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ORIGINAL ARTICLE

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Phase I trial of the matrix metalloproteinase inhibitor BAY12-9566 in patients with advanced solid tumors

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Abstract *Purpose*: Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that are believed to be involved in primary and metastatic tumor growth by degrading the basement membrane and changing the extracellular matrix to facilitate invasion of malignant cells and angiogenesis. Overexpression of MMPs has been documented in various solid tumors. BAY12-9566 is a selective inhibitor of MMPs, in particular MMP-2, -3, and -9. The purpose of this trial was to define the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), safety profile, pharmacokinetics and pharmacodynamics of orally administered BAY12-9566 in patients with incurable solid tumors. *Methods*: The starting dose of BAY12-9566 for this single institution, outpatient phase I study was 100 mg/day orally. Patients were allowed to receive drug for up to 12 months. A total of 27 patients with various solid malignancies including colorectal, breast, lung, cervical and ovarian cancers were enrolled at doses from 100 to 1600 mg/day. Patients were evaluated weekly while on treatment. Relevant radiologic examination was performed every 8 weeks to document and follow sites of measurable or evaluable disease. *Results*: Toxicities from BAY12-9566 included liver injury test abnormalities, anemia, shoulder and back pain, thrombocytopenia, mild nausea and fatigue, diarrhea, rash and deep vein thrombosis. No toxicity greater than grade III was observed. As doses were increased from 100 to 400 to 1600 mg/day, even in divided doses, less than proportional increases in AUC were observed. At the highest dose level of 1600 mg/day, the day 29 AUC (3778.00 mg·h/l) remained similar to the day 29 AUC (3312.60 mg·h/l) at the dose level of 1200 mg/day. No responses were seen, but 14 patients remained on study with stable disease for 4 to 26 months. *Conclusions*: BAY12-9566 was well tolerated at doses as high as 800 mg orally twice daily. Although mild alterations in liver injury tests, platelet count and hematocrit were noted, these were not dose-limiting. The drug was well absorbed. However, the absence of proportional increases in AUC with doses greater than 800 mg and the achievement of Css in the range associated with biologic activity in preclinical models led to the selection of 800 mg twice daily for further evaluation in phase III trials.

Keywords Matrix metalloproteinase inhibitor · Advanced solid tumors

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Introduction

Matrix metalloproteinases (MMPs) are a family of at least 16 different zinc- and calcium-containing proteolytic enzymes that play an important role in maintaining tissue homeostasis within the extracellular matrix. Although the members of this family share a highly conserved catalytic domain and a specific sequence in the prodomain, they differ in substrate specificity, inhibitor binding and matrix binding [4]. MMPs are believed to be

involved in primary and metastatic tumor growth by degrading the basement membrane and changing the extracellular matrix to facilitate invasion of malignant cells and angiogenesis. Overexpression of MMPs has been documented in various tumors, including breast, colon, gastric, head and neck, prostate and lung cancer [9]. Matrix metalloproteinase inhibitors (MMPIs) targeted against MMPs have been identified using several approaches for synthesizing and screening agents. BAY12-9566 is one of a series of MMPIs selected for inhibition of MMP-2, -3, and -9 with inhibitory constants of 11, 134 and 301 nmol/l.

In a B16.F10 murine melanoma model, growth of tumors implanted in mice was inhibited by a maximum of 50% when a 14-day course of oral twice-daily 100 mg/kg BAY12-9566 was administered [3]. When tumor cells were injected into the tail vein of B16.F10 mice 24 h before implantation, there was a 58% inhibition in the total number of metastases at the 100 mg/kg oral dose [7].

SCID mice with HCT 116 colon tumor fragments implanted in the cecum were treated with BAY12-9566 on day 5 at doses from 25 to 200 mg/kg [6]. There was inhibition of primary tumor growth of 35% at a dose of 100 mg/kg as well as a 50% reduction in the overall incidence of distant metastases. The size of the metastatic tumors was also smaller. In the H-23 human lung cancer xenograft model, BAY12-9566 was given with cisplatin. There was an increase in complete responses of established tumors with BAY12-9566 in combination with cisplatin compared to cisplatin alone.

