A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group


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Received 17 August 2012; revised 17 September 2012; accepted 18 September 2012

Background: There is no proven benefit of adjuvant treatment of uterine sarcoma (US). SARCGYN phase III study compared adjuvant polychemotherapy followed by pelvic radiotherapy (RT) (arm A) versus RT alone (arm B) conducted to detect an increase ≥ 20% of 3-year PFS.

Methods: Patients with FIGO stage ≤ III US, physiological age ≤ 65 years; chemotherapy: four cycles of doxorubicin 50 mg/m² d1, ifosfamide 3 g/m²/day d1–2, cisplatin 75 mg/m² d3, (API) + G-CSF q 3 weeks. Study was stopped because of lack of recruitment.

Results: Eighty-one patients were included: 39 in arm A and 42 in arm B; 52 stage I, 16 stage II, 13 stage III; 53 leiomyosarcomas, 9 undifferentiated sarcomas, 19 carcinosarcomas. Gr 3–4 toxicity during API (/37 patients): thrombopenia (76%), febrile neutropenia (22%) with two toxic deaths; renal gr 3 (1 patient). After a median follow-up of 4.3 years, 41/81 patients recurred, 15 in arm A, 26 in arm B. The 3 years DFS is 55% in arm A, 41% in arm B (P = 0.048). The 3-year overall survival (OS) is 81% in arm A and 69% in arm B (P = 0.41).

Conclusion: API adjuvant CT statistically increases the 3 year-DFS of patients with US.

Key words: adjuvant, chemotherapy, sarcoma, treatment, uterine

introduction

Uterine sarcomas (US) [leiomyosarcoma (LMS), carcinosarcoma (CS), and endometrial stromal sarcoma (ESS), according to traditional classification systems] are uncommon tumors and constitute only 3% of uterine malignancies. US are poor prognosis diseases, even at early stage, with a high risk of metastatic relapse. In the observational arm of the European Organization for Research and Treatment of Cancer (EORTC) study of adjuvant radiotherapy (RT), half of 112 patients with stage I–II USs relapsed after surgery alone, and the progression-free survival (PFS) at 3 years was 51.9%. Among the 112 patients who received pelvic RT after surgery, the 3-year PFS was increased to 57.7%, but the difference was not statistically significant [1].

In a French retrospective study [2], median overall survival of 157 patients with US was 33 months, with 3- and 5-year survival rates of 49% and 40%, respectively, and a median
event-free survival of 13 months. Among the 101 relapses, 70% were metastatic.

Given the absence of impact on overall survival of pelvic RT and the high risk of distant relapse, the role of adjuvant chemotherapy needed further investigations. Whether or not adjuvant therapy has an impact on the survival of patients with US is currently unclear. No benefit was shown with doxorubicin as an adjuvant treatment even though a trend emerged in favor of chemotherapy in the only randomized published study of adjuvant chemotherapy in early-stage US [3]. A chemotherapy protocol producing a higher response rate than doxorubicin alone may have better results in an adjuvant setting. In a case–control study of 36 patients with stage I–III US (including LMS, CS, and high-grade ESS), 18 received three cycles of API (doxorubicin, ifosfamide, and cisplatin) regimen followed by RT compared with an historical control group of 18 patients treated with postoperative RT alone; median event-free survival of the entire population (chemotherapy group and control group) was 33 months (11–45), and the 3-year disease-free survival rates in the control group and in the chemotherapy plus RT group were 43% and 76%, respectively [4]. Adjuvant API followed by RT is a feasible protocol in localized US and needs to be explored in a randomized trial to confirm or not a benefit in term of DFS and OS. From those results, we conducted a multicentric phase III study (SARGYN protocol), comparing API chemotherapy regimen followed by RT versus RT alone for patients with localized US after complete surgery.

patients and methods

eligibility

Patients were enrolled according to the following criteria: US (LMS, CS, high-grade ESS, according to histological classification at that time) histologically confirmed by a sarcoma pathologists experts panel, age between 18 and physiological 65 years; FIGO 1989 modified classification for endometrial carcinoma stage lower than or equal to III, with complete surgery (at least hysterectomy and bilateral oophorectomy); ECOG performance status of 0 or 1; adequate hematologic (granulocyte blood count and platelet count exceeded, respectively, 1500/μl and 100,000/μl); hepatic (total bilirubin < 1.5 times the upper limit of normal, transaminases < 2.5 N), renal (creatinin < 1.25 N) and cardiac (LVEF measurement (per ultrasound or scintigraphy) >50%) functions; normal thoracic, abdominal, and pelvic CT scans; and written informed consent form. Stages of disease were determined using an application of the FIGO staging classification used for carcinoma of the uterine corpus advocated by Salazar et al. [5]: stage I = sarcoma confined to uterine corpus; II = confined to corpus and cervix; III = confined to pelvis; and IV = extrapelvic sarcoma.

The clinicaltrials.gov identifier for this study was NCT00162721.

randomization and masking

Randomization was done centrally—so the next treatment was not known in advance—via a computer-generated system using permuted blocks of two and four patients. Stratification was done by histology (CS versus others) and brachytherapy (expected or not).

