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Clinical report

Phase I and pharmacologic study of BMS-181174 given as a 6 h infusion every 4 weeks to patients with advanced solid tumors

AST Planting,[1] JHM Schellens,[1,3] MEL van der Burg,[1] M de Boer-Dennert,[1] B Winograd,[2] G Stoter[1] and J Verweij[1]

[1]Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, 3008 AR Rotterdam, The Netherlands. [2]Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford CT 06492, USA. [3]Present address: Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands.

BMS-181174, a new mitomycin C (MMC) analog, showed more activity than the parent compound in tumor xenografts. In a phase I study with a 5–30 min slow bolus administration, hematologic and vascular toxicity were observed as major side effects. A prolonged infusion was suggested to circumvent the vascular toxicity. In this phase I study BMS-181174 was administered as a 6 h infusion every 4 weeks; the doses studied were 3.2, 6.4, 11.5, 19.0, 32.0, 50.0, 75.0 and 100 mg/m^2. Twenty-eight patients were enrolled in the study, the majority with colorectal cancer. Hematologic side effects consisted of thrombocytopenia, and mild leuko- and granulocytopenia. The most distressing non-hematologic side effect was vascular toxicity consisting of phlebosclerosis and phlebitis, becoming dose limiting at 100 mg/m^2. One patient developed a hemolytic uremic syndrome at a cumulative dose of 350 mg/m^2. Pharmacokinetic data are available for 24 patients. The AUC ranged from 3.35 to 41.49 (μg·h/ml) and was highly correlated with the dose administered (r=0.83). The kinetics appeared to be linear. One patient with metastatic colon cancer had a partial response of liver metastases. BMS-181174 is a MMC analog with a toxicity profile comparable to that of the parent compound. As doses above 50 mg/m^2 are complicated by vascular toxicity precluding multiple administrations, further exploration of BMS-181174 will not be performed. [© 1999 Lippincott Williams & Wilkins.]

Key words: BMS-181174, MMC analog, phase I study.

Introduction

Mitomycin C (MMC) is an antitumor antibiotic widely used in the treatment of gastrointestinal, gynecological and non-small cell lung cancer. Its pharmacology and molecular pharmacologic properties have been extensively described.[1,2] MMC toxicity, among others, consists of long-lasting and cumulative bone marrow suppression, especially thrombocytopenia, which frequently hampers repeated administration of the drug. This and other, less frequent but more serious, toxicities such as pulmonary fibrosis, vascular and skin toxicity, and hemolytic uremic syndrome contributed to the gradual loss of popularity of the drug.[3–8] The broad spectrum of antitumor activity of MMC and especially its activity against hypoxic tumor cells explains the continued interest in the development of MMC analogs.

BMS-181174 is a new semi-synthetic MMC analog. It differs from MMC by substitution of an amino group on the C6 position by a nitrophenyl ethyl disulfide group. The drug has a molecular weight of 547.61. The structure formula is given in Figure 1.

In vitro BMS-181174 showed activity against various murine and human tumor cell lines including B16 melanoma, M109 lung cancer and several colon cancer cell lines, including cell lines resistant to MMC. *In vivo* BMS-181174 was active against P388 and L1210 leukemia, but showed cross-resistance to MMC in this model. In the B16 melanoma model BMS-181174 was more active than MMC. Unlike MMC, BMS-181174 is not more toxic in hypoxic than in aerobic conditions.[9]

Toxicity studies in the mouse, rat and dog showed bone marrow suppression to be the dose-limiting toxicity. In rats the major non-hematologic side effect was cardiotoxicity with histologic features of myocardial degeneration with inter- and intracellular vacuolization, intercellular edema, fibrosis, inflammation, periarteritis and thrombosis. Cardiotoxicity was dose

Correspondence to AST Planting, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, PO Box 5201, 3008 AR Rotterdam, The Netherlands.
Tel: (+31) 10 4391733; Fax: (+31) 10 4391003;
E-mail: planting@onch.azr.nl

