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ORIGINAL ARTICLE

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A dose-finding and pharmacokinetic study of the matrix metalloproteinase inhibitor MMI270 (previously termed CGS27023A) with 5-FU and folinic acid

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Abstract The orally bioavailable matrix metalloproteinase inhibitor MMI270 reduces tumour growth metastasis in preclinical models. We assessed the feasibility and pharmacokinetic interactions of combining MMI270 with 5-fluorouracil (5-FU) and folinic acid (FA). Entered into the study were 33 patients with advanced colorectal cancer. They received FA 200 mg/m^2 over 2 h followed by 5-FU 400 mg/m^2 over 15 min and 5-FU 600 mg/m^2 over 22 h on days 1 and 2 of a 14-day cycle. MMI270 commenced with the second cycle at either 50 mg once daily, 150 mg three times daily or 300 mg twice daily. No dose-limiting toxicity was observed at any MMI270 dose level. Ten patients (61%) experienced joint symptoms independent of MMI270 dose, leading to interruption, modification, or discontinuation of treatment in seven patients (23%). MMI270 did not alter 5-FU pharmacokinetics. Six patients had a partial response and seven had stable disease. 5-FU/FA with MMI270 at a dose of 300 mg twice daily is well tolerated. MMI270 has no significant effect on 5-FU pharmacokinetics.

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Introduction

The matrix metalloproteinases (MMP) are a family of zinc-dependent enzymes involved in extracellular matrix (ECM) and basement membrane (BM) degradation [9, 12]. These proteins fall into three major subgroups: collagenases, stromelysins and gelatinases. In normal tissues they are involved in tissue remodelling, their activity being controlled by α 2-macroglobulin and a family of specific tissue inhibitors (TIMP). In malignancy, the normal control of MMP activity appears to be altered in three main ways: increased activation from latent proenzymes by proteolytic enzymes such as urokinase-like plasminogen activator (u-PA), increased expression of MMP and reduced expression of TIMP. The resulting change in balance, favouring increased MMP activity, is integral to the process of malignant cell invasion and metastasis. Also important are degradation of the basement membrane and the facilitation of endothelial cell invasion during tumour angiogenesis [2, 8, 15, 25].

A number of small molecular inhibitors of MMPs (MMPI) have been developed that reduce tumour growth, metastasis and angiogenesis in preclinical models [19]. These MMPIs fall into two classes, those which inhibit a broad range of target enzymes (e.g. marimastat), and those which show relative specificity (e.g. BAY12-9566). MMI270 is a potent, broad-spectrum, orally active, MMPI that inhibits the gelatinases MMP2 and MMP9 and the stromelysin MMP3 in low nanomolar concentrations. In rat tumour models of breast and endometrial cancer, MMI270 as a single agent or in combination with megestrol acetate has been

shown to significantly reduce tumour burden and number of lymph node and lung metastases [24]. Antimetastatic in vivo and antiangiogenic effects in vitro were also noted with MMI270 (Novartis MMI270 Investigator Brochure).

On the basis of these preclinical results, a single-agent phase I study of MMI270 was performed [10]. Patients received treatment with MMI270 for 4 weeks in the first instance with the option of continuing treatment if it was well tolerated. Pharmacokinetic data from this study indicated that MMI270 is rapidly absorbed following oral administration with a median t_{max} of 0.58 h (range 0.3–3 h) and a median half-life of 1.6 h. At the highest single-agent dose used (600 mg three times daily), a substantial proportion of patients experienced a reversible skin reaction. Arthralgia and/or myalgia in the upper limbs was observed in 40% of patients treated at all dose levels with the onset several weeks after the start of treatment with MMI270. The frequency and severity of arthralgia and myalgia did not appear to be dose related and symptoms settled over time after stopping the drug. This pattern of toxicity is similar to that described with other broad-spectrum MMPIs.

