Medical and Pediatric Oncology 27:145–148 (1996)

Response of Pediatric Malignant Solid Tumors Following Ifosfamide or Ifosfamide/Carboplatin/Etoposide: A Single Hospital Experience

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One hundred thirty-eight pediatric patients have received treatment for malignant solid tumors with ifosfamide with mesna, and 71 have received a combination with ifosfamide/carboplatin/etoposide (ICE). Responses were obtained in many types of pediatric tumors, yet comparison of responses was not possible because of inadequate numbers of tumors of differing histiotypes. Comparison of results between patients with all tumors treated with ifosfamide or ICE indicated that there was a higher response rate for patients treated with ICE, with an estimated odds ratio of 2.74 (95% C.I. 1.45–5.179). Excluding patients without prior chemotherapy and radiotherapy, the odds ratio for 2.801 (95% C.I. 1.45–5.4) suggests a similar result. There remain no guarantees that the more costly treatment with ICE, which requires cytokine support, will offer therapeutic benefits against resistant solid tumors.

Key words: ifosfamide, ifosfamide/carboplatin/etoposide, pediatric tumors

INTRODUCTION

In the United States, ifosfamide, an analogue of cyclophosphamide, has been utilized with the uroprotectant mesna in various pediatric clinical trials over the past 12 years [1,2]. Ifosfamide/mesna has been used alone or combined with other agents such as vincristine, dactinomycin, doxorubicin, cisplatin, carboplatin, and etoposide [2]. Significant responses have been demonstrated in rhabdomyosarcoma, Wilms' tumor, lymphoma, osteosarcoma, Ewing sarcoma, and other soft tissue sarcomas [2–5]. On the basis of these results, ifosfamide has been included in the standard Phase III therapy for such tumors as osteosarcoma [6,7]. Ewing sarcoma [8,9], and rhabdomyosarcoma [9–13].

This communication compares the response rates to ifosfamide/mesna versus ifosfamide/carboplatin/etoposide (ICE) with mesna in patients treated for various pediatric malignancies at St. Jude Children's Research Hospital between 1983 and 1992.

MATERIALS AND METHODS

Patients received ifosfamide/mesna on the Phase II protocol initiated in 1983 [14] or on one of two Phase I protocols initiated in 1989 and completed in 1991 [15,16]. These patients were treated with three different drug schedules of ifosfamide/mesna. On the Phase II study, patients received 1.6 g/m^2 per day × 5 [14]. The Phase I studies comprised two different dose escalation protocols with chemotherapy, given daily for 3 days [15], or every other day times 3 [16]. Dosages utilized in the single agent Phase I studies of ifosfamide started with 80% of the total dose delivered over 5 days in our Phase II study (8 mg/m^2). Initial dosage was 2,133 mg/m^2 daily × 3, followed by 2,560 mg/m^2 and 3,072 mg/m^2 daily × 3 for solid tumor patients. Patients with brain tumors received similar dosages every other day × 3. The recommended daily dose to be given to previously treated solid tumor patients (other than those with brain tumors) was 2,133 mg/m^2 daily × 3 for patients with prior cisplatin exposure, and 3,000 mg/m^2 daily × 3 for patients without prior exposure to cisplatin. For patients with brain tumors irrespective of prior platinate dosing, the recommended dosage was 3,000 mg/m^2 every other day × 3; this recommended dosage represented an increase of 1 g/m^2 total dosage over that delivered in the Phase II trial for patients with various solid tumors, including brain rumors. Successive treatments were given at approximately 3-week intervals. Patients who were treated with ifosfamide as a single agent for metastatic tumor may have had prior

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Received June 1, 1995; accepted December 11, 1995.