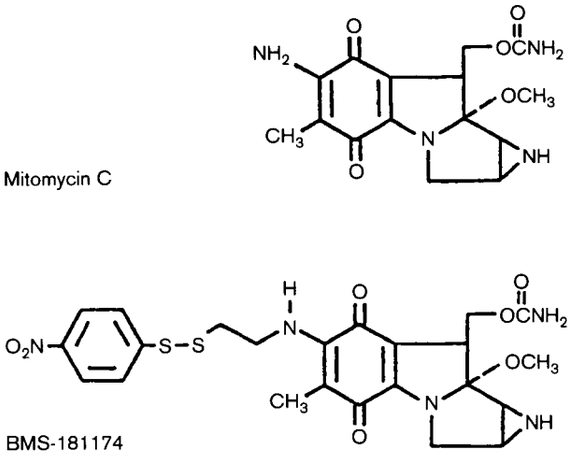

Figure 1. Chemical structure of BMS-181174 and MMC.

related and was irreversible at the highest dose levels studied. Other histopathologic changes observed in the rat were glomerulopathy, renal tubular degeneration, pulmonary inflammation, arteritis, thrombosis, lymphoid depletion and necrosis at the injection site. In the dog toxicity consisted of rapid reversible myelosuppression. Cardiac or renal toxicity were not observed in dogs.

In the first phase I study in man BMS-181174 was administered as a 5-30 min infusion every 4 weeks.[10] In this study 82 patients were entered. Thrombocytopenia and leukocytopenia were dose-limiting toxicities in pretreated patients at a dose of 75 mg/m^2 and thrombocytopenia was cumulative. Other toxicities observed were a decrease in the left ventricular ejection fraction (LVEF) in nine out of 62 evaluable patients, but this was reported not to be correlated to the dose level. Local cutaneous toxicity or phlebitis at the injection site was observed in 25% of the patients. Three patients developed a possibly drug-related pneumonitis. We performed a phase I study with BMS-181174 as a 6 h continuous infusion every 4 weeks in an attempt to avoid in this way the vascular toxicity reported in the study of Macaulay *et al.* which was ongoing when the present study started. Based on the safety data already obtained in the bolus phase I study the starting dose selected was 3.2 mg/m^2.

Patients and methods

Eligibility and follow up

All patients enrolled in the study had histologic proof of a metastatic solid tumor unresponsive to conventional therapy or with a tumor type for which a standard regimen did not exist. All patients had a life expectancy of at least 2 months, age 18-75 years, WHO performance status ≤ 2 and no prior chemotherapy with MMC, anthracyclins or nitrosoureas. Other chemotherapy was allowed as well as immuno- or radiotherapy provided that there was at least a 4 week interval and there was full recovery from toxicities of prior treatments. Prior radiotherapy to the chest involving the heart was not allowed. Further eligibility criteria included WBC $\geq 4.0 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, serum bilirubin <25 mmol/l, liver function tests <1.25 the upper level of normal (ULN) or <2.5 ULN in case of liver metastases, serum creatinine ≤ 120 μmol/l, a left ventricular ejection fraction (LVEF) $>55\%$ and no signs of CNS involvement. All patients gave written informed consent.

Prior to the first dose all patients had a full clinical work up consisting of a medical history, physical examination, complete blood counts, coagulation parameters, full serum chemistries, creatinine clearance, ECG, estimation of the LVEF by MUGA scan, a chest X-ray and a CT scan of the tumor-bearing areas.

During follow up patients had a weekly physical examination; serum chemistries were measured weekly, hematological counts twice weekly; MUGA scans were to be repeated before every cycle. From dose level 6 on all patients had a standard lung function test (Jaeger Masterlab) and a DLCO diffusion test by the single-breath method before the start of the first cycle and lung function tests were repeated every second cycle. Response to treatment was assessed after two cycles or earlier if considered indicated. The WHO guideliness were used for response evaluation and for grading of toxicity.[11]

Drug administration

Patients were hospitalized for the administration of BMS-181174. BMS-181174 was supplied in vials containing 20 mg lyophilized powder and was dissolved in 10 ml of 5% Tween 80 in phosphate buffer. The solution was further diluted with normal saline to a concentration of 0.1 mg/ml. The final solution was filtered over a disposable filter (poresize 0.22 μm, Millex GS; Millipore, Bedford, MA). The drug solution was administered over 6 h using a volumetric pump (IVAC 590) as a side infusion via a peripheral vein. Due to vascular toxicity, patients at the two highest dose levels received their infusions via long indwelling catheters (Intracath; diameter 0.16 inch). During preparation and administration the drug was protected from light.

