Doxorubicin and ifosfamide-mesna in advanced and recurrent uterine sarcomas

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Summary

Purpose of investigation: To report the experience of a single institution in the south of Israel with doxorubicin and ifosfamide-mesna in patients with advanced/recurrent uterine sarcomas.

Methods: The hospital records of five patients with advanced/recurrent uterine sarcomas who had combination chemotherapy with doxorubicin and ifosfamide-mesna were retrospectively reviewed. Doxorubicin 30 mg/m^2 was given on days 1 and 2 and ifosfamide 2,000 mg/m^2 (+ mesna, W/W 60%) was given on days 1, 2 and 3 of every 21 days. Dose intensity, relative dose intensity and average relative dose intensity (ARDI) of chemotherapy were calculated. Response was determined using clinical evaluation and radiological reports. Toxicity was graded using the National Cancer Institute (NCI) criteria.

Results: The median ARDI of the combination of doxorubicin and ifosfamide received by the patients was 0.68 (range, 0.53-0.74). One (20%) patient had disease complete response lasting three months and four (80%) patients had progressive disease. Toxicity was mainly hematological with grade 3 or 4 leukopenia – four (80%) patients, neutropenia – four (80%), thrombocytopenia – one (20%) and anemia – one (20%). Non-hematological toxicity was negligible. At follow-up, four (80%) patients had died of disease and one (20%) was alive with disease.

Conclusion: Although the combination of doxorubicin and ifosfamide has certain activity in advanced/recurrent uterine sarcomas, the toxicity is of much concern and the results of treatment in terms of response duration and survival are poor.

Key words: Uterine sarcoma; Chemotherapy; Doxorubicin; Ifosfamide; Disease response; Toxicity.

Introduction

Several studies have demonstrated the superiority of the combination of doxorubicin and ifosfamide over other chemotherapy regimens in the treatment of advanced/recurrent soft tissue sarcomas, with a disease overall response rate of 7%-45% (partial response rate, 3%-35%; complete response rate, 3%-16%) [1-8]. Nevertheless, the treatment with doxorubicin and ifosfamide is often limited by severe hematological and non-hematological toxicities. Doxorubicin can specifically cause damage to the myocardium and cardiac function (left ventricular ejection fraction, LVEF) should routinely be monitored during the administration of doxorubicin by multiple gated acquisition (MUGA) scan [9]. As a rule, patients are eligible to receive doxorubicin only if the LVEF is > 50% and the total cumulative dose of doxorubicin should not exceed 550 mg/m^2 [8, 9]. Ifosfamide, like its isomeric analogue cyclophosphamide (the oxazaphosphorines), does not possess in itself alkylating activity and is metabolized in the hepatic microsomes to produce the active alkylating compound phosphoramide mustard and a metabolite called acrolein [10]. Acrolein, which is excreted in the urine, can cause bladder toxicity ranging from mild cystitis to severe bladder damage with massive hemorrhage (hemorrhagic cystitis). Bladder toxicity caused by acrolein can be prevented, or markedly diminished, by adequate hydration, frequent bladder emptying and the administration of the sulphhydryl-containing compound mesna (2-mercaptoethane sulfonate) [10].

Uterine sarcomas are characterized by rapid clinical progression and poor prognosis. They are rare tumors, accounting for only 3%-7% of malignant tumors of the uterine corpus and for only about 1% of all female genital tract malignancies, with an estimated incidence of less than one in 100,000 women per year [11]. Since uterine sarcomas are uncommon and consequently very few individuals or even referral centers can build up an adequate experience of handling this disease, its optimal management has been a challenge and a subject of debate. Management of uterine sarcomas has traditionally followed that of endometrial adenocarcinoma with total abdominal hysterectomy and bilateral salpingo-oophorectomy being the mainstay of treatment. Adjuvant pelvic radiotherapy has generally been applied in early-stage disease, and systemic chemotherapy has generally been administered in advanced/recurrent disease [11].