In addition to promising preclinical data, a total 124 healthy volunteers have completed phase I studies with relatively little toxicity [2]. Pharmacokinetic analysis revealed a plasma half-life of 90–100 h, with protein binding of $>99.9\%$ [10]. Kinetics were determined to be linear up to the 100 mg dose level. Based on these data and on the safety record in human volunteers, 100 mg/day was determined to be the starting dose in this trial.

The objectives of this trial were: (1) to define the maximum tolerated dose (MTD) or to achieve the steady-state plasma concentration (Css) of BAY12-9566 in the range associated with biologic activity in preclinical models, (2) to determine the dose-limiting toxicity (DLT), if any, (3) to assess the safety profile, (4) to determine the pharmacokinetics of BAY12-9566 when administered orally on a daily schedule to patients with advanced incurable solid tumors, and (5) to observe any evidence of antitumor activity.

Materials and methods

Eligibility

All patients who were enrolled in this trial were more than 18 years of age, with an ECOG performance status of ≤ 2, and had a histologically or cytopathologically documented solid tumor that was refractory to conventional treatment. Life expectancy was required to be at least 12 weeks and patients were required to be capable of and willing to give written informed consent. Laboratory requirements included the following hematology and chemistry parameters: absolute neutrophil count (ANC) $>1500/\mu l$, platelets $>100{,}000/\mu l$, PT/PTT within normal limits, bilirubin <1.5 mg/dl, ALT, AST, and alkaline phosphatase less than twice the upper limit of normal, and creatinine <1.5 mg/dl.

Patients who had had major surgery within the past 14 days, had received large field radiation therapy or chemotherapy within 28 days, or had received mitomycin or nitrosoureas within the past 42 days were excluded from the study. Concurrent chemotherapy, radiation therapy, or immunotherapy were not allowed to be administered while on study. Any patients with brain or meningeal metastases, active infections or other severe psychological or social problems preventing full compliance were not eligible. Patients with a history of gastrointestinal disorder or gastric and small bowel resections that could result in incomplete absorption of the study medication, a history of major cardiovascular events, such as myocardial infarction or stroke in the past 3 months, as well as patients taking oral anticoagulants were excluded from the trial. Patients were required to practice adequate birth control; women were excluded if they were either pregnant or breast-feeding. Patients with hypersensitivity to BAY12-9566 or similar compounds, a significant history of drug allergies to multiple medications, or having taken investigational drugs in the past 30 days were not eligible to enroll.

Approval was granted by the Institutional Review Board and all patients signed informed consents prior to initiation of treatment.

Treatment

BAY12-9566 was supplied by Bayer Corporation, Pharmaceutical Division, (West Haven, Ct).

The initial oral daily dose of BAY12-9566 was 100 mg. At each dose level, patients received a single oral dose of study medication between 7 and 10 a.m. on day 1. A small breakfast was allowed prior to the first dose. The first dose was witnessed by either the investigator or the study nurse to ensure patient compliance. For the following 3 days, patients received twice-daily dosing to more rapidly achieve steady-state blood levels. On day 5, patients reverted to once-daily dosing. The study was initiated with 28 days of therapy followed by 2-week treatment breaks. After the first six patients were observed, patients received continuing daily doses.

Study design

DLT was defined as one of the following toxicities that were possibly or probably related to the study medication: (1) any toxicity greater than grade 3, (2) symptomatic grade 2 toxicity that required holding or reducing a dose, (3) any grade 2 biochemical toxicity which persisted for more than 7 days, (4) other toxicities of concern to the investigator/sponsor. MTD was defined as the dose level at which the dose-limiting toxic events occurred in two patients. The NCI Common Toxicity Criteria were used to determine grade of toxicity.

