Original article

IMPACT OF CHEMOTHERAPY IN UTERINE SARCOMA (UtS): REVIEW OF 13 CLINICAL TRIALS FROM the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) INVOLVING ADVANCED/metastatic UtS COMPARED TO OTHER SOFT TISSUE SARCOMA (STS) patients treated with first line chemotherapy.

I Ray-Coquard[1], E Rizzo[2], JY Blay[1], P Casali[3], I Judson[4], A Krarup Hansen[5], LH Lindner[6], AP dei Tos[7], H Gelderblom[8], S Marreaud[2], S Litière[2], P Rutkowski[9], P Hohenberger[10], A Gronchi[3], W.T. van der Graaf[11].

[1] Département de Cancérologie médicale, Centre Léon Bérard, Lyon, France
[2] European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium
[3] Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy
[4] Royal Marsden Hospital, Chelsea, London, UK
[5] Herlev Hospital, Copenhagen University, Herlev, Denmark
[6] Klinikum der Universitaet Muenchen, Campus Grosshadern, Muenchen, Germany
[7] Ospedale Regionale "Ca' Foncello", Treviso, Italy
[8] Leiden University Medical Centre, Leiden, the Netherlands
[9] Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, Poland
[10] Mannheim University Medical Center, Mannheim, Germany
[11] The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, London, UK.

Corresponding author:
Dr Isabelle Ray-Coquard
Medical oncology department
Centre Léon Bérard
28, rue Laennec, 69373 – Lyon CEDEX 08- France
Phone : +33 (0)4 78 78 28 88
Fax : +33 (0)4 78 78 27 16
Email : isabelle.ray-coquard@lyon.unicancer.fr

Abstract

Objective: UtS are a group of uncommon tumors representing 1% of malignant neoplasms of the female genital tract, and 7% of sarcomas. The objective of this study was to evaluate the factors associated with the clinical behavior UtS.

Methods: Information on 269 patients with advanced or metastatic first line UtS treated by chemotherapy was available in a database containing information on 3270 patients with advanced soft tissue sarcomas (STS) entered in EORTC-STBSG clinical trials between 1977 and 2010. The chemotherapy was aggregated in 4 categories: anthracyclines alone, ifosfamide alone, the combination of doxorubicin and ifosfamide, and CYVADIC.

Results: Among the 269 UtS pts, there were 231 deaths (median OS 10.4 months, 95% CI: 9.1-11.9) and 257 progressions and/or deaths (median PFS 4.1 months, 95% CI: 3.5-4.9). Multivariate analyses reported PS ($p < 0.001$) only to be a statistically significant prognostic factor for OS in UtS; for PFS, LMS histology ($p = 0.025$) is associated with a better outcome. There was no relationship between the 4 groups of chemotherapy regimens and impact on clinical outcomes. Histological subtype was significantly correlated with response to chemotherapy (RR: LMS 19% vs other 33%, $p = 0.026$). Ifosfamide single agent yielded only 5% of RR.

Conclusions: Clearly, UtS are very aggressive neoplasms with poor outcome when treated with chemotherapy consisting of anthracyclines with or without ifosfamide or cyclophosphamide. New strategies are urgently needed.

Key words: sarcoma, uterine, treatment, chemotherapy.

INTRODUCTION

Soft tissue sarcomas (STS) are rare tumors, and globally account for less than 1% of all malignancies. Uterine sarcomas (UtS) are rare malignancies representing approximately 8–10% of all uterine malignancies (1;2). Compared with the more common uterine carcinomas, UtS are more aggressive and have typically a worse prognosis. Their histopathological classification was revised by the World Health Organization (WHO) in 2003 including leiomyosarcomas (LMS) (70%), low grade endometrial stromal sarcomas (20%) and undifferentiated or poorly differentiated endometrial sarcomas (6%). More unusual UtS subtypes, such as liposarcoma, rhabdomyosarcoma, angiosarcoma, PEComa, representing all together less than 5% of all UtS, have also been reported (1).

Because of their rarity and heterogeneity, no consensus has yet emerged on prognostic factors for clinical outcome and treatment strategy. There are actually several papers attempting to address prognostic factors in uterine sarcoma subtypes more specifically for LMS at initial diagnosis (2). In metastatic phase, systemic treatment is the recommended approach for the majority of patients (3). However, as for other STS, patients with metastatic disease should be evaluated to determine whether resection of metastases may be appropriate (4).

