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Ifosfamide in pediatric malignant solid tumors*

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Summary. Ifosfamide/mesna was given to 97 patients who had malignant solid tumors diagnosed before they were 21 years of age. Patients received 1.6 g/m^2 ifosfamide daily $\times 5$, given i.v. over 15 min, followed by 400 mg/m^2 i.v. mesna at 15 min and 4 and 6 h after ifosfamide. Responses were noted in patients with osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma and other soft-tissue sarcomas, rhabdoid tumor, neuroblastoma, Wilms' tumor, primitive neuroectodermal tumor, retinoblastoma, germ-cell tumors, and B-cell lymphoma. Toxicity included mild to moderate nausea and vomiting, transient, reversible myelosuppression, transient elevations of serum blood urea nitrogen (BUN) and creatinine and liver enzymes, infections, and self-limiting neurotoxicity characterized by changes in mental status, motor dysfunction, cranial nerve palsy, cerebellar dysfunction, and seizures. Neurotoxic symptoms were generally seen in patients who had previously received cisplatin. Ifosfamide is an important alkylating agent that should be combined with other agents in phase II and III trials. Alternate dose schedules should also be investigated.

Introduction

Few clinical trials of ifosfamide with or without mesna, involving patients who had malignant solid tumors diagnosed before they were 21 years old, have been reported [2, 13, 14, 16, 19, 23]. Scant information existed on the activity of ifosfamide in these pediatric neoplasms prior to the initiation of phase II and III studies using ifosfamide in combination therapy [14, 17]. To date, no phase I clinical trials of this drug have been carried out in pediatric patients. On the basis of early adult trials, which indicated that ifosfamide was better tolerated when given over 5 days than when given over a shorter period [24], we began a phase II study in November 1983, with the objective of determining both response and toxicity. Because of previously reported bladder toxicity, we included the administration of mesna following ifosfamide delivery.

Patients and methods

A total of 97 patients diagnosed as having malignant solid tumors before they were 21 years old were admitted to this study. Table 1 indicates the characteristics of these patients, for which the median age at the initiation of ifosfamide treatment was 12.2 years (range, 1–24 years). The diagnoses of these individuals were histologically confirmed; all had nonresectable or metastatic tumors and measurable disease. Of the 97 patients, 93 had received prior chemotherapy; the exceptions had malignant Schwanoma and multifocal, metastatic, or nonresectable osteosarcoma. The median performance status of these patients was 2 (range, 0–3), according to Eastern Cooperative Oncology Group criteria [18]. At the time of admission to this study, all patients had normal hemograms and urinalysis as well as hepatic, renal, and cardiac function. Consent for treatment was obtained from the patient and/or parent/guardian.

Prior to treatment, the extent of disease was assessed with conventional diagnostic imaging studies, radionuclide bone scans, and computed tomography or ultrasonography of affected areas. Bone marrow aspirates were obtained as necessary. Urinalysis was carried out daily on the days of ifosfamide delivery, and the agent was given only if urine contained <50 RBCs/high-power field. Hemograms were repeated weekly, and tests of renal and hepatic function were repeated as necessary.

Ifosfamide was supplied by the National Cancer Institute (Bethesda, Md), and mesna was supplied by Asta-Werke A. G. Bielefeld, FRG and by the National Cancer Institute. A dose of 1.6 g/m^2 ifosfamide (in sterile water for injection, 50 mg/ml) was infused over 15 min for 5 consecutive days, and 400 mg/m^2 mesna was given i.v. at 15 min and 4 and 6 h after ifosfamide. All patients received 1,000 ml/m^2 0.33 *N* saline containing 5% dextrose by i.v. infusion between the first and third mesna infusions. During the following 18 h, patients were required to receive 1,000–2,000 ml/m^2 fluids orally or by infusion. As necessary, i.v. or oral antiemetics or narcotics were delivered.

