Adjuvant chemotherapy following surgery in the management of uterine sarcomas

A. Szánthó, *M.D., Ph.D.*; **J. Bálega,** *M.D.*; **I. Szabó,** *M.D.*; **A. Demeter,** *M.D.*; **N. Sipos,** *M.D.*; **Z. Csapó,** *M.D., Ph.D.*; **Z. Papp,** *M.D., Ph.D., D.Sc.*

Ist Department of Obstetrics and Gynecology, Faculty of Medicine, Semmelweis University, Budapest (Hungary)

Summary

Objective: The aim of this study was to investigate the use of imaging tools in the diagnosis of uterine sarcomas, and to evaluate the effect of the adjuvant chemotherapy for uterine sarcomas.

Patients and Methods: The data of 29 patients with uterine sarcomas who received cytostatic polychemotherapy between 1990 and 2000 at the Oncological Division of the I[st] Department of Obstetrics and Gynecology, Semmelweis University were evaluated by the authors. Symptoms leading to diagnosis and methods of diagnosis were examined. Vascular changes shown by two-dimensional, color and pulsed Doppler ultrasonography were observed. For staging the currently accepted FIGO method was adopted. Most of the patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH & BSO). In each case we administered adjuvant combination chemotherapy according to the CYVADIC-protocol. The effect of adjuvant chemotherapy was evaluated.

Results: Six patients had Stage I, ten had Stage II, 11 had Stage III, and two had Stage IV disease. The mean age of the patients was 53.6 years with a range of 22 to 77 years. Histopathologic distribution included nine leiomyosarcomas (LMS), 13 mixed mesodermal sarcomas (MMS), and seven endometrial stromal sarcomas (ESS). Although most patients experienced neutropenia following cytotoxic chemotherapy, other non-hematologic adverse effects were easy to control. The average progression-free interval was 22.14 months, in which no significant difference was found between the histologic types. Different stages showed highly varied responses; surprisingly, patients in Stage IV with lung metastases were documented to have the longest progression-free survival. The three-year survival rate for all stages was demonstrated in 34.4% of cases. Patients with progressive disease had an average survival period of 4.4 months.

Conclusions: These findings suggest that adjuvant cytostatic therapy for patients with distant metastasis confined to a single organ may produce better results than expected.

Key words: Uterine sarcoma; Cytostatic treatment, CYVADIC.

Introduction

Uterine sarcomas are rare neoplasms, a fortunate circumstance keeping in mind their poor prognosis. The annual incidence of sarcomas ranges between 0.5 and 3.3 cases per 100,000 women. They constitute approximately 1% of all gynecological cancer and comprise about 3-5% of malignant tumors of the uterus [1-3]. This variance is due to imprecise histopathological reports on tumors excised as benign fibroids and then, much later, diagnosed correctly as malignant. Uterine sarcomas arise primarily from two tissue types: endometrial sarcomas from the endometrial glandulae and stroma and leiomyosarcomas from the myometrium itself.

Surgery, i.e., total abdominal hysterectomy and salpingo-oophorectomy (TAH & BSO), which is the mainstay of the therapy, has not proved to be effective enough; and several authors have claimed that there is no proven benefit to postoperative radiotherapy either [4-7]. There is evidence that cytostatic chemotherapy provides an increased survival benefit to patients [8-15], so we started to treat our sarcoma patients with adjuvant cytostatic polychemotherapy following surgery. The aim of this study was to retrospectively evaluate the results of the management of patients with uterine sarcoma at our department.

Patients and Methods

From 1990 through 2000 a total of 29 patients with uterine sarcoma underwent adjuvant cytostatic polychemotherapy following surgery at the I[st] Department of Obstetrics and Gynecology, Semmelweis University, Budapest. Diagnosis was confirmed preoperatively by D & C in nine patients, and postoperatively by TAH & BSO in 17 patients. Of these 26 patients, 23 underwent TAH & BSO and three explorative laparotomy. There were three patients who had previously undergone TAH & BSO at public hospitals with negative histological results. When a recidivistic tumor developed, excision of the tumor was carried out. According to this and the revised former histologic block, it could be assumed that sarcomatous changes might have already taken place at the time of hysterectomy.