Systemic treatment options for advanced or metastatic disease have most frequently been evaluated in phase II trials dedicated to UtS, or retrospective series (5). For monotherapeutic regimens such as doxorubicin, gemcitabine, ifosfamide, or trabectedin, a response rate lower than 25% was observed (6). Response rates are slightly better (25 to 50%) for combinations such as doxorubicin plus ifosfamide, gemcitabine plus docetaxel, gemcitabine plus dacarbazine, and more recently doxorubicin plus trabectedin (6-11).

The objective of this study was to perform an exploratory, retrospective analysis of differences in patient and disease characteristics as compared to other STS sub-types, and to evaluate factors associated with the clinical outcome of patients with advanced or metastatic UtS treated by first line chemotherapy, using pooled data of patients registered in EORTC-STBSG sarcoma trials from 1977 to 2010.

PATIENTS AND METHODS

Patients included in the analysis

The pooled database contains information on 3238 eligible chemotherapy-naïve patients out of 3460 treated in thirteen EORTC-STBSG advanced STS trials (see ST1). UtS patients only (269 pts) were considered for the prognostic factor analysis.

End points of the analysis

The end points were overall survival (OS), progression free survival (PFS) and response rate to chemotherapy (RR). OS was computed from the date of randomisation (in randomised trials) or the date of prospective registration (in nonrandomised trials) to the date of death. Patients reported to be alive at the time of last follow-up were censored. PFS was defined from the date of randomisation/prospective registration to the date of progression or death, whichever occurred first. Patients alive and progression-free at the last follow-up were censored. RR was evaluated in all trials using WHO response criteria (12) or RECIST (13).

Covariates

We considered general patient characteristics such as age and baseline performance status (PS, measured on the WHO scale except for two trials in which it was retrospectively converted from the Karnofsky scale), variables related to the disease history, histopathological grade (as

the histological grading system was not homogeneous defined among the different trials and because of change of definition over time, it was decided to separate the low histopathological grade (grade I) vs other grade (grade II and III) or missing) and histology (whereby, if available, the diagnosis by a panel of reference pathologists was preferred over the local assessment). Adenosarcoma and carcinosarcoma were not included in the different trials as stated in the inclusion or exclusion criteria.

Other variables related to the history of sarcoma were prior surgery, prior radiotherapy, and extent of disease at time of the inclusion. Treatment was aggregated in 4 categories: anthracyclines alone (doxorubicin 75 mg/m², caelyx 50mg/m², epirubicin 75 mg/m², epirubicin 3*50 mg/m², epirubicin 150 mg/m²), ifosfamide alone (ifosfamide 5 g/m², ifosfamide 3*3 g/m², ifosfamide 9 g/m² cont., ifosfamide 12 g/m²), the combination of doxorubicin and ifosfamide (doxorubicin 50mg/m² with ifosfamide 5 g/m², doxorubicin 75 mg/m² with ifosfamide 5 g/m², doxorubicin 75 mg/m² with ifosfamide 10 g/m²) and CYVADIC (Adriamycin, 50 mg/m2, Cyclophosphamide, 500 mg/m2, Vincristine, 1.5 mg/m2 and Dacarbazine, 750 mg/m2).

Statistical methods

Categorical variables were summarized by frequencies and percentages, continuous covariates by median, range and interquartile range (IQR). The variables were presented according to primary tumor site (UtS versus other) and compared using either chi-square tests (categorical variables) or Kruskal-Wallis tests (continuous variables). Survival data was estimated by the Kaplan–Meier method.

To identify significant prognostic factors among the baseline covariates, first univariate log rank tests were performed for OS and PFS and univariate logistic regression analyses for RR. Secondly, all factors were included in multivariate Cox (for OS and PFS) and logistic (for RR) regression models. Important factors were identified by a backward selection procedure. The

substantial amount of missing data in the variables prior surgery and histopathological grade leads to a considerable loss of information for the multivariate analyses. In the case of surgery, excluding the missing information would result in the exclusion of the most recent trial of the database. We thus considered “missing data” for these two factors as a separate category in the models. The statistical significance was set at 0.05 for all analyses in this report.

