The treatment of uterine leiomyosarcoma: Clinical outcomes of 18 cases and the effectiveness of chemotherapy

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Summary

Purpose: To investigate clinical outcomes with respect to the effectiveness of chemotherapy in the treatment of uterine leiomyosarcoma. *Methods:* Study subjects were 18 patients with uterine leiomyosarcoma treated surgically at our hospital between February 1986 and December 2007. A chemotherapy regimen that combined ifosfamide, epirubicine, and cisplatin (IEP) was used as the main first-line chemotherapy. *Results:* FIGO disease stages were as follows: Stage I (n = 11), Stage II (n = 1), Stage III (n = 3), Stage IV (n = 3). Five-year overall survival of patients with Stage I-III disease was 65.3% (95% CI: 46.1-92.4%). None of patients with Stage IV disease survived for more than two years. Of seven patients who suffered advanced or recurrent disease, six received IEP; the response rate was 50%, one complete response and two partial responses. *Conclusions:* The combination of surgery and chemotherapy seems to be an acceptable treatment for uterine leiomyosarcoma. IEP may be an active regimen for this aggressive disease.

Key words: Uterine leiomyosarcoma; Chemotherapy; Surgery; Survival; Response rate.

Introduction

Uterine leiomyosarcoma (LMS) is a rare, aggressive and high-risk gynecological malignancy. Most cases of early-stage LMS are diagnosed by pathologic assessment of surgical specimens [1]. Distant metastasis is characteristic of the disease, even if total surgical resection is achieved. The treatment of choice for LMS is complete resection, but treatment of advanced-stage disease or recurrence is often difficult. Gadducci *et al*. reported that tumor stage is the strongest prognostic variable and that treatment of patients with advanced or recurrent LMS becomes mainly palliative [2].

Treatment of LMS remains controversial, particularly with respect to adjuvant therapy. Some studies have shown that adjuvant chemotherapy added to surgery is useful for LMS. Hensley *et al*. reported that gemcitabine plus docetaxel for unresectable LMS yielded a response rate of 53% [3] and that gemcitabine plus docetaxel was effective as adjuvant chemotherapy following complete resection of LMS [4]. On the contrary, Omura *et al*. reported no benefit from adriamycin as adjuvant therapy for LMS in a randomized clinical trial [5].

Our strategy for treatment of uterine LMS is a combination of surgery and chemotherapy. Patients with advanced-stage disease frequently undergo preoperative chemotherapy for reduction of tumor volume. We investigated clinical outcomes among patients who were treated for LMS at our hospital between February 1986 and December 2007. We looked particularly at the effectiveness of chemotherapy for this aggressive disease.

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Materials and Methods

Between February 1986 and December 2007, 18 patients with uterine LMS were treated at our Cancer Institute Hospital (Tokyo, Japan). None of the 18 patients underwent radiotherapy as initial treatment. Follow-up ranged from 3.2 to 102 months. Under approval from our hospital ethics committee, the medical records of all 18 patients were obtained and reviewed. Staging was according to the modified International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer. Treatment outcomes were investigated. Overall survival curves were drawn per clinical stage according to the Kaplan-Meier method.

During the study period, ifosfamide, epirubicine and cisplatin (IEP) were used in combination as the main first-line chemotherapy for uterine sarcomas. The method has been described elsewhere [6]. Briefly, ifosfamide is administered intravenously at 1 g/body on days 1-4, epirubicin at 50 mg/m^2 on day 5, and cisplatin at 15 mg/m^2 on days 1-5. This cycle is repeated every four weeks. In a small proportion of patients, ifosfamide and cisplatin (IP) were used together without epirubicin (n = 1), or adriamycin at 60 mg/m^2 and cisplatin at 50 mg/m^2 (AP) were both used on day 1 (n = 1).