Staging for the extent of the disease was retrospectively performed according to the modified FIGO classification for endometrial cancer, but without subdividing Stage I into IA and IB. Preoperative evaluation consisted of physical examination, a complete blood and platelet count, a screening metabolic profile (electrolytes, bilirubin, blood urea nitrogen, creatinine), microscopic urine analysis, two-dimensional and color Doppler ultrasonography, chest X rays, and occasionally computer tomography or magnetic resonance imaging scans.

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All 29 patients received combination cytostatic chemotherapy according to the CYVADIC protocol (500 mg/m^2 cyclophosphamide + 50 mg/m^2 adriamycin on the first day, 1.0 mg/m^2 vincristine on the first and fifth days and 250 mg/m^2 dacarbazin from the first to the fifth day) [13, 14]. The treatment was repeated every 28 days for a total of six cycles. All necessary information was given to the patients regarding the expected use and possible adverse effects of the cytostatic treatment. Eligibility criteria included values between 50 and 100 on the Karnofsky scale for overall physical condition and adequate hematological levels (white blood count = 4,000; platelet count = 200,000), hepatic, and renal function tests.

Responses were assessed by clinical examinations and imaging technologies (color Doppler ultrasonography, chest radiograph and computed tomography) after the third and last cycles.

Results

The average age of the study population was 53.6 years (range 22 to 77). The mean age of patients with mixed mesodermal tumors was 62.3 years, more than ten years older than that of endometrial stromal sarcoma (45 years) and leiomyosarcoma (49.4 years) patients (Table 1). Mean age was similar for all four stages (Table 2), as in endometrial carcinoma patients, but differed greatly in cases with cervical cancer, where higher stages were concurrent with a higher median age.

Sixty-five percent of the patients presented with abnormal vaginal bleeding, which occurred similarly in all three histologic subtypes. Abdominal pain occurred in 55% of the cases, and women with leiomyosarcoma often presented with complaints of increasing abdominal girth, a sign of a rapidly growing tumor (Table 1). We found six patients in Stage I, ten in Stage II, 11 in Stage III, and two in Stage IV (Table 2). Both patients in Stage IV had lung metastasis.

We found color Doppler ultrasonography an extremely significant tool, since it often suggested the presence of uterine sarcoma preoperatively. Two-dimensional ultrasonography revealed the following signs typical of tumors: lack of typical morphological signs, disintegration of the myometrial structure, masses with irregular borders in the myometrium producing irregular muscle echoes, and deformed uterine contour and cavity. Pulsed Doppler signals obtained from intratumoral vessels showed nodular or diffuse hypervascularization. Irregular, thin, randomly dispersed vessels could be identified in peripheral and/or central locations. High diastolic flow and low resistance were recorded in these intratumoral vessels (RI < 0.4; PI < 0.8 where RI = resistance index; PI = pulsatility index). There were significant differences between the impedance parameters of the two main uterine arteries, which were characterized by a decrease of vascular impedance (RI < 0.75; PI < 1.6). In low grade endometrial stromal sarcomas degenerative vascular structure and reduced vascular impedance were found.

Combination chemotherapy according to the CYVADIC protocol was administered in an average of six cycles (range 4-12 cycles) and in 158 cycles altogether. Adverse effects of the chemotherapy were graded by the WHO standards. Severe, grade 4 hematologic toxicity was noted in only one patient, while grade 3 was noted in four patients. In these cases granulocyte colony-stimulating factor (G-CSF) prophylaxis was instituted. Neutropenia never reached a stage which caused septic conditions. Seven patients developed anemia severe enough to require blood transfusion. Complete alopecia (grade 4 toxicity) occurred in five patients. Other adverse effects were graded 1 or 2 (Table 3). No deaths ascribable to complications arising from chemotherapy were observed.

