Phase I Study of Intraperitoneal Metalloproteinase Inhibitor BB94 in Patients with Malignant Ascites

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ABSTRACT

This was an open Phase I study of i.p. matrix metalloproteinase inhibitor BB94 in patients with malignant ascites. The objective of the study was to determine the effect of increasing i.p. doses of BB94 with reference to the tolerance, safety, and pharmacokinetics of the compound. Twenty-three patients with malignant ascites had BB94 instilled into the peritoneal cavity after paracentesis. The compound was well tolerated; no serious adverse events were seen, and no specific toxicities were observed. High plasma concentrations were seen an hour after dosing, and BB94 was still present in the plasma at day 28 after treatment at levels in excess of the IC50 identified in preclinical studies. Five of the 23 patients neither reaccumulated ascites nor died up to 112 days after dosing. Seven patients died without reaccumulating ascites. Although the study was not designed to demonstrate clinical efficacy, the results were encouraging and support the further therapeutic evaluation of matrix metalloproteinase inhibitors in the management of malignant ascites.

INTRODUCTION

Matrix metalloproteinases are a family of homologous enzymes capable of degrading components of the extracellular matrix (1). They all contain a zinc atom at their active site. These enzymes can be divided into five classes on the basis of their sequence homology and substrate specificity.

With the exception of the fibrillar collagenases (class I), the preference of these enzymes for particular matrix substrates in vivo remains poorly defined. However, it is clear that collectively they are capable of degrading all components of the extracellular matrix (2-8).

BB94 is a low molecular weight (M, 478,000) synthetic compound that inhibits a broad spectrum of matrix metalloproteinases. The molecule is a peptide mimetic containing a hydroxamate group. This is the active region of the molecule, in that it is this group that is responsible for binding the zinc atom at the active site of the metalloproteinase and thereby inhibiting the enzyme.

BB94 is a potent but reversible MMPI and displays IC50s in the low nanomolar range against the various classes of enzymes but has no activity against unrelated metalloproteinases such as encephalinase or angiotensin-converting enzyme.

INo initial studies were carried out in the HU xenograft model of human ovarian carcinoma malignant ascites. In brief, 106 cells of the xenograft were introduced directly into the peritoneal cavity of nude mice on day 0, where they formed malignant ascites and became life threatening within 16-25 days. Histological assessment of a control group of mice thus treated confirmed extensive peritoneal tumors and malignant ascites. Mice treated with BB94 (40 mg/kg) on a daily basis from days 3-20 after introduction of the xenograft showed resolution of the ascites. By day 21, the ascites had resolved into small avascular nodules comprising a dense stromal capsule surrounding small islands. The control group that was given a diluent alone had a median survival of only 18.5 days, whereas mice treated with BB94 had a median survival of 120 days, representing a 6.5-fold increase in survival (9).

In animal studies, single acute i.p. administrations of BB94 resulted in no treatment-related deaths at doses of 250 mg/m2 in mice, 3120 mg/m2 in rats, and 5880 mg/m2 in dogs.

Doses in excess of those described above were not achievable due to technical problems related to the solubility of the drug and the resultant distension of the abdomen.

In light of these animal studies, we report the results of the first study in which i.p. BB94 was given to a series of patients with malignant ascites.

PATIENTS AND METHODS

Twenty-three patients with malignant ascites were recruited to the study. Patients required a predicted survival of 1 month or more and gave written informed consent to take part in the study. Patients with an obstructive jaundice or a history of significant cardiac disease were excluded, as were patients currently receiving i.p. therapy or who had undergone surgery in the preceding month.

Trial medication was supplied in 20-ml vials containing 20 mg/ml BB94. The excipients in the formulation were ethanol, polyethylene glycol 400 Ph Eur, methyl cellulose Ph Eur, and water for injection. Patients were treated at five dose levels. In view of the lack of toxicity in animal studies and the inability to achieve a LD100 standard toxicological principles could not be applied to calculate the first dose level. A very conservative first

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2 The abbreviation used is: MMPI, matrix metalloproteinase inhibitor.
dose was selected at about one-thirtieth of the maximum dose given to dogs. The other four dose levels were based on a standard modification of the Fibonacci series. Three patients were treated at each of the first three dose levels, and seven patients each were treated at the fourth and fifth dose levels. During the study, the next dose level was not started until a 28-day follow-up period was complete.

The primary objective of the study was to evaluate toxicity and monitor pharmacokinetics, with end points being dose-limiting toxicity and/or pharmacological levels appropriate to effective therapeutic doses in preclinical studies.

Concentrations of BB94 in plasma samples were determined using a validated analytical procedure involving solid-phase extraction and high-performance liquid chromatography mass spectroscopy conducted in the Department of Cellular Biochemistry, British Biotechnology, Ltd. (Cowley, Oxford, United Kingdom).