RESULTS

Table 1 lists the 3238 patient characteristics considered in this analysis by tumor origin (269 UtS patients vs. 2969 patients with other primary tumors gathered as ‘other types’). In this patient population, the expert panel reviewed 68% of initial histological diagnoses and 31% were discordant (see SF1). The majority of cases which were reclassified were leiomyosarcomas (106 or 16%), MFH (98 or 15%) and tumors which were considered unclassifiable after central review (91 or 14%); 28% of tumors were reclassified as miscellaneous, for which in the majority of cases no further information was available. In the specific case of the uterine sarcomas, 12 were leiomyosarcomas; 9 of which were reclassified as part of the miscellaneous category.

Patients with UtS have generally different characteristics compared to those with other sites of tumor origin: the median age of the uterine sarcoma patients at registration was 53 years which is 3 years older than the median age of other patients. The extent of disease involved the primary site in 37.5% of UtS patients, while in 46% of the other patients. Disease free interval between diagnosis and registration for first line metastatic chemotherapy did not differ from other STS and in the majority of patients did not surpass 18 months. Furthermore, UtS patients had more often metastases in the lungs (68.8% vs 54.8%) but less often in the liver (12.3% vs 17.4%). The majority of UtS patients (70.6%) had a leiomyosarcoma and none had synovial sarcoma while among the other patients only 26.7% had a leiomyosarcoma and 10.1% had

synovial sarcoma. Table ST2 reports details of histology: 53 (20%) of UtS patients were classified as miscellaneous sarcoma (more details were unfortunately not available in the databases).

As the analysis is based on patients treated over 30 years, the impact of time effect on diagnosis and on outcome was investigated. The Uts patients were divided in two groups: 208 patients enrolled before 2000 and 61 after 2000. The majority of uterine sarcoma patients enrolled after 2000 had age between 50-60 (54.1%) and in contrast to the patients registered before 2000 none had PS 2 or greater (0 vs 10.1%). Data for primary surgery are often missing for patients enrolled after 2000 because this was not collected in the most recent trial. There was no significant difference between the survival of patients enrolled after 2000 vs before (p=0.493).

Survival data of UtS compared to other STS

Among the UtS patients, there were 231 deaths (median OS 10.4 months, 95% CI: 9.1-11.9) and 257 progressions and/or deaths (median PFS 4.1 months, 95% CI: 3.5-4.9). Figure 1A & 1B reported OS and PFS for UtS versus other STS patients. There was no significant difference between the two groups (log rank test OS p = 0.098, PFS p = 0.183).

Prognostic factors for overall survival in UtS patients

Results of the univariate analyses of prognostic factors for OS are shown in table 2. PS and histopathological grade were found to be significant at a 5% level (see SF2 A & B). No impact of types of chemotherapy regimens (chemotherapy regimens containing doxorubicin versus no) by histological subtype (LMS versus other) on survival was observed (see SF3 A). In the multivariate model, only PS remained significant. The backward selection and the fit of the multivariate model were found to be somewhat unstable due to the amount of missing information for histopathological grade and prior surgery. Note that the results observed for the category of "missing information" on prior surgery (outcome similar to the outcome of

patients with "known" surgery) seems to suggest that, at least in this subgroup of patients, the majority of these patients are likely to have received some surgery.

Prognostic factors for progression free survival in UtS patients

Results of the univariate analyses of prognostic factors for PFS are shown in table 3. PS and histological subtype are significant factors. No impact of types of chemotherapy regimens (chemotherapy regimens containing doxorubicin versus no) by histological subtype (LMS versus other) on PFS was observed (see SF2 B). Also here, the subgroup of patients for whom the surgery status is unknown had a similar outcome as those with known surgery.

The multivariate model included factors identified as significant from backward selection. Histology (other vs LMS: HR 0.72, 95% CI 0.54 – 0.96, p=0.025) was significant. For PFS also, the multivariate analyses was found to be unstable due to missing data in the covariates.

