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Early phase II Gynecologic Oncology Group experience with ifosfamide/mesna in gynecologic malignancies*

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Summary. Starting in July 1985, the Gynecologic Oncology Group conducted a series of phase II trials with ifosfamide/mesna in advanced or recurrent gynecologic malignancies. Previously untreated patients received 1.5 g/m^2 i.v. ifosfamide daily for 5 days. Mesna was given i.v. q4h × 3 following ifosfamide; each dose was 20% of the daily ifosfamide dose. All patients with ovarian and 87% of those with cervical cancer had previously undergone platinum-based therapy. Because of the toxicity encountered in previously treated patients with ovarian carcinoma, the dose of ifosfamide was reduced to 1.2 g/m^2 daily in all patients who had received prior chemo- or radiotherapy. In epithelial ovarian carcinoma, responses were observed in 8 (20.0%) of 41 evaluable patients, with 3 (7.0%) complete responses. Response duration was 2.1–20.3+ months, with a median of 6.9+ months. In squamous-cell carcinoma of the cervix, 3 (11.1%) of 27 evaluable patients showed partial responses of 1.8, 2.2, and 3.1 months' duration. Of 26 untreated patients with mixed mesodermal tumors of the uterus, 5 (19.2%) achieved complete and 3 (11.5%) showed partial responses, for an overall response rate of 30.7%. Response duration was 1.4+–8.6 months, with a median of 3.8 months. Toxicity included two deaths due to renal insufficiency and a third related to neurologic impairment. Hematologic toxicity was manageable. Ifosfamide/mesna has activity in a wide range of gynecologic malignancies.

Introduction

Founded in 1970, the Gynecologic Oncology Group (GOG) is a multicenter cooperative organization sponsored by the National Cancer Institute and dedicated to clinical trial of surgery, radiotherapy, and chemotherapy in the treatment of gynecologic cancer. Phase II trials of chemotherapeutic agents in malignancies that are non-amenable to surgical or radiotherapeutic control have been a GOG priority since its inception. The activity of ifosfamide in the treatment of malignant lymphomas [5], pancreatic [12] and testicular [17] carcinomas, and soft-tissue sarcomas [3] led the GOG to initiate a series of phase II trials of this drug in advanced or recurrent gynecologic malignancies in July 1985.

Patients and methods

Three separate GOG studies accrued patients from July 1985 to March 1988. Protocol 26U involved previously treated malignancies of a variety of primary sites. The epithelial ovarian carcinoma and squamous-cell cervical carcinoma arms have since been closed to accrual and are summarized in this report. Chemotherapy-naive patients with squamous-cell carcinoma of the cervix were treated on protocol 76I, and protocol 87B included subjects with advanced or recurrent uterine sarcomas who had not received prior chemotherapy. All patients with refractory epithelial ovarian carcinoma had previously undergone treatment with cisplatin and cyclophosphamide with or without doxorubicin. In all, 87% of patients with resistant squamous-cell carcinoma of the cervix had received prior therapy with cisplatin, carboplatin, or iproplatin as well as radiotherapy. Patients with mixed mesodermal tumors and leiomyosarcomas of the uterus had not received prior chemotherapy.

Biopsy or hysterectomy specimens from all patients were reviewed by the GOG Pathology Committee. Additional eligibility criteria included disease measurable by physical examination or medical imaging techniques; ascites and pleural effusions were not considered to be measurable disease. Also required were a GOG performance status of 2 or less; an interval of at least 3 weeks since any prior tumor-directed therapy; the absence of significant infection; recovery from recent surgery, radiotherapy, or chemotherapy; and adequate hematologic (WBC count of ≥ 3,000/mm^3; platelet count of ≥ 100,000/mm^3), hepatic (serum bilirubin, SGOT, and alkaline phosphatase values of ≤ 2× normal levels), and renal (serum creatinine value of ≤ 2.0 mg% or creatinine clearance of ≥ 50 ml/min) function tests. Informed consent was obtained from all patients and none was treated until the study had been approved by the Human Investigations Committee of the participating institution.

