A Retrospective Review of Metastatic or Recurrent Uterine Sarcomas Treated with Ifosfamide and Doxorubicin (IMA)

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ABSTRACT

The prognosis of metastatic uterine sarcoma is poor with median survival reported between 4 to 26 months. We evaluated the efficacy and toxicity of ifosfamide (I), mesna (M) and doxorubicin (A) (IMA) chemotherapy regimen retrospectively in patients with metastatic or recurrent uterine sarcomas.

Forty-two patients were enrolled in this study. The median age was 53 years (range, 18-72). Thirty-seven patients were assessable for response and survival; forty patients were assessable for toxicity. A total of 162 cycles of chemotherapy were introduced and for each patient and median number of chemotherapy cycles were 4 (range, 1-6). We observed complete response (CR) in 3 patients; partial response (PR) in 14 patients. Objective RR was 46% (95% CI, 30% to 62%). The median progression-free survival time of the responders was 8.0 months (range, 4-35). The median progression-free survival time of all patients was 5.0 months. Febrile neutropenia was encountered in 6 patients. Dose modifications were required in 4 patients due to myelotoxicity. Central nervous system (CNS) toxicity was observed in three patients. IMA regimen has moderate anti-tumor activity (46%) with acceptable toxicity in patients with recurrent or metastatic uterine sarcomas.

Key Words: Metastasis, Recurrent, Uterine sarcoma, Ifosfamide, Doxorubicin, Chemotherapy

ÖZET

Metastatik ya da Rekürren Uterin Sarkomlarında İfosfamid-Adriamisin (İMA) Tedavisinin Retrospektif Analizi

Metastatik ya da rekürren uterin sarkomların prognozu kötüdür. Yapılan çalışmalarda ortanca sağkalım 4-26 ay olarak bildirilmiştir. Bu çalışmada metastatik ya da rekürren uterin sarkomlu hastalarda ifosfamid ve adriyamisin kombinasyon tedavisinin etkinliğini ve toksisitesi retrospektif olarak incelenmiştir.

Çalışmaya 42 uterin sarkomlu hasta alındı. Hastaların ortanca yaşı 53 (aralık, 18-72) idi. Otuz yedi hasta yanıt, sağkalım; 40 hasta ise toksisite açısından değerlendirilebildi. Toplam 162 kür kemoterapi, hasta başına ortanca kür sayısı 4 (aralık; 1-6) olacak şekilde uygulandı. Üç hastada tam yanıt, 14 hastada ise parsiyel yanıt gözlendi. Objektif cevap oranı %46 (%95 GA, %30 - %62) idi. Yanıt alınan hastalarda ortanca progresyonsuz sağkalım 8.0 (4-35) aydı. Hastaların tamamı değerlendirildiğinde ise progresyonsuz sağkalım 5.0 aydı.

Altı hastada febril nötropeni gelişti. Dört hastada miyelotoksisite nedeniyle doz modifikasyonu yapıldı. Santral sinir sistemi toksisitesi 3 hastada gözlenmiştir. İMA rejimi ileri evre uterin sarkomlu hastalarda orta derecede etkili (%46) ve tolere edilebilen bir rejimdir.

Anahtar Kelimeler: Metastaz, Rekürren, Uterin sarkom, İfosfamid, Adriamisin, Kemoterapi

INTRODUCTION

Uterine sarcomas are rare and highly malignant tumours of the female genital tract. They account for <1% of all gynecological malignancies and 2-5% of all uterine cancers. Their incidence is 1-2/100.000 of the female population and they are twice more common in black than white women (1). Due to the rarity of these tumours and the different characteristics and prognosis of the various histological subtypes, it has been difficult to reach conclusions about the effect of various treatments on survival. There are three major types of uterine sarcoma; leiomyosarcomas (LMS), endometrial stromal sarcomas (ESS), and mixed mullerian tumours, (now called carcinosarcomas, CS). The management of these tumours is a challenge as they are aggressive in behaviour and metastatic disease is common (1).

In this retrospective analysis, we investigate the efficacy and toxicity of the combination of ifosfamide and doxorubicin in patients with recurrent or metastatic uterine sarcomas.

PATIENTS AND METHODS

From January 1999 to September 2005, a total of 42 patients with recurrent and/or metastatic uterine sarcoma, treated with ifosfamide (I), mesna (M) and doxorubicin (A) (IMA) regimen were retrospectively analyzed.

Patients must have met the following eligibility criteria: histologically confirmed recurrent or metastatic uterine sarcoma, measurable disease in two dimensions on physical examination or imaging, ECOG performance status 0-2, and adequate bone marrow, renal, and hepatic functions. Adequate function was defined as: WBC ≥3000/ml; platelets ≥100.000/ml, granulocyte count ≥1500/ml, creatinine ≤1.5 mg/dl, bilirubin ≤1.5x institutional normal, and SGOT and alkaline phosphatase ≤3x institutional normal.