Response to chemotherapy

The analysis of response to chemotherapy identified 60 (22.3%) responders among UtS patients (Table 4), however no significant difference was observed between the RRs observed from the different treatments (p=0.056). Table 5 summarizes the results of the univariate analyses of potential prognostic factors. Again, only histology remained significant in multivariate analysis. No impact of the type of chemotherapy regimen (doxorubicin containing regimen versus no doxorubicin) by histology on RR was noted.

DISCUSSION

This is the first study comparing the outcome of patients with advanced UtS with those with other STS histological subtypes. UtS patients in this retrospective analysis had a median PFS of 4.1 months and a median survival time of 10.4 months, with no difference compared to other STS. These survival data may be supportive to include UtS patients in randomized trials

exploring new options in metastatic phase for all STS patients. The univariate and multivariate analyses for overall survival demonstrated a prognostic impact of PS. As for PFS, a better outcome was observed for uterine patients with different histology from LMS. Compared to a previously reported subgroup analysis of MPNST using the EORTC databases (14), there was no significant effect of treatment regimen observed neither for PFS nor OS. A multivariate logistic regression analysis of response to chemotherapy identified only histology as a significant factor. The RR using doxorubicin alone or in combination is relatively low (but not so different compared to other STS subtypes), compared to the RR with ifosfamide alone, which is really low. Therefore, it should be recommended to avoid ifosfamide alone for patients in situations where achieving response is of clinical relevance, e.g. to reduce symptoms or to improve surgical resectability. On the other hand, CYVADIC regimen using dacarbazine in combination (8;15) with other drugs provided the highest RR (35%) compared to others.

The low RR reported for UtS patients included in these large randomized phase III trials (except 3 non randomized) contrasted with the higher RR published or reported in non-randomized very selected phase II trials using doxorubicin plus or less other compounds such as trabectedin (17;18), gemcitabine and docetaxel (7), or gemcitabine and dacarbazine (11) (S3).

Randomised trials are needed to confirm results from non-randomised phase II studies (specifically when using combination chemotherapy regimens vs monotherapy) before considering one rather than the other.

Considering OS data of the current analysis and previously reported prospective randomized trials, single-agent doxorubicin is still considered the standard chemotherapy. The Cochrane review in 2006 concluded that combination regimens, compared with single-agent doxorubicin, produced only marginal increases at the expense of increased toxic effects, with no improvements in overall survival (19). Recent results of the EORTC 62012 trial in advanced STS

confirmed such analysis for all STS (20). Initial combination therapy may be considered appropriate only for those patients with good PS, no comorbidity and who would be expected to tolerate the increased toxicity, particularly if objective response is considered important for symptomatic improvement or patients with high grade undifferentiated sarcoma.

The weakness of this study lies in its being a retrospective analysis using data from patients treated up to more than 30 years ago with only 68% reported histological review for initial diagnosis. In several of the (older) trials histology was reported using a limited level of detail (often at most 10-12 categories, including “miscellaneous” and “unclassifiable”). During this period the tumor histology classification has undergone several changes, with the most recent WHO classification released in 2013 containing a reclassification of MFH tumors. Nevertheless, fewer patients with uterine sarcoma were reclassified as compared to the general patient population considered in this study (14% versus 31%). This increases our confidence in the results of the analyses looking at the prognostic value of histology on the outcome of uterine sarcoma patients.

Other possible prognostic factors that could not be studied as cofactors are: mitotic index, molecular classification, initial surgery quality (free margins or not) and initial FIGO stage (21). The apparent differences of RR between therapeutic regimens may be explained by selection bias and should be confirmed on the basis of randomized data.

The benefit of chemotherapy for metastatic disease should be weighed against the possible side-effects. New drugs and drug combinations with promising targeted therapies, such as pazopanib (22), sorafenib & bevacizumab reported marginal effects, while cabozantinib and trabectedin are currently being studied in advanced STS including UtS (NCT 01979393, NCT02249702). The data extracted from EORTC databases greatly support that doxorubicin alone or in combination with ifosfamide could be the best control arm in first line treatment to

explore new combinations or treatment, such as gemcitabine-docetaxel or doxorubicin-trabectedin, specifically in the field of LMS.