The aim of this study is to report the experience of a single institution in the south of Israel with the combination of doxorubicin and ifosfamide-mesna in five patients with advanced/recurrent uterine sarcomas and discuss the efficacy of this combination chemotherapy in uterine sarcomas based on review of pertinent literature.

Patients and methods

The hospital records of patients who had combination chemotherapy with doxorubicin and ifosfamide-mesna for advanced/recurrent uterine sarcomas between October 1999 and

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October 2004 at the Unit of Gynecologic Oncology, Soroka Medical Center, Beer-Sheva, Israel were retrospectively reviewed. Doxorubicin was planned to be given at a dose of 30 mg/m^2 in 100 ml NaCl 0.9% by a 15-minute intravenous infusion on days 1 and 2 of every 21 days. Ifosfamide was planned to be administered at a dose of 2,000 mg/m^2 in 1,000 ml standard solution by a 60-minute intravenous infusion on days 1, 2 and 3 of every 21 days. On days 1 and 2, ifosfamide was given immediately after doxorubicin. On days 1, 2 and 3, mesna (2-mercaptoethan sulfonate) was given at a dose of 400 mg/m^2 in 100 ml NaCl 0.9% by a 15-minute intravenous infusion thrice as follows: at the beginning of ifosfamide infusion and four and eight hours after the beginning of ifosfamide infusion. Every 21-day cycle was accepted as one course.

The method of dose intensity calculations suggested by Levin and Hryniuk [12, 13] for platinum-containing chemotherapy was adopted for the doxorubicin and ifosfamide regimen as follows: 1) The planned standard dose intensity (DI) of each drug was expressed in the form of mg/m^2/week. The results were for doxorubicin: 60 mg/m^2: 3 = 20 mg/m^2/week and for ifosfamide 6,000 mg/m^2: 3 = 2,000 mg/m^2/week; 2) The dose intensity actually received by the patient of each drug (expressed in mg/m^2/week) was calculated by dividing the cumulative absolute dose of each drug (expressed in mg/m^2) by the total number of weeks of the treatment period; 3) Each of the dose intensities actually received by the patient was calculated as a decimal fraction of the dose intensity of the respective drug in the planned standard regimen, which gave the relative dose intensity (RDI) for each drug; 4) For each patient, the relative dose intensities were added and divided by two (number of drugs in the planned standard doxorubicin and ifosfamide regimen). This gave the average relative dose intensity (ARDI) for the entire doxorubicin and ifosfamide regimen received by the patient compared with the planned standard doxorubicin and ifosfamide regimen.

Disease status was determined using clinical evaluation and imaging studies. The following criteria were used for disease response: 1) Complete response – disappearance of all lesions without evidence of any new lesions for ≥ 4 weeks; 2) Partial response – ≥ 50%-reduction in the size of the lesions without evidence of any new lesions for ≥ 4 weeks; 3) Stable disease – < 50%-reduction or ≤ 25%-increase in the size of the lesions, without evidence of any new lesions; 4) Progressive disease – > 25%-increase in the size of the lesions or evidence of any new lesions. Hematological and non-hematological toxicities were graded using the common terminology criteria for adverse events of the National Cancer Institute (NCI) [14].

Results

During the five-year period from October 1999 through October 2004, five patients with advanced/recurrent uterine sarcomas were treated with the combination of doxorubicin and ifosfamide. Patient characteristics are summarized in Table 1. The median age of the patients was 52 (range, 42-55) years. The median time from initial diagnosis to detection of recurrent disease was 16.5 (range, 2-40) months.

The details of doxorubicin and ifosfamide treatment are displayed in Table 2. The median number of doxorubicin and ifosfamide courses per patient was four (range, 1-6) courses and the median duration of doxorubicin and ifosfamide treatment was 17 (range, 3-20) weeks. The median average relative dose intensity (ARDI) of the doxorubicin and ifosfamide treatment received by the patients was 0.68 (range, 0.53-0.74).