Exclusion criteria were the absence of measurable disease, prior chemotherapy in patients with mixed mesodermal tumors and leiomyo-

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Table 1. Hematologic toxicity according to GOG criteria

Site	Toxicity grade:					Total
	0	1	2	3	4	
	Leukocytopenia:					
Ovary	12	4	7	12	6	41
Sarcoma	17	1	16	13	9	56
Cervix	13	1	4	4	5	29
Total (%)	42 (33.3)	6 (4.8)	27 (21.4)	29 (23.0)	20 (15.9)	126 (100)
	Granulocytopenia:					
Ovary	26	2	5	3	5	41
Sarcoma	44	1	2	3	6	56
Cervix	21	0	1	4	3	29
Total (%)	91 (72.2)	3 (2.4)	8 (6.3)	10 (7.9)	14 (11.1)	126 (100)
	Thrombocytopenia:					
Ovary	24	7	6	2	2	41
Sarcoma	49	5	0	1	1	56
Cervix	28	0	1	0	0	29
Total (%)	101 (80.2)	12 (9.5)	7 (5.6)	3 (2.4)	3 (2.4)	126 (100)

sarcomas only, more than one prior chemotherapeutic regimen in those with ovarian and cervical tumors only, a GOG performance status of f 3, the presence of a second malignancy excluding squamous or basal skin lesions, and the presence of microhematuria in excess of the lowest normal institutional range. Ifosfamide was given i.v. daily × 5 every 4 weeks at a dose of 1.5 g/m^2; this dose was reduced to 1.2 g/m^2 in patients who had received prior radiotherapy or chemotherapy. Mesna was given i.v. at 300 mg/m^2 q 4 h for three doses following ifosfamide.

History and physical examination, with assessment of evaluable lesions and GOG performance status, chemical analyses, measurement of blood urea nitrogen (BUN) and creatinine values, and microscopic urinalysis were carried out before each cycle of therapy, and WBC, differential, and platelet counts were obtained weekly. Abdominopelvic computerized tomographic (CT) scans were used in all patients, unless tumor parameters were measurable by examination or chest radiograph.

Drug administration was delayed after hematologic toxicity until the WBC count was f 3,000/mm^3, the platelet count, f 100,000/mm^3 and the granulocyte count, f 1,500/mm^3. Patients were considered to be evaluable for toxicity if only one course of therapy was given and evaluable for response after a single course of therapy if there was clear-cut progression. In other cases, patients remained on study until either disease progression was noted or adverse effects prevented further therapy. Response duration was calculated from the date of response until documentation of disease progression. Standard GOG response criteria [2] were applied.

Results

Of 46 patients with epithelial ovarian cancer who were entered in the study, 4 were determined to be ineligible due to either a wrong primary or more than one prior chemotherapy regimen. Another patient was ineligible because of an inadequate trial of therapy. In addition to cisplatin combination therapy, 7 patients had received radiotherapy and 11 had previously undergone hormonal therapy. A total of 41 patients were evaluable for response and toxicity; their mean age was 54.4 years. Three patients (7.0%) achieved complete and five (13.0%) showed partial responses to therapy, for a response rate of 20.0%. Response duration was 2.1–20.3+ months, and six patients were progression-free at 5, 6, 7.8, 9.6, 12.3, and 20.3 months. Five of eight responses were observed in patients with pelvic disease, and three were seen in patients with extrapelvic metastases.

A total of 30 patients with advanced squamous-cell carcinoma of the cervix were entered in the study. In all, 13 subjects had previously received cisplatin; 10, carboplatin; and 3, iproplatin. All but two patients had received radiotherapy to the pelvis as primary treatment. Surgery had been carried out with curative intent in 12 patients whose median age was 47 years. Three patients (11.1%) responded to ifosfamide therapy and responses were observed in both pelvic and extrapelvic disease. Response duration was 1.8, 2.2, and 3.1 months. Previous chemotherapy in responding patients included cisplatin in two and carboplatin in one.