The last question is how to evolve in future clinical trials dedicated to UtS? The options are to perform 1) either large (and thus most probably, global) phase III trials including all high grade UtS to evaluate the best chemotherapy regimen compared to standard chemotherapy (a doxorubicin based regimen), or 2) stratified clinical trials including all uterine subtypes (LMS, high grade undifferentiated sarcoma, high grade adenosarcoma with overgrowth) or 3) separate clinical trials asking several questions (one major endpoint and several secondary endpoints) but more dedicated to each subtypes. Results of ongoing trials will hopefully help to address these burning questions in this group of patients with such an overt need for improvement in outcome.

CONCLUSIONS

This study reports the outcome of a really important series of UtS patients in first line treatment with advanced or metastatic disease within randomised trials. The results in term of PFS, OS and RR highlight the poor prognosis of this population, low RR to chemotherapy with doxorubicin alone or in combination with ifosfamide and the need to confirm results about RR, PFS or OS of published non-randomised phase II trials in selected population of patients. These results clearly show the urgent need for innovative new strategies including new compounds in this group of patients for whom OS is less than 10 months.

Acknowledgment

This publication was supported by a donation from the French National Ligue against Cancer (La Ligue Nationale contre le Cancer) through the EORTC Charitable Trust. Elisa Rizzo's work as Fellow at EORTC Headquarters was supported by a grant from the EORTC Soft Tissue and Bone

Sarcoma Group. We also thank all investigators who have put their efforts in participation in the EORTC clinical studies that were described in this paper.

Disclosure

The authors have declared no conflict of interest

Reference List

(1) Ducimetière F, Lurkin A, Ranchère-Vince D, Decouvelaere AV, Péoc'h M, Istier L, Chalabreysse P, Muller C, Alberti L, Bringuier PP, Scoazec JY, Schott AM et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PLoS ONE 2011;6(8):e20294.

(2) Zivanovic O1, Jacks LM, Iasonos A, Leitao MM Jr, Soslow RA, Veras E, Chi DS, Abu-Rustum NR, Barakat RR, Brennan MF, Hensley ML. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. Cancer. 2012 Feb 1;118(3):660-9.

(3) Gupta AA, Yao X, Verma S, Mackay H, Hopkins L. Chemotherapy (gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) in inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a clinical practice guideline. Curr Oncol 2013 October;20(5):e448-e454.

(4) Stojadinovic A, Yeh A, Brennan MF. Completely resected recurrent soft tissue sarcoma: primary anatomic site governs outcomes. J Am Coll Surg 2002 April;194(4):436-47.

(5) Casali PG, Jost L, Sleijfer S, Verweij J, Blay JY. Soft tissue sarcomas: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008 May;19 Suppl 2:ii89-ii93.

(6) Hensley ML. Role of chemotherapy and biomolecular therapy in the treatment of uterine sarcomas. Best Pract Res Clin Obstet Gynaecol 2011 December;25(6):773-82.

(7) Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008 June;109(3):329-34.

(8) Maki RG. Gemcitabine and docetaxel in metastatic sarcoma: past, present, and future. Oncologist 2007 August;12(8):999-1006.

(9) Pautier P, Floquet A, Penel N, Piperno-Neumann S, Isambert N, Rey A, Bompas E, Cioffi A, Delcambre C, Cupissol D, Collin F, Blay JY et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist 2012;17(9):1213-20.

(10) Monk BJ, Blessing JA, Street DG, Muller CY, Burke JJ, Hensley ML. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a gynecologic oncology group study. Gynecol Oncol 2012 January;124(1):48-52.

(11) Losa R, Fra J, López-Pousa A, Sierra M, Goitia A, Uña E, Nadal R, Del Muro JG, Gión M, Maurel J, Escudero P, Esteban E et al. Phase II study with the combination of gemcitabine and DTIC in patients with advanced soft tissue sarcomas. Cancer Chemother Pharmacol 2007 February;59(2):251-9.

(12) World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland: 1979.

(13) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada [see comments]. J Natl Cancer Inst 2000 February 2;92(3):205-16.

(14) Kroep JR, Ouali M, Gelderblom H, Le Cesne A, Dekker TJ, Van Glabbeke M, Hogendoorn PC, Hohenberger P. First-line chemotherapy for malignant peripheral nerve sheath tumor (MPNST) versus other histological soft tissue sarcoma subtypes and as a prognostic factor for MPNST: an EORTC soft tissue and bone sarcoma group study. Ann Oncol 2011 January;22(1):207-14.