Table 1. — *Patient characteristics.*

Patient's initials and age	Initial surgery	Histologic type	Stage at diagnosis	Pelvic radiotherapy	Time to recurrence (months)	Site(s) recurrence
E.M. 49	TAH + BSO	LMS (homologous)	I	None	40	Pelvis, abdomen, lung and mediastinum
I.M. 42	TAH + BSO + PLNS	LMS (heterologous [rhabomyosarcoma]) + HG-ESS	I	XRT (5040 cGy)	3	Pelvis and abdomen
P.K. 54.	TAH + BSO + PLNS	HG-ESS	I	XRT (5040 cGy) + brachytherapy (4000 cGy)	4	Lung and bone
R.D. 52	TAH +BSO + omentectomy + PLNS	LMS	I	XRT (5040 cGy)	29	Abdomen and lung
A.S. 55	TAH +BSO + partial resection of pelvic and abdominal masses	Carcinosarcoma (homologous)	III	XRT (3700 cGy) after one course of doxorubicin and ifosfamide	– (PD)	PD in pelvis and abdomen

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LMS, leiomyosarcoma; HG-ESS, high-grade endometrial stromal sarcoma; PLNS, pelvic lymph node sampling; XRT, external pelvic radiotherapy; PD, progressive disease.

Table 2. — *Details of doxorubicin and ifosfamide-mesna treatment.*

Patient	No. of courses	Duration (weeks)	Doxorubicin DI	RDI	ADPC	CDPP	Ifosfamide DI	RDI	ADPC	CDPP	ARDI
E.M.	4	17	13.2	0.66	56.2	225	1411.7	0.70	6000	24000	0.68
I.M.	6	20	12.5	0.62	41.8	251	1410.0	0.70	4700	28200	0.66
P.K.	4	16	14.0	0.70	56.2	225	1500.0	0.75	6000	24000	0.72
R.D.	4	20	11.7	0.58	58.7	235	961.7	0.48	4808	19235	0.53
A.S.	1	3	14.6	0.73	44	44	1500	0.75	4500	4500	0.74

DI, dose intensity (mg/m^2/week); RDI, relative dose intensity, ARDI, average relative dose intensity; ADPC, average dose per course (mg/m^2); CDPP, cumulative dose per patient (mg/m^2).

Disease response to doxorubicin and ifosfamide, further treatment and outcome of patients are summarized in Table 3. One patient (20%) had a disease complete response lasting for three months and in four patients (80%) the disease progressed during doxorubicin and ifosfamide treatment. Further treatment included weekly gemcitabine in three patients, VIP (VP-16 [etoposide], ifosfamide and cisplatin) in two patients, cytoreductive surgery and continuous hyperthermic peritoneal perfusion with mitoxantrone in one patient, irradiation to the pelvis in one patient and irradiation for distant metastases in two patients. At follow-up, four patients had died of disease three to 62 months after the initial diagnosis and one patient was alive with disease 39 months after initial diagnosis.

The toxicity of doxorubicin and ifosfamide treatment was mainly hematological (Table 4): four patients (80%) had grade 3 or 4 leukopenia and neutropenia necessitating the administration of granulocyte colony-stimulation factor (G-CSF) and dose reduction in subsequent courses, one patient (20%) had grade 3 anemia necessitating the administration of blood transfusions and one patient

Table 3. — *Disease response to doxorubicin and ifosfamide-mesna, further treatment and outcome of patients.*

Patient	Response to doxorubicin and ifosfamide	Duration of response to doxorubicin and ifosfamide	Further treatment	Response to further treatment	Follow-up from initial diagnosis (months)	Outcome
E.M.	PD	–	Gemcitabine x 6, VIP x 1	PD	62	DOD
I.M.	CR	3 months	Cytoreductive surgery + CHPP with mitoxantrone, radiotherapy to liver, gemcitabine x 6	PD	22	DOD
P.K.	PD	–	VIP x 4, gemcitabine x 4, radiotherapy to spine	PD	16	DOD
R.D.	PD	–	–	–	39	AWD
A.S.	PD	–	XRT	PD	3	DOD

VIP, VP-16 (etoposide), ifosfamide and cisplatin; PD, progressive disease; CR, complete response; DOD, died of disease; AWD, alive with disease; CHPP, continuous hyperthermic peritoneal perfusion; XRT, external pelvic radiotherapy.