The efficiency of therapy was evaluated on the basis of the length of time to progression (TTP). Progression-free periods were evaluated in the different stages and histological types. When examined by different stages, progression-free periods were found to be increasingly shorter in higher stages (Table 2). A surprising exception was Stage IV, where the highest progression-free period was achieved, even though these patients had extrauterine disease. By the time of surgery, both patients had already develo-

Table 1. — *Patient characteristics.*

Histologic distribution	LMS 9 patients	MMS 13 patients	ESS 7 patients	Total 29 patients
Symptoms				
Vaginal bleeding	5/9	8/13	6/7	19/29
Lower abdominal pain	6/9	4/13	5/7	15/29
Enlarged uterus	5/9	3/13	5/7	13/29
Surgery				
TAH & BSO*	8/9	11/13	7/7	26/29
Tumor excision by laparotomy	1/9	2/13	0/7	3/29
Average age	49.3 years	62.3 years	45 years	53.6 years
Time to progression	24.5 months	18.8 months	22.8 months	22.1 mo.

*TAH & BSO: Total abdominal hysterectomy and bilateral salpingo-oophorectomy; LMS = leiomyosarcoma; MMS = mixed mesodermal sarcoma; ESS = endometrial stromal sarcoma.

Table 2. — *Staging for uterine sarcoma.*

	Cases	Average age (yrs)	TTP* (mos)
Stage I			
Sarcoma confined to the corpus	6	45.6	32.3
Stage II			
Sarcoma confined to the corpus and cervix	10	59.0	19.3
Stage III			
Involvement of other pelvic tissues	11	53.7	15.7
Stage IV			
Extrapelvic disease	2	50.3	43.5
Total	29	53.6	22.1

*TTP = time to progression.

Table 3. — *Adverse effects.*

WHO Grade	0	1	2	3	4
Myelosuppression	8	7	9	4	1
Nausea and vomiting	9	10	8	2	0
Cardiac symptoms	16	8	5	0	0
Alopecia	0	2	8	14	5

ped lung metastases. After hysterectomy, metastatic disease had high sensitivity to cytotoxic chemotherapy; in these two cases, the TTP was over 43.5 months. Time to progression was in the case of leiomyosarcoma 24.5 months, followed by endometrial stromal sarcoma (22.8 months) and mixed mesodermal sarcoma (18.8 months) (Table 1). These differences are, however, rather insignificant (p, 0.82; p, 0.59; p, 0.45). Median TTP for all three tissue types and all stages was 22.1 months. The three-year survival rate for all stages was demonstrated in 34.4% of cases. Patients with progressive disease had a median survival of 4.4 months. Twelve of our patients are still alive. Five patients with recurrence were treated with second-line cytostatic therapy using the VIP protocol (vepesid, ifosfamid+mesna and cisplatin), one patient with brain metastasis underwent successful stereotaxical radiotherapy.

Discussion

Mesenchymal tumors of the uterus present a particularly challenging problem for the oncologist. Since these tumors are uncommon, most practicing clinicians do not have extensive experience in their treatment.

Uterine sarcomas tend to occur in postmenopausal women [16]. According to the literature the median age for leiomyosarcoma is around 55 years; for mixed mesodermal sarcoma it is even higher, approximately 65 years [16]. It should be noted that women with MMT tended to be older than those with LMS. In women with MMT, 91% were postmenopausal while only 58% of women diagnosed with LMS were postmenopausal. Ours study confirms the observation published by others, that the mean age is different for the three histologic types. The average age of the study population was 53.6 years (range 22-77). The mean age of patients with mixed mesodermal tumors was 62.3 years, more than ten years higher than that of endometrial stromal sarcoma (45 years) and leiomyosarcoma (49.4 years) (Table 1). Premenopausal patients with leiomyosarcoma have better prognosis than postmenopausal patients [17].

Clinical symptoms are usually the same as symptoms for other uterine tumors; most characteristic of these are metrorrhage or postmenopausal bleeding [1, 3]. Sarcomas are usually accompanied by abdominal complaints. Often the patient herself feels a palpable lower abdominal mass or senses a sudden increase in abdominal girth [18]. In approximately 10% of all cases, urological complaints are the first indicators of the disease [1]. Symptoms depend largely on the place of the tumor; one growing towards the uterine cavity causes bleeding as a primary symptom, while a fast growing stromal sarcoma is accompanied by pain. Similarly to the literature, the leading symptoms of our patients were irregular vaginal bleeding, lower abdominal pain, as well as an enlarged, palpable uterus (Table 1).