The combination of ifosfamide 2500 mg/m^2 d 1-3, mesna 2500 mg/m^2 d 1-3, doxorubicin 60 mg/m^2 d 1 (IMA) was repeated every 3 wk. A total of two to six cycles were administered depending on response. Patients who achieved at least stable disease after two cycles of IMA were given additional two cycles of treatment. In responders, a maximum of six cycles were given irrespective of the response at

Table 1. Patient Characteristics

Characteristics	Value
Median age in years (range)	53 (18-72)
Histological subtype	
Leiomyosarcoma	20 (48%)
Malignant mixed mesodermal tumor	6 (14%)
Endometrial stromal sarcoma	6 (14%)
Carcinosarcoma	5 (12%)
Adenosarcoma	4 (10%)
High grade undifferentiated sarcoma	1 (2%)
ECOG	
0	15 (36%)
1	16 (38%)
2	11 (26%)
Primary treatment	
Surgery	42 (100%)
Chemotherapy	10 (24%)
Radiotherapy	7 (17%)
Site of disease	
Pelvic and extrapelvic	24 (57%)
Pelvic	15 (36%)
Extrapelvic	3 (7%)
Distant metastatic sites	
Lung	10 (23.8%)
Liver	8 (19.4%)
Bone	2 (4.7%)
Brain	1 (2.3%)
Median time from diagnosis to initiation of IMA therapy	6.0 months

Table 2. Treatment Characteristics and Toxicities

Characteristics	Value
1 cycle	4 patients
Lost the follow up	2 patients
Ifosfamide encephalopathy	2 patients
2 cycles	11 patient*
3 cycles	2 patients
4 cycles	8 patients
5 cycles	4 patients
6 cycles	13 patients
Median IMA cycle/patient	4.0
Treatment related death	0/42 patients
Ifosfamide encephalopathy	3/42 patients
Neutropenic fever episode	6/42 patients
Gross hematuria	1/42 patients
RBC transfusion	6/42 patients
Platelet transfusion	0/42 patients
Requiring G-CSF	4/42 patients
Cardiotoxicty	1/42 patients
Dose modification due to toxicity	4/42 patients

* One patient developed ifosfamide encephalopathy during 2nd cycle of chemotherapy

the end of treatment. Treatment was discontinued when response assessment after two cycles showed progressive disease, when there was evidence of disease progression at any time, or after six cycles of chemotherapy.

RESULTS

Forty-two patients (20 leiomyosarcoma [LMS], 6 malignant mixed mesodermal tumor [MMMT], 6 endometrial stromal sarcoma, 5 carcinosarcoma, 4 adenosarcoma, and 1 high grade undifferentiated sarcoma) were enrolled in this study. The median age was 53 years (range, 18-72). Two patients were lost to follow up after the first cycle; 3 patients had ifosfamide encephalopathy on the first and second cycles (2 patients on first cycle, 1 on second cycle) on the second and third day of the cycle. Thirty-seven patients were assessable for response and survival; forty patients were assessable for toxicity. Ten patients had received prior cytotoxic therapy and 7 had undergone prior radiotherapy [external radiotherapy (n= 5) and brachytherapy (n= 2)]. The prior cytotoxic regimens included paclitaxel and carboplatin [n= 3], ifosfamide and doxorubicin [n= 1], doxorubicin [n= 1], cisplatin and doxorubicin [n= 1], and other doxorubicin-based regimens [n= 4]. Performance status of the patients was as follows: 0 (n= 15), 1 (n= 16), and 2 (n= 11). The predominant sites of measurable disease in 24 (57%) patients were pelvic and extrapelvic, in 15 (36%) patients were pelvic disease and 3 (7%) patients had only extrapelvic disease. Most frequent metastatic sites were peritoneum, lung and liver. Median period of time from the diagnosis to starting IMA regimen was 6.0 months (range, 1-131). A total of 162 cycles of chemotherapy were introduced and for each patient median number of chemotherapy cycles were 4 (range, 1 to 6 cycles). We observed CR in 3 (8.1%) patients; PR in 14 (37.8) patients. Objective RR was 46% (95% CI, 30% to 62%). In addition, 10 (27.0%) patients had stable disease and 10 (27.0%) patients progressive disease. Of 20 pts with LMS, 3 CR and 6 PRs were observed. The median progression-free survival time of the responders was 8.0 months (range, 4-35). The median progression-free survival time of all patients was 5.0 months. Febrile neutropenia was encountered in 6 patients. Dose modifications were required in 4 patients due to myelotoxicity. CNS toxicity was observed in three patients.

There were no treatment-related deaths. The details of adverse effects and treatment characteristics are illustrated in Table 2. As Table 3 illustrates treatment responses according to histological subtypes,

Table 3. Treatment outcome based on radiographic and clinical assessments according to histological subtype

	Best response during treatment				
	CR	PR	SD	PD	NA
Leiomyosarcoma (n=20)	3	6	6	3	2
MMMT (n=6)	-	3	2	1	-
ESS (n=6)	-	2	-	2	2
Carcinosarcoma (n=5)	-	-	2	2	1
Adenosarcoma (n=4)	-	3	-	1	-
HGUS (n=1)	-	-	-	1	-
Total (n=42)	3	14	10	10	5

MMMT; Malignant mixed mesodermal tumor, ESS; Endometrial stromal sarcoma, HGUS; High-grade undifferentiated sarcoma, NA; not assessable, CR; complete response, PR; partial response, SD; stable disease, PD; progressive disease.