Groups of at least three patients were treated and evaluated at each dose level. The dose escalation paradigm was as follows. (1) If no DLT was observed in the three patients who were treated for 28 days, then the next cohort of patients were treated at the next dose level. Dose escalations proceeded as follows: 100 mg daily, 400 mg daily, 400 mg twice daily, 400 mg three times daily, 400 mg four times daily, and 800 mg twice daily. (2) If one DLT occurred within the first 28 days of treatment, then the next three patients were enrolled at the same dose level. If only one of the six patients at this dose level experienced DLT, then dose escalation continued. If two or more of the six patients experienced DLT, then this dose was declared the MTD. (3) If two DLTs occurred within the first 28 days of treatment, then three more patients were enrolled at the same dose level and this dose was declared the MTD.

For dose reductions due to late toxicities (beyond the first 28 days), BAY12-9566 was restarted either at the same or lower dose as decided by the investigator and sponsor. There were no intrapatient dose escalations allowed. Dose ranging was to continue until the MTD was defined or until a dose was achieved that produced BAY12-9566 trough plasma concentrations of approximately 360 mg/l, which was equivalent to ten times the minimal plasma concentrations found to be efficacious in preclinical mouse models.

Study procedures

History, including adverse event assessments and brief physical examinations, were performed every 4 weeks. Patients were instructed not to take any other concomitant medications in the 8-h period prior to, or the 4-h period after dosing on days 1 or day 28. Any concomitant medications taken were recorded.

Laboratory analyses included weekly CBC with differential, liver injury tests, serum chemistry panel (sodium, potassium, chloride, bicarbonate, glucose, creatinine, blood urea nitrogen, calcium, phosphorus, uric acid), urinalysis, and coagulation profile. Imaging studies included CT scans, abdominal ultrasound, radiography or other radiologic studies as clinically indicated to document all sites of disease. EKG was obtained prior to initiation of therapy.

Pharmacokinetics

Patients were instructed to fast for 2 h before samples were obtained. Venous blood samples (7 ml each) for BAY12-9566 were collected by venipuncture at the following time-points for cycle 1: days 1 and 28 at 0 (predose), 1, 2, 4, and 8 h; days 2 and 29 (24-h trough samples); days 15 and 43 predose; day 71 (24-h trough sample). Within 20 min of blood draw, each sample was centrifuged for 10 min at 4°C and 2800 *g* to separate the plasma. The plasma was transferred to a polypropylene tube and kept frozen (at –20°C or lower).

Plasma samples were prepared as described by Agarwal et al. [1]. BAY12-9566 was analyzed by high-performance liquid chromatography using a Beckman Ultrasphere C8, 5 μ*M*, 100A, 250×4.6 mm analytical column at a temperature of 40°C. The precipitation of plasma proteins required the use of acidified acetonitrile. A gradient elution was necessary to separate all analytes from the endogenous constituents of the plasma. The UV detection was performed at 290 nm. Retention times of metabolites M1, M2, and M3, BAY12-9566 and BAY13-8825 (internal standard) were approximately 9, 12, 14, 16, and 20 min, respectively.

Pharmacokinetic parameters were calculated using KinCalc. The observed maximum concentration was recorded as C_{max}. Normalized C_{max} was obtained by dividing C_{max} by the dose in milligrams per kilogram. T_{max} was the time at which the maximum concentration was observed. $AUC_{(0\text{-}tau)}$ was the area under the plasma BAY12-9566 concentration-time curve from zero to the end of the dosing interval (tau). AUC values were calculated by using the linear trapezoidal rule in the ascending portion of the plasma concentration-time curve. $AUC_{(0\text{-}tau)}$ was normalized by the dose in milligrams per kilogram to obtain normalized $AUC_{(0\text{-}tau)}$. If BAY12-9566 was administered twice daily, three times daily or four times daily, the $AUC_{(0\text{-}tau)}$ on day 29 was multiplied by 2, 3 or 4, respectively, to obtain $AUC_{(0\text{-}24)}$ at steady state. This conversion allowed a comparison of the total daily dose and the associated steady-state AUC.