Accurate preoperative diagnosis is difficult. In cases of endometrial stromal sarcoma and leiomyosarcoma cytological diagnosis might be helpful [18]. Final diagnosis is often gained by dilatation and curettage (D & C). In a rather high number of cases, only the histologic diagnosis of the surgical sample is definitive. In cases of sarcomas extruding into the peritoneal cavity, uterine curettage will not necessarily detect malignant tissue in the uterus. Sometimes early stage intramural leiomyosarcoma is not diagnosed correctly after hysterectomy, however, later locoregional recurrence proves the malignant nature of the tumor [18]. We also had three patients from other hospitals with recurrence following TAH & BSO with negative histological results, although the revision of the original blocs revealed a sarcomatous lesion in the fibroids. That is why precise histologic analysis of each fibroid-like surgical sample is of extreme importance. Today color Doppler ultrasonography also contributes to the diagnostic procedure [19, 20]. Transvaginal ultrasonography is a non-invasive technique, highly accepted by patients, which affords detailed delineation of the uterus, the myometrium, and the main uterine vessels [21]. Varying in histological origin, different cellular atypia and mitotic rates of uterine sarcomas can all significantly affect the intratumoral vascularity and blood flow characteristics detected by color Doppler [22, 23]. Our results suggest that when using intratumoral RI alone for discrimination an overlap can be found between uterine leiomyomas and uterine sarcomas [22].

Concerning the treatment, hysterectomy with or without radiotherapy may be curative in a number of patients with uterine sarcomas limited to the uterus at the time of diagnosis [24]. Reported 5-year survival rates are typically in the 50% range [5]. Inoperable cases used to be submitted to primary radiation therapy [6], while recently cytostatic chemotherapy has gained ground both in the postoperative period and as a primary treatment in inoperable cases. For the medication of uterine sarcomas, protocols that have been proven efficient in the treatment of other soft tissue sarcomas are generally used. Doxorubicin has been considered the "standard" therapy, although the results with this agent are poor. In a randomized trial by the GOG, single agent doxorubicin was compared to doxorubicin plus cyclophosphamide for women with MMS, LMS or ESS. Both arms of this trial had an overall response rate of 19% [25]. Another "standard" sarcoma drug is dimethyl-triazeno imidazole carboxamide (DTIC). In another randomized GOG trial with similar eligibility criteria, DTIC plus doxorubicin had an overall response rate of 24.2% versus a response rate of 16.3% for doxorubicin alone [26]. Combination chemotherapy in uterine sarcomas has been reported by a number of authors [8, 9]. Yap *et al.* administered the CYVADIC regimen for the treatment of advanced sarcomas [10]. Piver *et al.* reported a 23% response rate with 12% complete responses to a combination of cyclophosphamide, adriamycin, vincristine and dacarbazine (DTIC) [11]. Fukunishi presented that CYVADIC-etoposide chemotherapy was an optional effective treatment for lung metastasis in the uterine myxoid leiomyosarcoma patients [27]. Although we had only two patients with lung metastases, we achieved similarly good results (Table 2).

Piver and co-workers have compared the survival rate of patients who received only surgical treatment with those who received adjuvant chemotherapy. While surgery had a 36% survival rate, adriamycin therapy was associated with a survival rate of 63% and the CYVADIC protocol with an even higher 89% [13]. According to Piver the CYVADIC protocol following surgery seemed to be the most promising combination [14].

According to these results in 1990 we introduced the adjuvant CYVADIC protocol for patients with uterine sarcomas. With controllable adverse effects and a generally good response we were able to achieve an average two-year progression-free survival rate.

Although several authors have questioned the efficiency of adjuvant chemotherapy in early stage [9, 28], we believe that by using cytostatic chemotherapy, the outcome of patients with metastatic uterine sarcoma can be better. Most recently taxans have been supposed to achieve the best results [29]. For reinforcement of the results of our retrospective review, prospective randomized investigations would be necessary.

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Address reprint requests to:
A. SZANTHO, M.D., PH.D.
Ist Dep. of Obstetrics and Gynaecology
Semmelweis University Medical School
Baross UTCA 27
Budapest H 1088 (Hungary)