Of 64 patients who received ifosfamide therapy for advanced or metastatic sarcomas of the uterus, 56 were evaluable for toxicity. One patient each was ineligible because of wrong primary or was inevaluable because treatment was never started. For six patients it is too early for analysis, and two are inevaluable for response. A total of 41 patients had undergone prior hysterectomy, 2 underwent laparotomy only, and 11 had no previous surgery; 20 subjects had received prior radiotherapy. Of the mixed müllerian tumors, 14 were homologous and 15 contained heterologous elements. Among the patients with leiomyosarcomas, 29 were evaluable for toxicity and 28 for response; 4 (14.3%) of the latter experienced partial responses to therapy. Of the patients with mixed müllerian tumors, five (19.2%) achieved complete responses to ifosfamide therapy and three (11.5%) showed partial responses, for a response rate of 30.7%. Response duration was 1.4+–8.6 months, with a median of 3.8 months.

Toxicity

Initially, 1.5 g/m^2 ifosfamide was given daily to previously treated patients with ovarian carcinoma. Because of death due to renal toxicity in one patient with no known underlying renal disease as well as several cases of grade 4 hema-

Table 2. Other toxicity according to GOG criteria

Site	Grade: 0	1	2	3	4	Total
GI	62	13	47	2	2	126
Renal	93	23	7	1	2	126
Neurologic	104	7	5	7	3	126
Anemia	102	5	9	10	0	126

tologic toxicity, the initial dose of ifosfamide was reduced to 1.2 g/m^2 per day in patients who had previously undergone chemotherapy or radiotherapy. A second patient with ovarian carcinoma died of renal failure while receiving the reduced dose and was found to have chronic pyelonephritis and pyonephrosis at autopsy. One patient with squamous-cell carcinoma of the cervix developed grade 3 renal toxicity that was reversed by supportive measures alone. Three patients with ovarian cancer developed microscopic hematuria. No other significant renal or urothelial toxicity was encountered. Initially, microscopic examination of the urine was required on a daily basis; the lack of urothelial toxicity enabled urinalysis to be done prior to each course of therapy.

An additional death occurred. After 3 days of ifosfamide therapy, one patient with a mixed mesodermal tumor of the uterus developed cerebellar dysfunction, left hemiparesis, and progressive coma and succumbed. A brain CT scan was done and showed no organic lesion. Lumbar puncture was not carried out, nor was a postmortem examination. This patient had normal renal and hepatic function by laboratory evaluation. Neurologic toxicity was also observed in 14 patients (14%) who experienced somnolence or a decreased level of responsiveness, which reversed with discontinuation of ifosfamide therapy.

Hematologic toxicity was acceptable. Of the patients evaluable for toxicity, GOG grade 3 and 4 leukopenia was observed in 23.0% and 15.9%, respectively. Only 19% of patients developed GOG grade 3 or 4 granulocytopenia, and none developed granulocytopenic fever or evidence of sepsis. Only 19.9% of patients had thrombocytopenia; 2.4% each had grade 3 or grade 4 thrombocytopenia, with no thrombocytopenic hemorrhage being reported in any patient. Although more patients with ovarian cancer experienced leukocytopenia than did those with mixed mesodermal tumors or cervical cancers, no other difference in hematologic toxicity was observed relative to the site of disease. WBC counts of <3,000/mm^3 (grade 2 or more) were more often reported ($P = 0.04$) among patients over 65 years of age (78%) than among those who were younger (54%). The results of hematologic toxicity are outlined in Table 1. In all, 18 patients (18%) required transfusion during therapy with ifosfamide. GOG grade 3 or 4 gastrointestinal (GI) toxicity was observed in only 4% of the patients treated (Table 2).