For patients who underwent chemotherapy, response rates, progression-free survival and overall survival were determined. Response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST). Disappearance of all target and non-target lesions and no evidence of a new lesion was classified as complete response (CR). A ≥ 30% decrease in measurable lesions was classified as partial response (PR). A > 20% increase in measurable lesions was classified as progressive disease (PD), and any situation that did not qualify as response or progression was classified as stable disease (SD).

Results

Patient characteristics are listed in Table 1. Median age of the patients was 55 years (range, 35-77 years). The most common symptom was vaginal bleeding. Fourteen

Table 1. — *Patient characteristics (n = 18).*

Characteristic	
Median age (range)	55 (35-77) years
FIGO stage	
I	11
II	1
III	3 (IIIa,1; IIIb,1; IIIc,1)
IV	3
Symptom	
Vaginal bleeding	8
Palpable mass	4
Abdominal pain	3
Tumor size	
< 5 cm	4
≧ 5 cm	14

Number of patients is shown unless otherwise indicated.
FIGO: International Federation of Gynecology and Obstetrics.

Table 2. — *Initial treatment per FIGO disease stage (n = 18).*

Treatment	Stage I (n = 11)	Stage II (n = 1)	Stage III (n = 3)	Stage IV (n = 3
Surgery				
TAH+BSO (or USO)	7	1	1	2
TAH+BSO+LDN	4	–	1	–
TAH+BSO+LDN+LAR	–	–	1	–
Chemotherapy	2	1	3	3
Preoperative	–	–	1	3
Postoperative	2	1	2	–

FIGO: International Federation of Gynecology and Obstetrics; BSO: bilateral salpingo-oophorectomy, USO: unilateral salpingo-oophorectomy; TAH: total abdominal hysterectomy; LDN: lympadenectomy; LAR: low anterior resection.

Table 3. — *Adjuvant chemotherapy of patients with Stage I-III disease§.*

Patient	Stage	Adjuvant chemotherapy	Courses	Recurrence-free survival (months)	Site of recurrence	Overall survival (months)	Outcome
1	I	IEP	3	–	–	56.4	NED
2	I	IEP	6	27	Pelvic mass	46.7	DOD
3	II	IEP	5	–	–	74.1	NED
4	IIIa	AP	3	26	Lung	50.6	DOD
5	IIIc	IEP	4	–	–	61.6	NED

§Five out of 15 patients with Stage I-III disease were treated with adjuvant chemotherapy. IEP: ifosfamide, epirubicine, cisplatin; AP: adriamycin, cisplatin; NED: no evidence of disease; DOD, died of disease.

patients had a tumor larger than 5 cm. FIGO stages were as follows: Stage I (n = 11), Stage II (n = 1), Stage III, (n = 3) and Stage IV (n = 3). All 15 patients with Stage I-III disease underwent total resection, and 5 of these patients received adjuvant chemotherapy. Details of initial treatment are listed in Table 2. Pelvic lymphadenectomy was performed in two patients, and pelvic and paraaortic lymphadenectomy was performed in four patients. Lymph node metastasis was found in one of these six patients.

Adjuvant chemotherapy was used in five patients with Stage I-III disease: IEP in four patients and AP in one patient (Table 3). Two of these five patients had recurrences. Median progression-free survival in patients who received adjuvant chemotherapy was 56.3 months. Of the ten patients with Stage I-III disease who did not undergo adjuvant chemotherapy, two had a recurrence. Overall, of