3 (8.1%) patients attained a complete response and 14 (37.8%) patients achieved a partial response, for an overall response rate of 46%.

DISCUSSION

The standard treatment for metastatic and or recurrent uterine sarcoma is chemotherapy and/or surgery. Chemotherapy seems to have a limited impact on the clinical outcome. The poor effect of chemotherapy represents an insidious problem for patients with metastatic or unresectable disease and, indeed, new therapeutic approaches are clearly required to improve survival of these patients (1).

The Gynecologic Oncology Group (GOG) has actively pursued through a series of phase II and III studies dating to the early 1980s (2). Omura et al. studied doxorubicin with or without dacarbazine in women with advanced or metastatic uterine sarcomas and reported response rates of 30% and 25%, respectively, among women with leiomyosarcomas (3). The activity of doxorubicin was confirmed in a subsequent phase III study by the GOG. Muss et al. reported doxorubicin alone or in combination with cyclophosphamide administered to patients with advanced uterine sarcomas (4). Twenty-three patients with leiomyosarcomas were evaluable for response and three partial responses (response rate 13%) were observed (5,6). In a phase II study of ifosfamide, 17.2% patients responded (7). In a subsequent study, ifosfamide and doxorubicin were combined to yield a 30.3% response rate (8). Paclitaxel produced a response rate of 12% in another GOG trial (9). Gemcitabine has been one of the few agents with activity in these tumors with an observed response rate of 20.5% (10). Hensley et al. combined gemcitabine with docetaxel and reported a response rate of 53% in 34 patients, some of whom had failed doxorubicin therapy (11). Other agents that have been studied, including mitoxantrone, diaziquone, aminothiadiazole, and cisplatin, have yielded disappointing results with response rates less than 5% (12-15). The only other agent with potential for activity in the treatment of patients with uterine LMS was etoposide, with a response rate of 11% (16). In the present trial, the response rate for ifosfamide and doxorubicin was 46%.

Estimates of outcomes among women with leiomyosarcomas of the uterus vary widely. Five-year survival rates range from 25 to 75%. The reported risk of recurrence varies from 45 to 73%, and the

proportion of these recurrences that occur in the pelvis ranges from 14 to 64%. Tumor grade and stage (using modified criteria for endometrial cancer) appear to be valid prognostic indicators for LMS of the uterus (17).

In our study, the results were satisfactory in patients with leiomyosarcoma histology. Overall, the response rate was 50% with three complete and six partial responses. The median progression-free interval and survival were 11 months and 29 months, respectively. We did not observe any responses among the patients with carcinosarcomas histology. We observed three and two partial responses in patients with MMMT and ESS, respectively. Furthermore, this regimen was associated with mild toxicity (including CNS toxicity and neutropenic fever). Although our study contains a limited number of patients with a variety of gynecological sarcomas, our review has led us to continue using IMA in patients with leiomyosarcomas histology. Future studies should account for differences in natural history and clinical response of different histologic subtypes of malignant uterine sarcoma either by histological stratification or by designing studies targeted to specific histologies.

Uterine sarcomas are a heterogeneous group of tumors with a propensity for metastasis and resistance to conventional therapy. Recent success in the treatment of other solid tumors with the targeted therapies offers new avenues for investigation. Adams et al. studied expression of c-kit, PDGFR-á, and PDGFR-â in these tumors as a preliminary step to determining their susceptibility to targeted therapy. However, c-kit and PDGFR-â are unlikely to represent primary treatment targets in uterine sarcomas. The strong expression of PDGFR-á in uterine sarcoma specimens suggests a role for this receptor in tumor development, although its potential as a therapeutic target requires further investigation (18).

Raspollini et al. analyzed another potential target; HER-2/neu overexpression in 28 uterine carcinosarcomas. They observed HER-2/neu overexpression in nine cases (32.1%). Hence, the results of this analysis may support the challenge of a new therapeutic approach, which could test the role of anti-HER-2 (trastuzumab) in patients with advanced or metastatic uterine carcinosarcoma (19). Livasy et al. evaluated for HER2 and EGFR expression in cases of endometrial carcinosarcoma. EGFR expression was identified in the majority of tumors (45/55, 82%). HER2 overexpression (3+) was seen in 14/55 (25%) cases and HER2 gene amplification was seen in 11 (20%) cases. EGFR and HER2 appear to play a role in the carcinogenesis of endometrial carcinosarcomas. The carcinomatous and sarcomatous elements of these tumors showed consistent differences in HER2 and EGFR expression patterns supporting biologic differences between these components. Studies evaluating the clinical utility of HER2 or EGFR targeted therapy in these tumors appear warranted (20).

Since chemotherapy for metastatic or recurrent uterine sarcoma is still essentially a palliative treatment for the majority of cases, quality of life measurement besides response and survival is an important end point. Given the respectable response rate and safe toxicity profile, IMA combination chemotherapy should be tested in a randomized setting especially in patients with leiomyosarcoma histology.

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