Phase I Study of Intrapleural Batimastat (BB-94), a Matrix Metalloproteinase Inhibitor, in the Treatment of Malignant Pleural Effusions

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ABSTRACT

Tumor cells and associated stromal cells secrete matrix metalloproteinases (MMPs), contributing to invasion, angiogenesis, and metastasis. Batimastat (BB-94) is a broad-spectrum MMP inhibitor that causes resolution of ascites and/or tumor growth delay in animal models of breast, ovarian, and colorectal cancer. We recruited 18 patients with cytologically positive malignant pleural effusions into a Phase I study of intrapleural BB-94. Three patients received single doses of BB-94 at each dose level: 15, 30, 60, 105, 135, and 300 mg/m². Two patients were retreated with a second course at 60 and 105 mg/m². BB-94 was detectable in plasma 1 h after intrapleural administration, and peak levels of 20–200 ng/ml occurred after 4 h to 1 week. BB-94 persisted in the plasma for up to 12 weeks, at levels exceeding the IC_{50} for target MMPs. Peak values were higher, and persistence in the plasma was longer after higher doses of BB-94. The treatment was well tolerated. Toxic effects included low-grade fever for 24–48 h (6 of 18 patients, 33%) and reversible asymptomatic elevation of liver enzymes (8 patients, 44%). Toxicity seemed unrelated to BB-94 dose or plasma levels. Sixteen patients evaluable for response required significantly fewer pleural aspirations in the 3 months after BB-94 compared with the 3 months before. Seven patients (44%) required no further pleural aspiration until death/last follow-up. After 1 month, patients treated with 60–300 mg/m² BB-94 had significantly better dyspnea scores, indicating improved exercise tolerance, compared with baseline scores the day after BB-94. The maximum tolerated intrapleural dose remains to be defined, but it is clear that intrapleural BB-94 is well tolerated, with evidence of local activity.

INTRODUCTION

Malignant pleural effusions are common in patients with advanced cancer, occurring in almost half of all patients with lung and breast carcinoma. When the effusion is diagnosed, 75% of patients have respiratory symptoms including dyspnea, cough, and chest pain. Malignant effusion is a poor prognostic factor; ~20% of patients die within 1 month, and the median survival is only a few months (1). However, some survive for many months or years, and the effusion is often an important source of morbidity. Pleural drainage relieves breathlessness, but most effusions recur within a few days, and 90–100% within 1 month (2, 3). Various sclerosing or cytotoxic agents have been used to obliterate the pleural space (pleurodesis). Talc insufflation seems to be 90–100% effective (4–6), although thorascopy under general anesthetic may be inappropriate in patients with advanced cancer. Other agents including Corynebacterium parvum, the tetracyclines, and bleomycin achieve successful pleurodesis in 30–75% of patients, but often require repeat administration (7, 8).

MMPs are a family of structurally related zinc-atom-dependent endopeptidases that include the interstitial collagenases, stromelysins, gelatinases, and membrane-type MMPs. These enzymes are responsible for the turnover and remodeling of extracellular matrix proteins (9). MMP activity is tightly controlled in several ways: at a transcriptional level; by regulation of latent proenzymes; and by the presence of natural inhibitors, both general, such as a2 macroglobulin and specific tissue inhibitors of metalloproteinases (10, 11). MMPs are involved in the formation of new vessels, mediating the remodeling of the extracellular matrix that accompanies new vessel growth (12). Many tumors are characterized by deregulated MMP activity, either in the tumor cells themselves or, more often, in adjacent stroma. Higher levels of activated MMPs have been demonstrated in more invasive and/or metastatic tumors and may give prognostic information independent of stage (13–18).

BB-94 [(4-N-hydroxyamino)-2R-isobutyl-3S-(thiopen-2-ylthiomethyl)-succinyl]-l-phenylalanine-N-methylamide] is a substituted peptide analogue of the peptide residues on one side

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3 The abbreviations used are: MMP, matrix metalloproteinase; LFT, liver function test; AP, alkaline phosphatase; AST, aspartate aminotransferase; BB-94, batimastat.
of a principle cleavage site in type I collagen. The hydroxamate group binds the zinc atom in the active site, resulting in potent, reversible inhibition. BB-94 inhibits the activity of a broad spectrum of MMPs, with IC₅₀s of 1.5–10 ng/ml (3–20 nM; Ref. 19). BB-94 has weak cytostatic effects against cancer cell lines in vitro, but is not cytotoxic (20, 21). i.p. BB-94 treatment results in resolution of ascites, tumor growth delay, and dose-dependent increase in survival of nude mice bearing human ovarian cancer xenografts (22). In a rat breast cancer model, BB-94 inhibited lung colonization and spontaneous lymphatic metastases (23). BB-94 also retarded the growth of human breast cancer xenografts and delayed locoregional regrowth of resected tumors, but did not suppress ascites formation (24, 25).

