Adjuvant chemotherapy in early stage uterine sarcomas: An open question

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Summary

Uterine sarcomas are aggressive gynecological cancers even at early stage of disease. The most common histological types are represented by leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma. The mainstay of treatment of stage I-II disease is total hysterectomy with bilateral salpingo-oophorectomy. Adjuvant radiotherapy may decrease local recurrence rates without any significant impact on survival. Adjuvant chemotherapy is a logical approach, since distant recurrences are more frequent than local failures. The chemotherapy regimens commonly used in advanced uterine sarcomas are similar to the ones for advanced soft tissue sarcomas, with anthracyclines and ifosfamide as the most active drugs. However, carcinosarcomas respond better to cisplatin-based regimens. It is advisable to design international cooperative randomized trials with the aim of defining the role of adjuvant chemotherapy in the treatment of early stage uterine sarcomas.

Key words: Uterine sarcoma; Radiotherapy; Chemotherapy; Failure.

Introduction

Uterine sarcomas are rare gynecological tumors, with an annual incidence rate of 1.6-3.3/100,00 women [1, 2]. The most common histological types are represented by leiomyosarcoma, endometrial stromal sarcoma, and mixed mullerian tumors (carcinosarcomas) [2-6]. Endometrial stromal sarcomas include low-grade and high-grade categories, mainly according to the mitotic counts [7-9]. Uterine sarcomas have generally an aggressive clinical behaviour, with a great tendency to local recurrence, and, even more, to distant spread. In a series including 250 patients with recurrent uterine sarcomas of different histological types, the sites of failure were pelvic in 14% of cases, distant in 33%, and both pelvic and distant in 53% [5]. Most distant relapses involve lungs and upper abdomen, while brain metastases are uncommon. Median time to recurrence is less than two years, and such interval is as short as tumor stage is high.

Stage is the most important prognostic factor. As reported by Salazar and Dunne [5] 5-year survival was: for leiomyosarcoma 53% for the 113 stage I patients compared to 8% for the 50 stage II-IV patients; for endometrial stromal sarcoma 55% for the 23 stage I patients compared to 12% for the 42 stage II-IV patients; for carcinosarcoma 50% for the 82 stage I patients and 12% for the 100 stage II-IV patients.

The prognostic value of histologic type has not yet been defined. However most authors failed to detect significant differences in the outcome according to this variable, excluding low-grade endometrial stromal sarcoma which showed and excellent prognosis [1, 4-6, 10-14]. Conversely, Olah *et al.* [15] reported that the prognosis of leiomyosarcoma, when adjusted for stage, age and grade, is poorer than that of carcinosarcoma. All authors agree that low-grade endometrial stromal sarcoma has a quite different biological behaviour characterized by an indolent growth pattern associated with 80-100% 5-year survival, although about 37-60% of patients eventually recur after a very long time [7, 8, 16-18].

Total abdominal hysterectomy and bilateral salpingo-oophorectomy represents the standard treatment [4-6, 9, 10, 12, 16, 18-24]. However the need to remove ovaries in premenopausal patients with leiomyosarcoma is still controversial, since some authors found that ovarian tissue preservation did not change recurrence risk [19, 22, 25, 26]. As far as endometrial stromal sarcoma is concerned, Norris and Taylor [7] reported that the addition of bilateral salpingo-oophorectomy to hysterectomy provided no benefit. Conversely, Berchuck *et al.* [16] observed that recurrent disease was less frequent after removal of both ovaries. Some authors consider bilateral salpingo-oophorectomy as mandatory in low-grade endometrial stromal sarcomas since these tumors often express receptors for estrogens and antiestrogenic treatment may be of some clinical benefit for advanced or recurrent disease [17, 27-31].

