Unexpected Toxicity in Patients Treated with Iphosphamide

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SUMMARY

A derivative of cyclophosphamide, 2,3-(N, N1-bis(2-chloroethyl)diamido-1,3,2-oxazaphosphoridinoxyd (Iphosphamide), was less toxic in experimental systems than cyclophosphamide, while it had a broader antitumor spectrum. We studied this agent in a clinical trial of 37 patients with histologically proved, far-advanced malignant disease. The study was designed mainly to determine toxicity and dosimetry of Iphosphamide. Curative effect of Iphosphamide in experimental animals depends on concentration rather than on total dose; therefore, single large doses of the agent were investigated in the first 31 patients. Side effects include nausea, vomiting, alopecia, uremia, hematuria, dysuria and frequency, urinary incontinence, hemopoietic suppression, elevated alkaline phosphatase and transaminase, and mental confusion. Because of nephrotoxicity at high single doses, a further 6 patients received smaller daily doses; however, at the small daily dose levels tubular damage also occurred, as evidenced by granular cylinders in the urine of all 6 patients. At the smaller dose range, nephrotoxicity was the only toxic manifestation. Therapeutic benefit was obtained only with high doses. In view of kidney toxicity at all dosage levels, attention should be given to urine microscopy and other kidney function tests in all patients being treated with Iphosphamide.

INTRODUCTION

A derivative of cyclophosphamide, 2,3-(N, N1-bis(2-chloroethyl)diamido-1,3,2-oxazaphosphoridinoxyd (Iphosphamide, Z4942) was synthesized at Asta-werke AG, Brackwede, Germany. The chemical structure of this agent differs from other nitrogen mustard compounds in that the 2 functional chloroethyl groups are not attached to the same nitrogen atom (see Chart 1). Iphosphamide is more stable in aqueous solution than cyclophosphamide, and the 50% lethal dose in rats is almost twice that of cyclophosphamide. The antitumor effect of this agent in experimental animals was very encouraging; the effect on Yoshida sarcoma, Walker 256 carcinoma, and Jensen sarcoma was similar to that of cyclophosphamide. However, in DS carcinosarcoma, resistant to all other drugs tested, a single dose of Iphosphamide, 120 mg/kg, cured 9 out of 10 treated rats (1).

The effectivity of Iphosphamide in DS carcinosarcoma (2) resistant to all other chemotherapeutics prompted the present clinical trial. This trial was designed to assess toxicity of the agent in patients with malignant disease.

MATERIALS AND METHODS

Thirty-seven patients with far-advanced, histologically proved malignant disease were treated. There were 25 bronchus carcinomas, 3 carcinomas of the breast, 3 carcinomas of the ovaries, 2 lymphosarcomas, and 1 case each of reticulum cell sarcoma, hemangioendothelioma, Ewing sarcoma, and acute lymphatic leukemia. Of these, 33 patients were considered to have received adequate treatment for therapeutic evaluation. (Treatment was considered to have been adequate if at least 1 course was given to the point of toxicity and if the patient was observed for at least 2 weeks following treatment.) In 4 patients, the drug trial was considered inadequate for therapeutic evaluation because the patient died within 2 weeks of administration of the 1st dose. However, some parameters of toxicity could be observed in these 4 patients, and they are included for analysis of toxicity of Iphosphamide.

All patients had measurable metastatic disease; none had received chemotherapy for at least 3 weeks prior to the start of Iphosphamide treatment. All patients were hospitalized for several days following an injection. At the start of treatment patients had a complete physical examination, including measurement of metastases, appropriate roentgenograms, and the following laboratory investigations: hemoglobin level, total and differential white blood cell count, platelet count, reticulocyte count, sedimentation rate, total serum protein, serum albumin, globulin, electrophoretic pattern, bilirubin, alkaline phosphatase, urea, uric acid, creatinine, and transaminase. Daily urinalysis was done during the period of hospitalization, and biochemical determinations were repeated every 14 days, or more often if abnormalities were noted. Hematological studies were repeated twice weekly. Roentgenograms were repeated as necessary.

Iphosphamide was supplied by Asta-werke AG, in ampuls containing 500 mg of active substance per ampul. Each ampul was dissolved in 25 ml of sterile water, and because of the large volume of the total injection it was administered as a short i.v. infusion.

As experimental evidence indicated that the curative effect of Iphosphamide depends on concentration rather than on total dose (2), this trial was started with large doses. The first 7 patients received 50 or 80 mg/kg every 14 days. Two patients received only 1 injection, 2 patients received 3
courses, and the other 3 patients had 4, 5, and 6 courses, respectively.