BB-94 has shown antitumor effects in animal models of human colorectal cancer (26), murine melanoma, and hemangioma (20, 21).

There is no animal model of pleural effusion. However, the pleural and peritoneal cavities are functionally analogous and are lined by cells of similar histology and embryological origin. High levels of activated MMPs have been detected in malignant pleural effusions (27). These findings, together with the efficacy of BB-94 in the treatment of malignant ascites in animal models and in three Phase I trials in patients with malignant ascites (28–30), led to the present study evaluating the efficacy of intrapleural BB-94 in an open Phase I dose-escalating study in patients with cytology-positive malignant pleural effusions.

PATIENTS AND METHODS

Pretreatment Evaluation. Patients were eligible for the study if they had a cytologically positive malignant pleural effusion where standard management would involve drainage and pleurodesis. Eligibility also required that they had received no prior intrapleural therapy and had a predicted survival of >1 month. Patients were ineligible if they had a history of cardiac disease, obstructive jaundice, or surgery within the previous month. Pretreatment assessment was performed during admission and included history and physical examination, full blood count, liver biochemistry, electrocardiogram, chest X-ray, and other imaging as clinically indicated. An intercostal drain was inserted under local anesthetic, and a sample of fluid was sent for cytological analysis. The pleural effusion was drained to dryness usually over 1–3 days, initially by gravity and followed, if necessary, by suction from a wall-mounted suction pump using a pressure of 20 cm of H₂O for 12–24 h. After pleural ultrasound confirmation that negligible fluid remained, the BB-94 was administered as described below. This study was approved by the Central Oxford Research Ethics Committee, and patients were included after giving their written informed consent.

Study Design and Treatment. This was a Phase I dose-escalation study. Six dose levels of BB-94 were administered: 15, 30, 60, 105, 135, and 300 mg/m². Three patients were recruited to each dose level, with sequential assignment from low to high dose levels. At each dose level, there was an option to give a second dose of BB-94, between 28 and 84 days after the initial administration. Dose escalation was based on satisfactory safety data on the preceding dose level.

BB-94 was administered as a suspension via the intercostal drain in 50 ml of 5% dextrose over 5 min. The tubing was flushed with 10 ml of sterile saline, and the drain was removed. A chest X-ray was performed to check for pneumothorax. Patients remained in the hospital for an additional 24 h and were monitored for pulse, blood pressure, temperature, and for pleural pain using a 4-point verbal rating (no pain, grade 0; mild pain, grade 1; moderate pain, grade 2; severe pain, grade 3).

Pharmacokinetics. Blood samples were taken into lithium heparin tubes before BB-94 treatment and at 1, 4, 6, and 24 h and weekly for 12 weeks after treatment. Within 15 min of collection, samples were centrifuged at 4°C at 2000 rpm for 5 min, and the plasma was stored at -70°C. The samples were analyzed at British Biotech Pharmaceuticals Limited (Oxford, United Kingdom). BB-94 was extracted from plasma (1 ml/sample) at acidic pH using C18 solid phase extraction cartridges using an automated system. The cartridges were washed with di ammonium hydrogen phosphate, methanol/water (10%/90%, v/v) and hexane/ethyl acetate (90%/10%, v/v). The analytes were eluted with methanol. The methanol fractions were dried in a vacuum centrifuge and reconstituted in mobile phase. The chromatographic system comprised a C18 reversed phase high-performance liquid chromatography column and a mobile phase of methanol/water/acetonitrile (60%/30%/10%, v/v/v). BB-94 and the internal standard were detected using a Finnigan TSQ 700 mass spectrometer in MS/MS mode. The analytical procedure was developed and validated, as described (31, 32).

