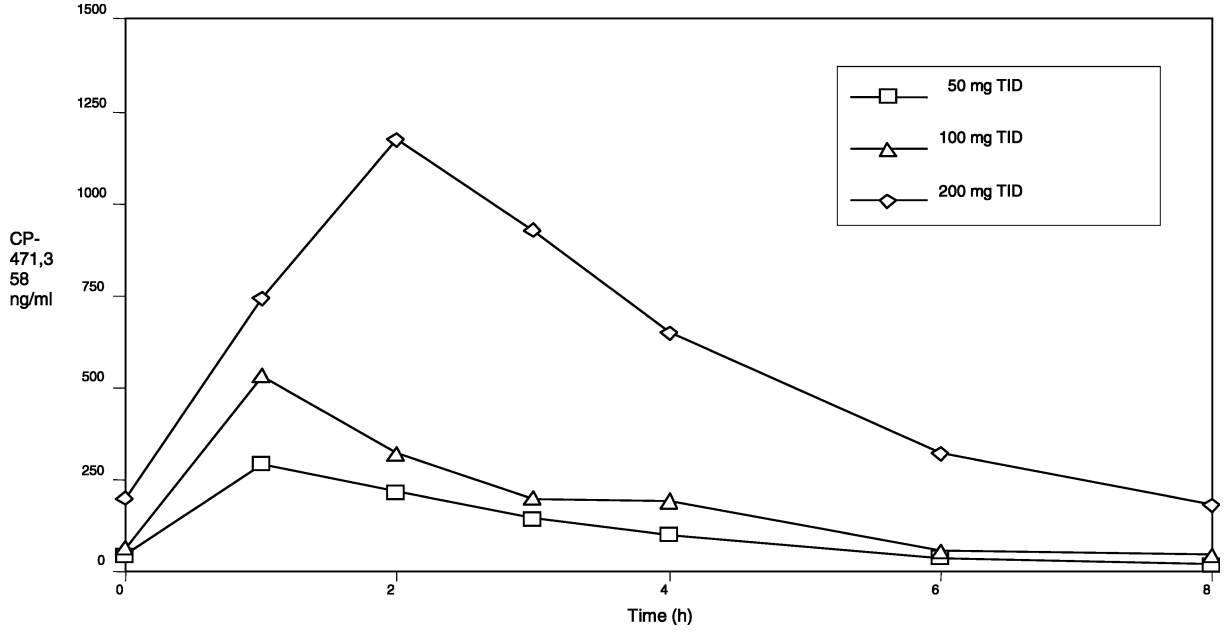
Fig. 2 Day-15 geometric mean concentration–time plots for CP-471,358 administered TID. The plots are for the a.m. dose (50 mg $n=6$; 100 mg $n=12$; 200 mg $n=6$)

Responses

No partial or complete responses were observed. Eight patients had stable disease of different durations (colon cancer and sarcoma each two patients; non-small-cell lung cancer, melanoma, mesothelioma and ovarian cancer each one patient).

Discussion

We conducted a phase I study with CP-471,358, a MMPI. MMPs are likely to be involved in the early stages of tumor development and in the process of metastasis. Their exact role and their complex interaction with integrins, cytokines, sheddases and adhesion



molecules have not yet been elucidated [7]. The first MMPIs that entered clinical trials were batimastat and marimastat. Batimastat is only applicable for intracavitary use because of insolubility in water, and further development was therefore halted. Marimastat is a relatively nonspecific MMPI that inhibits the activity of MMPs 1, 2, 3, 7, 9 and 12. The DLT of marimastat is polyarthritis. Marimastat was studied versus placebo as maintenance therapy in small-cell lung cancer after induction chemotherapy [20]. In this study 63% of the patients reported musculoskeletal side effects (18% grade 3 or 4) and 32% of the patients on marimastat stopped treatment as a result of this adverse event. No improvement of progression-free or overall survival was demonstrated. In a randomized study in advanced pancreatic cancer comparing the efficacy of gemcitabine with that of marimastat at three dose levels (5, 10 and 25 mg BID continuously) the risk of musculoskeletal complaints appeared to be correlated with the marimastat dose and increased from 39% with the 5 mg BID dose to 55% with the 25 mg BID dose. Grade 3 or 4 toxicity was reported in 7% in the 5 mg BID arm versus 12% in the 25 mg BID arm [4]. In a placebo-controlled trial in locally advanced pancreatic cancer comparing gemcitabine in combination with marimastat 10 mg BID versus the combination of gemcitabine and placebo, grade 3 or 4 musculoskeletal toxicity was limited to 4% of the patients [5]. It was suggested that the dose-limiting polyarthritis is linked to the inhibition of MMP-1 [11].

CP 471,358 is a more selective MMPI sparing MMP-1; therefore it was anticipated that it would result in fewer musculoskeletal adverse events. However, the clinical profile of arthralgia/myalgia observed in this study is similar to that of marimastat. Myalgia/arthralgia was observed at nearly all dose levels with a suggestion that the severity increased at the higher dose levels of 300 mg and 400 mg daily.

Other recently developed MMPIs also frequently result in myalgia/arthralgia as an adverse effect. Col-3, a tetracycline derivative, is a competitive inhibitor of MMP-2. In a phase I study cutaneous phototoxicity was the DLT. Three out of 37 patients developed drug-induced systemic lupus erythematosus (SLE) accompanied by arthralgia and fever. In these three patients, SLE was confirmed by a positive antinuclear antibody test [18]. Rheuma serology was performed in patients entered in the latter part of our study, but positive reactions were not observed. MMI270 (CGS27023A), another oral MMPI, also resulted in musculoskeletal events reported in 39 out of 92 patients treated in the phase I study, and this adverse effect was not dose-related but correlated with treatment duration [15]. Also, prinomastat, which was studied as adjunctive treatment to chemotherapy in non-small-cell lung cancer and glioblastoma multiforme resulted in musculoskeletal toxicity and failed to demonstrate any greater benefit in antitumor activity than chemotherapy alone [2].

Since there have been suggestions that, in part, these adverse events could be decreased or alleviated by introducing drug holidays, intermittent dosing was assessed in the current study. Unfortunately, musculoskeletal events nevertheless persisted.

MMPIs, without or with fewer musculoskeletal adverse effects are BAY 12-9566 and BMS-275291. BAY 12-9566 does not inhibit MMP-1 and is devoid of musculoskeletal side effects. DLT for this agent is hematologic (thrombocytopenia) and other major adverse effects are fatigue and diarrhea [8, 12]. BAY 12-9566 has been studied in placebo-controlled trials in pancreatic, ovarian and small-cell lung cancer. Due to lack of clinical activity the BAY 12-9566 studies were prematurely closed [13, 16].

BMS-275291 is a broad-spectrum MMPI that also inhibits MMP-1 but spares sheddases [14]. In a phase I study, this agent resulted in CTC grade 1and 2 myalgia in 49% of patients, but caused no grade 3 myalgia or arthritis (although one case of tenosynovitis was observed). This finding suggests that inhibition of MMP-1 is indeed not the only explanation for the occurrence of the arthralgia/myalgia syndrome. Further randomized studies may assess whether patients will tolerate milder adverse events. Since MMPIs are agents that will likely require chronic dosing, adverse events such as arthralgia/myalgia, even if less than grade 2, may not allow long term administration. For CP-471,358 the frequency of arthralgia/myalgia and the challenge in controlling these symptoms prompted us not to recommend further study in cancer patients.

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