The starting dose of BMS-181174 was 3.2 mg/m^2. Three patients were planned per dose level for a minimum of four evaluable cycles per dose level. For dose escalation a modified Fibonacci schema was used. The maximal tolerated dose (MTD) was defined as the highest dose producing manageable, tolerable and reversible toxicity WHO grade III in three out of six patients at that dose level.

Pharmacokinetics

Blood samples for pharmacokinetics were taken from the contralateral arm at 0, 2, 4, 6 (end of infusion), 6.25, 6.5, 7, 8 and 24 h. Per sample, 10 ml of venous blood was collected in EDTA containing Vacutainer tubes and stored on ice until centrifugation. The samples were centrifuged within 30 min in a refrigerated centrifuge at 1000 *g* for 15 min. The plasma layer was collected in a polyprolene tube and kept frozen at −80°C until analysis. Plasma concentrations were analyzed by a quantitative reverse-phase HPLC assay employing UV detection at 370 nm and precolumn derivatization, according to a method developed by Gaver and Deeb.[12] In brief, the plasma protein bound thioethyl MMC moiety was reduced by adding tributylphosphate (25 μmol in 0.05 ml dimethylsulfoxide) to 0.5 ml of plasma containing 12.5 μmol EDTA. Two minutes later, 5 μmol maleimide in 2 ml acetone added to trap the free thiol. After 30 min, the liquid phase was removed and evaporated under nitrogen at 48°C. The residue was dissolved in 0.25 ml 2 mM KH_2PO_4:acetone (7:3 v/v) and injected on a Shandon Hypersil RP18 (10 cm, 4.6 mm internal diameter, 5 μm particle size; Astmoor, Cheshire, UK). The photometric UV response was linear between 50 and 10 000 ng/ml BMS 181174 equivalent. Precision at the lower limit of quantitation of 50 ng/ml was 7% and accuracy 98%. At the lowest two dose levels blood samples were taken from the start until the end of infusion. At the higher dose levels samples were taken up to 24 h after the start of the infusion.

The area under the curve (AUC) was determined using noncompartmental pharmacokinetics (Siphar, release 3.0; SIMED, Creteil, France).

Results

A total of 28 patients were entered in the study and all were eligible. The patient characteristics are given in Table 1. The dose levels studied, the numbers of patients and cycles per dose level are specified in Table 2. Eighteen patients received more than one cycle. The total number of cycles administered was 52.

Table 1. Patient characteristics

No. of patients entered	28
Male:female	18:10
Median age (range)	57 years (37–73)
Median performance status (range)	1 (0–2)
Tumor types	
colorectal cancer	13
carcinoma of unknown primary	4
non-small cell lung cancer	2
renal cell cancer	2
cholangiocarcinoma	2
miscellaneous	5
Previous chemotherapy	
yes	26
no	2
Previous radiotherapy	
yes	6
no	22

Table 2. Hematologic toxicity (WHO grading; worst toxicity per cycle)

Dose level	Dose (mg/m^2)	No. patients/ no. cycles	Anemia					WBC					Granulocytes					Platelets				
			0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3.2	4/6	–	3	3	–	–	5	1	–	–	–	6	–	–	–	–	6	–	–	–	–
2	6.4	3/5	–	4	1	–	–	5	–	–	–	–	5	–	–	–	–	5	–	–	–	–
3	11.5	3/6	3	2	1	–	–	6	–	–	–	–	6	–	–	–	–	6	–	–	–	–
4	19	3/10	3	2	5	–	–	8	2	–	–	–	1	–	–	–	–	1	–	–	–	–
5	32	3/5	–	2	3	–	–	4	1	–	–	–	5	–	–	–	–	4	–	–	1[a]	–
6	50	3/4	–	2	2	–	–	2	2	–	–	–	4	–	–	–	–	4	–	–	–	–
7	75	6/10	–	9	1	–	–	9	1	–	–	–	9	1	–	–	–	7	2	1	–	–
8	100	3/6	–	5	1	–	–	3	1	2	–	–	3	2	1	–	–	2	3	–	1[b]	–

[a]Patient with intravascular coagulation.
[b]Patient developed HUS.