Discussion

Phase II trials carried out by the GOG have extensively tested various drugs in epithelial ovarian carcinoma, squamous-cell carcinoma of the cervix, and mixed mesodermal tumors of the uterus. Ifosfamide is among the most active agents tested in these disease sites.

In ovarian epithelial carcinoma, cisplatin was the second in a series of salvage agents tested by the GOG. A response rate of 24% was observed in 37 patients, who relapsed after alkylating-agent or anthracycline therapy [15]. Since the incorporation of cisplatin into first-line therapeutic regimens in ovarian cancer, reports of active salvage agents have been few. Tamoxifen and dianhydrogalactitol have produced response rates of 17.0% and 15.4%, respectively [1, 14]. No drug tested by the GOG has resulted in a response rate exceeding 20%. The activity of ifosfamide in ovarian cancer, suggested by Bruehl et al. [4] and Yazigi et al. [18] was confirmed by the present study. The activity of this drug in patients who had previously received cyclophosphamide also suggests the lack of cross-resistance between these two agents. It is apparent that an ifosfamide dose of 1.5 g/m^2 per day in patients who have previously received intensive combination chemotherapy may produce unacceptable toxicity.

Other authors [6] have suggested that ifosfamide is active against previously treated squamous-cell carcinoma of the cervix. The three partial responses observed in the present study confirm this impression, although the response rate was low (11.1%). Other agents studied by the GOG that have shown activity exceeding 10% in patients who had failed cisplatin therapy include dianhydrogalactitol [14] and rozoxane [10]. The lack of significant toxicity observed in the present study among patients with cervical cancer suggests that a trial of ifosfamide in untreated patients could be conducted at a higher dose level and that the agent may be given at 3-week intervals.

Agents used by the GOG in the treatment of mixed mesodermal tumors of the uterus include doxorubicin with or without DTIC [13], piperazinedione [11], cisplatin [16], and etoposide [19]. Of these drugs, doxorubicin plus DTIC produced a 22.6% response rate and cisplatin yielded a 17.9% response rate; neither result approaches the 32.2% rate observed in the present study. The GOG is studying ifosfamide with or without cisplatin in a phase III study in untreated patients with advanced or recurrent mixed mesodermal tumors of the uterus.

The dominant hematologic toxicity observed in this study was leukocytopenia with relative platelet sparing. Nadir counts were modestly low, and neither granulocytopenic fever nor thrombocytopenic hemorrhage was observed. Deaths due to renal failure occurred in two patients. Renal failure attributable to ifosfamide therapy is felt to be less common and less predictable than urothelial toxicity [19], although the use of mesna has markedly reduced the latter. Goren et al. [9] have suggested that nephrotoxicity may be more common in patients who have previously received cisplatin therapy, and other investigators [17] have suggested an increased risk of toxicity in patients whose renal function is impaired by other factors. The death due to renal failure observed in the present study at the lower starting dose of ifosfamide was probably related to renal insufficiency resulting from chronic infection.

The incidence of neurotoxicity (14%) in the present study is similar to that observed by others [7]; however, it

is possible that neurotoxicity was underreported in the early portion of our study. Mild neurotoxicity consisting of somnolence alone was difficult to detect in the presence of lorazepam, used frequently as an antiemetic in the present study. The neurotoxicity of ifosfamide is not well understood but may be related to accumulation of the metabolite chloracetaldehyde [8], which is related to the known central-acting depressants acetaldehyde and trichloroacetaldehyde (chloral hydrate). Neurologic impairment by ifosfamide is usually global in nature, and it is uncertain whether the death in the present study was directly related to ifosfamide or to an undetected vascular event. The encephalopathic death of one patient who was ineligible for this study because of severely compromised hepatic function underscores the need for adequate renal and hepatic reserves in patients receiving ifosfamide therapy.