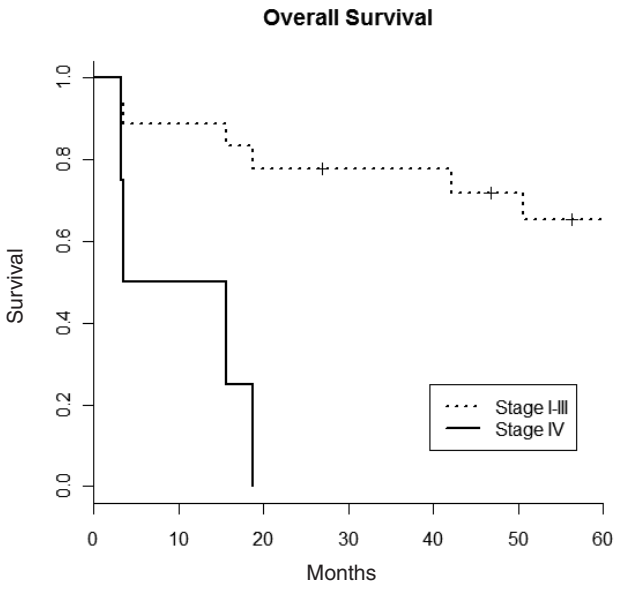

Figure 1. — Overall survival of patients with Stage I-III disease and patients with Stage IV disease.

the 15 patients with Stage I-III disease, four had recurrences during the follow-up period. One patient with Stage IIIc disease who showed lymph node metastasis has remained well for 70 months with no evidence of recurrence. Five-year overall survival of patients with Stage I-III disease was 65.3% (95% CI: 46.1-92.4%). None of patients with Stage IV disease survived more than two years (Figure 1). Among patients with Stage I-III disease, there was no significant difference in overall survival between those who received adjuvant chemotherapy (n = 5) and those who did not (n = 10) (5-year overall survival; 67.4% and 66.6%, respectively, $p = 0.712$).

Treatment and outcome of the seven patients with advanced or recurrent disease are summarized in Table 4. Six of these patients received IEP, and one received IP. Responses to chemotherapy among these patients were CR (n = 1), PR (n = 2), SD (n = 2) and PD (n = 2). The rate of response to IEP was 50%. Two patients with Stage IV disease received preoperative IEP and abdominal total hysterectomy. PR was achieved in one of these patients, and SD was achieved in the other. Median progression-free survival and overall survival in the seven patients were 15.0, and 18.7 months, respectively.

Discussion

There is little doubt that primary surgical resection is the best first-line therapy in patients with uterine LMS. In a study of 1,396 patients, Kapp *et al*. found that oophrectomy and lymphadenectomy had no independent effect on survival [7]. Thus, for premenopausal women with early-stage uterine LMS, total abdominal hysterectomy is usually recommended. Of our study patients, however, six underwent lymphadenectomy, and only one showed

Table 4. — *Treatment and outcome of patients with advanced or recurrent disease (n = 7).*

Patient	Stage	Initial treatment	Site of metastasis	CT (months)	Courses	Response	Progression-free survival (months)	Overall survival (months)	Outcome
1	Rec. I	Surgery	Liver	IEP	3	PD	16	67.4	DOD
2	Rec. I	Surgery+CT	Pelvic mass	IEP	7	PR	27	46.7	DOD
3	Rec. IIIa	Surgery+CT	Lung	IEP	6	SD	15	50.6	DOD
4	Rec. IIIb	CT+Surgery	Vagina	IEP	3	CR	15.5	15.5	DOC
5	IV	CT+Surgery	Lung	IEP	3	PR	2	4.5	DOD
6	IV	CT+Surgery	Liver/Muscle	IEP	4	SD	12	18.7	DOD
7	IV	CT	Lung/Vagina	IP	1	PD	3	3.2	DOD

Rec: Recurrent disease, CT:Chemotherapy, DOD: Died of disease, DOC: Died of other cause. PD: progressive disease, PR: partial response, SD: stable disease, CR: complete response.