Hematologic toxicity was analyzed as worst WHO grade per treatment cycle and is shown in Table 2.

Anemia was frequently observed, did not exceed grade 2, was not dose-related and reflected the pre-existing disease state rather than treatment related toxicity. Leukocytopenia, with the exception of a heavily pretreated patient at the first dose level, was only observed from the dose of 19 mg/m^2 on and reached grade 2 only at the highest dose level, varying in duration from 7 to 28 days. Granulocytopenia, not exceeding grade 2, was also observed at the two highest dose levels only. Thrombocytopenia was first observed at the dose of 32 mg/m^2 in a patient who developed a clinical picture compatible with diffuse intravascular coagulation (DIC). As this DIC developed in the first week after the first administration of the study drug and the patient had a rapid progressive poorly differentiated lung cancer this DIC was considered disease related and not drug related. At 75 mg/m^2 thrombocytopenia grade 1 or 2 developed in three out of six patients with a median nadir on day 26 (range 18–33). In one patient the thrombocytopenia developed after the third cycle suggesting cumulative toxicity. At the dose of 100 mg/m^2 thrombocytopenia grade 1 was observed in all three patients. One patient developed thrombocytopenia grade 3 after the third cycle, starting on day 22 with recovery to normal on day 43 also suggesting cumulative toxicity. As this patient had a response in liver metastases of colon cancer, he received a fourth cycle at a reduced dose of 50 mg/m^2. After this cycle, at a cumulative dose of 350 mg/m^2, a hemolytic uremic syndrome (HUS) with ARDS developed leading to death despite intervention with heparin and plasmapheresis. The HUS presented with microscopic hematuria and proteinuria on day 40 after the fourth cycle, followed by a rise in serum creatinine from 66 to 1065 μmol/l shortly before death. Autoantibodies against erythrocytes were not detected. Since antibodies against hepatitis A, B or C and antibodies against cytomegalovirus and Epstein-Barr virus were also not detected an infectious origin for the HUS was considered unlikely. At autopsy the kidneys showed intima fibrosis of vessels, sclerosis of the mesangium of glomeruli, narrowing of capillaries and fibrinoid deposition in the mesangium. The glomeruli reacted positive for fibrin and complement with immunofluorescence techniques. In the lungs alveolar edema with fibrin-rich eosinophilic hyaline membranes were found with interstitial edema, infiltrates and hemorrhages compatible with a terminal ARDS during uremia.

The most serious non-hematologic toxicity observed was vascular toxicity (Table 3) presenting as phlebitis, from the dose of 11.5 mg/m^2 on, leading to phlebosclerosis or venous thrombosis in the infusion arm making further administration of the drug via peripheral veins impossible. Long indwelling catheters via antecubital veins were used in all patients from the dose of 75 mg/m^2 on in combination with 15 000 U of heparin i.v. for 24 h. Nevertheless, phlebosclerosis developed in five and a venous thrombosis in two patients (one at dose level 75 and 100 mg/m^2, in both patients after the third cycle). At 100 mg/m^2 this side effect was considered dose limiting since it precluded multiple drug administrations in all patients.

The LVEF was measured at the start of treatment in all patients and repeated before every cycle; for 17 out of 18 patients who received more than one cycle follow-up LVEFs are available. A drop of more than 15% from the base line value was observed in four patients: one patient at the lowest dose level at a cumulative dose of 6.4 mg/m^2, one patient at 19 mg/

Table 3. Non-hematologic toxicity (WHO grading: worst toxicity per cycle)