Monitoring. Assessments made on the day after BB-94 administration were used as baseline measurements against which to gauge subsequent changes in pleural effusion and its symptoms. Two measures were used, one subjective and one objective. First, patients were asked to rate their degree of dyspnea using the oxygen cost visual analogue scale. The subject marked the central line at a level above which he/she could not perform because of breathlessness. The distance of the patient’s mark from the origin gave a numerical dyspnea score, ranging from 0 cm for “extreme breathlessness disturbing sleep” to 10 cm for “brisk walking uphill” (33, 34). This measure has been shown to be appropriate for assessment of response to therapy (35). Second, patients underwent pleural ultrasound to measure the extent of the effusion. All ultrasound scans were performed by the same radiologist (F.G.) and were performed with the patient sitting erect, measuring the vertical height of the effusion in millimeters from the lateral aspect of the diaphragm in the mid-axillary line.

Patients were followed up for 12 weeks after BB-94 administration with weekly outpatient assessment as follows: history (including assessment of pleural pain and dyspnea score), examination, blood count, liver biochemistry, chest X-ray, and pleural ultrasound. Toxic effects were graded according to the Cancer and Leukemia Group B Common Toxicity Criteria. Other investigations were performed as clinically indicated. Patients were readmitted for pleural aspiration or drainage as required on conventional clinical grounds, namely radiological evidence of accumulating effusion accompanied by increased dyspnea and reduced exercise tolerance.

Patients had to be followed up for a minimum of 4 weeks to be eligible for response assessment. Patients were considered to have had a complete response when no radiological recurrence of fluid was seen from the time of pleurodesis until death.
RESULTS

or the date of last follow-up. Partial responders were defined as having recurrence of fluid, but without the need for further treatment. Treatment was considered to have failed if there was symptomatic reaccumulation of fluid confirmed radiologically and requiring reaspiration (4).

Pharmacokinetics. Because it is a poorly soluble material, BB-94 was administered as a suspension into the pleural cavity. From such a depot, the drug slowly dissolves and can gain access to the systemic circulation. We assessed the extent to which this occurred by measuring plasma BB-94 levels; samples were analyzed on 17 patients. No plasma samples were available for BB-94 assay in one patient treated at 15 mg/m² (case 1; Table 1). All samples were assayed in a total of six analytical sessions. The standard curves were linear over a 2–250 ng/ml concentration range (low range assay) and over 20–1000 ng/ml (high range assay). For the low range assay, the intraday variation of the calibration standards ranged from 3.4–15.5%, and the interday variation was 4.4–14.2%. Equivalent values for the high range assay were 3.4–18.1% for the intraday variation and 3.4–14.1% for the interday variation. The limit of detection was 2 ng/ml. Stability assessments showed no evidence of degradation at any of the quality control concentrations after 1–24-h storage at room temperature or up to three freeze-thaw cycles. The quality control data indicated adequate accuracy and precision during the analysis.

Table 1 Patients, diagnosis, and pleural effusion assessment

| Patient no. | Diagnosis    | Dose (mg/m²) | Dyspnea score (%)
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<tr>
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<td>Breast</td>
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<td>Breast</td>
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| Effusion height (%)
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<td>2/NE</td>
<td>0/NE</td>
</tr>
<tr>
<td>2/NE</td>
<td>0/NE</td>
<td>PR</td>
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<td>NR</td>
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<tr>
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<td>NR</td>
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<tr>
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<td>0/0</td>
<td>PR</td>
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<th>Pleural response</th>
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<tr>
<td>PR</td>
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</tr>
<tr>
<td>NR</td>
<td>42</td>
</tr>
<tr>
<td>PR</td>
<td>42</td>
</tr>
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<sup>a</sup> Value 1 month after BB-94, expressed as a percentage of baseline value on day 1. Rising dyspnea score indicates improvement in exercise tolerance.

<sup>b</sup> Incidence of pleural aspiration/drainage 1 month/3 months before BB-94 and 1 month/3 months after BB-94 administration.

<sup>c</sup> Survival in weeks from BB-94 treatment.

<sup>d</sup> NE, not evaluable; NR, no response (fluid reaccumulated and required reaspiration); PR, partial response (fluid reaccumulated but did not require reaspiration); ND, not done; ACUP, adenocarcinoma of unknown primary site.