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TABLE I. Demographics of Patients Treated With Ifosfamide or Ifosfamide/Carboplatin/Etoposide

209 Patients
160 Caucasian
44 Black
5 Hispanic
Male: female = 99:110
Median age = 8.5 years (range, 0.2–21.5) at diagnosis
Treatment
Ifosfamide alone = 138
Ifosfamide/carboplatin/etoposide = 71

TABLE II. Number of Patients Treated by Tumor Type

	Treatment	
Tumor type	Ifosfamide	ICE
Brain	23	7
Ewing sarcoma	11	5
Germ cell	4	6
Hodgkin	5	—
Hepatic	2	—
Melanoma	1	—
Neuroblastoma	18	24
Nasopharyngeal carcinoma	2	—
Osteosarcoma	27	2
Primitive neuroepithelioma	2	1
Rhabdomyosarcoma	8	3
Retinoblastoma	3	—
Synovial sarcoma	3	2
Wilms	10	8
Other	19	13
Total	138	71

treatment with chemotherapy which included ifosfamide, etoposide, cisplatin, or carboplatin, and may or may not have received irradiation. In all, 138 patients were treated with ifosfamide/mesna as a single agent.

Seventy-one patients were treated on studies that combined targeted doses of carboplatin administered with fixed doses of ifosfamide/mesna and etoposide [17], sometimes in combination with GM-CSF [18,19] or interleukin-1α [20]. In these studies, the carboplatin dose was targeted to an area under the concentration vs. time curve (AUC) based on the individual glomerular filtration rate (GFR) as determined by 99 m technetium-DTPA plasma clearance [17–20].

In this analysis, we considered patients who were from the one population, solid tumor patients, and differences from different diseases were due by chance. Responses to treatments were defined as CR/PR and NR. The frequencies of responses by strata defined by treatment group and the status of prior radiation therapy and prior chemotherapy were calculated. Zelen's test [21] was used to check homogeneity among strata. Stratified Mantel-Haenszel test [22] was used to compare the difference between treatment groups.

We did not compare the results of ifosfamide/mesna or ICE with ifosfamide/etoposide because so few patients (n = 20) were treated with this 2-drug combination of agents.

RESULTS

Demographics of the patient populations are presented in Table I. Table II lists the numbers of patients with specific tumor types treated with ifosfamide/mesna and with ICE.

Table III indicates the responses following treatment with ifosfamide and with ICE. Responses were defined as complete response, partial response, and no response. Complete response indicated complete disappearance of all tumor for at least one month, partial response was defined as greater than 50% reduction of all tumor masses for more than one month, and no response was recorded for lesions that did not progress, had less than 25% reduction in mass size, or progressive enlargement of tumor size. There were not enough patients to draw conclusions about responses in specific disease types and varying prior treatment modalities.

There was no statistically significant evidence for lack of homogeneity among strata ($P = 0.38$). Stratified Mantel-Haenszel test showed there was a significant difference in responses between the ifosfamide and ICE group and the estimated odds ratio (2.74, 95% C.I. 1.45–5.179) suggested an association between the ICE group and higher response rate.

Excluding patients without prior radiotherapy and prior chemotherapy, similar results were obtained. There was no statistically significant evidence for lack of homogeneity among strata ($P = 0.22$). Stratified Mantel-Haenszel test showed there was a significant difference of responses between the ifosfamide and ICE groups and the estimated odds ratio (2.801, 95% C.I. 1.45–5.4) suggested an association between the ICE group and higher response rate.

Responses were also examined in relationship to prior treatment, as shown in Table IV. Of those with no prior radiation or chemotherapy, half responded favorably to ICE. However, too few patients who had had no prior treatment received ifosfamide/mesna for comparison. Among these with no prior radiation, but with prior chemotherapy, response rates were 3% for patients receiving ifosfamide/mesna compared to 43% for patients receiving ICE. Of those who received prior radiation but no prior chemotherapy, too few had received ICE to be comparable to the few who received ifosfamide/mesna. For the group who had had both prior irradiation and chemotherapy, there was a large difference in response rates, 55% versus 22% in favor of those patients receiving ICE.

