Cancer Chemother Pharmacol (1986) 18 (Suppl 2): S 51–S 54

Cancer Chemotherapy and Pharmacology



# Ifosfamide chemotherapy for pancreatic carcinoma*

**Lawrence H. Einhorn**[**1, 2] and Patrick J. Loehrer[***]**

Department of Medicine, Indiana University Hospital, N582, Indianapolis, IN 46223, USA

**Summary.** From April 1982 through February 1984, 29 patients with pancreatic cancer were treated with ifosfamide (1.25–1.5 g/m$^2$ on days 1–5) + *N*-acetylcysteine (NAC) 2 g p.o. every 6 h on days 1–7 every 3 weeks. In responding patients without serious toxicity, subsequent courses of ifosfamide were escalated every 3 weeks by 0.25 g/m$^2$ per day to a maximum of 2 g/m$^2$ per day, with escalation of NAC to 12 g/day. Patients with KPS <50, serum creatinine or bilirubin >2 mg/d l, or obstructive uropathy were ineligible. The median age was 54 (range 36–78), median KPS 70, and median pretreatment weight loss 9 kg. Toxicity included nausea, vomiting, moderate myelosuppression, and occasional mental confusion. Hematuria (>11 RBC/HPF) developed in only 1/29 courses (17 patients) of ifosfamide at ≥1.75 g/m$^2$ per day, and in 7/52 courses (27 patients) overall (13%). Of 27 evaluable patients 6 responded (22%), including 1 with complete response. The median survival was 6 months. Based upon these results, we are currently evaluating ifosfamide + 5-fluorouracil in pancreatic cancer.

## Introduction

Adenocarcinoma of the pancreas is the fourth most common cause of cancer-related death in the United States. Chemotherapy has had a minimal role in the treatment of pancreatic cancer. 5-Fluorouracil remains the most active drug in this disease, with a response rate of approximately 15% and no apparent impact on the expected median survival time of 4–6 months [12].

A combination regimen using 5-fluorouracil, doxorubicin, and mitomycin C (FAM) was initially reported by investigators at Georgetown to produce remissions in 10 of 25 (40%) patients with measurable pancreatic cancer [19]. Although responding patients lived for approximately 1 year, the median survival for all patients in this study was still only 5.5 months. Subsequent trials at Georgetown using the same FAM regimen with the addition of chlorozotocin [20] or hexamethylmelamine [21] have shown lower response rates (13% and 21%, respectively) with similar median survival times. Recently the FAM regimen failed to demonstrate an improved response rate or survival advantage over 5-fluorouracil alone or in combination with adriamycin in a randomized prospective trial [6].

Regimens containing streptozotocin in place of doxorubicin have had similar response rates to FAM with no apparent impact on median survival [5, 16, 24]. Thus, it is obvious that new active chemotherapeutic agents are needed for the treatment of this disease.

The role of alkylating agents in pancreatic cancer has hitherto been poorly defined. Although data have suggested activity for nitrogen mustard [11], chlorambucil [14], and cyclophosphamide [22], the information has been anecdotal prior to the establishment of more rigid response criteria. More recently, in a randomized phase II trial melphalan was found to be devoid of activity [9]. A further trial, which compared streptozotocin with either 5-fluorouracil or cyclophosphamide in the treatment of pancreatic cancer, revealed only a 12% response rate in 93 evaluable patients [13].

In 1976, Brühl and his group reported 8 partial and 2 complete remissions in 13 patients with pancreatic cancer treated with ifosfamide [1–3]. The mean survival was still only 8.6 months, but he did note a complete responder alive at 24 months. Following this result and other European data which suggested activity of ifosfamide in this disease, Gad-El-Mawla et al. found 6 partial responses in 10 patients with pancreatic cancer treated with this drug [7]. However, at the dosage of ifosfamide used (2.0 g/m$^2$ per day on days 1–5), all but two patients developed hemorrhagic cystitis. Certain thiol compounds, such as *N*-acetylcysteine and mesna, have been demonstrated to be effective in decreasing the urotoxicity of the oxazphosphorines (e.g., cyclophosphamide, ifosfamide) [18, 23]. A trial was therefore initiated of ifosfamide with *N*-acetylcysteine (NAC) for the treatment of pancreatic adenocarcinoma.