Sixteen of the patients had ovarian carcinoma. Of the remaining seven patients, two had sarcoma, one had breast cancer, one had colon cancer, one had endometrial cancer, one had renal cancer, and one had pancreatic cancer. All patients with ovarian cancer had been heavily pretreated with platinum-containing chemotherapy. The mean age of the patients was 66 years, ranging from 46–84 years. Twenty-one of the patients were female. All patients had a performance status of 2, in that they were symptomatic requiring therapeutic paracentesis. The patient demographics are summarized in Table 1.

After drainage of ascites by means of a peritoneal dialysis catheter inserted under local anesthetic, BB94 was instilled into the peritoneal cavity in 500 ml of 5% dextrose over approximately 40 min. The catheter was then removed. All diuretic therapy was stopped. The patients were observed closely in hospital for 24 h after treatment before being discharged. They were seen weekly for 4 weeks and monthly thereafter. At each visit, a full physical examination was performed, clinical toxicity was recorded, and blood was taken for a hematological and biochemical evaluation including cardiac enzymes.

RESULTS

Toxicity Results. The tolerability of i.p. BB94 was good. Twenty subjects experienced at least one adverse event within the 28-day study period. The toxicities were recorded using common toxicity criteria scales. The most common event was vomiting, which was experienced by 12 patients (six grade 1, five grade 2, and one grade 3). Fatigue occurred in nine patients (two grade 1, four grade 2, and three grade 3), with abdominal pain being recorded in eight patients (three grade 1, three grade 2, and two grade 3). Eight patients experienced fever (three grade 1 and five grade 2). Nausea occurred in six patients (four grade 1 and two grade 2), as did diarrhea (five grade 1 and one grade 2). Three patients experienced a bowel obstruction, but in all cases, this resolved on conservative therapy.

Two patients developed anemia, and one patient, an insulin-dependent diabetic, experienced an increased requirement for insulin during the first 72 h after infusion. Fatigue and abdominal pain were more common at higher dose levels. Events considered at least possibly related to treatment occurred in 16 patients, the most common of which were fatigue (9 cases), fever (7 cases), vomiting (6 cases), and abdominal pain (5 cases). Laboratory tests indicated no adverse effects of BB94 on liver and renal function, and there was no evidence of cardiac toxicity. Aside from 2 cases of anemia, there were no significant changes in any of the standard hematological and biochemical parameters assessed.

Pharmacokinetic Results. Sustainable plasma concentrations of BB94 in excess of 10 ng/ml were achieved for up to

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Tumor site</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level 1 (150 mg/m²)</td>
<td>F</td>
<td>54</td>
<td>Ovary</td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>Dose level 2 (300 mg/m²)</td>
<td>M</td>
<td>73</td>
<td>Pancreas</td>
<td>Serous cystadenocarcinoma</td>
</tr>
<tr>
<td>Dose level 3 (600 mg/m²)</td>
<td>F</td>
<td>78</td>
<td>Uterus</td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>Dose level 4 (1050 mg/m²)</td>
<td>F</td>
<td>65</td>
<td>Ovary</td>
<td>Serous cystadenocarcinoma</td>
</tr>
<tr>
<td>Dose level 5 (1350 mg/m²)</td>
<td>F</td>
<td>84</td>
<td>Ovary</td>
<td>Serous cystadenocarcinoma</td>
</tr>
</tbody>
</table>

Table 1 Patient demographics and BB94 dose levels
DISCUSSION

BB94 is the first MMPI to enter clinical trials. This study documents the results of the first Phase I study of i.p. administration in patients with malignant ascites. MMPIs represent a new class of compounds with potential therapeutic efficacy in malignant disease. The tolerability of i.p. BB94 was good. Although a number of subjects experienced at least one adverse event within the 28-day study period, the majority of these adverse events, in particular, nausea and vomiting, were con-

28 days in four of the six patients treated at the first two dose levels. Of note, these levels were well above the IC50 of the drug. With the exception of one patient, sustainable plasma concentrations in excess of 100 ng/ml were achieved in all patients at the three highest dose levels.

High plasma concentrations of BB94 were demonstrated 1 h after dosing. The highest mean concentrations were seen at 1 h after 150 mg/m², at 4 h after 300 mg/m², and at 24 h after all other doses.

BB94 was still present in plasma at day 28 at concentrations ranging from a mean of 19.8 ng/ml after 150 mg/m² BB94 to 226.1 ng/ml after 1350 mg/m² BB94 (Fig. 1). Blood concentrations fell with a half-life of 19.1 days overall. The area under the curve seemed to increase linearly with dose.

Clinical Results. Of the 23 patients in the study, 16 did not require redrainage within 28 days of initial treatment. Seven patients reaccumulated ascites and required redrainage within 28 days. By the end of the 112-day follow-up period, 11 patients had reaccumulated ascites. Fourteen patients died within this period, 7 patients died without reaccumulation, and 5 neither died nor reaccumulated ascites. Of the five patients who neither died nor reaccumulated ascites, four had been drained within 4 months of the start of the study, with three of them having been drained on more than one occasion before entry.

ACKNOWLEDGMENTS

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REFERENCES


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