Levitt et al. [10] concluded that the maximum tolerated dose (MTD) of MMI270 is 300 mg twice daily. At this dose and also at 150 mg twice daily, maximum plasma concentrations of MMI270 are greater than 80 ng/ml (about 200 n *M*), a concentration which, based on their IC_{50} values, should result in full inhibition of the target enzymes. The trial reported here consequently was designed to determine the MTD of MMI270 in combination with 5-fluorouracil (5-FU) and to investigate any potential pharmacokinetic interaction between MMI270 and 5-FU. Preclinical data, which became available during the conduct of this trial, suggested that MMI270 had antimetastatic effects in vivo and antiangiogenic effects in vitro. These effects occurred at very low doses (equivalent to an estimated 25 mg daily in humans). These data suggest that lower doses and less-frequent schedules of administration may be appropriate for further investigation. Although MMPIs may be active as single agents, it is likely that they will be more effective in combination with chemotherapy. We conducted this dose-finding study of MMI270 combined with 5-FU and folinic acid to determine the tolerability of the combination and exclude any clinically significant pharmacokinetic interaction.

Materials and methods

Eligibility criteria

The Local Research Ethics Committee in each of the participating centres approved this study. All patients entered into the study gave written informed consent and had a histologically or cytologically confirmed diagnosis of malignancy for which chemotherapy with 5-FU and folinic acid was considered appropriate. Eligibility criteria included an estimated life expectancy ≥12 weeks, WHO performance status of ≤ 2, adequate hepatic function (serum bilirubin less than 1.5 times the upper limit of the reference range; transaminases less than 2.5 times the upper limit of the reference range), and adequate haematological function (haemoglobin ≥9 g/dl; neutrophil count $\geq 1.0\times10^9$ l^{-1}; platelets $\geq 100\times10^9$ l^{-1}).

Patients were considered ineligible if they had cerebral metastases, received chemotherapy or radiotherapy within the previous 28 days, had undergone previous treatment with an investigational agent within 30 days, or had a history of prior adverse reaction to fluoropyrimidines. Those with previous upper gastrointestinal surgery or concurrent upper gastrointestinal disease potentially affecting the administration or absorption of oral medication were also excluded.

Treatment

5-FU with folinic acid was administered as a 48-h i.v. infusion [4]. On day 1 of each treatment cycle, folinic acid 200 mg/m^2 in 250 ml normal saline was administered over 2 h, followed by a bolus injection of 5-FU 400 mg/m^2, then by an infusion of 5-FU 600 mg/m^2 in 500 ml normal saline over 22 h. This was repeated on day 2 of each cycle with cycles given every 14 days.

MMI270 was administered orally at one of three dose levels in successive cohorts of patients. The starting dose level of MMI270 was 150 mg three times daily and dose escalation was planned when three patients at the previous dose level had completed at least three cycles (42 days) of treatment. The subsequent dose levels of MMI270 were to be based on the results of preclinical studies and the single agent phase I study that were anticipated to become available during the course of this study and also on the pattern of toxicities seen. When the recommended dose was reached an expanded cohort was to be enrolled to fully evaluate the toxicity and efficacy of the combination.

MMI270 was commenced with the second cycle of 5-FU chemotherapy and continued until toxicity was observed, disease progression noted or until further treatment was declined. The reason for this delay in commencing MMI270 administration was twofold. Firstly, the administration of a single cycle of 5-FU alone allowed the assessment of toxicity due to 5-FU alone and the exclusion of any patient who experienced unexpectedly severe side effects. Secondly, this allowed the assessment of toxicity in patients participating in the pharmacokinetic sub-study, where this delay was necessary, in the same way as for others in the study.

Treatment toxicity was assessed according to NCI Common Toxicity Criteria version 2 [20] and response according to WHO criteria.