Table 5. — *Reported responses to chemotherapy regimens for advanced-stage or recurrent uterine leiomyosarcoma.*

First author (year)	Chemotherapy regimen	Number of patients	Respone rate	PFS (months) treated	OS (months)
Omura G.A. [14] (1983)	Doxorubicine 60 mg/m^2, day1 every 3 weeks	28	25%	10.8	12.1
Slayton RE [15] (1987)	Etoposide 100 mg/m^2, days 1-3 every 4 weeks	28	11%	–	–
Sutton G. [16] (1992)	Ifosfamide 1.5 g/m^2, days 1-5 every 4 weeks	35	17.2%	–	–
Sutton G. [11] (1996)	Doxorubicine 50 mg/m^2, day1 Ifosfamide 5 g/m2/24 hr and mesna, 6 g/m^2/36 hr every 3 weeks	33	30.3%	–	9.6
Currie J.L. [17] (1996)	Hydroxyurea 2 g/body, days 1, 2 Dacarbazine 700 mg/m^2, day 2 Etoposide 300 mg/m^2, days 2-4 every 4 weeks	38	18.4%	–	15.0
Sutton G. [18] (1999)	Paclitaxel 175 mg/m^2, day 1 every 3 weeks	34	9%	10.7	–
Hensley M.L. [13] (2002)	Gemcitabine 900 mg/m^2, days 1,8 Docetaxel 100 mg/m2, day 8 every 3 weeks	34	53%	5.6	17.9
Sutoon G. [19] (2005)	Liposomal doxorubicin 50 mg/m^2, day 1 every 4 weeks	35	14%	–	–
Hensley M.L. [13] (2008)§	Gemcitabine 900 mg/m^2, days 1, 8 Docetaxel 100 mg/m^2, day 8 every 3 weeks	48	27%	5.6	–

§Regimen was used as second-line chemotherapy. PFS: progression-free survival, OS: overall survival.

lymph node metastasis. It is somewhat surprising that recurrence did not develop in the node-positive patient. Perhaps it was because of the adjuvant chemotherapy.

It remains controversial whether adjuvant treatment is of clinical value for uterine LMS. Reed *et al*. [8] reported the results of their phase III randomized trial, concluding that adjuvant pelvic radiation provided no benefit toward overall or disease-free survival of patients with Stage I-II LMS. Pautier *et al*. reported that adjuvant chemotherapy with ifosfamide, doxorubicin and cisplatin followed by radiation is a feasible protocol, resulting in a 3-year disease-free survival rate of 76% in their patients [9]. With respect to adjuvant chemotherapy, Wu *et al*. [10] were the first to report that adjuvant chemotherapy is effective for uterine LMS. However, Giuntoli *et al*.1 reported that adjuvant therapy did not appear to significantly affect survival. Although our study was limited by the small patient group, no significant difference was found in overall survival between those who received adjuvant chemotherapy (n = 5) and those who did not (n = 10). Prospective studies are needed to clarify whether adjuvant chemotherapy is beneficial in patients with LMS.

Chemotherapy regimens have been examined for their effect on advanced or recurrent uterine LMS (Table 5). Ifosfamide combined with doxorubicin was evaluated in a phase II study; the regimen showed promise for patients with recurrent disease, with a response rate of 30.3% [11]. Hirota *et al*. described a case of metastatic LMS (treated 5 times surgically) in which CR was achieved with a combination of ifosfamide, pirarubicin and cisplatin after a cyclophosphamide, pirarubicin and cisplatin combination proved to be ineffective [12]. A novel combination of gemcitabine and docetaxel yielded a 53% response rate among 29 patients with advanced or recurrent disease [3]. A phase II trial of this combination, conducted by the Gynecologic Oncology Group, yielded a response rate of 27%, even when the regimen was used as second-line chemotherapy [13].

In our study group, however, of four patients who received IEP as adjuvant chemotherapy, only one suffered recurrence, and in the treatment of advanced or recurrent uterine LMS, the response to IEP was 50%. These results suggest that IEP is active against LMS and that it a potential candidate for first-line chemotherapy.

In conclusion, our strategy for treatment of uterine LMS, i.e., the combination of surgery and chemotherapy, seems to be effective. IEP may be an active regimen for this aggressive disease. Further studies are needed to confirm the effectiveness of such adjuvant chemotherapy for uterine LMS.

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