Courses of ifosfamide were delivered at 21-to 28-day intervals, depending on recovery of the WBC count to

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Table 1. Characteristics of 97 patients receiving ifosfamide/mesna

Boys/Girls	51/46
Median age (range)	12.2 years (1.9–24.5)
Prior chemotherapy	93
Prior alkylating agents	71
Cyclophosphamide	68
Cisplatin	60
Melphalan	6
Dacarbazine	4
Mechlorethamine	2
Prior radiation therapy	47
Prior surgery	93

$>2\times10^9$/l and the platelet count to $>100\times10^9$/l. Additional criteria before retreatment included a total granulocyte count of $<1\times10^9$/l. Treatment was witheld in the presence of significant neurotoxicity or hematuria. Response was assessed by physical examination and appropriate diagnostic imaging studies after the delivery of two 5-day courses of ifosfamide/mesna. Additional courses of this treatment were given unless there was evidence of progressive disease after the first or subsequent treatment courses. For individuals undergoing complete or partial responses following two treatment courses, treatment was continued for 12 months or until there was evidence of progressive disease.

In all, 22 patients were evaluated with daily EEGs to assess neurotoxicity [22, 23]. Other toxicity was quantitated using the criteria of the Pediatric Oncology Group [29]. Subclinical nephrotoxicity was evaluated by measuring the excretion of the urinary enzymes *N*-acetyl-β-D-glucosaminidase and alanine aminopeptidase in urine samples obtained prior to and during the treatment courses of 20 patients [11].

A complete response was defined as the disappearance of all measurable lesions for $\geqslant6$ weeks. A partial response was defined as a reduction of $\geqslant50\%$ in the perpendicular diameters of all measurable lesions, lasting more than 6 weeks. A mixed response was defined as a reduction of $>50\%$ in the perpendicular diameters of some measurable lesions but a change of $<50\%$ in other lesions for more than 6 weeks. Stable disease was defined as a decrease of $<25\%$ in the size of measurable lesions. Progressive disease was defined as an increase of $>25\%$ in the size of measurable lesions or the development of new lesions. The duration of response was calculated from the initiation of chemotherapy to the documentation of disease progression.

Of the 97 patients who entered this study between November 1983 and August 1986, 6 (3 with neuroblastoma, 2 with Hodgkin's disease, and 1 with nasopharyngeal carcinoma) could not be evaluated for tumor response because of early death due to tumor or infection and, in one instance, failure to return for reevaluation.

A total of 253 treatment courses were delivered to 97 patients. Subsequent to the initial course, 65 patients had 2 courses, 32 had 3 courses, 22 had 4 courses, 10 had 5 courses, 8 had 6 courses, 5 had 7 courses, 4 had 8 courses, 3 had 9 courses, 3 had 10 courses, 3 had 11 courses, and 1 patient received 12 courses. In all, 135 courses were delivered in an outpatient setting, whereas 118 were given in an inpatient setting. Eight treatment courses were abbreviated due to early death (1), severe nausea and vomiting (1), progressive disease (1), seizures (2), and other neurotoxicity (3).

Table 2. Responses to ifosfamide/mesna

Diagnosis	Evaluable patients (*n*)	CR	PR	MR	SD	NR
Osteosarcoma	22	2	3	4	5	8
Neuroblastoma	14	–	3	–	–	11
Ewing's sarcoma	9	–	1	1	1	6
Wilms' tumor	9	–	2	–	–	7
Rhabdomyosarcoma	8	–	2	–	–	6
Germ-cell tumors	4	–	2	–	–	2
Brain tumors	4	–	–	–	1	3
Sarcoma, NOS[a]	3	–	1	1	1	–
Malignant fibrous histiocytoma	2	–	–	–	–	2
Schwannoma	2	1	1	–	–	–
Primitive neuroectodermal tumors	2	–	1	–	–	1
Synovial sarcoma	1	–	1	–	–	–
Leiomyosarcoma	1	–	–	–	1	–
Fibrosarcoma	1	–	–	1	–	–
Chondrosarcoma	1	–	–	–	–	1
Rhabdoid tumor	1	–	1	–	–	–
Retinoblastoma	1	–	1	–	–	–
Hepatoblastoma	1	–	–	–	–	1
Hepatocellular carcinoma	1	–	–	–	–	1
Nasopharyngeal carcinoma	1	–	–	–	–	1
Hodgkin's disease	1	–	–	–	–	1
B-cell lymphoma	1	1	–	–	–	–
Melanoma	1	–	–	–	–	1
Totals	91	4	19	7	9	52