Selective pelvic and/or para-aortic lymphadenectomy may be useful for carcinosarcoma which shows a relatively high incidence of lymph node metastases [21, 23, 24, 32], but not for leiomyosarcoma and endometrial stromal sarcoma in which retroperitoneal involvement is rare [22, 24, 26, 32, 33]. Carcinosarcoma requires an aggressive surgical staging, including peritoneal cytology, omentectomy, peritoneal biopsies, and when appropriate tumor debulking [21, 23, 24, 34].

External pelvic irradiation has been widely employed as adjuvant treatment in uterine sarcomas [1, 4-6, 10-12, 16, 18, 20-23, 35-46]. Postoperative irradiation doses between 50 and 60 Gy have been recommended and in selected cases brachytherapy has been performed [36]. According to most authors, adjuvant irradiation may decrease local re-

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currence rates without any significant impact on survival since most patients with relapsed disease have distant failures (Table 1). Some authors reported that carcinosarcoma and endometrial stromal sarcoma are more radiosensitive than leiomyosarcoma [42-44]. It is worth noting that, with regard to early stage carcinosarcoma, Gerszten *et al.* [39] and Manchul *et al.* [45] recently reported that adjuvant radiotherapy improves both local control and overall survival, whereas in the series of Larson *et al.* [46] surgery and intracavitary plus external irradiation gave a lower local failure rate (p = 0.006) and better overall survival (p = 0.001) than surgery in combination with either intracavitary or external irradiation.

A randomized European Organization for Research and Treatment of Cancer (EORTC) study is comparing adjuvant pelvic radiotherapy versus observation only in patients with totally resected stage I-II high-grade uterine sarcoma [47].

Because of the aggressiveness and tendency for early distant spread, uterine sarcoma cannot be considered a local disease even in early stages [10]. Therefore treatment planning should include systemic therapy.

Before assessing the role of adjuvant chemotherapy in uterine sarcomas, it is worthwhile to analyze the clinical trials of adjuvant chemotherapy in soft tissue sarcomas of different sites.

Table 1. — *Effect of adjuvant radiotherapy on local control and survival in uterine sarcoma.*

Author	Decrease in local failure	Improvement in survival
George [1]	yes	no
Salazar [4, 5]	yes	no
Kahanpaa [6]	yes	no
Wheelock [10]	yes	no
Covens [11]	yes	no
Echt [12]	yes	no
Tinkler [20]	no	no
Ali and Wells* [21]	yes	no
Sartori* [23]	yes	no
Chi* [37]	yes	no
Gerszten* [39]	yes	yes
Ferrer [40]	yes	yes
Manchul* [45]	yes	yes

*carcinosarcoma only.

Table 2. — *Randomized trials comparing doxorubicin- and ifosfamide-based regimens versus non-ifosfamide-containing regimens in advanced soft tissue sarcomas.*

Author	Regimens	Patients (n.)	Response rate	Median survival
Antman [56]	DOX 60 mg/m²+ DTIC 1000 mg/m² vs	170	17%	13 months
	DOX 60 mg/m²+ IFO 6-7.5 g/m² + DTIC 1000 mg/m²	170	32% (p=0.005)	12 months (p=ns)
Edmonson [57]	DOX 80 mg/m² vs	90	20%	9 months
	DOX 60 mg/m² + IFO 7.5 g/m² vs	88	34%*	11 months
	MITO 8 mg/m² + DOX 40 mg/m² CDDP 60 mg/m²	84	32%	9 months
	(*versus DOX alone, p = 0.03)			(p=ns)
Santoro [58]	DOX 75 mg/m² vs	263	21.3%	52 weeks
	DOX 50 mg/m² + IFO 5 g/m² vs CTX 500 mg/m² +	258	25.2%	55 weeks
	VCR 1.5 mg/m² + DOX 50 mg/m² + DTIC 750 mg/m²	142	26.8% (p=ns)	51 weeks (p=ns)

Chemotherapy in soft tissue sarcomas

The two most active drugs are doxorubicin and ifosfamide, which demonstrated a dose-response relationship with response rates between 20% and 35% when doxorubicin is used at >75 mg/m² and ifosfamide is used at >10 g/m² [48-51]. Ifosfamide appears to be more active when given as a 2- to 3-hour infusion compared with a 24-hour infusion [49, 50, 52].