Evaluation of response

Tumor response criteria were based on the overall sum of measurable disease. Complete response was defined as the disappearance of all clinical and radiologic evidence of tumor, determined by two observations not less than 4 weeks apart. The patient must also have been free of all tumor-related symptoms. Partial response was defined as 50% or greater decrease in the overall sum of measurable lesions determined by two observations not less than 4 weeks apart. No simultaneous increase in the size of any lesion or the appearance of any new lesions may have occurred. Stable disease was defined as the steady state of disease less than partial response. Progressive disease was defined as an unequivocal increase of at least 25% in the overall sum of measurable lesions as compared to baseline or the appearance of any new lesions.

Patient compliance was monitored by drug administration diaries which were evaluated at each outpatient visit. Administration of study drug was also monitored by study staff on days 1 and 28.

Treatment termination criteria

Treatment termination criteria included: (1) clinical or radiologic evidence of disease progression, (2) intercurrent illness that compromised the patient's participation in the trial, (3) patient voluntary withdrawal, and (4) discretion of the treating physician. If a patient was discontinued from the study drug due to noncompliance during cycle 1, then a replacement patient was allowed to be enrolled.

Statistics

No formal sample size estimation was made for this phase I study with cohorts of three or four patients at each dose level. Descriptive summary statistics were utilized for demographic variables, adverse events, and laboratory parameters.

Results

A total of 27 patients were enrolled on the study between December 1996 and January 1998. Patient characteristics are detailed in Table 1. Overall, there were 12 males (44%) and 15 females (56%) with advanced solid tumors. The majority (96%) had an ECOG performance status of 0 or 1. Breast and colon cancer were the most common diagnoses represented. The majority of patients (96%) had received prior chemotherapy, while only 11%

Table 1 Patient characteristics

Gender	
Male	12
Female	15
ECOG status	
0	12
1	14
2	1
Race	
Caucasian	24
African American	2
Asian	1
Primary tumor site	
Colon	9
Breast	6
Ovary	3
Cervix	2
Kidney	2
Lung	2
Gallbladder	1
Mediastinum	1
Mesothelioma	1
Total	27

had received prior radiation therapy and 4% had received prior surgery. No patients were treated with prior immunotherapy, hormonal therapy, or biologic therapy. All patients were assessable for laboratory and radiologic studies as well as for toxicity evaluation in the first cycle of therapy.

Toxicity

Hematologic toxicity of a mild degree was seen frequently. Seven patients (26%) experienced grade I platelet toxicity and all 27 patients had a decline in platelet count, even though the values remained within normal limits. No grade II or III thrombocytopenia was observed. Ten patients (37%) experienced grade I anemia, while 11 (41%) and 3 (11%) experienced grade II and III anemia, respectively. All had preexisting anemia. Six patients (22%) required red cell transfusions. Of the 11 patients with grade II anemia or greater, two received 100 mg daily, two received 150 mg, two received 400 mg, two received 800 mg and three received 1600 mg total daily dose. All three patients with grade III anemia received the 1600 mg daily dose. The anemia occurred at different times in the treatment cycle. Grade I neutropenia occurred in three patients (11%). One patient (4%) experienced grade II neutropenia at 400 mg and one patient (4%) experienced grade III neutropenia at 1600 mg. There were no episodes of febrile neutropenia.

Liver injury test abnormalities included five patients (19%) with grade II alkaline phosphatase toxicity, four patients (15%) with grade II bilirubin toxicity, one patient (4%) with grade I SGOT toxicity, and two patients (8%) with grade I SGPT toxicity. All patients with grade II liver function toxicity had liver metastases. There were two dose reductions secondary to hepatic injury test abnormalities. One patient had resolution of the toxicities to baseline and the other did not. These two patients with bilirubin and alkaline phosphatase toxicity were dose-reduced from 1200 mg and 1600 mg to 800 mg daily, respectively.