## Materials and methods

From April 1982 to February 1984, in all 29 patients with biopsy-proven locally unresectable or metastatic adenocarcinoma of the pancreas were considered eligible for this study. Characteristics of the patients entered on this study are shown in Table 1. The median age was 54 (range 36–78) years. The median pretreatment weight loss was 20 lbs (range 0–53 lbs). All patients had a Karnofsky performance status of 50 or greater, and demonstrated at least one bidimensionally measurable lesion. Malignant hepa-

* This work was supported in part by NCI grant # 1R35 CA 39844-01

** American Cancer Society Clinical Professor of Oncology

*** American Cancer Society Junior Faculty Fellow

*Offprint requests to:* L. H. Einhorn

**Table 1.** Patient characteristics

| 1. Characteristic | Patients ($n$ = 29) |
|---|---|
| Sex: male/female | 18/11 |
| Performance status | |
| 90–100 | 4 |
| 70– 80 | 15 |
| 50– 60 | 9 |
| Sites of measurable disease | |
| Liver | 13 |
| Pancreatic mass | 14 |
| Lymph nodes | 2 |
| Prior chemotherapy | 2 |

tomegaly could be considered measurable disease if the liver edge was palpated in quiet respiration at least 5 cm below the costal margin at the midclavicular line or xiphoid process prior to treatment. No chemotherapy or radiotherapy was permitted within 3 and 4 weeks, respectively, before entry to this study. All patients had a serum creatinine of 2 mg/dl or less and adequate bone marrow reserve (granulocyte count greater than 2000/μLl, platelet count greater than or equal to 125000/μl).

Pretreatment studies included a history and physical examination, checks on SMA-12, electrolytes, BUN, creatinine, CEA, and EKG, urinalysis, and chest X-ray. Abdominal computed tomographic scanning was performed for baseline tumor measurements in all patients.

Pretreatment hydration consisted of 1 l 5% dextrose in 0.45 normal saline. Ifosfamide was then administered at 1.25 g/m$^2$ in 500 ml 5% dextrose in water infused over approximately 1 h for 5 consecutive days. Further hydration with two additional 12-h infusions of 1 l 5% dextrose in 0.45 normal saline was administered during each 24-h period. When no significant toxicity was noted in the first six patients treated, the starting dose of ifosfamide was increased to 1.5 g/m$^2$ per day on days 1–5 in newly entered patients. Patients voided at least every 2 h while awake and at least once during the night. NAC was taken orally at a dosage of 2 g at least 1 h before ifosfamide treatment, and continued every 6 h until 2 days after the last ifosfamide dosage. In patients receiving more than 1.5 g/m$^2$ ifosfamide, NAC was increased to 2 g every 4 h for the same duration. Daily urinalysis demonstrating no more than 10 red blood cells/per high-power field (grade 0–I) was required before administration of ifosfamide.

If no toxicity worse than grade I (Table 2) was noted, subsequent courses of ifosfamide were administered in a similar fashion every 3 weeks, with a dosage escalation (by increments of 0.25 g/m$^2$ per day for 5 days) to a maximum dosage of 2 g/m$^2$ per day. Responding patients were continued on study at the maximal tolerated dosage for a maximum of 1 year or withdrawn sooner, at the discretion of the physician. If a grade II or greater hematuria developed, the subsequent NAC dose was increased (see Table 2), and when hematuria resolved ifosfamide was resumed at the previous dosage. If subsequent grade II or greater hematuria again developed, NAC was escalated to a maximum of 3.0 g every 4 h [18]. If grade II or grade III hematologic or urothelial (after maximum NAC dosage) toxicity developed, subsequent doses of ifosfamide were decreased by 25% and 50%, respectively.

A complete response (CR) is defined as complete resolution of abnormalities noted on physical examination, CT scan, and serum CEA determinations. A partial response (PR) is defined as a greater than 50% decrease in the sum of the product of two perpendicular diameters of all measurable disease for at least 1 month. When hepatomegaly was used as the criterion of response, a decrease of at least 30% in the sum of the measurements below the right and left costal margins at the midclavicular line and xiphoid process was required. Stable disease was a decrease by less than 50% and an increase of no greater than 25% in the size of measurable lesions for at least 2 months. When CT scan was used for tumor measurements, subsequent measurements were accomplished by using comparable field cuts using the same definition for responses. Response duration and survival were calculated from the first day of treatment to the day of relapse and death, respectively.

**Table 2.** *N-A*cetylcysteine dosages

| 1. *Ifosfamide dosage* | *NAC dosage* |
|---|---|
| 1.25–1.5 (g/m$^2$ per day) | 2.0 g p.o. every 6 h |
| 1.75–2.0 (g/m$^2$ per day) | 2.0 g p.o. every 4 h |

2. With grade II or greater hematuria – ifosfamide delayed until hematuria resolved, then reinstituted at the same dosage). NAC was increased as stated below:

| *Grade* | *NAC dosage p.o. every 4 h* |
|---|---|
| II (11–50 RBC/HPF) | 2.5 g |
| III (>50 RBC/HPF) | 3.0 g |

3. If further grade II or III hematuria developed upon rechallenge, and patient was receiving maximum NAC dosage (18 g/day), subsequent dosages of ifosfamide were decreased by 25% (for grade II toxicity) or 50% (grade III toxicity)

## Results

Of the 29 patients who entered the study, 2 were inevaluable for response: 1 of these received 2 days of therapy, developed hemorrhagic cystitis, and refused further treatment, while the other developed acute renal failure after the third day of treatment with ifosfamide and died prior to an evaluation of response. Both are considered evaluable for toxicity. The median number of courses administered for responders was 6.5 (range 4–8) and for non-responders, 2 (range 1–6).