The initial single dose was then increased to 150 mg/kg for the next 24 patients. With the administration of such a large single dose hemorrhagic cystitis might be expected; therefore, bladder instillations were given with every dose of Iphosphamide. These concomitant instillations were given as follows. A urinary catheter was passed and left in position for 36 hr. Before the injection of Iphosphamide, 10 ml Reducdyn\(^2\) diluted with 10 ml of sterile water were instilled and retained in the bladder. The Reducdyn solution was renewed every 2 hr during the first 36 hr after the Iphosphamide injection. The catheter was then removed, and the patient was kept on a very high fluid intake for several days. Thirteen of these patients received 2 or 3 injections of Iphosphamide, 150 mg/kg, usually repeated at monthly intervals. In 9 of the patients in whom a clinical remission was obtained with the large initial doses, maintenance treatment with 20 mg/kg was given on an outpatient basis.

Because of renal toxicity encountered with the higher dose ranges, a further 6 patients were given 10 mg/kg per day for 5 days a week; this was stopped in each patient when granular cylinders appeared in the urine.

RESULTS

Toxic Effects

Of the 31 patients receiving single large doses, the most frequent toxic manifestations included nausea and vomiting (29 patients), alopecia (21 patients), uremia (22 patients), hematuria (17 patients), dysuria and frequency (17 patients), urinary incontinence (4 patients), leukopenia (18 patients), fall in hemoglobin (9 patients), thrombocytopenia (4 patients), increased alkaline phosphatase and transaminase (10 patients), and mental confusion (7 patients).

Hematuria. Hematuria occurred in about one-third of patients receiving Iphosphamide, 80 to 150 mg/kg. Chart 2 shows the incidence and severity of hematuria with Iphosphamide. Onset of hematuria was within 1 or 2 days of the injection, except in 1 patient with impaired renal function, where the onset was delayed for 7 days. Duration varied from 1 to 25 days (average, 5.1 days). None of the patients receiving 10 mg/kg/day had hematuria.

Dysuria and Frequency. Observations on dysuria and frequency closely parallel those on hematuria. The onset was usually within 1 or 2 days after the injection; the duration tended to be longer in most cases and varied from 1 to 41 days (average, 8.6 days). Hematuria was not always associated with dysuria and frequency.

Leukopenia. A fall in white blood cell count to below 4000/cu mm was not observed after administration of 10, 20, 50, or 80 mg/kg, but occurred after 81% of the doses of 150 mg/kg. It was the 2nd most frequent toxic manifestation following doses of 150 mg/kg. The severity of leukopenia is shown in Table 1. The lowest white cell count was always

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\(^2\) Nordmark-werke GmbH, Hamburg, Germany. Composition of each ampul of 10 ml: N-acetylamide-thiolactone, 50 mg; L-cysteine, 150 mg; D-fructose, 2000 mg.

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![Diagram of chemical structures](chart1.png)

Chart 1. Chemical structure of cyclophosphamide and Iphosphamide. They differ only in the position of the 2 functional chloroethyl groups.

![Graph showing incidence of severity of hematuria with Iphosphamide](chart2.png)

Chart 2. Incidence of severity of hematuria with Iphosphamide. The incidence is shown and graded: 0, normal; 1, mild; 2, moderate; 3, severe; 4, very severe or life threatening. Patients receiving 150 mg/kg all received bladder instillations of Reducdyn.

<table>
<thead>
<tr>
<th>WBC (× 10(^3))</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1.0</td>
<td>7</td>
</tr>
<tr>
<td>1.1–2.0</td>
<td>26</td>
</tr>
<tr>
<td>2.1–3.0</td>
<td>35</td>
</tr>
<tr>
<td>3.1–4.0</td>
<td>13</td>
</tr>
<tr>
<td>4.0–</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 1

 Severity of leukopenia after doses of 150 mg/kg
reached within 1 to 2 weeks of the injection, with an average of 10.6 days. Leukopenia lasted from 6 to 17 days (average, 9.7 days). Three patients remained leukopenic until death.

**Fall in Hemoglobin.** A fall in hemoglobin of more than 2 g/100 ml was never caused by any of the lower doses but it occurred after 32% of doses of 150 mg/kg. After 22% of doses, the fall was between 2.1 and 3 g/100 ml, and after 10% of doses, the fall was between 3.1 and 4 g/100 ml. The duration of suppression varied from 7 to 30 days (average, 19 days). A reticulocytosis was noted in 16 patients.

**Thrombocytopenia.** A fall in platelet count to below 100,000/cu mm was observed after 13% of doses of 150 mg/kg and was never caused by any of the lower doses. The lowest value reached within 1 or 2 weeks. The platelet count never fell to below 50,000/cu mm.

**Nephrotoxicity.** Uremia was defined as an elevation of blood urea above the highest normal value of our laboratory, namely, 45 g/100 ml. It occurred after 13% of doses of 20 mg/kg, 43% of doses of 50 mg/kg, and 66% of doses of 150 mg/kg. The severity of uremia following doses of 150 mg/kg is shown in Table 2. Onset of uremia varied between 1 and 5 days (average, 3.1 days) after the injection. In 3 patients, concomitant marked elevations of creatinine and uric acid were noted.