<sup>e</sup> Patient developed empyema.

RESULTS

Patients. Eighteen patients were entered into the study, including 12 women and 6 men with a median age of 57 years (range, 39–72). All patients had WHO performance status 0–2. The primary tumors were breast cancer (eight patients), adenocarcinoma of unknown primary site (four patients), non-small cell lung cancer (three cases, one of whom also had prostate cancer), and one case each of melanoma, renal cell cancer, and mesothelioma (see Table 1). All patients had a cytologically positive pleural effusion causing symptoms. Three patients had bilateral effusions. One patient (case 16; Table 1) had a left pleural effusion treated by bleomycin pleurodesis 2 years previously, without recurrence. She subsequently developed a right-sided effusion and was entered into this study. Two additional patients (cases 3 and 5) had bilateral effusions at the time of trial entry. In both cases, the right effusion was the largest and was the site of BB-94 instillation.

Two patients died within 1 month of therapy, in both cases due to progressive systemic disease and without reaccumulation of pleural fluid. Of the remaining 16 patients, 8 completed the 12 week follow-up period. The other eight patients were withdrawn from the study because of progressive disease, from which four patients died and the other four went on to further systemic treatment.
BB-94 for Malignant Pleural Effusion

After administration of 300 mg/m² BB-94, plasma levels including paracetamol. Fever was seen in patients, which was treated by drainage and systemic antibiotics. In the other six cases (33%), no cause was identified, and in these the fever was controlled without further complication, using simple measures including paracetamol. Fever was seen in patients treated at the lowest and highest dose levels, with no clear dose relationship.

In 8 of the 18 patients (44%), we noted asymptomatic elevation of liver enzymes after BB-94 (Table 2). With the exception of one patient treated at 15 mg/m², all cases of LFT abnormality occurred at dose levels of 60 mg/m² and above. Perhaps because of small numbers, there was no statistical difference between the incidence of liver toxicity in the lower dose group (6 patients, one with toxicity, at 15–30 mg/m²) and those treated at 60–300 mg/m² (12 patients, 7 with toxicity; P = 0.152 by Fisher’s exact test). Included here is a patient who was retreated at 105 mg/m² (case 10; Table 1); having had no LFT toxicity after the first course, we noted grade 2 LFT toxicity after the second course. The other patient who had a second course (at 60 mg/m²; case 7) experienced no liver toxicity after either course. The LFTs began to rise on the day after BB-94 treatment, and involved AP, AST, and γ glutamyl transferase. In most cases, there were equivalent changes in transaminases and AP. In two patients, there was a discrepancy between the extent of elevation of AP and AST. Case 2 (dose level 15 mg/m²) had grade 1 AST elevation and grade 2 AP elevation. Case 10 (dose level 105 mg/m²) had grade 2 toxicity, as judged by AP, and grade 3 toxicity, as judged by AST. In each case, Table 2 lists the worst grade of toxicity experienced by each patient. Peak values were noted between days 1–21, usually days 7–14. In five of the eight cases, the values were falling but still abnormal 1–5 months after BB-94, in the absence of concurrent computed tomography or ultrasound evidence of metastases. One of these patients with resolving LFT changes (case 9; Table 1) developed hepatomegaly 1 month after BB-94 and died of progressive disease after an additional 3 weeks. In the remaining three cases with evidence of liver toxicity, the LFTs returned to normal 2 weeks to 2 months after BB-94. Two of these patients later developed scan evidence of liver metastases, 2 months and 1 year after treatment.

Of these eight patients with possible BB-94-related LFT changes, four had posttreatment fever and four did not. No correlation was found between the extent of liver enzyme elevation and the peak plasma level of BB-94 achieved. We saw no drug-related changes in hemoglobin levels, white cell counts, or platelet counts.

Other symptoms that followed BB-94 administration included nausea (six patients, 33%), malaise/fatigue (six patients, 33%), pleural pain (five patients, 28%), and cough (four patients, 22%). These symptoms could have been secondary to the underlying disease. Three patients (17%) had complications of intercostal drain insertion, including a case of hydro pneumothorax after a second BB-94 treatment at 105 mg/m², empyema requiring drainage and antibiotics in a patient treated at 135 mg/m², and a small pneumothorax (<10%) not requiring drainage after BB-94 at 300 mg/m².