Pharmacokinetics

Pharmacokinetics of MMI270 and 5-FU were assessed in a subset of 12 patients treated at the recommended dose of MMI270 to be given with 5-FU. MMI270 was administered for 48 h between 7 and 5 days prior to the administration of the first cycle of chemotherapy. MMI270 was then recommenced with the second cycle of chemotherapy. Pharmacokinetic sampling for MMI270 was undertaken before taking the dose of MMI270 and then at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h. After collection, heparinized blood specimens were centrifuged at 2500 rpm for 15 min at room temperature. Plasma was then separated and immediately frozen at −20°C until analysis.

MMI270 concentrations were determined in plasma using a validated HPLC method described previously [10]. In brief, after acidification of plasma with 0.1 *M* potassium phosphate, MMI270 was extracted from plasma with ether/methylene chloride (2:1). The organic layer was extracted, evaporated to dryness and reconstituted in 200 ml of HPLC mobile phase. HPLC was then performed using a 5 μm Zorbax SB-C_{18} analytical column and analytes measured using UV detection at a wavelength of 242 nm. The lower level of quantification of MMI270 is 20 ng/ml.

On day 1 of the first cycle of chemotherapy, heparinized blood samples were taken to assess 5-FU pharmacokinetics before dosing and then 1, 2, 8 and 20 h after the start of the i.v. infusion on day 1 (5-FU alone) and on day 29 (5-FU and MMI270). The specimens were centrifuged at 2500 rpm for 15 min at room temperature and the resulting plasma samples were transferred by pipette into screw-cap plastic tubes. Samples were immediately frozen to −20°C and maintained frozen until analysis. 5-FU was determined in plasma by a validated method utilizing HPLC with UV detection [21]. The lower limit of quantification was 25 ng/ml.

Pharmacokinetic analyses were performed by non-compartmental methods using WinNonlin Professional (v. 3.1) software (Scientific Consulting). Calculated parameters included maximum concentration (C_{max}), time of maximum concentration (t_{max}), terminal elimination half-life ($t_{1/2}$) and area under the concentration–time curve (AUC). For MMI270, AUC was calculated over the time interval 0–8 h after dosing. For 5-FU, AUC was calculated over the time interval 2–20 h after the start of infusion. Pharmacokinetic sampling was repeated for both MMI270 and 5-FU as described above on day 1 of the third cycle of chemotherapy.

Dose modifications

If significant musculoskeletal toxicity (grade 2 or 3) was observed with MMI270, it was discontinued until symptoms abated before restarting at half the dose. If symptoms returned after therapy had resumed then MMI270 was discontinued, but chemotherapy could continue.

Evaluation of response

Pretreatment evaluation included a full medical history and examination, full blood count and biochemical profile including urea, electrolytes, and liver function tests. CT scan of the abdomen and other sites of disease was performed as appropriate prior to starting treatment and repeated after 4, 8 and 12 cycles of chemotherapy to assess response. Serum levels of the tumour marker CEA were assessed, if appropriate, prior to each cycle of chemotherapy. Evaluation of response was based on WHO criteria [22]; response rates are based on the total number of patients entered into the study, regardless of whether they received MMI270.

Results

Thirty-three patients were entered into the study, all of whom had metastatic colorectal cancer; their characteristics are shown in Table 1. One patient received the initial cycle of 5-FU, but did not start treatment with MMI270 due to a deterioration in his general condition precluding further treatment, and was withdrawn from the study. This patient was included in the analysis of response but not included in the toxicity analysis. Eleven patients had received previous adjuvant chemotherapy with a 5-FU-based regimen and one had received previous adjuvant immunotherapy with Edrocolomab. Six patients had received previous therapy for metastatic