The combination of doxorubicin plus ifosfamide plus dacarbazine has been found to obtain a 25-52% response rate in patients with advanced or recurrent soft tissue sarcomas [53-55]. However, this regimen often causes febrile neutropenia and nonhematologic toxicities that may require a dose reduction [51]. Many of these side-effects are probably due to dacarbazine, which is the least active drug in the three-agent regimen.

Three large randomized trials failed to show a survival advantage for the combination doxorubicin plus ifosfamide, with or without dacarbazine, versus non-ifosfamide-containing regimens [56-58]. The lack of survival improvement with ifosfamide plus doxorubicin could be due to the relatively low doses of these two drugs, or, alternatively, to the inclusion of gastrointestinal sarcomas which are known to be resistant to chemotherapy.

By giving 75-90 mg/m²/cycle of doxorubicin as a continuous 24-48-hour infusion (to minimize cardiotoxicity) plus 10 g/m²/cycle of ifosfamide by a bolus schedule, Patel [51] obtained a 65% response rate in 79 patients with soft tissue sarcomas. Therefore the combination of an anthracycline plus ifosfamide at appropriate doses and schedules is the most active systemic therapy for these malignancies. However a study of the Italian Group on Rare Tumors did not support an increasing dose of continuous infusion ifosfamide over 9 g/m²/cycle with bolus epidoxorubicin 120 mg/m² in two daily doses [59].

Recently Papai *et al.* [60] reported a 46% objective response rate (with a complete response in 10% of cases), with moderate toxicity, in a series of 104 patients with inoperable, metastatic or locally recurrent soft tissue sarcomas treated with etoposide (100 mg/m² for 5 days) plus ifosfamide (2 g/m² for 2 days) plus cisplatin (20 mg/m² for 5 days). This new combination seems to be promising.

Paclitaxel 250 mg/m² 3-hour infusion obtained a partial response in 7% of 28 patients with advanced soft tisse sarcoma [61]. This drug seems to have substantial activity against angiosarcoma of the scalp or face [62]. The regi-

men of doxorubicin (50 mg/m^2) plus paclitaxel (150 mg/m^2 24-hour infusion) showed no more activity than single agent-doxorubicin in advanced sarcoma [63]. Docetaxel is inactive in these malignancies [64, 65].

Adjuvant chemotherapy is considered useful for rhabdomyosarcomas, osteosarcomas, and Ewing's sarcomas, but remains controversial for other adult sarcomas [66]. Only two of the 14 randomized trials of adjuvant chemotherapy in soft tissue sarcomas reported a significant improvement in overall survival in favor of the chemotherapy arm. However, many of these trials show trends towards improvement in disease-free survival and overall survival in favor of chemotherapy without reaching a statistical significance, mainly because of the limited number of patients, suboptimal chemotherapy regimens used, and a mixture of low- and high-risk disease [67]. A recent meta-analysis by the Cochrane group assessed 14 trials of doxorubicin-based adjuvant chemotherapy including 1,568 adults with localised resectable soft tissue sarcoma [68]. The hazard ratio with chemotherapy was 0.73 (95% CI, 0.56-0.94) for local recurrence-free interval, 0.70 (95% CI, 0.57-0.85) for distant recurrence-free interval, and 0.75 (CI 95%, 0.64-0.87) for overall recurrence-free survival. These results correspond to an absolute benefit of 6-10% at ten years. For overall survival the hazard ratio with chemotherapy was 0.89 (95% CI, 0.76-1.03), which was not significant but potentially represents an absolute benefit of 4% at ten years. The strongest evidence of a beneficial effect on survival was seen in patients with sarcomas of the extremities. These positive results reflect the efficacy of the chemotherapy regiomens employed in the 1970s and 1980s [69]. The study of contemporary adjuvant chemotherapy of the Italian Cooperative Group showed a statistically significant advantage in both disease-free survival and overall survival for patients treated with adjuvant chemotherapy [70]. This study was a prospective randomized trial of five cycles of adjuvant epidoxorubicin (60 mg/m^2 for 2 days) plus ifosfamide (1.8 g/m^2 for 5 days) versus observation in 104 patients with high-grade, primary or locally recurrent soft tissue sarcomas of the extremities. After a median follow-up of 36 months there was a significant improvement in local control (p = 0.05), disease-free survival (p = 0.02), and overall survival (p = 0.01) in favor of the chemotherapy arm.