Three patients (11%) experienced deep venous thrombosis. One patient had a prior history of deep venous thrombosis, but was not anticoagulated during the study. The second patient, despite being on coumadin therapy for atrial fibrillation which developed while on study, developed a deep venous thrombosis and was diagnosed with Trousseau's syndrome. The third patient with metastatic colon cancer developed renal failure secondary to bilateral ureteric obstruction while on study and developed a deep venous thrombosis. This third patient also experienced cardiac arrest at the time of the renal failure and was successfully resuscitated. It was determined that the cause of the cardiac arrest was hyperkalemia. Other toxicities included three patients (11%) with grade I headaches, two patients (7%) with grade III musculoskeletal back pain, and one patient (4%) with grade III nausea and vomiting (Table 2).

Table 2 Drug-related toxicities versus dose

	Dose (mg)						Total
	100	125	150	400	1200	1600	
Diarrhea	–	1	1	–	2	3	7
Nausea	1	1	–	–	2	3	7
Asthenia	1	–	1	–	1	3	6
Vomiting	2	1	–	–	–	1	4
Abdominal pain	–	1	–	1	–	1	3
Dyspepsia	–	2	1	–	–	–	3
Headache	1	–	–	–	–	2	3
LFT abnormal	1	–	–	–	1	1	3
Flatulence	–	1	1	–	–	–	2
Total	7	8	5	3	7	21	51

There were no partial responses and no complete responses on this study. There were 14 patients (48%) with stable disease, and 10 patients (37%) with progressive disease. Three patients (15%) were discontinued from the trial, and were therefore nonevaluable, one after 4 days due to newly discovered brain metastases, one after 2 days due to disease progression by CT scan and the last after 18 days because of gastrointestinal toxicities. Of the 14 patients with stable disease, 11 remained stable for more than 4 months and 3 had stable disease for more than 7 months. The median time to tumor progression was 4 months. One patient with mesothelioma remained on study for 26 months with stable disease.

Pharmacokinetic results

The first cohort of patients received an oral dose of 100 mg/day. The mean AUC on day 1 was 183.52 mg·h/l (Table 3). This value remained similar in the next two cohorts at 125 mg and 150 mg daily, respectively. There was a fourfold increase in the day 1 AUC at the 400 mg daily dose, but the day 29 AUC remained relatively stable when compared to the other lower dose levels. With a threefold increase in dose (1200 mg daily), there was a proportional increase in the day 29 AUC. At the highest dose level of 800 mg twice daily, the day 29 AUC remained similar to the one at the dose level of 400 mg thrice daily. The 800 mg twice daily dosing schedule was found to be more convenient than the 400 mg four times a day dosing and the calculated $AUC_{(0\text{-}24)}$ on day 29 was highest with the 800 mg twice-daily dose. T_{max} did not appear to be affected by multiple dosing. BAY12-9566 is absorbed relatively rapidly into the systemic circulation. The accumulation factor, which is defined as the ratio of $AUC_{(0\text{-}tau)}$ on day 29 to that on day 1, appeared to be similar across doses, suggesting that there was no dose-dependent change in drug accumulation in the systemic circulation.

With regard to the day 1 C_{max}, there was a fourfold increase in value which correlated with a fourfold increase in dose. However, as the dose escalation continued, the day 1 C_{max} reached a plateau and the day 1

Table 3 Mean and standard deviation (SD) BAY12-9566 plasma pharmacokinetic parameters following administration of oral doses of BAY12-9566 to cancer patients for 29 days