Table 1 Patient characteristics

	Dose level			
	50 mg once daily	150 mg three times daily	300 mg twice daily	Overall
Age (years)				
Median	52	49	62	61
Range	34–75	48–70	41–76	34–76
Sex				
M	5	2	17	24
F	4	1	4	9
PS				
0	7	1	10	18
1	2	2	9	13
2	–	–	2	2
Primary site				
Colon				22
Rectum				11
Previous chemotherapy				
Adjuvant	3	–	8	11
Palliative	–	1	5	6
Previous radiotherapy				
Adjuvant	1	1	2	4
Palliative	1	–	8	9

disease, the median number of previous treatment regimens being 1.5 (range 1–3). Three patients were treated at the initial MMI270 dose of 150 mg three times daily. At this point the phase I single-agent study of MMI270 indicated that reversible skin toxicity occurred in patients treated at doses of 600 mg twice daily and above. Furthermore, it was apparent that doses of MMI270 greater than 300 mg twice daily were not well tolerated over protracted periods with around 40% of patients treated in the single-agent phase 1 study experiencing moderate to severe arthralgia or myalgia [10]. Therefore, the target dose of MMI270 in the current study was defined as 300 mg twice daily. We expanded the number of patients treated at this dose level to 12 and studied their pharmacokinetics.

During the course of this study, preclinical data became available suggesting that MMI270 inhibited tumour metastasis in a mouse model over the dose range of 5–120 mg/kg per day, with a dose of 20 mg/kg per day being maximally effective. This is equivalent to a human dose of between 50 and 100 mg/day. A further nine patients were, therefore, enrolled at an MMI270 dose of 50 mg daily in case chronic administration of higher doses proved impractical. These patients received a median of 152.5 days on treatment with MMI270 (range 28–309 days).

A total of 249 cycles of combined treatment with the MMPI and 5-FU/folinic acid were administered in three dose levels. Patients received a median of 112 days (range 112–140 days), 92 days (range 0–266 days) and 152 days (range 28–309 days) of MMI270 at the 150 mg three times daily, 300 mg twice daily and 50 mg once daily dose levels, respectively. In all three cohorts the most common reason for discontinuing treatment was disease progression (18/33 patients, 56.25%), however, seven patients stopped study treatment due to toxicity (21.87%). Two patients, one each at the 50-mg daily and 300-mg twice-daily MMI270 dose level died during the study; in both cases death was due to disease progression.

Compliance

Compliance with MMI270 treatment was monitored using a dosage record form, which 17 patients (52%) returned. Of those patients who returned a form, 14 (82%) appeared to have complied fully with treatment. Data on the number of capsules returned to pharmacy from 18 patients (54%) confirmed that compliance was good; the median proportion of drug taken by patients (actual dose/target dose) was 0.96.

Toxicity

Toxicity due to 5-FU chemotherapy alone was evaluated following the first cycle of chemotherapy. Any nausea with 5-FU alone was experienced by 24 patients (73%), but only 3 (9%) vomited. Diarrhoea occurred in 11 patients (33%) and stomatitis in 7 patients (21%). These toxicities were mild and in no case worse than CTC grade 2.

In the second and subsequent treatment cycles with 5-FU, administered along with MMI270, the pattern of toxicity was similar to that seen with 5-FU alone. Nausea (CT grade 1 or 2) was observed in 15 patients (45%), the reduced incidence being due to the use of prophylactic antiemetic therapy; 4 patients (12%) vomited. Diarrhoea occurred in 17 patients (51%) and stomatitis in 12 patients (36%). Although patient numbers were small, there was no evidence that MMI270 affected the frequency or severity of 5-FU toxicity; however, we cannot exclude the possibility of a toxicity interaction between these agents.

Toxicities potentially associated with MMI270 were assessed in the context of side effects associated with the drug given as a single agent. Overall, 20 patients (60.6%) experienced musculoskeletal symptoms during treatment with MMI270, most commonly pain (11 patients) or stiffness (10 patients). There was no clear difference in the incidence of these toxicities between dose levels. Five

Table 2 Treatment toxicity (all cycles)