Chemotherapy in uterine sarcomas

Antiproliferative agents most commonly used in uterine sarcomas are the same delivered in adult soft tissue sarcomas. In a randomized study of the Gynecologic Oncology Group (GOG) on 146 advanced uterine sarcomas, response rates were 16.3% in patients treated with doxorubicin compared to 24.2% (p = NS) in those treated with doxorubicin + dacarbazine [71]. In detail, single agent-doxorubicin achieved an objective response in 25.0% of patients with leiomyosarcoma compared to 9.8% of those with carcinosarcoma. Response rates to the combination regimen for these two histotypes were 30.0% e 22.6%, respectively.

In phase II studies on the activity of ifosfamide in gynecological cancer, the GOG found that this agent (1.5 g/m^2 daily for 5 days) obtained an objective response in 17.2% of 35 patients with leiomyosarcoma [72], 33.3% of 21 patients with endometrial stromal sarcoma [73], and in 32.2% of 28 patients with carcinosarcoma [74]. Sutton *et al.* [75] reported that the combination of doxorubicin (50 mg/m^2) plus ifosfamide (5 g/m^2/24-hour continuous infusion) achieved a 30.3% response rate in 33 patients with leiomyosarcoma.

In a multicenter study using doxorubicin (30 mg/m^2 for 3 days) plus ifosfamide (10 g/m^2 continuous infusion for 5 days), Leyvraz *et al.* [76] reported a 55% response rate among 31 evaluable patients with advanced sarcomas of different sites. Response rates were similar in gynecological sarcomas and soft tissue sarcomas of other sites.

Cisplatin has a good activity in carcinosarcoma but not in leiomyosarcoma. As second-line treatment, this drug (50 mg/m^2) achieved an objective response in 17.9% of 28 patients with carcinosarcomas [77] and 5.3% of 19 with leiomyosarcoma [78]. In a first-line treatment study cisplatin (50 mg/m^2) obtained an objective response in 19.0% of 63 patients with carcinosarcoma and in 3.0% of 33 patients with leiomyosarcoma [79].

Combination regimens with cisplatin plus doxorubicin achieved a response rate of approximately 60-70% (range = 33.3-85%) among patients with advanced carcinosarcomas (23,80-85). For instance in the CTF experience, a clinical response was obtained in 64.7% of the 17 patients treated with a cisplatin-containing regimen and in 30.0% of the 20 patients who received doxorubicin-containing regimens (without cisplatin), whereas survival curves were overlapping in the two groups [23]. The GOG is comparing chemotherapy with ifosfamide and cisplatin versus whole abdominal radiotherapy in patients with optimally debulked stage I, II, III or IV carcinosarcoma of the uterus [86].

Very few data are currently available about the activity of paclitaxel in uterine sarcomas [87, 88]. In the GOG experience first-line paclitaxel (175 mg/m^2 3-hour infusion) obtained an objective response and a stabilization of disease in 9.1% and 24.2%, respectively, of 33 patients with advanced or recurrent uterine leiomyosarcoma [87]. The GOG is carrying out a phase III randomized study of ifosfamide with or without paclitaxel in patients with advanced, refractory or recurrent carcinosarcoma of the uterus [89].