Assessment of Response. Two patients were not evaluable for radiological response because they died within 4 weeks of BB-94 administration (cases 6 and 11; Table 1). The remaining 16 evaluable patients received 18 doses of BB-94 (see Table 1). Using conventional radiological criteria (4), these resulted in...
administration of BB-94, graded according to Cancer and Leukemia Group B Common Toxicity Criteria. In the remaining 9 patients (56%). The median survival of the patients who received 135–300 mg/m2 BB-94 survived for at least 42 weeks. However, there was no evidence of systemic tumor reaccumulation with a need for aspiration.

Table 2  Fever and LFT abnormality after treatment with BB-94

| Dose (mg/m2) | No. of patients | Fever | LFTs
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<tr>
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<td></td>
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<tr>
<td>15</td>
<td>3</td>
<td>0</td>
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</tr>
<tr>
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</tr>
<tr>
<td>300</td>
<td>3</td>
<td>2</td>
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a Grade 1, elevation of AP and AST 2.5 × normal; grade 2, 2.6–5 × normal; grade 3, 5.1–20 × normal.  
b One patient developed empyema 1 week after BB-94 treatment.

d a partial pleural response in 7 of 16 evaluable patients (44%) and no response (i.e., reaccumulation with a need for aspiration) in the remaining 9 patients (56%). The median survival of the entire cohort of patients was 19 weeks (range, 3–93); all patients who received 135–300 mg/m2 BB-94 survived for at least 42 weeks. However, there was no evidence of systemic tumor regression after intrapleural BB-94.

To quantify the effect on the reaspiration rate, we compared the number of repeat pleural aspirations before and after BB-94 administration (see Table 1 and Fig. 2). In the month before BB-94, the 16 evaluable patients (following 18 evaluable treatments) underwent pleural aspiration/drainage on 42 occasions compared with 10 occasions in the month after BB-94 (P = 0.0004 by Wilcoxon matched pairs signed rank test). Including only the 12 patients who survived ≥3 months after BB-94, equivalent figures for reaspiration rates 3 months before and 3 months after BB-94 are 43 and 14, respectively (P = 0.0045). Two of the patients failing treatment required a single pleural aspiration for control of dyspnea in the month after BB-94. Four patients (cases 3, 5, 16, and 17) required more than one repeat aspirate; all of these had breast cancer. Cases 3 and 5 had bilateral effusions, and both had received BB-94 into the right hemithorax. After this treatment, there was evidence of accumulation in the left-sided effusion in both patients, and case 3 required aspiration on the left- as well as the right-sided drainage detailed above. This was not included in the numbers of aspirations listed in Table 1, which shows only the reaspirations of the hemithorax treated with BB-94. There was no clear difference in reaspiration rates between patients treated at different dose levels of BB-94.

Table 1 also shows the dyspnea scores and effusion heights at 1 month after treatment, expressed as a percentage of the baseline measurement 1 day after BB-94 administration. Effusion heights were assessible at baseline and after 1 month in 15 patients (17 treatments). Pleural ultrasound showed that in five patients (cases 5, 6, 10, 12, and 13) the effusion had been drained to dryness, and in the remainder there was residual fluid before BB-94 administration. On the day after BB-94, most patients had a baseline effusion height of 60–100 mm, comprising the 50-ml volume of BB-94 suspension, the 10-ml saline line flush, and any residual pleural fluid. Serial measurements of effusion height showed a trend to increase in all but two patients (cases 4 and 17), and one of these (case 17) had required two reaspirations during this period. Compared with the baseline value, and taking all 15 evaluable patients together, the mean effusion height increased by 184 ± 24% 1 month after BB-94.

Dyspnea scores were assessible in 13 patients (15 treatments). One month after treatment, the overall change in dyspnea score in the entire group of 13 patients was 109 ± 10% of the baseline value. Table 1 shows that the dyspnea scores were stable or increasing in 10 patients (12 treatments). Only three patients (cases 1, 4, and 5) had a major fall in dyspnea score, indicating a reduction in exercise tolerance. These three patients had been treated with 15 or 30 mg/m2 BB-94. Taking these two low-dose cohorts as a separate subgroup, the four assessible patients treated with 15–30 mg/m2 BB-94 had a mean dyspnea score of 69 ± 25%. This was not significantly different from the baseline value (100%; P = 0.194 by Student's t test). The 10 evaluable patients treated at 60–300 mg/m2 showed stable or increasing scores, with a mean value at 1 month of 125 ± 7%. This was higher than the baseline value (P = 0.0085), although not significantly different from the 1-month value in the lower dose group (127 ± 7 versus 69 ± 25; P = 0.107), perhaps because of the small numbers and large SE in the latter group.