DISCUSSION

We have described the experience of our institution between 1983 and 1992 in treating individuals with ifos-

TABLE III. Responses Following Ifosfamide and ICE

	Ifosfamide			ICE[a]		
Tumor	CR[b]	PR[c]	NR[d]	CR	PR	NR
Neuroblastoma		4	14	2	12	10
Brain		2	21		1	6
Osteosarcoma	3	7	17		1	1
Wilms		2	8	3	4	1
Ewing		1	10	1	1	3
Rhabdomyosarcoma		2	6		1	2
Germ cell		2	2	1	2	3
Hodgkin			5			
Synovial	1	1	1			2
MTPNS[e]		2				2
Sarcoma, N.O.S.[f]		1	2			1
Rhabdoid		1	1		2	
NHL[g]	1	1	1		1	
Retinoblastoma		2	1			
Primitive neuroepithelioma		1	1		1	
Epithelioid sarcoma			1		1	
ASPS[h]						2
MFH[i]			2			
Leiomyosarcoma			1			1
Fibrosarcoma			2			
NPC[j]			2			
Mesothelioma	1		1			
Angiosarcoma			1			
Triton					1	
Melanoma			1			
Clear cell sarcoma						1
Papillary serous carcinoma						1
Hepatocellular			1			
Hepatoblastoma			1			
Total	6	29	103	7	28	36

[a]ICE, Ifosfamide, carboplatin, etoposide.
[b]CR, Complete response.
[c]PR, Partial response.
[d]NR, No response.
[e]MTPNS, Malignant tumor of peripheral nerve sheath.
[f]N.O.S., Not otherwise specified.
[g]NHL, Non-Hodgkin lymphoma.
[h]ASPS, Alveolar soft part sarcoma.
[i]MFH, Malignant fibrous histiocytoma.
[j]NPC, Nasopharyngeal carcinoma.

famide/mesna and with the ICE regimen. In the past several years, ifosfamide has been used in combination with other agents for the primary treatment of rhabdomyosarcoma [13], osteosarcoma [6], and Ewing sarcoma [8] at this institution. We had only 20 patients who were treated with ifosfamide plus etoposide, an active combination known to be of value in the treatment of Ewing sarcoma as well as other tumors. We did not include these subjects in this analysis, but results of this combination in treating recurrent or resistant solid tumors have been reported by Miser et al. [23], Kung et al. [24], Horowitz et al. [25], and others [26]. The results of ICE chemotherapy, with and without cytokines, for pediatric malignant tumors have been reported from this institution [17–20].

We found that patients with neuroblastoma, Ewing sarcoma, germ cell tumor, non-Hodgkins lymphoma, osteosarcoma, primitive neuroepithelioma, rhabdomyosarcoma, synovial sarcoma, and Wilms' tumors responded to ifosfamide/mesna, and that patients with brain tumors, Wilms' tumor, Ewing sarcoma, germ cell tumors, neuroblastoma, primitive neuroepithelioma, and synovial sarcoma responded to ICE. However, despite the large number of patients included in this analysis, we cannot conclusively recommend one treatment over the other for specific disease types. The combination with ICE had a higher percentage of responses, yet we cannot get a statistical comparison in specific tumor types since comparable numbers of patients were not treated with ifosfamide and ICE, and because the analysis was based on one population of solid tumors. However, it appears (Table III) that in selected tumor types, ICE has no greater response rates than ifosfamide/mesna.

In the treatment of patients with unresponsive childhood cancer, we recommend that ICE be used in individuals who have received ifosfamide as part of their initial therapy, rather than retreating with ifosfamide alone. However, this significantly more myelotoxic treatment may require the utilization of cytokines, and there remains no guarantee that this more costly treatment will offer improved therapeutic effects against resistant solid tumors.

TABLE IV. Responses to Treatment by Ifosfamide/Mesna and ICE

		Complete or Partial response	No response	Total
No prior radiation/ no prior chemotherapy	Ifosfamide/mesna	1	2	3
	ICE	8	8	16
No prior radiation/ with prior chemotherapy	Ifosfamide/mesna	18	41	59
	ICE	12	16	28
Prior radiation/ no prior chemotherapy	Ifosfamide/mesna	2	7	9
	ICE	1	0	1
Prior radiation/ prior chemotherapy	Ifosfamide/mesna	14	53	67
	ICE	14	12	26
		70	139	209

ACKNOWLEDGMENTS

The authors express their appreciation to Sharon Naron for editorial assistance and Jan Kelley and Imella Herrington for word processing. This work was supported by USPHS Childhood Cancer Center Support (CORE) Grant CA-21765 and Solid Tumor Program Project Grant CA-23099 from the National Cancer Institute, and by the American Lebanese Syrian Associated Charities (ALSAC).

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