Table 4. — *Toxicity of doxorubicin and ifosfamide treatment.*

Patient	Hematological toxicity (grade)	Non-hematological toxicity	LVEF B.T.	LVEF A.T.	Treatment of toxicity
E.M.	Thrombocytopenia (1)	Alopecia	65%	69%	–
I.M.	Anemia (3) Leukopenia (4) Neutropenia (4) Thrombocytopenia (2)	Alopecia	69%	64%	Blood, G-CSF
P.K.	Leukopenia (3) Neutropenia (3) Thrombocytopenia (1)	Alopecia	70%	67%	G-CSF
R.D.	Anemia (2) Leukopenia (4) Neutropenia (4)	Alopecia	58%	60%	G-CSF
A.S.	Anemia (2) Leukopenia (4) Neutropenia (4) Thrombocytopenia (3)	None	65%	NA	G-CSF

LVEF, left ventricular ejection fraction; B.T., before treatment; A.T., after treatment; G-CSF, granulocyte colony stimulating factor; NA, not assessed.

(20%) had grade 3 thrombocytopenia. Neutropenic fever requiring hospitalization was observed in two patients. Non-hematological toxicity, apart from alopecia, was negligible. In none of the patients was the LVEF < 50%. None of the patients experienced allergic reactions to doxorubicin, ifosfamide or mesna.

Discussion

The rarity of uterine sarcomas has made assessment of the efficacy of doxorubicin and ifosfamide in the treatment of advanced/recurrent uterine sarcomas difficult. Omura *et al.* [15] treated patients with advanced uterine leiomyosarcomas and mixed mesodermal sarcomas with single-agent doxorubicin 60 mg/m^2 every 21 days and demonstrated a response rate of 25% and 9.8%, respectively. Sutton *et al.* [16] treated patients with advanced or metastatic uterine mixed mesodermal sarcomas and leiomyosarcomas with single-agent ifosfamide 1,500 mg/m^2/day for five days every 28 days and documented a response rate of 32.2% and 17.2%, respectively. Hawkins *et al.* [17] compared ten patients with advanced uterine leiomyosarcomas who received ifosfamide (5,000-7,500 mg/m^2 per course) alone with 11 patients with advanced uterine leiomyosarcomas who received doxorubicin (40-60 mg/m^2 per course) and ifosfamide (5,000 mg/m^2 per course). Of the ten patients who received ifosfamide alone, one patient experienced partial response lasting six months. Of the 11 patients who received the combination of doxorubicin and ifosfamide, one had complete response lasting 11 months. The authors have concluded that ifosfamide has only modest activity in uterine sarcomas [17]. Sutton *et al.* [18] evaluated the activity and toxicity of ifosfamide in 35 women with advanced/recurrent uterine leiomyosarcomas not previously exposed to chemotherapy. Ifosfamide was administered at 1,500 mg/m^2 on days 1-5 of every 21 days. Disease partial response was observed in six (17.2%) patients. Grade 3 or 4 neutropenia occurred in four (11%) patients and grade 4 neurotoxicity in one (2.8%) patient. It has been concluded that ifosfamide has modest activity in patients with advanced/recurrent uterine leiomysarcomas [18]. In another study, Sutton *et al.* [19] assessed the effectiveness and toxicity of ifosfamide in 21 patients with recurrent or metastatic endometrial stromal sarcomas previously unexposed to chemotherapy. Four (19%) patients experienced partial response and three (14.3%) had complete response, for an overall response rate of 33.3%. Grade 3 or 4 neutropenia occurred in four (19%) patients, grade 2 anemia – one (4.7%), and bladder toxicity – one (4.7%). The authors have concluded that ifosfamide is active in the treatment of recurrent or metastatic endometrial stromal sarcomas [19]. In 1996, the Gynecologic Oncology Group (GOG) evaluated in a phase II study the efficacy and toxicity of ifosfamide and doxorubicin in 34 patients with advanced or metastatic uterine leiomyosarcomas who had not received prior chemotherapy [20]. Doxorubicin was administered at 50 mg/m^2 on day 1 and ifosfamide at 5,000 mg/m^2 (+ mesna 6,000 mg/m^2, 120% W/W) on day 1 of every 21 days. The overall response rate was 30.3% (partial response – 27.3% and complete response – 3%), stable disease – 51.7%, and progressive disease – 18%. Median response duration was 4.1 months in partial responders and response duration was 8.7 months in the patient with complete response. Partial responders received a median of eight cycles of chemotherapy (range, 3-11 cycles), with a median of five cycles until the response was documented. Median survival for responders was 11.1 months and 9.6 for the group as a whole. Almost 50% of the patients experienced grade 3 or 4 neutropenia. Neutropenic fever was observed in two patients and one died of sepsis. One patient died because of doxorubicin-related cardiac toxicity and one patient had ifosfamide-related grade 2 renal toxicity. It has been concluded that although the combination of doxorubicin and ifosfamide is moderately active, it is unclear whether this regimen has an advantage over doxorubicin alone [20]. In 2000, Sutton *et al.* [21] reported an overall response rate of 36% (partial response, 12% and complete response, 24%) in a group of 102 patients with advanced/recurrent uterine mixed mesodermal sarcomas who were treated with ifosfamide 1,500 mg/m^2/day for five days with mesna uroprotection every 21 days. Grade 3 or 4 leukopenia was observed in