Toxicity was predominately urothelial and hematologic. In 14 courses (12 pts) of ifosfamide at 1.25 g/m$^2$ per day only one case of grade II hematuria developed, in a woman with a concurrent urinary tract infection. Six episodes of grade III and one episode of grade II hematuria occurred during 52 courses (27 pts) of ifosfamide at 1.5 g/m$^2$ per day (total incidence grade II/III: 7/52 or 13%). In 29 courses of ifosfamide at 1.75 g/m$^2$ per day (11 pts) or 2 g/m$^2$ per day (6 pts) only one episode of grade III hematuria developed (total incidence of grade II/III: 1/29 or 3.5%). Hemorrhagic cystitis was the principle reason for 4 patients failing to attain or maintain the maximum dosage of ifosfamide (2 g/m$^2$ per day). In general, hematuria occurred during the 5-day treatment course, but one patient developed gross hematuria 3 weeks after his eight cycle of ifosfamide. Hematuria generally resolved in 24–72 h after the cessation of ifosfamide. Subsequent successful re-

treatment with the same dose of ifosfamide with increased NAC was achieved in only 1 of 3 patients.

Myelosuppression was generally mild, although severe leukopenia (WBC less than 1000/mm$^3$) and thrombocytopenia (<50000/mm$^3$) occurred on the first day of the next treatment course in two patients at ifosfamide dosages of 1.5 g/m$^2$ or less. One of these patients had a pretreatment bilirubin of 6.8, while the other had had extensive prior treatment with chemotherapy (fluorouracil, doxorubicin and mitomycin C). Two patients had episodes of Klebsiella pneumoniae bacteremia following treatment with ifosfamide. In neither case was sepsis associated with granulocytopenia, and it resolved with appropriate antibiotics in both. One case of granulocytopenic fever of unknown etiology resolved with antibiotics. Ifosfamide dosages were not escalated in patients because of myelosuppression (low nadir (<2500) 4 pts; <2500 on day of treatment, 3 pts; granulocytopenic fever, 1 pt).

Nausea and vomiting occurred in nearly three-quarters of the treated patients. This side-effect appeared to be associated with the ingestion of NAC rather than with the ifosfamide infusion. Gastrointestinal toxicity was dose-limiting in 4 patients.

Five patients demonstrated central nervous system disturbances, which included disorientation, cognitive dysfunction, mild memory disturbances, and hallucinations. Dosages of ifosfamide at the times of these occurrences ranged from 1.25 to 2 g/m$^2$ per day. Although most of these patients were taking antiemetics and narcotics concomitantly with the ifosfamide treatment, all patients noted improvement of these symptoms within 24–48 h upon discontinuation of the ifosfamide. This was the dose-limiting toxicity in one patient.

Acute renal failure requiring dialysis occurred in one patient treated with ifosfamide for only 3 days at a dosage of 1.5 g/m$^2$ per day. This patient had no known pre-existing renal dysfunction. The patient succumbed eventually when further dialysis was refused by the patient and family. In addition to the nephrotoxicity experienced by this patient, confusion, gross hematuria, and profound myelosuppression (WBC 100 cells/mm$^3$, platelet count 32000/mm$^3$) occurred.

Among the 27 patients evaluable for response, there were 1 CR and 5 PRs (22% response rate; 95% confidence limits 6% and 38%). The complete responder had disappearance of a 5 × 5 cm supraclavicular lymphnode (an abdominal CT scan was normal prior to treatment whithout change during therapy). All the partial responders had improvement of liver metastasis noted on CT scan. One of the partial responders demonstrated complete resolution of hepatic metastases in CT scan, but the CEA failed to normalize completely (from 160 ng/ml to 10.8 ng/ml). Five patients demonstrated stable disease for 3+, 5, 6, 7+, and 11 months. The pancreas was the site of the primary measurable lesion in 4 of these 5 patients. Responders were treated with a median of 6.5 courses (range 4–9) and nonresponders with a median of 2 courses (range 1–6).