**DISCUSSION**

Experimental studies have shown that BB-94 inhibits several aspects of the malignant phenotype, including invasive tumor growth, metastasis, and tumor-induced angiogenesis (36). Inhibition of ascites accumulation was one of the most striking effects in preclinical studies of ovarian cancer (22), although the precise mechanism by which MMPs contribute to ascites formation is unclear.

BB-94 cannot be given systemically because it is insoluble. It shows low bioavailability when given p.o., but it can be given with effect as a suspension into the peritoneal cavity (36). i.p. BB-94 has been evaluated in three Phase I trials in patients with symptomatic malignant ascites. The drug seemed to reduce the need for repeat paracentesis and generated sustained plasma BB-94 levels (28–30). Two of these studies reported that i.p. BB-94 was well-tolerated at doses up to 1350 mg/m2 (28, 30). In the third study, using BB-94 doses of 600-1800 mg/m2, all nine patients experienced abdominal pain/cramping, which at the highest dose level required opiate infusion, and one patient developed chemical peritonitis causing small bowel obstruction (29).

In selecting a dose range for evaluation of intrapleural BB-94 treatment, we aimed to reach the therapeutic dose in animal models (90–120 mg/m2) within four escalations of the starting dose. In general, the treatment was very well tolerated. We noted two toxic effects of BB-94: fever and hepatotoxicity. The fever was mild, brief, and unrelated to dose, consistent with previous reports (29, 30). Asymptomatic elevation of liver enzymes, which has not been reported after i.p. treatment, occurred in 44% of our patients within 1 day of BB-94 administration. Values fell to normal in some patients within 2 months, but in others there was persisting abnormality, although continuing to decline, for up to 5 months in the absence of ultrasound and/or computed tomography evidence of metastases. All but one of the patients experiencing hepatotoxicity had received...
BB-94 for Malignant Pleural Effusion

Fig. 2 Pleural aspirations 1 and 3 months before and 1 and 3 months after intrapleural BB-94 at 15–300 mg/m². Bars, total numbers of pleural aspirations/cohorts of three patients at each dose level.

at least 60 mg/m² BB-94, but statistical analysis did not confirm that this was a significantly higher incidence than in the lower dose group. Indeed, within the 60–300 mg/m² dose range, the severity of LFT elevation did not increase with dose. We observed no other toxicity attributable to the drug. In particular, any pleural pain reported by our patients was consistent with the extent of intrathoracic disease and the discomfort of thoracocentesis. We saw no local pleural equivalent of the severe abdominal pain reported after i.p. instillation of BB-94 (29). Neither did we see any signs of the musculoskeletal toxicity reported after a related MMP inhibitor, marimastat (37). In the absence of significant grade 3 toxicity, we conclude that the maximum tolerated intrapleural dose of BB-94 was not reached.

In most patients, we were able to detect BB-94 in the plasma 1 h after treatment, and peak values occurred between 4 h and 1 week. There was considerable individual variation in the extent of systemic absorption of BB-94 from the pleural cavity. However, peak values were higher and more persistent in the plasma longer after higher doses of BB-94. Plasma BB-94 levels exceeded the IC₅₀’s for the main target enzymes, including interstitial collagenase (IC₅₀ 1.5ng/ml), gelatinases A and B (2ng/ml), matrilysin (3ng/ml), and stromelysin-1 (10ng/ml). At the highest dose level, 300 mg/m², plasma BB-94 levels exceeded these IC₅₀’s were detectable throughout the 12-week study period. Such prolonged persistence in plasma after a single intrapleural administration is probably attributable to the fact that the drug was administered as a suspension, which acted as an intrapleural depot, as has been suggested for i.p. administration (36). We have no experimental data to assess whether these levels did indeed inhibit MMPs in vivo. The drug is 95% protein bound in human plasma, and this is likely to reduce access to extravascular sites. It is possible that higher levels would be needed to achieve systemic MMP inhibition in man. Future studies would be strengthened by the inclusion of assays for MMP activity, to confirm the mode of activity in the pleural space and to clarify the significance of the systemic BB-94 levels we detected in our patients.