	Dose level					
	50 mg once daily ($n=9$)		150 mg three times daily ($n=3$)		300 mg twice daily ($n=21$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Nausea	5		2		9	
Vomiting	1		1		1	1
Diarrhoea	5		2		10	
Anorexia	1				1	
Palmar/plantar syndrome	4				3	
Lethargy	2		1		5	1
Stomatitis	4		1		6	1
Conjunctivitis	3				1	
Arthralgia	3				6	2
Joint stiffness			3		4	3
Myalgia					2	
Skin rash	1				3	

patients (55.6%) treated at the lowest dose level (50 mg once daily) had joint symptoms, which in two patients were attributed to MMI270 and led to discontinuation of treatment in one patient. All three patients treated at the intermediate dose (150 mg three times daily) experienced joint symptoms related to MMI270 but none required interruption or cessation of treatment. At the highest dose level (300 mg twice daily), 12 patients (57%) had joint symptoms which in 11 patients were attributed to MMI270; this led to permanent discontinuation of drug in three patients and temporary interruption in a further three. Overall, the median time from commencing treatment with MMI270 until the onset of joint symptoms was 98 days (range 5–221 days). The median time to onset of joint symptoms was 75 days, 98 days and 62 days in the 50 mg once daily, 150 mg three times daily and 300 mg twice daily groups, respectively; and these did not differ significantly.

Four patients experienced a mild transient skin rash during the study. Three were receiving 300 mg twice daily of MMI270, the other 50 mg once daily. The rash was thought to be due to MMI270 in only two of these patients, both at the 300 mg twice daily dose.

Seven patients stopped treatment due to toxicity. In five patients this was due to musculoskeletal toxicity with arthralgia and join stiffness. One patient developed ataxia, ascribed to 5-FU, which improved on stopping treatment. A further patient developed severe fatigue (grade 3) which led to the discontinuation of chemotherapy. The treatment toxicities over all cycles are summarized in Table 2.

Pharmacokinetics

The mean concentration–time profiles of MMI270 in the absence and presence of 5-FU for the 12 patients treated with an MMI270 dose of 300 mg twice daily are shown in Fig. 1. The AUC, C_{max} and t_{max} for MMI270 (with and without 5-FU), and also for 5-FU are detailed in Table 3. Overall, there was a 15% decrease in AUC but a 43% decrease in C_{max} for MMI270 in the presence of 5-FU. Interpatient variability, however, was high, and these differences were not statistically significant. The mean concentration–time profiles for 5-FU in the presence and absence of MMI270 are shown in Fig. 2. The