References

1. Beecham J, Blessing J, Creasman N (1988) Tamoxifen responsiveness, hormone receptors and tumor grade: a prospective study of 105 advanced ovarian cancer patients (abstract). Proceedings, Society of Gynecologic Oncology meeting February
2. Blessing JA (1984) Design, analysis and interpretation of chemotherapy trials in gynecologic cancer. In: G Deppe (ed) Chemotherapy of gynecologic cancer. AR Liss, New York, pp 49–83
3. Bramwell VH, Mouridsen HT, Santoro A, Blackledge G, Somers R, Verwey J, Dombernowsky P, Onsrud M, Thomas D, Sylvester R, van Oosterom A (1987) Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcoma. Eur J Cancer Clin Oncol 23: 311–321
4. Bruehl P, Guenther U, Hoefer-Janker (1976) Results obtained with fractionated ifosfamide massive dose treatment in generalized malignant tumors. Int J Clin Pharmacol 14: 29–30
5. Cabanillas F, Hagemeister FB, Bodey GP, Freireich EJ (1982) IMVP-16: an effective regimen for patients with lymphoma who have relapsed after initial combination chemotherapy. Blood 60: 693–697
6. Coleman RE, Harper PG, Gallagher C, Osborne R, Rankin EM, Silverstone AC, Slevin ML, Souhami RL, Tobias JS, Trask CW (1986) A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother Pharmacol 18: 280–283
7. Fossa SK, Talle K (1980) Treatment of metastatic renal cancer with ifosfamide and mesnum with and without irradiation. Cancer Treat Rep 64: 1103–1108
8. Goren MP, Wright RK, Pratt CB, Pell FE (1986) Dechloroethylation of ifosfamide and neurotoxicity. Lancet II: 1219–1220
9. Goren MP, Wright RK, Pratt CB, Horowitz ME, Dodge RK, Viar MJ, Kovnar EH (1987) Potentiation of ifosfamide neurotoxicity, hematotoxicity, and tubular nephrotoxicity by prior *cis*-diamminedichloroplatinum(II) therapy. Cancer Res 47: 1457–1460
10. Homesley HD, Blessing JA, Berman M (1986) ICRF-159 (rozoxane) in patients with advanced nonsquamous cell carcinoma of the cervix. Am J Clin Oncol (CCT) 9: 325–326
11. Lagasse L, Thigpen JT, Morrison F (1979) Phase II trial of piperazinedione in treatment of advanced endometrial carcinoma, uterine sarcoma, and vulvar carcinoma (abstract). Proc Am Soc Clin Oncol 400
12. Loehrer PJ, Williams SD, Einhorn LH, Ansari R (1985) Ifosfamide: an active drug in the treatment of adenocarcinoma of the pancreas. J Clin Oncol 3: 367–372
13. Omura GA, Major FJ, Blessing JA (1983) A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer 52: 626–632
14. Stehman FB, Blom J, Blessing J (1983) Phase II trial of galactitol 1,2:5,6-dianhydro (NSC 132313) in the treatment of advanced gynecologic malignancies: a Gynecologic Oncology Group study. Gynecol Oncol 15: 381–390
15. Thigpen T, Lagasse L, Homesley H (1983) Cis-platinum in the treatment of advanced or recurrent adenocarcinoma of the ovary. Am J Clin Oncol (CCT) 6: 431–435
16. Thigpen JT, Blessing JA, Orr JW, DiSaia PJ (1986) Phase II trial of cisplatin in the treatment of patients with advanced or recurrent mixed mesodermal sarcomas of the uterus: a Gynecologic Oncology Group study. Cancer Treat Rep 70: 271–274
17. Wheeler BM, Loehrer PJ, Williams SD, Einhorn LH (1986) Ifosfamide in refractory male germ cell tumors. J Clin Oncol 4: 28–34
18. Yazigi R, Wild R, Madrid J, Arraztoa J (1984) Ifosfamide treatment of advanced ovarian cancer. Obstet Gynecol 63: 163–166
19. Zalupski M, Baker LH (1988) Review: ifosfamide. J Natl Cancer Inst 80: 556–566