(15) Hempling RE, Piver MS, Baker TR. Impact on progression-free survival of adjuvant cyclophosphamide, vincristine, doxorubicin (adriamycin), and dacarbazine (CYVADIC) chemotherapy for stage I uterine sarcoma. A prospective trial. Am J Clin Oncol 1995 August;18(4):282-6.

(16) Piver MS, Rose PG. Advanced uterine sarcoma; response to chemotherapy. Eur J Gynaecol Oncol 1988;9(2):124-9.

(17) Blay JY, von Mehren M, Samuels BL, Fanucchi MP, Ray-Coquard I, Buckley B, Gilles L, Lebedinsky C, Elsayed YA, Le Cesne A. Phase I combination study of trabectedin and doxorubicin in patients with soft-tissue sarcoma. Clin Cancer Res 2008 October 15;14(20):6656-62.

(18) Pautier P, Floquet A, Cupissol D, Lcas B, Bompas E, Chevreau C, Selle F,Weber BE, Guillemet C, Penel N, Duffaud F. LMS-02: A phase II single-arm multicenter study of doxorubicin in combination with trabectedin as a first-line treatment of advanced uterine leiomyosarcoma (u-LMS) and soft tissue LMS (ST-LMS): First results in patients with u-LMS. J Clin Oncol. 31. 2013.
Ref Type: Abstract

(19) Bramwell VH, Anderson D, Charette ML. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Cochrane Database Syst Rev 2003;(3):CD003293.

(20) Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, Kerst JM, Sufliarsky J, Whelan J, Hohenberger P, Krarup-Hansen A, Alcindor T at al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014 April;15(4):415-23.

(21) Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009 May;105(2):103-4.

(22) Van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012 May 19;379(9829):1879-86.

(23) Miller DS, Blessing JA, Kilgore LC, Mannel R, Van LL. Phase II trial of topotecan in patients with advanced, persistent, or recurrent uterine leiomyosarcomas: a Gynecologic Oncology Group Study. Am J Clin Oncol 2000 August;23(4):355-7.

(24) Sutton G, Blessing J, Hanjani P, Kramer P. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol 2005 March;96(3):749-52.

Figures and Tables

<u>Table 1:</u> Patient, tumor and treatment characteristics of UtS patients compared to patients with tumors in other sites of origin (a = Kruskal-Wallis test; b = Chi-square test, IQR = Interquartile range).

	Tumor site			
	Uterine sarcoma (N = 269)	Other types (N = 2969)	Total (N = 3238)	p-Value
	N (%)	N (%)	N (%)	
Performance status				0.299b
PS 0	128 (47.6)	1251 (42.1)	1379 (42.6)	
PS 1	117 (43.5)	1350 (45.5)	1467 (45.3)	
PS 2+	21 (7.8)	277 (9.3)	298 (9.2)	
Unknown	3 (1.1)	91 (3.1)	94 (2.9)	
Treatment				0.015b
Anthracyclins	119 (44.2)	1146 (38.6)	1265 (39.1)	
DOX+IFO	87 (32.3)	1040 (35.0)	1127 (34.8)	
CYVADIX	23 (8.6)	429 (14.4)	452 (14.0)	
IFO ALONE	40 (14.9)	354 (11.9)	394 (12.2)	
Histopathological grade				0.035b
Low	12 (4.5)	262 (8.8)	274 (8.5)	
Intermediate/high	178 (66.2)	1810 (61.0)	1988 (61.4)	
Unknown	79 (29.4)	897 (30.2)	976 (30.1)	
Histology				<0.001b
Leiomyosarcoma	190 (70.6)	792 (26.7)	982 (30.3)	
Synovial sarcoma	0 (0.0)	300 (10.1)	300 (9.3)	
Other	69 (25.7)	1730 (58.3)	1799 (55.6)	
Unknown	10 (3.7)	147 (5.0)	157 (4.8)	
Prior surgery				<0.001b
No surgery	10 (3.7)	337 (11.4)	347 (10.7)	
Non optimal surgery	40 (14.9)	484 (16.3)	524 (16.2)	
Complete surgery	117 (43.5)	856 (28.8)	973 (30.0)	
Unknown	102 (37.9)	1292 (43.5)	1394 (43.1)	
Prior radiotherapy				0.527b
No	186 (69.1)	2104 (70.9)	2290 (70.7)	
Yes	81 (30.1)	839 (28.3)	920 (28.4)	
Unknown	2 (0.7)	26 (0.9)	28 (0.9)	
Extent of disease				
Primary	101 (37.5)	1366 (46.0)	1467 (45.3)	<0.001b
Liver metastases	33 (12.3)	518 (17.4)	551 (17.0)	0.022b
Lung metastases	185 (68.8)	1626 (54.8)	1811 (55.9)	<0.001b
Bone metastases	22 (8.2)	308 (10.4)	330 (10.2)	0.148b
Other metastases	105 (39.0)	1120 (37.7)	1225 (37.8)	0.782b
Age at registration (years)				<0.001a
Median (IQR)	53 (47–59)	50 (39–59)	51 (40–59)	
Range	22–76	10–80.0	10–80	
N obs	262	2905	3167	
Time between initial diagnosis and registration (months)				0.673a
Median (IQR)	6.8 (1.7–15.3)	6.2 (1.3–18.4)	6.3 (1.4–18.0)	
Range	0.0–199.5	0.0–346.5	0.0–346.5	
N obs	266	2766	3032	