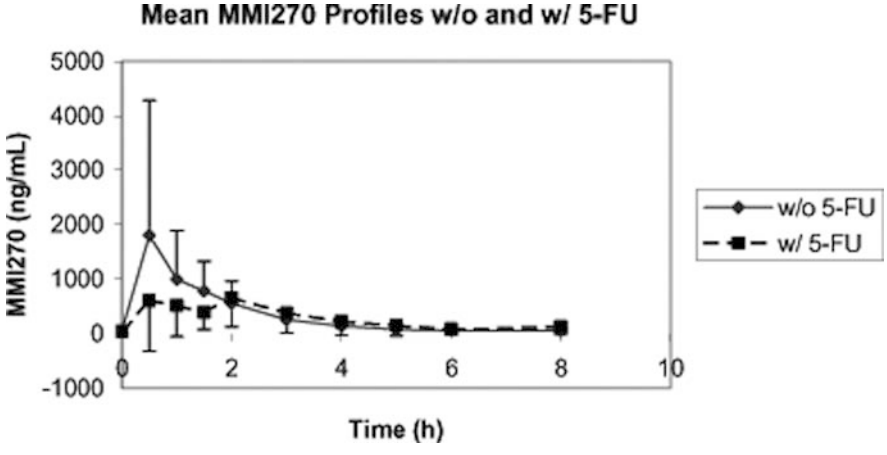

Fig. 1 Concentration versus time plots for MMI270 with and without 5-FU

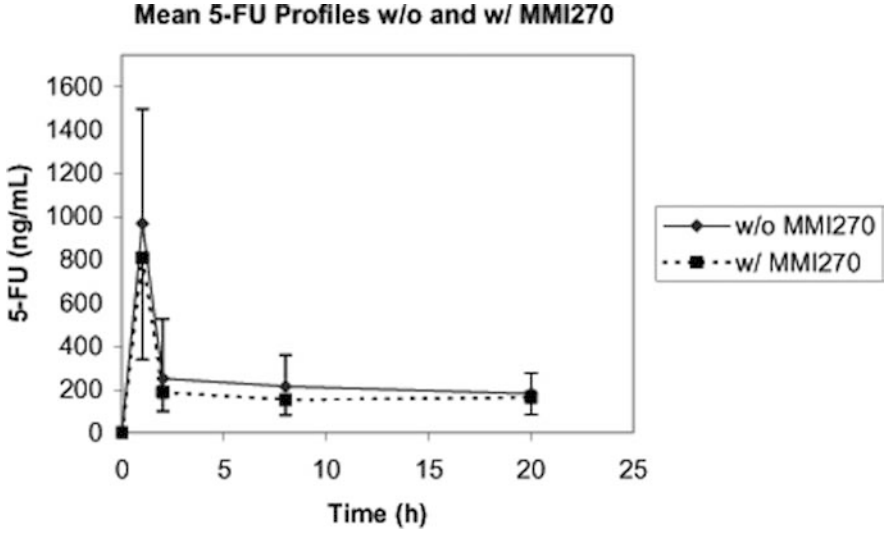

Fig. 2 Concentration versus time plots for 5-FU with and without MMI270

Table 3 Pharmacokinetic parameters of 5-FU and MMI270 following separate and concurrent administration

	MMI270		5-FU	
	Without 5-FU	With 5-FU	Without MMI270	With MMI270
AUC (ng Eh/ml) (95% confidence interval)	2875 (1745–4005)	2284 (1491–3077)	3675 (2574–4776)	3344 (2736–3952)
Median C_{max} (ng/ml) (range)	1559 (629–7525)	1031 (315–2603)	968 (436–1590)	809 (430–1368)
t_{max} (h) (range)	0.78 (0.5–3.0)	1.61 (0.42–2.8)		

administration of MMI270 did not result in any marked change in 5-FU pharmacokinetics.

Response

Response could be assessed in 30 of the 33 patients in the study. Six (18.2%) had a partial response, 17 (51.5%) had stable disease, and (21.2%) had disease progression on treatment. The three patients who were not evaluable for response did not have bidimensionally measurable disease.

Discussion

We established that MMI270 can be safely administered in conjunction with 5-FU and folinic acid over a range of dose levels. Dose-limiting toxicity was not encountered in this study. The most significant toxicity related to the MMI270 was arthralgia and joint stiffness. This was reversible in all cases, but 10% of patients had to discontinue treatment with MMI270 at the maximum dose assessed.

The pattern of toxicity observed did not suggest any clinically relevant interaction between 5-FU and MMI270. There was an increased incidence of diarrhoea associated with the second and subsequent treatments with 5-FU and folinic acid compared to the first cycle of chemotherapy (administered without MMI270), although it was not more frequent than that found in other clinical trials [4]. Moreover, the response rate is consistent with that seen in a similar group of patients at this centre treated with 5-FU and folinic acid alone [11]. This study did not achieve the conventional endpoint in a phase I trial of determining the MTD of MMI270 in combination with 5-FU and folinic acid. There is, however, little evidence that the maximum benefit from MMPI therapy occurs at the highest doses. Therefore, design of trials to optimally assess the activity of these drugs remains a significant challenge. During the course of this trial, ongoing preclinical studies suggested that the effect of MMI270 occurs with serum concentrations significantly lower than those achieved at the highest dose of MMI270 used in this study. Furthermore, activity appeared greatest when serum concentrations fell below the IC_{50} for MMP inhibition during a significant proportion of the day. It is, therefore, not possible to define the optimal therapeutic dose of MMI270 for future studies on the basis of this trial. This problem is common to the design of other trials to determine the optimum dose of cytostatic rather than cytotoxic agents and emphasizes the need to investigate pharmacokinetics and validated surrogate markers in addition to dose-limiting toxicity when assessing the profile of such drugs.