Postmortem examinations performed on 7 patients who died within 15 days of the administration of the large dose of Iphosphamide showed that 4 had evidence of acute tubular necrosis in the kidney, 1 patient had chronic pyelonephritis with hydronephrosis, and another patient had no abnormalities of the kidneys; in the other patient, autolysis obscured the histological picture.

**Granular Cylinders in the Urine.** In the 6 patients who were given 10 mg/kg/day for 5 days/week, the only toxic effect observed was the appearance of large numbers of granular cylinders in the urine. Granular cylinders in the urine appeared within 22 days in all 6 patients. The average time to development of granular cylinders was 13 days. The treatment was stopped when excess cylinders appeared, and the cylinduria cleared in all cases within 10 days.

**Alopecia.** Two of the 4 patients receiving single doses of up to 80 mg/kg developed alopecia on Days 56 and 29, respectively. Nineteen of the 24 patients receiving single doses of 150 mg/kg developed alopecia 11 to 32 days (average, 18.5 days) after the start of treatment. The patients who did not develop alopecia all died within 19 days after start of treatment.

**Enzyme Changes.** This consisted of an abnormal elevation of alkaline phosphatase and/or serum transaminase. In many patients this elevation returned to normal again later during the study, and in 1 patient more than 1 transient elevation was observed. Enzyme changes occurred in 10 patients.

**Confusion.** Mild to severe degrees of confusion developed in all 7 patients above 60 years of age who received 150 mg/kg. It was not observed following lower doses. In 2 of these patients brain metastases were found at postmortem examination.

**Other.** Other side effects observed and possibly attributable to drug effect included urinary incontinence in 4 patients, urinary retention in 1 patient, bladder spasms in 1 patient, diarrhea in 1 patient, and general malaise without uremia in 1 patient.

**Therapeutic Effects**

Among the 7 patients who received a single dose of 80 mg/kg or less, there were 6 evaluable cases; all had bronchus carcinoma. One patient with undifferentiated small-cell carcinoma had objective and subjective improvement lasting 2 months, and 1 patient with an undifferentiated carcinoma had only subjective improvement lasting 1 month, but his tumor masses remained unchanged. Among the 24 patients who received initial single doses of 150 mg/kg, 21 were evaluable. Therapeutic effect could not be evaluated in 3 patients because they died within 6 days of start of treatment. Ten of the 21 patients had objective and subjective improvement lasting 1 to 3 months.

Analysis of the 21 evaluable cases initially treated with 150 mg/kg shows that 7 of 11 cases with bronchus carcinoma improved, 1 of 3 cases with ovarian carcinoma improved, 1 of 2 cases of lymphosarcoma improved, and 1 case of Ewing sarcoma improved. The improvement consisted of tumor shrinkage of more than 50% plus subjective improvement lasting more than 1 month. No response was seen in 2 cases with breast carcinoma and 1 case each of reticulum cell sarcoma and malignant hemangioendothelioma.

The 6 patients with bronchus carcinoma who received daily doses of 10 mg/kg did not benefit therapeutically.

**DISCUSSION**

Iphosphamide was shown to be less toxic in experimental animals, while it had a broader therapeutic spectrum than cyclophosphamide. Furthermore, experimental evidence that definite cures can be achieved in transplantable tumors by 1 dose alone prompted this clinical trial with single large doses of Iphosphamide in patients with far-advanced metastatic disease. As the curative effect of Iphosphamide in experimental animals depends on concentration rather than on total dose administered, it seemed logical in clinical toxicity studies to determine the largest single dose that can safely be given to patients. The dose was gradually increased, and it seemed safe to move up to 150 mg/kg. At this dose level measurable side effects, nausea, and vomiting were severe, but not intolerable. In addition, therapeutic effects of measurable nature were observed at this dose level. It was
possible to counteract bladder toxicity by using prophylactic Reducdyn instillations with large Iphosphamide doses.

The unexpected and most severe side effect encountered at what was hoped to be optimal dose range was kidney damage. In view of the serious nephrotoxicity at high doses, a last group of patients received only 10 mg/kg of Iphosphamide 5 times per week. In all 6 patients treated at this dosage range, granular cylinders were found in the urine; no hemopoietic toxicity occurred. The occurrence of granular cylinders in the urine during treatment with an agent was considered to be evidence of tubular damage. As extensive clinical trials are underway with this agent in Europe and as a clinical trial has recently been started at the National Cancer Institute in Washington, this side effect warrants further investigation. The present study was aimed at investigating the toxicity of the drug. Therapeutic activity was seen and should be further investigated.

As German clinicians had not reported kidney toxicity with Iphosphamide, samples of the agent were sent back to Germany in order to determine whether chemical changes may have taken place during transport of the drug. Laboratory investigations showed that the Iphosphamide used in South Africa was not chemically changed and no impurities resulted because of the transport.

REFERENCES
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