Phase II trial of intravenous hexamethylmelamine in patients with advanced ovarian cancer

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Abstract

A Phase II trial of an intravenous preparation of Hexamethylmelamine was performed in ovarian cancer. Patients who had received prior Platinum based chemotherapy and had measurable disease were eligible. Among 15 evaluable patients, there were no objective responses. Two patients did show clinical and laboratory evidence of improvement. Toxicity was predominantly nausea and vomiting with minimal other toxicity. This intravenous form of Hexamethylmelamine has not shown meaningful activity in ovarian cancer patients who have failed prior platinum treatment.

Introduction

Hexamethylmelamine is an active agent against ovarian cancer [1]. All clinical trials of hexamethylmelamine have utilized oral dosage regimens because of lack of aqueous solubility. Administration of intravenous hexamethylmelamine hydrochloride caused severe local irritation and phlebitis. The oral form is well-absorbed, but undergoes extensive first-pass metabolism. Oral hexamethylmelamine is usually given by prolonged daily administration. Nausea, vomiting, myelosuppression and peripheral neuropathy are common toxicities, and depend on dosage and duration of treatment.

A stable parenteral form of hexamethylmelamine was developed by Ames and Kovach [2], using a fat emulsion (Intralipid) as a vehicle. This preparation completed phase I testing at Mayo Clinic utilizing two schedules [3]. A day 1 and a daily times 5 regimen every 4 weeks were studied. Dose limiting toxicity was nausea and vomiting, with myelosuppression being insignificant and no neurologic, hepatic or renal toxicity seen. There were no objective responses seen in 47 patients, but these included only 2 patients with ovarian cancer.

We performed a phase II study using the 5-day regimen of intravenous hexamethylmelamine as second line chemotherapy in advanced ovarian cancer.

Patients and methods

Patients with measurable advanced ovarian cancer who had failed one prior cisplatin or carboplatin-containing regimen were eligible. ECOG performance status of 0–2, satisfactory blood counts, liver function, and a creatinine less than 1.9 were required. Hexamethylmelamine was prepared in In-
Table 1.

Duration of treatment

<table>
<thead>
<tr>
<th># of courses</th>
<th># of patients</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2–4</td>
<td>5</td>
</tr>
<tr>
<td>5–8</td>
<td>2</td>
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<tr>
<td>&gt; 8</td>
<td>1</td>
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</tbody>
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Toxicity

Nausea/vomiting

- grade 1 or 2: 11
- grade 3 or 4: 4

Leukopenia (WBC nadir 2.8–8.7 x 10^9/liter with median 4.4)

- grade 1 or 2: 6
- grade 3 or 4: 0

Thrombocytopenia (Platelet nadir 85–505 x 10^9/liter with median 217)

- grade 1 or 2: 5
- grade 3 or 4: 0

Neurologic

- grade 1 or 2: 1
- grade 3 or 4: 0

Tralipid to a concentration of 4 mg/mL. The drug was given in a dosage of 600 mg/m^2 intravenous (I.V.) daily × 5 days every 4 weeks. The infusion rate was 2 mL/minute. Dosage adjustments were specified based on toxicity. Dosage was increased 10% in subsequent courses if the white blood cell nadir was greater than 2,500 and the platelet nadir was above 100,000, as long as no other significant toxicity occurred. Dosage reductions were made for any toxicity grade III or IV, based on National Cancer Institute (NCI) common toxicity criteria. Treatment was continued until progression. Standard response criteria for measurable disease were used.

Sixteen patients were entered on study. Fourteen of these had prior cisplatin treatment and two had prior carboplatin. Ten of the patients had progressed on Platinum therapy or not responded to it. Six patients were not proven Platinum refractory. Four patients had prior whole abdominal radiotherapy.

Results

One patient did not return for evaluation and was declared inevaluable. Among the 15 evaluable patients there were no partial or complete responses. Two patients did show evidence of improvement. One had resolution of cytology-positive ascites and reduction of her CA-125 from 12,000 to 31 with 8 cycles of treatment. This patient’s pretreatment measurable mass on computerized tomography (CT) scan proved to be a benign cyst on subsequent laparotomy, so this patient was declared non-measurable (ascites and CA-125 elevations were not considered measurable). This patient had microscopic residual disease at laparotomy, so subsequently treated with whole-abdomen radiotherapy, but progressed nine months later. A second patient had stable disease on treatment for 33 months, then progressed. This patient’s ascites and pleural effusions did improve with treatment. Both patients that showed improvement were not proven Platinum refractory.

Toxicity from treatment was mild to moderate and consisted mostly of nausea and vomiting. Myelosuppression was minimal. Most patients who received multiple courses of treatment had dosage increases because of high nadir blood counts. Only one patient had a dosage reduction, this for thrombocytopenia. Several patients had some degree of neurotoxicity from prior Platinum treatment; this did not worsen with Hexamethylmelamine. One patient was coded for mild neurotoxicity which may have been related to this treatment. Further information regarding results and toxicity is given in Table 1.

Median time to progression of study patients was 2.4 months and median survival was 5.9 months.

Discussion

Although there was a hint of activity seen in two patients, the absence of a measurable objective response in 15 patients caused termination of the study. This gives a 95% confidence of ruling out a true response rate of greater than 16.6%.

Newer, more effective antiemetic regimens might