Attempts have been made in a number of studies to evaluate surrogate endpoints for the biological activity of MMPI. Early studies suggested that plasma MMP levels were elevated in patients with colon and breast cancer [25]. It was hoped that changes in MMP levels might act as a marker of a biologically effective dose. However, no consistent changes in the activity or plasma levels of MMP2 or 9 were seen in a phase I trial [23]. Subsequently, marimastat was reported to significantly reduce the rate of rise of tumour markers in a number of solid tumours [14, 16, 17]. In patients with pancreatic cancer, the Ca19-9 tumour marker level stabilized or fell in 30% of evaluable patients treated with marimastat, this was associated with a twofold improvement in median survival compared to those with a rising Ca19-9 [6]. The clinical significance of this finding is unclear as there is little clinical literature evaluating the rate of rise of tumour markers in common solid tumours over time. Indeed, a placebo-controlled randomized study has shown no improvement in outcome with the addition of marimastat to gemcitabine [13].

When two or more drugs are given concomitantly, it is possible that one could affect the pharmacokinetics of another. It may be particularly important to exclude such an interaction where chronic administration and late-onset toxicity are anticipated, as these may not be clinically detectable in a phase I trial of limited size. In this study, the determination of the pharmacokinetics of drug alone always preceded the determination of kinetics in combination, rather than randomizing the sequence of treatments. Nevertheless, the concomitant administration of MMI270 did not have a significant effect on 5-FU pharmacokinetics. Thus, there is no pharmacokinetic basis for an adjustment of 5-FU dose during concomitant treatment with MMI270. By contrast, concomitant administration of 5-FU was associated with a marked decrease in the C_{max} of MMI270, but only a small decrease in AUC and a slight increase in t_{max}. There have been very few reports on the effect of 5-FU and/or leucovorin on the pharmacokinetics of other drugs, and there are no reports of an effect on plasma concentration. The concomitant administration of MMI270 with food also results in a decrease in C_{max} and increase in t_{max} with no effect on AUC [5]. The similarity of the pharmacokinetic results raises the

possibility that 5-FU/leucovorin may slow the absorption of MMI270, possibly through an effect on the mucosa of the gastrointestinal tract. It is unlikely, however, that the small fall in AUC of MMI270 is clinically significant when administered with 5-FU. This trial demonstrates the tolerability of MMI270 and 5-FU over a range of potential doses that require further evaluation. The most appropriate design would be a randomized phase II study covering a range of MMI270 doses along with 5-FU.

The role of MMPI therapy, alone or in combination with chemotherapy, in the treatment of cancer is unclear. A recent study of marimastat in patients with unresectable gastric cancer demonstrated a small benefit in overall survival compared to treatment with placebo. Subgroup analysis revealed that this improved survival was primarily seen in patients entered into the study following a response to chemotherapy [3]. By contrast, interim analysis of two large phase III studies in patients with non-small-cell lung cancer and prostate cancer of the broad-spectrum MMPI, AG3340, or placebo in addition to chemotherapy showed no differences in progression-free survival or response rate [1, 18]. BAY12-9566, an MMPI with a limited spectrum of activity against MMP2, 3 and 9, has been compared to placebo in patients with small-cell lung cancer and with pancreatic cancer [7, 13]; in both studies MMPI treatment was associated with an inferior outcome.

The current study showed that MMPI270 and 5-FU can be given together with no additional toxicities and no significant pharmacokinetic interaction. Although to date the results of phase III trials of MMPIs have been disappointing, optimizing combinations of cytotoxic chemotherapy and chronically administered novel agents remain an important challenge.

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