Published studies suggest that, untreated, at least 90% of effusions will recur and require reaspiration within 1 month of the initial thoracocentesis (2, 3). We observed that patients required significantly fewer pleural aspirations after intrapleural BB-94 than they had done before. Using conventional criteria for pleural response (4), BB-94 achieved a partial response in 7 of 16 evaluable patients, giving a response rate of 44%. In addition to this qualitative measure, we also attempted to make quantitative serial measurements of effusion height and dyspnea score. Regular ultrasound assessment clarified the extent to which radiological shadowing was due to solid and/or fluid components and permitted serial measurements of effusion height, although the continuity of this measure was affected by any repeat thoracocentesis. We also monitored serial dyspnea scores using a previously validated visual analog scale (34). Despite the ultrasound evidence of continued fluid accumulation, many patients documented an increase in dyspnea scores, indicating a rise in exercise tolerance. Here, there was evidence of a possible dose-related effect: 1 month after treatment, patients who received 60–300 mg/m² BB-94 reported dyspnea scores that improved significantly compared with baseline values after BB-94 administration. In the context of the changes in effusion height, it is possible that a patient may adapt symptomatically to the presence of a stable or slowly increasing effusion. In addition to reflecting the extent of effusion, the dyspnea scores were likely to be influenced by pulmonary involvement (malignant deposits, lymphangitis), nonmalignant lung disease (e.g., obstructive airways disease), or nonpulmonary conditions (e.g., anemia).

From the patients’ perspectives, the most significant measure was probably the reaspiration rate, because this reflected the point at which the symptoms of the effusion became sufficiently troublesome to warrant intervention. It is possible that physician bias could have influenced the timing and frequency of pleural aspiration. We attempted to minimize this by ensuring that the timing of reaspiration was patient-led, dictated by the severity and rate of change of symptoms. Intrapleural BB-94 significantly reduced the need for pleural reaspiration, with a similar effect at all doses within the range tested. During the 12-week follow-up period of this study, four patients with breast cancer fared less well than the others, each requiring two reaspirations within a month of treatment. We note that in an animal model of human breast cancer, where BB-94 retarded solid tumor growth, there was no effect on ascites formation despite the presence in ascites fluid of two potential host-derived BB-94 targets, gelatinases A and B (25). It is possible that effects in breast cancer depend on the nature of the deposit, whether solid or liquid, and the anatomical site of metastatic disease.

In general, the efficacy of BB-94 seems to be comparable with that of other agents given intrapleurally (8). We noted that the baseline ultrasound revealed the presence of residual fluid in the pleural cavity in all but five of our patients before BB-94 instillation. Previous reports have stressed the need to drain the pleural cavity to dryness to achieve successful pleurodesis by a sclerosing agent (7). We observed a pleural response to BB-94 in patients with residual fluid, consistent with a mode of action other than simple chemical sclerosis. This may make MMP
inhibition a more valuable approach than conventional sclero-
sants, given that inability to drain to dryness is a common cause
of failure of pleurodesis. However, we cannot exclude the
possibility that the drug could have been acting as a local
sclerosant, and it was to reduce the likelihood of this nonspecific
mode of action that we elected to limit the local dose to 300
mg/m².

Aside from its pleural effects, we saw no systemic antitu-
tumor responses to BB-94, despite documenting significant
plasma levels of the drug after intrapleural treatment. It is clear,
however, that conventional responses would be unlikely because
the drug is not cytotoxic and caused tumor growth delay rather
than regressions in animal models (22, 24). The inadequacy of
conventional response criteria for monitoring cytostatic thera-
pies has already been noted, and it may be more appropriate to
focus on the attainment and duration of stable disease (36). In
this regard, we observed longer survival in patients treated with
135–300 mg/m² BB-94 than in those treated at lower doses, but
the significance of this finding will require study of larger
numbers of patients. The recent availability of orally active
MMP inhibitors (37, 38) should facilitate further evaluation of
these interesting new agents.