There are very few clinical studies on adjuvant chemotherapy in uterine sarcomas. Some nonrandomized studies on small series seemed to show that adjuvant chemotherapy with the combination of vincristine plus actinomycin-D plus cyclophosphamide (VAC regimen) improved the outcome of patients with early stage uterine sarcomas of different histological types [90-92]. Buchsbaum *et al.* [90] reported that the addition of adjuvant VAC after total abdominal hysterectomy and bilateral salpingo-oophorectomy improved the 5-year survival rate of patients with stage I-II uterine sarcomas from 7% to 63%. Marchese *et al.* [91] found that adjuvant VAC produced an increase in the 5-year survival rate from 15% to 61%. In the analysis of van Nagell *et al.* [92] on patients with

stage I sarcoma having ten or more mitoses per 10 HPF, the recurrence rate after adjuvant VAC was significantly reduced when compared to that of similar patients treated by surgery alone or surgery plus pelvic irradiation [28% versus 78%, $p < 0.02$). Similarly Wong *et al.* [93] reported that adjuvant combination chemotherapy with vincristine (1 mg/m^2 days 1 and 4) plus doxorubicin (40 mg/m^2 day 2) plus cyclophosphamide (400 mg/m^2 day 2) plus dacarbazine (200 mg/m^2 days 1-4) was associated with a 5-year disease-free survival of 80.3% and a 5-year overall survival of 84.1% in 28 patients with stage I uterine sarcoma.

Conversely in other studies adjuvant chemotherapy with VAC or single agent doxorubicin or doxorubicin-based regimens failed to impact on survival [94-97]. In detail, a randomized trial conducted by the GOG on 156 stage I-II uterine sarcoma patients after surgery with or without radiotherapy did not show any significant difference in disease-free survival and overall survival between the patients who received doxorubicin 60 mg/m^2 every three weeks for eight cycles and those who did not [96].

Peters *et al.* [83] delivered adjuvant chemotherapy with cisplatin (100 mg/m^2) plus doxorubicin (45-60 mg/m^2) to 17 patients with endometrial stromal sarcoma or carcinosarcoma. After a median follow-up of 34 months, only four (23.5%) patients developed a recurrence and actuarial 5-year survival was 75%. Resnik *et al.* [98] gave combination chemotherapy with cisplatin (50 mg/m^2 day 1) plus doxorubicin (50 mg/m^2 day 1) plus etoposide (100 mg/m^2 days 1-2) to 23 patients with stage I-II carcinosarcoma, and found that the 2-year survival rate was 92%.

The GOG has carried out a clinical study to assess adjuvant chemotherapy with cisplatin (20 mg/m^2 for 5 days) and ifosfamide (1.5 g/m^2 for 5 days), repeated every 3 weeks for 3 cycles, in stage I-II uterine carcinosarcoma [99]. After a minimum follow-up of two years, 63.1% and 73.8% of 65 evaluable patients were progression-free and alive, respectively.

Kushner *et al.* [100] delivered three cycles of adjuvant ifosfamide (1.5 g/m^2 for 3 days, repeated every 4 weeks) to 13 consecutive patients with completely resected, moderate- to high-grade uterine sarcoma. For the ten early stage patients, the 2-year progression-free survival was 60% and the 2-year overall survival was 100%, dropping to 67% at three years. Early stage patients with carcinosarcoma had a significantly longer time to progression than those with leiomyosarcoma (2-year progression-free survival of 100% versus 33%, $p = 0.019$).

Conclusion

The mainstay of treatment of early stage uterine sarcoma is surgery. Adjuvant pelvic irradiation reduces the risk of local recurrence, but it does not seem to significantly impact on overall survival. International cooperative randomized clinical trials are warranted to investigate the role of adjuvant chemotherapy. A combination chemotherapy with adequate doses of anthracyclines plus ifosfamide could represent a rational adjuvant treatment for leiomyosarcoma and high-grade endometrial stromal sarcoma, whereas adjuvant cisplatin-based regimens could be of benefit for carcinosarcoma.

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