Table 2: Univariate analyses of potential prognostic factors for overall survival of UtS patients (a = These missing values were considered as a separate category to avoid a considerable loss of patient information from the analyses).

Covariates		Patients (N)	Observed Events (O)	Hazard Ratio (95% CI)	p-Value (logrank test)
Performance status	PS 0	128	102	1	<0.001 (df=2)
	PS 1	117	105	1.61 (1.22, 2.12)	
	PS 2+	21	21	3.16 (1.96, 5.09)	
	Missing	3			
Prior Surgery	No surgery	10	10	1	0.633 (df=3)
	Non optimal surgery	40	32	0.64 (0.31, 1.31)	
	Complete surgery	117	99	0.66 (0.34,1.27)	
	Missinga	102	90	0.69 (0.36, 1.33)	
Prior radiotherapy	No	186	155	1	0. 782
	Yes	81	74	1.04 (0.79, 1.37)	
	Missing	2			
Primary site involved	No	145	124	1	0. 829
	Yes	101	86	0.97 (0.73, 1.28)	
	Missing	23			
Histopathologicalgrade	Low	12	8	1	0.040 (df=2)
	Intermediate/high	178	160	2.55 (1.19, 5.47)	
	Missinga	79	63	2.27 (1.04, 4.98)	
Treatment	Anthracyclins	119	104	1	0.945 (df=3)
	DOX+IFO	87	78	1.08 (0.80,1.45)	
	CYVADIX	23	20	0.96 (0.59, 1.55)	
	IFO ALONE	40	29	1.00 (0.66, 1.52)	
Age (cat)	<40yrs.	26	20	1	0.101 (df=3)
	40–50yrs.	72	63	1.66 (0.99, 2.78)	
	50–60yrs.	102	88	1.81 (1.10, 2.99)	
	≥60yrs.	62	54	1.86 (1.10, 3.15)	
	Missing	7			
Histology	Leiomyosarcoma	190	166	1	0.111
	Other	69	56	0.78 (0.57,1.06)	
	Missing	10			

Table 3: Univariate analyses of potential prognostic factors for PFS in UtS patients (a = These missing values were considered as a separate category to avoid a considerable loss of patient information from the analyses).