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REFERENCES

1. Miles, D. W., and Knight, R. K. Diagnosis and management of
2. Anderson, C. B., Philpott, G. W., and Ferguson, T. B. The treatment
3. Sarma, P. R., and Moore, M. R. Approach to the management
4. Fentiman, I. S., Rubens, R. D., and Hayward, J. L. A comparison of
intracavitary t alc and tetracycline for the control of pleural effusions
1986.
5. Aelony, Y., King, R., and Boutin, C. Thorascopic talc poudrage
J. W., and Mathur, P. N. Comparison of insufflated talc under thorasc-
copic guidance with standard tetracycline and bleomycin pleurodesis for
7. Evans, T. R. J., Stein, R. C., Pepper, J. R., Gazet, J-C., Ford, H. T.,
and Coombes, R. A. A randomized prospective trial of surgical against
medical tetracycline pleurodesis in the management of malignant pleural
1993.
metalloproteinases and tumor invasion: from correlation and causality to
P. E., and Harris, T. J. R. Sequence of human tissue inhibitor of
metalloproteinases and its identity to erythroid-potentiating activity.
Tissue inhibitors of metallo-proteinases—structure, regulation and bio-
angiogenesis on the human amniotic membrane: requirement of basic
682, 1989.
A novel metalloproteinase gene specifically expressed in stromal cell
15. Brown, P. D., Bloxidge, R. E., Stuart, N. S. A., Gatter, K. C., and
Carmichael, J. Correlation between expression of activated 72-kDa
16. Davies, B., Miles, D. W., Happerfield, L. C., Naylor, M. S.,
Bobrow, L. G., Rubens, R. D., and Balkwill, F. R. Activity of type
IV collagenases in benign and malignant breast disease. Br. J. Cancer,
Expression and localization of matrix-degrading metalloproteinases during
18. Murray, G. I., Duncan, M. E., O’Neil, P., Melvin, W. T., and
Fothergill, J. E. Matrix metalloproteinase-1 is associated with poor
19. Talbot, D. C., and Brown, P. D. Experimental and clinical studies
on the use of matrix metalloproteinase inhibitors for the treatment of
20. Chirivì, R. G. S., Garofalo, A., Criminin, M. J., Bawden, L. J.,
Stopacciaro, A., Brown, P. D., and Giavazzi, R. Inhibition of the
metastatic spread and growth of B16-BL6 murine melanoma by a
synthetic matrix metalloproteinase inhibitor. Int. J. Cancer, 58: 460–
21. Tarabotti, G., Garofalo, A., Belotti, D., Drudis, T., Borsotti, P.,
Scanziani, E., Brown, P. D., and Giavazzi, R. Inhibition of angiogenesis
and murine hemangioma growth by batimastat, a synthetic inhibitor of
22. Davies, B., Brown, P. D., East, N., Criminin, M. J., and Balkwill,
F. R. A synthetic matrix metalloproteinase inhibitor decreases tumor
burden and prolongs survival of mice bearing human ovarian carcinoma
23. Eccles, S. A., Box, G. M., Court, W. J., Bone, E. A., Thomas, W.,
and Brown, P. D. Control of lymphatic and hematogenous metastases of
a rat mammary carcinoma by the matrix metalloproteinase inhibitor
24. Sledge, G. W., Qulali, M., Goulet, R., Bone, E. A., and Fife, R.
Effect of matrix metalloproteinase inhibitor batimastat on breast cancer
growth and metastasis in athymic mice. J Natl Cancer Inst, 87:
25. Low, J. A., Johnson, M. D., Bone, E. A., and Dickson, RB. The
matrix metalloproteinase inhibitor batimastat retards human breast cancer
26. Watson, S. A., Morris, T. M., Robinson, G., Criminin, M. J.,
Brown, P. B., and Hardcastle, J. D. Inhibition of organ invasion by the
matrix metalloproteinase inhibitor batimastat in two human colon car-
27. Hurewitz, A. N., Zucker, S., Mancuso, P., Wu, C. L., Dimassimo,
B., Lysik, R. M., and Moutsakis, D. Human pleural effusions are rich
intraperitoneal metalloproteinase inhibitor batimastat in patients with
malignant ascites. Abstract presented at the 8th NCI-EORTC Symposi-


Phase I Study of Intrapleural Batimastat (BB-94), a Matrix Metalloproteinase Inhibitor, in the Treatment of Malignant Pleural Effusions

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