The median duration of survival for the entire group was 6 months (range 1–15+ months). Responders and nonresponders had median survival times of 8 months and 5 months, respectively. The median duration of response was 7 months (range 4–12 months). The two patients with a history of prior chemotherapy did not respond to treatment. All patients who demonstrated a response to treatment had an improved performance status and decreased pain. All but one of the responding patients demonstrated either stable or increasing weight during treatment.

## Discussion

Ifosfamide is an alkylating agent which is a structural analogue of cyclophosphamide. In phase I trials ifosfamide was found to differ from its parent compound in that it caused substantially less myelosuppression, but it had a marked incidence of hemorrhagic cystitis. Although the administration of ifosfamide in divided doses over 5 days, hydration, and frequent voiding has minimized the urothelial damage, hematuria has remained the dose-limiting toxicity [22].

The exact mechanism by which ifosfamide induces hematuria is unclear. Following administration, ifosfamide is metabolized in the liver to various active and inactive forms. The final metabolic products include acrolein and chloroacetic acid. Although acrolein is thought to be the major compound causing urothelial damage, several other compounds may be responsible [1, 15]. Compounds such as *N*-acetylcysteine and mesna form sulfhydryl bonds with acrolein, and perhaps these other compounds in the urine to minimize this toxicity [2, 4, 8, 15, 16, 23]. A dose-response relationship of NAC for the prevention of ifosfamide-induced hematuria has been suggested in previous reports [10, 18].

Oral *N*-acetylcysteine was associated with bladder protection in the majority of patients in this study, but temporary symptoms of cystitis still occurred in some patients. In general, cystitis was symptomatic with dysuria prior to the onset of hematuria and resolved within 1 to 2 days of discontinuation of ifosfamide. Upon resolution of the cystitis, further treatment with the same dosage of ifosfamide at increased dosage of NAC was possible in only one patient. As the NAC was associated with nausea and vomiting in most patients in this study, increased dosages of the oral agent were poorly tolerated. Parenteral forms of urothelial protective agents (i.e., NAC, mesna) might minimize this toxicity.

The major symptomatic toxicity in this study was gastrointestinal (nausea and vomiting). Gastrointestinal disturbances seemes to correlate strongly with the ingestion of the NAC capsules. Although most patients did manage to continue to take the NAC, antiemetics were frequently used.

Since 1984, we have had access to mesna, a new uroepithelial protector. We feel this agent is preferable to NAC because it can be given i.v., is as effective as NAC, and is not associated with nausea or vomiting.

Myelosuppression was generally mild in patients without prior chemotherapy or hyperbilirubinemia. Only one patient developed granulocytopenic fever during therapy. The one drug-related mortality in this study was a result of renal failure. Renal toxicity associated with ifosfamide is an uncommon finding [23]. Nephrotoxicity has usually been observed in patients with pre-existing renal disease. As ifosfamide is metabolized by the liver but excreted into the urine, acute renal failure with ifosfamide is often associated with severe and prolonged myelosuppression. With adequate support the renal dysfunction usually reverses [15].

The development of confusion during treatment with ifosfamide has been observed before [17, 23]. Van Dyk et al. reported confusion in 7 patients above the age of 60 years who received dosages of ifosfamide of 150 mg/kg every 2 weeks [17]. CNS toxicity was not observed in patients receiving lower dosages of ifosfamide, suggesting that this was a dose-related toxicity. No information was given on concurrent medications, but 2 patients had brain metastases found at postmortem examination. In our study, CNS toxicity occurred at dosages of 1.25–2 g/m$^2$, which does not necessarily support a dose-related toxicity.

This study confirms early results showing activity for ifosfamide in the treatment of pancreatic cancer. The response rate in this study, however, is less than the 60% (6 out of 10 patients) reported by Gad-El-Mawla et al. [7]. The daily dosage of ifosfamide in the Egyptian study was 2 g/m$^2$ in contrast to the initial starting dose in this study of 1.25–1.5 g/m$^2$. Only 6 patients were subsequently given the higher dosage of 2 g/m$^2$, because of tumor progression, myelosuppression, or hematuria at lower dosages. In the six responders in this study maximum dosages of ifosfamide were 1.5 g/m$^2$ (2 patients), 1.75 g/m$^2$ (2 patients), and 2 g/m$^2$ (2 patients). A dose-response relationship for ifosfamide may explain this difference but was not examined by this study.

In summary, ifosfamide is an active agent for the treatment of adenocarcinoma of the pancreas. Dosages above 1.2 g/m$^2$ per day can usually be administered safely in the majority of patients when strict attention is paid to hydration and frequent voiding. The administration of NAC also appears to minimize the urothelial toxicity but is often associated with at least a moderate degree of nausea and vomiting. Intravenous preparations of urothelial protective agents may minimize the gastrointestinal toxicity associated with this treatment. Further trials of ifosfamide for the treatmet of pancreatic cancer are warranted.

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