Covariates		Patients (N)	Observed Events (O)	Hazard Ratio (95% CI)	p-Value (logrank test)
Performance status	PS 0	128	118	1	0.038 (df=2)
	PS 1	117	115	1.23 (0.95,1.59)	
	PS 2+	21	21	1.76 (1.10, 2.80)	
	Missing	3			
Prior Surgery	No surgery	10	10	1	0.094 (df=3)
	Non optimal surgery	40	35	0.41 (0.20, 0.83)	
	Complete surgery	117	113	0.49 (0.26, 0.95)	
	Missinga	102	99	0.50 (0.26, 0.97)	
Prior radiotherapy	No	186	176	1	0.912
	Yes	81	79	1.02 (0.78, 1.32)	
	Missing	2			
Primary site involved	No	145	139	1	0.759
	Yes	101	96	0.96 (0.74, 1.25)	
	Missing	23			
HistopathologicalGrade*	Low	12	11	1	0.066 (df=2)
	Intermediate/high	178	172	2.04 (1.11, 3.77)	
	Missinga	79	74	1.92 (1.02, 3.63)	
Treatment	Anthracyclins	119	112	1	0.303(df=3)
	DOX+IFO	87	84	1.18 (0.89, 1.56)	
	CYVADIX	23	23	0.83 (0.53, 1.31)	
	IFO ALONE	40	38	1.25 (0.86, 1.81)	
Age	<40yrs.	26	21	1	0.070 (df=3)
	40–50yrs.	72	70	1.76 (1.07, 2.89)	
	50–60yrs.	102	100	1.89 (1.17, 3.05)	
	≥60yrs.	62	59	1.79 (1.08, 2.97)	
	Missing	7			
Histology	Leiomyosarcoma	190	185	1	0.024
	Other	69	63	0.72 (0.54, 0.96)	
	Missing	10			

Table 4: Response to chemotherapy regimen.

		Treatment				
		Anthracyclins (N = 119)	DOX + IFO (N = 87)	CYVADIC (N = 23)	IFO alone (N = 40)	Total (N = 269)
		N (%)	N (%)	N (%)	N (%)	N (%)
Best overall response	Complete response	3 (2.5)	2 (2.3)	3 (13.0)	0 (0.0)	8 (3.0)
	Partial response	26 (21.8)	19 (21.8)	5 (21.7)	2 (5.0)	52 (19.3)
	No change	51 (42.9)	29 (33.3)	7 (30.4)	15 (37.5)	102 (37.9)
	Progression	33 (27.7)	28 (32.2)	5 (21.7)	17 (42.5)	83 (30.9)
	Non evaluable	6 (5.0)	9 (10.3)	3 (13.0)	6 (15.0)	24 (8.9)

<u>Table 5</u>: Univariate analyses of potential prognostic factors for RR in UtS patients (a = These missing values were considered as a separate category to avoid a considerable loss of patient information from the analyses).

Covariates		Response (N)	Response rate (%)	OR	OR (95% CI)	p-Value
Performance status	PS 0	32	25	1	1	0.479 (df=2)
	PS 1	22	18.8	0.69	(0.38, 1.28)	
	PS 2+	4	19.1	0.71	(0.22, 2.25)	
Missing	3					
Prior surgery	No surgery	2	20	1		0.849 (df=3)
	Non optimal surgery	10	25	1.33	(0.24, 7.35)	
	Complete surgery	28	23.9	1.26	(0.25, 6.27)	
	Missinga	20	19.6	0.98	(0.19, 4.95)	
Prior radiotherapy	No	44	23.7	1		0.483
	Yes	16	19.8	0.79	(0.42, 1.51)	
	Missing	2				
Primary site involved	No	30	20.7	1		0.452
	Yes	25	24.8	1.26	(0.69, 2.31)	
	Missing	23				
Histopathological grade	Low	3	25	1		0.962 (df=2)
	Intermediate/high	39	21.9	0.84	(0.22, 3.26)	
	Missinga	18	22.8	0.89	(0.22, 3.62)	
Treatment	Anthracyclins	29	24.4	1		0.056 (df=3)
	DOX+IFO	21	24.1	0.99	(0.52, 1.88)	
	CYVADIX	8	34.8	1.66	(0.64, 4.3)	
	IFO ALONE	2	5	0.16	(0.04, 0.72)	
Age	<40yrs.	8	30.8	1		0.588 (df=3)
	40–50yrs.	17	23.6	0.7	(0.26, 1.88)	
	50–60yrs.	19	18.6	0.52	(0.20, 1.36)	
	≥60yrs.	14	22.6	0.66	(0.24, 1.83)	
	Missing	7				
Histology	Leiomyosarcoma	36	19	1		0.016
	Other	23	33.3	2.14	(1.15, 3.97)	
	Missing	10				

Figure 1: Overall survival (A) and progression-free survival (B) by tumor origin.