58% of the patients, neutropenia – 36%, and thrombocytopenia – 5%. Grade 3 neurotoxicity occurred in 19% of the patients, severe nausea and vomiting – 4% and gross hematuria – 4%.

In this small series of five patients with advanced/recurrent uterine sarcomas treated with the combination of doxorubicin and ifosfamide, we have shown a disease complete response lasting for three months in one (20%) patient and progressive disease in all other four (80%) patients. Toxicity was mainly hematological with four patients (80%) experiencing grade 3 or 4 leukopenia and neutropenia. We are not aware of previous studies reporting dose intensity calculations of the combination of doxorubicin and ifosfamide. In this study, we have calculated the dose intensity and relative dose intensity of each drug and the average relative dose intensity (ARDI) of the combination of these drugs. We have shown that the patients received doxorubicin and ifosfamide with an ARDI ranging from 53% to 74% (median, 68%) of the planned standard dose intensity. The main reason for dose intensity reduction was severe hematological toxicity. Dose intensity reduction was executed by reducing the dose per m^2 and/or delaying the administration of the next course. Like others [15-21], we have shown that although the combination of doxorubicin and ifosfamide-mesna exhibits noticeable activity in patients with advanced/recurrent uterine sarcomas, the toxicity is high, the response duration is short and the prognosis is dismal.

Conclusion

The treatment of uterine sarcomas continues to be a challenge. Although postoperative adjuvant pelvic radiotherapy may reduce the risk of local recurrence in patients with early-stage disease (Stage I and II), it can not prevent the development of recurrent disease in distant sites. Although the combination of doxorubicin and ifosfamide-mesna is considered the best available regimen in the treatment of advanced/recurrent uterine sarcomas in terms of response rate, the toxicity is of much concern and the results of treatment in terms of response duration and patient survival are poor. There is a need for the development of other more active and less toxic agents in the treatment of advanced/recurrent uterine sarcomas.

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