[a] NOS = not otherwise specified
CR, complete response; PR, partial response; MR, mixed response; SD, stable disease; NR, no response

Results

Characterization of the responses is shown in Table 2. Four complete responses were attained by two patients with osteosarcoma and one each with Schwannoma and B-cell lymphoma. The complete response for the patient with Schwannoma persisted for 12 months before evidence of recurrent pulmonary metastases. The pulmonary and brain metastases of a patient with osteosarcoma responded completely for >3 years. Responses were observed in more than one-third of the patients with osteosarcoma. Patients with other types of sarcomas, blastemic tumors, and germ-cell tumors also developed partial responses.

Some evidence of myelosuppression followed most treatment courses (Table 3). The median WBC nadir following the first course of ifosfamide/mesna was 1.3×10^9/l (range, 1.0–7.6) on day 11, and it was 1.9×10^9/l (range, 0.2–5.0) on day 12 of course 2. Of 91 patients, 55 had WBC counts of $<2.0\times10^9$/l during the first course, and 32 of 51 evaluable patients who received a second course had WBC counts of $<2\times10^9$/l following this treatment. Although thrombocytopenia rarely occurred following the first or second courses of treatment, a fall of >2 g/dl in hemoglobin values commonly occurred. There was no evidence of cumulative myelosuppression with the delivery of

Table 3. Comparison of the toxicity of the first and second courses of ifosfamide/mesna

Toxicity	Course 1	Course 2
Anemia (↓ Hb >2 g/dl)	45%	27%
Leukopenia (WBC $<2\times10^9$/l)	70%	51%
Thrombocytopenia (platelets $<100\times10^9$/l	20%	12%
Nausea, vomiting:		
Mild to moderate	68%	61%
Severe	7%	6%
Renal:		
Hematuria	0	1%
BUN >40, creatinine >2 mg/dl	9%	5%
Hepatic:		
SGOT, SGPT >2 × normal values	4%	7%
Infections	12%	9%

Hb, hemoglobin

successive courses. Severe nausea and vomiting were rarely encountered following treatment with ifosfamide/mesna; many individuals did not develop these symptoms at all.

After the first course of treatment had been delivered to the 97 patients, 12 episodes of infection were documented, for which 6 patients required hospitalization (Table 3). Following the second course of treatment, 5 of 65 patients required hospitalization for infections, fever, and/or neutropenia. The only significant infection in patients who received more than two courses of treatment was infection of the Hickman line site in the patient with osteosarcoma, who underwent a complete remission of pulmonary and brain metastases.

Mesna (as well as hydration) was successful in preventing hematuria due to hemorrhagic cystitis in all but one patient [5, 25]. Hemorrhagic cystitis developed following the second course of treatment of an 8-year-old boy with multifocal osteosarcoma [21]. Another patient developed hematuria following the third dose of ifosfamide during his first course of treatment; various evaluations failed to determine the etiology. This patient subsequently received ten additional, full courses of ifosfamide/mesna without recurrence of hematuria. Other causes of hematuria in two patients included known renal tumor infiltration and atonic bladder secondary to a tumor involving the presacral area and prostate.

The frequency of impaired glomerular filtration, measured by increases in BUN and serum creatinine levels, is shown in Table 3. Subclinical nephrotoxicity was noted by an increase in the excretion of urinary enzymes, as previously reported [11]. Elevations of serum transaminase levels were rarely encountered.