Dose level	Dose (mg/m^2)	No. patients/ no. cycles	Nausea/vomiting					Vascular toxicity					ASAT/ALAT elevation[a]				
			0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3.2	4/6	6	–	–	–	–	6	–	–	–	–	5	1	–	–	–
2	6.4	3/5	5	–	–	–	–	5	–	–	–	–	4	1	–	–	–
3	11.5	3/6	5	1	–	–	–	6	–	–	–	–	5	1	–	–	–
4	19	3/10	9	1	–	–	–	8	–	2	–	–	3	2	5	–	–
5	32	3/5	–	3	1	1	–	5	–	–	–	–	3	1	1[d]	–	–
6	50	3/4	1	2	1	–	–	3	1	–	–	–	2	1	1[b]	–	–
7	75	6/10	1	9	1	–	–	2	–	7	1	–	5	3	1	–	1[c]
8	100	3/6	4	2	–	–	–	1	–	4	1	–	5	–	1[e]	–	–

[a]Liver toxicity: if pre-existing ASAT/ALAT elevation, toxicity was evaluated as worsening of one grade (grade 1) or two grades (grade 2).
[b]Progressive liver metastasis.
[c]Progressive cholangiocarcinoma.
[d]Patient developed intravascular coagulation.
[e]Patient developed HUS.

m^2 at a cumulative dose of 38 mg/m^2 (reversible) and one patient at 50 and 100 mg/m^2 each, both with a cumulative dose of 100 mg/m^2. None of these patients were pretreated with cardiotoxic cytostatics or with radiotherapy to the chest. In three of these four patients no subsequent LVEF is available because of rapidly progressive disease. In five patients, one patient each at the dose level of 11.5, 19 and 50 mg/m^2, and two patients at 100 mg/m^2, chest pain was reported. This chest pain was described as 'wrapping', and was accompanied by shortness of breath and extreme tiredness. During these complaints no ECG changes were observed, neither at rest nor at exertion. Also, the LVEF measured at rest and during monitor-guided exercise tests did not show signs of a decreased cardiac function in these patients.

Evaluation of pulmonary toxicity was performed in all patients from dose level 6 on. In the patient developing the HUS, the DLCO deteriorated from 97% at baseline to 48% after the fourth administration, accompanied with a deterioration of the vital capacity and FEV_1. In none of the other patients studied were changes in pulmonary function observed. In the patients complaining of dyspnea or chest tightness also no lung function abnormalities were detected.

Nausea and vomiting were rarely reported as side effects, and were easily controlled with ondansetron or metoclopramide.

Renal toxicity was not observed, with the exception of the patient developing the HUS. Hepatic toxicity was not observed; all patients with deterioration in liver function had progressive liver metastases. One patient had a partial response of liver metastases from colon cancer; this patient continued treatment and developed the fatal HUS.

Pharmacokinetics

The median infusion duration was 6.27 h (range 5.85–7.33). The maximal plasma concentration (C_{max}) ranged from 93 ng/ml at the lowest dose-level to 3687 ng/ml at 100 mg/m^2 and appeared to be linearly related to the dose administered (Pearson r=0.86; Figure 2). The correlation coefficient with the dose in mg/m^2 was 0.90. The AUC was calculated up to the latest measured time point (AUC[t]), which was 24 h. As the $t_{1/2}$ turned out to be longer than the originally anticipated 4–6 h, the duration of the pharmacokinetic sampling was too short for calculation of a more precise curve. The curves were therefore not extrapolated to infinity, because the percentage of the area obtained by extrapolation was greater than 25% of the total area in the majority of patients. For this same reason distribution volume and clearance could not reliably be calculated. The AUC[t] ranged from 3.35 to 41.49 (μg·h/ml) and was linearly related with the dose administered (r=0.83; Figure 3) and with the dose/m^2 (r=0.89). C_{max} and AUC[t] were highly correlated (r=0.96). An example of a representative pharmacokinetic profile is given in Figure 4.