Dose level	C_{max}				T_{max} (h)		$AUC_{(0\text{-tau})}$ (mg·h/l)		$AUC_{(0\text{-}24)}$ (mg·h/l)
	Observed (mg/l)		Normalized (kg/l)		Day 1	Day 29	Day 1	Day 29	Day 29
	Day 1	Day 29	Day 1	Day 29					
100 mg daily	10.02 (2.37)	43.80 (8.75)	5.93 (1.89)	26.64 (7.39)	10.96 (8.86)	3.56 (0.99)	183.53 (30.62)	960.40 (263.55)	960.40 (263.55)
125 mg daily	16.59 (5.28)	46.19 (8.26)	11.07 (3.31)	31.48 (6.45)	3.30 (1.09)	2.88 (1.30)	283.60 (83.69)	948.30 (204.64)	948.30 (204.64)
150 mg daily	11.58 (5.44)	59.11 (12.98)	4.64 (1.47)	24.46 (2.13)	11.95 (10.62)	4.04 (0.09)	215.60 (97.05)	1234.50 (230.00)	1234.50 (230.00)
400 mg daily	49.25 (7.24)	101.66 (17.91)	7.23 (0.83)	16.01 (3.00)	5.48 (2.05)	4.23 (3.41)	933.98 (174.09)	1987.33 (321.48)	1987.33 (321.48)
400 mg three times daily	36.84 (7.8)	150.40 (19.05)	2.77 (0.76)	11.01 (2.23)	3.94 (0.11)	4.28 (0.27)	208.13 (26.95)	1104.20 (151.27)	3312.60 (453.80)
400 mg four times daily	29.57 (10.71)	132.88 (20.53)	1.28 (0.15)	5.18 (0.81)	4.78 (1.80)	3.89 (2.67)	117.95 (53.75)	724.85 (101.61)	2899.40 (406.44)
800 mg twice daily	37.01 (18.48)	176.83 (35.20)	1.98 (1.42)	8.88 (1.14)	4.48 (2.37)	3.37 (1.18)	349.82 (114.76)	1889.00 (489.17)	3778.00 (978.34)

C_{max} value at dose 800 mg twice daily was similar to that at the 400 mg daily dose. A similar trend was seen in the day 29 C_{max} data. However, only a doubling of the day 29 C_{max} was achieved with the fourfold increase in dose. Eventually, at the higher dose levels, similar C_{max} values were achieved. These results show that BAY12-9566 plasma C_{max} and AUC values increased less than proportionally with dose.

Discussion

BAY12-9566 is a novel nonpeptidic matrix metalloproteinase inhibitor with selectivity against MMP-2, -3, and -9, and antitumor activity in preclinical murine models. This report describes the results of a phase I trial with this drug in patients with incurable solid tumors. BAY12-9566 was generally well tolerated and displayed minimal toxicities. Mild dose-related toxicities, particularly grade I anemia and thrombocytopenia, were evident in patients taking the 1600 mg daily dose. Decreases in platelet counts were generally not clinically significant and were not associated with any bleeding episodes. All patients experiencing anemia had preexisting anemia prior to the start of the study. In addition, patients with liver metastases had liver injury test abnormalities. Three patients developed deep venous thrombosis.

There was a striking absence of musculoskeletal side effects, which distinguishes this compound from other MMPIs. The selectivity of this compound for MMP-2, -3 and -9, and not MMP-1 may explain why musculoskeletal side effects were not present, in contrast to the findings of studies with other similar compounds. For a drug that may be used for long periods of time, minimizing this particularly debilitating side effect is important.

Although there were no complete or partial responses in this trial, 48% of the patients experienced stable disease, including one patient who remained on study for 26 months. Based on their mechanism of action, MMPIs such as BAY12-9566 are not expected to cause a tumor to shrink, but rather to slow the growth and spread of a tumor. In a patient population with multiple prior therapy and advanced disease, the number of patients with stable disease is an important and worthwhile outcome.

The pharmacokinetics of BAY12-9566 in cancer patients appear to be similar to those in healthy volunteers. There were less than proportional increases in plasma BAY12-9566 C_{max} and AUC values with dose. Steady-state levels of BAY12-9566 were reached at the optimal dosing schedule of 800 mg twice daily. These levels are in the range of the target plasma levels of BAY12-9566 that demonstrated efficacy in preclinical models [5, 8]. The MTD was not reached in this study, as further dose escalation was limited by a plateau in plasma concentration despite dose increases. The data obtained from this study have been used to determine the optimal

dosing schedule of BAY12-9566 for subsequent studies. The dose of 800 mg twice daily was chosen as it gave the best overall combination of maximal plasma levels that can be achieved in a dosing schedule that was convenient for patients. Currently, further development of BAY12-9566 in clinical trials has been on hold, and analysis of phase III trial results is awaited.

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