Neurotoxicity, as previously described to include disturbances of mental status, the motor system, cranial nerves, and cerebellar function or seizures [22], was observed in 22 of 97 patients (23%) at some time during their treatment. Of the 56 courses of treatment given to these 22 patients, 36 were associated with evidence of neurologic dysfunction. Thus, 14% (36/253) of courses delivered were associated with neurotoxicity. The affected patients showed complete recovery from all dysfunction within 3 days of completion of the 5-day courses of treatment. There was no evidence that prior courses of ifosfamide predisposed patients to develop more severe neurotoxicity, yet patients who had neurologic dysfunction with their first 5-day course were at greater risk for recurrence of this abnormality with their second and subsequent courses [23]. The direct association of neurotoxicity, myelosuppression, and nephrotoxicity with the cumulative dose of prior cisplatin has been observed for our patients [10, 20]. The median age of the 22 patients who developed neurotoxicity was 14.2 years (range, 2.2–21.4 years), compared with 9.9 years (range, 2.1–24.5 years) for the 44 patients who had also received prior cisplatin but did not develop neurotoxicity. Of the 22 patients who developed neurotoxicity, 4 had not previously received cisplatin. Their neurotoxic features were in no way different from those in patients with neurotoxicity who had previously been given cisplatin.

As previously reported, EEGs were obtained during 51 courses delivered to 23 patients [23]. EEGs became abnormal during the 5-day courses of treatment in four patients with observed neurotoxicity. However, abnormal EEGs were also observed during 14 of 42 courses given to 19 asymptomatic patients. The usual EEG changes were the slowing of the baseline rhythm, followed by an increase in delta range activity, then by high-voltage rhythmic delta discharges occurring either anteriorly, posteriorly, or in generalized areas. Such changes developed in individuals with and without clinical evidence of neurotoxicity.

Discussion

With the addition of 36 patients to our previous report [23], we continued to confirm the activity of ifosfamide against tumors generally considered resistant to conventional modalities of treatment. Responses were observed in patients with various types of pediatric neoplasms. In addition to 31 patients who had evidence of complete, partial, or mixed responses, 8 individuals had stable disease for 6 weeks or longer. Ifosfamide is the only alkylating agent with predictable activity against osteosarcoma; its response rate in previously treated patients is similar to that previously observed after other single-agent treatment such as high-dose methotrexate, doxorubicin, or cisplatin [23]. Of 11 patients with soft-tissue sarcomas other than rhabdomyosarcoma, 6 also showed evidence of response, indicating the usefulness of ifosfamide in treating these rarer types of sarcomas.

Neurotoxicity, as quantitated in a previous publication [22], was shown to be most significantly related to prior treatment with cisplatin at doses of >300 mg/m^2. Young patients with disseminated neuroblastoma [13], treated elsewhere with ifosfamide as initial therapy, demonstrated no evidence of neurotoxicity. In our patient population, there was no evidence of associated acidosis [2] and no correlation with the presence of bulky pelvic disease or intercurrent treatment with antiemetics or narcotics [22].

The metabolism of ifosfamide [3] produces higher levels of a potentially neurotoxic metabolite, chloroacetaldehyde, than that of cyclophosphamide. Micromolar levels of this metabolite have been demonstrated in the blood of individuals following treatment with ifosfamide [9]. The

ifosfamide dose schedule involving daily doses of >2 g/m^2 may well predispose patients who had previously received cisplatin to develop signs of neurotoxicity.

Hemorrhagic cystitis definitely attributed to ifosfamide was encountered following only 1 of 253 treatment courses delivered to our patients, indicating the value of mesna in protecting the bladder [7]. A recent publication [1] has indicated the protective nature of mesna in other oxazaphosphorine therapy following cyclophosphamide-associated hematuria and hemorrhagic cystitis [1], yet mesna has not offered protection against clinical nephrotoxicity [28]. Although the use of mesna does not protect the kidneys from evidence of subclinical nephrotoxicity [11], the frequency and severity of changes in serum creatinine levels are lower than those reported in the absence of mesna [28].

The demonstration of the antitumor activity of ifosfamide in various pediatric malignant solid tumors [3, 15, 16, 19, 27] previously considered to be resistant to cyclophosphamide and/or cisplatin makes the use of this agent a viable alternative following the failure of treatment with these two agents. Studies of adults with soft-tissue sarcomas [4, 26] have suggested the superiority of ifosfamide over cyclophosphamide in patients who have not previously been treated with these agents. Delivery of ifosfamide with other active agents such as etoposide and doxorubicin may provide rational front-line therapy in pediatric patients with various malignant neoplasms including osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, and other soft-tissue sarcomas [8, 17]. Alternative schedules for the delivery of ifosfamide in pediatric patients should continue to be explored.

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