Discussion

MMC, one of the most active antitumor antibiotics, was frequently used in the 1960s and 1970s in combination chemotherapy regimens. Cumulative bone marrow suppression, thrombocytopenia in particular, rendered the drug rather difficult for combination regimens. With an increasing number of

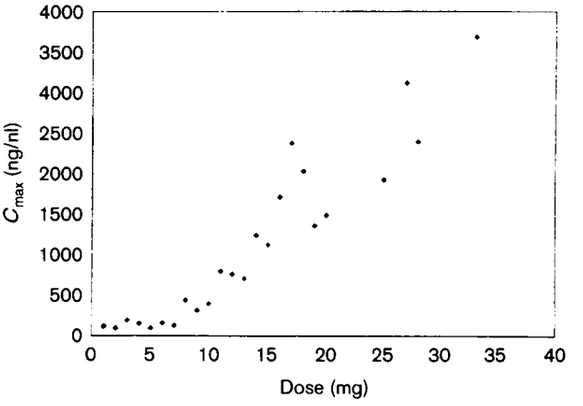

Figure 2. Relationship between the maximal plasma concentration (C_{max}) and the absolute dose given (Pearson correlation test r=0.86).

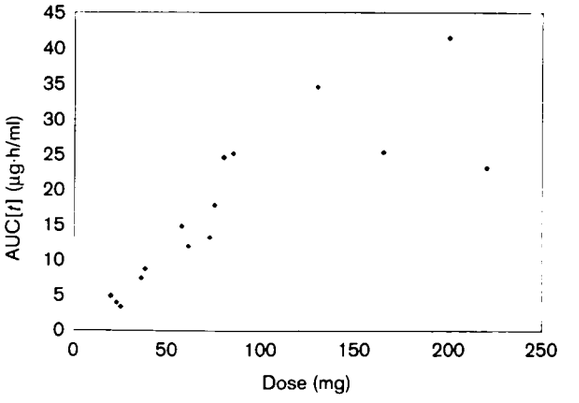

Figure 3. Relationship between the area under the curve (0–24 h) for the 6 h infusion (AUC[t]) and the absolute dose given (r=0.83).

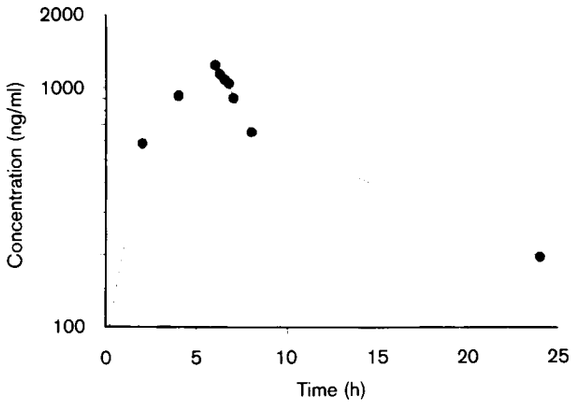

Figure 4. AUC of BMS-111874 administered at a dose of 30 mg/m^2.

reports on serious unpredictable side effects, especially HUS in up to 10% of patients even after cumulative doses as low as 30 mg/m^2,[4-8,13-19] but also reports on pneumonitis,[3,20,21] and vascular and skin toxicity,[22] the popularity of MMC gradually waned.

BMS-181174, a new MMC analog, was selected for phase I studies because of an improved antitumor activity over MMC in preclinical studies. In the first phase I study with BMS-181174 administered as a slow i.v. bolus, thrombophlebitis was a major side effect especially in patients treated with doses of 65-75 mg/m^2, of whom 25% experienced grade 3-4 vascular toxicity.[10] In our study we tried to circumvent this toxicity by administering BMS-181174 as a 6 h infusion and, at higher dose levels, by administering the drug via long indwelling central catheters in combination with low-dose heparin. Despite these measures, thrombophlebitis and phlebosclerosis continued to develop, and precluded administration of multiple cycles in all patients at the highest dose levels. Vascular toxicity can therefore be considered as the dose-limiting toxicity for BMS-181174 in this study. The second prominent side effect observed was thrombocytopenia. In contrast to Macaulay *et al.* we could not relate the dyspnea complaints objectively to pulmonary toxicity, except in the patient with HUS. In four patients a decline in the LVEF was observed, which was reversible in one patient. One patient developed a lethal HUS considered to be drug related.

The pharmacokinetics of BMS-181174 appeared to be linear. C_{max} as well as the AUC up to 24 h after start of the infusion were highly correlated with the dose administered, indicating relatively little interpatient pharmacokinetic variability.

We conclude that BMS-181174 is a drug with side effects not very dissimilar to the mother compound MMC. Because of the vascular side effects phase II studies will not be initiated.

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