Random assignment was required within 8 weeks after complete surgery; the eligibility was checked centrally in the coordinating center by a faxed checklist before treatment allocation.

treatment

Patients were randomly assigned to receive chemotherapy followed by RT (arm A) or RT alone (arm B). Patients had to be randomized and to begin the treatment within 8 weeks following surgery.

Chemotherapy consisted in four cycles of API regimen: doxorubicin 50 mg/m² day 1, ifosfamide 3 g/m² per day, days 1 and 2, with mesna 3 g/m² per day, days 1 and 2, cisplatin 75 mg/m² day 3, and lenograstim 150 μg/m² per day, days 7–14; API regimen was administered every 3 weeks. When the absolute neutrophil count was less than 1500/μl and/or the platelet count less than 100,000/μl, chemotherapy was delayed by 1 week. In case of febrile neutropenia or grade 4 hematological toxicity, cisplatin, and ifosfamide doses were reduced by 20% for the further cycles. If severe hematotoxicity occurred again, despite those doses reductions, investigators could either stop the therapy or reduce the doses of doxorubicin at convenience.

External pelvic RT was delivered for a total dose of 45 grays in 5 weeks (1.8 grays per fraction), starting 4 weeks after the last administration of chemotherapy in arm A or within 8 weeks following surgery in arm B. After the RT completion, vaginal brachytherapy was optional (choice of each center at the beginning of the study).

statistical analysis

end points

The primary end point was difference in the 3-year disease-free survival (DFS) between the two treatment arms. DFS was defined as time from the randomization to disease progression, or death before the development of disease progression. Secondary end point was overall survival (OS) defined as time from randomization to death from any cause.

Patients with no event at the time of analysis were censored at date of last follow-up.

sample size

A sample size of 256 patients (128 in each arm) was required to give 80% power to detect a treatment related difference of 20% between the arms (from 35% to 55%), using a two-sided 5% significance level.

interim analyses

An interim analysis was planned when two-thirds of patients were recruited, and the final analysis was planned when all surviving patients had achieved at least 3 years follow-up and included all patients randomized into the study, regardless of their compliance with treatment (intention to treat analysis).

randomization

Randomization was stratified by histology (CS versus others) and brachytherapy (expected or not).

statistical analysis

Overall survival and DFS curves were calculated using the Kaplan–Meier method [6].

Comparability of groups was checked, and comparison of DFS was made with a log-rank test.

Two hundred fifty-six patients had to be included. However, study was stopped in August 2009 because of lack of recruitment. Results are then based on the 81 patients who entered the study.

The starting point for survival was the date of the initial diagnosis, whereas the closing date for the statistical analysis was May 2011.

results

Between October 2001 and July 2009, 81 patients were randomized in 19 institutions, 39 in the chemotherapy plus RT
neutropenia, 24% a febrile neutropenia, 76% a grade 3–4 anemia, 58% a grade 3–4 neutropenia, 24% a febrile neutropenia, 76% a grade 3–4 thrombocytopenia, and 1% a grade 3 renal toxicity. Two toxic deaths occurred from a septic shock after the fourth cycle. One of these occurred after a protocol major violation without hypoplasia, and 2 for another reason. Seventeen percent of patients have started their RT >6 weeks after their last cycle of CT.

toxicity
Severe and acute toxic effects during CT are shown in Table 2.

arm A (CT and RT)
Among the 38 patients who received at least one cycle of CT, 58% experienced a grade 3–4 anemia, 58% a grade 3–4 neutropenia, 24% a febrile neutropenia, 76% a grade 3–4 thrombocytopenia, and 1% a grade 3 renal toxicity. Two toxic deaths occurred from a septic shock after the fourth cycle. One of the two occurred after a protocol major violation without dose reduction for a grade IV toxicity.

There were no peripheric neurological complications, no encephalitis, and no bladder toxicity.

Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Arm A, CT + RT</th>
<th>Arm B, RT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>FIGO Stage (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>55</td>
<td>54.5</td>
</tr>
<tr>
<td>range</td>
<td>40–69</td>
<td>39–66</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>High-grade stromal sarcoma</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Vaginal brachytherapy (n)</td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>

During RT, one patient presented a grade 3 and another one a grade 4 gastrointestinal toxicity. There were no grade 3 or 4 cutaneous, urinary or other toxic effects.

arm b (RT)
Only one patient presented a grade 3 gastrointestinal toxicity, and there were no grade 3 or 4 cutaneous, urinary or other toxic effects in the 39 patients treated with RT alone.

Among the 81 patients, two (one in each arm) developed a breast cancer (4 years after the end of treatment), and 1 (arm B) a renal cell carcinoma (4 months after the end of treatment).

survival
Forty-one patients have relapsed at a median time of 13 months (range 5–43 months), 15 in the CT arm, and 26 in the RT alone arm (Table 3). Seventy-three percent of first relapse were metastatic (n = 30) with three local and metastatic relapses among them, and 27% local relapses alone (n = 11). Twenty-five of 30 patients with metastatic disease had lung metastasis. Three patients died without disease in arm A, two from a septic shock at the fourth cycle and one from pulmonary embolism (70 months after inclusion without relapse), and none in arm B.

The median disease-free survival (DFS) is 33 months in the entire population. There is a significant difference in the 3-year DFS with 55% in arm A and 41% in arm B (P = 0.048; Figure 1). There is no difference in overall survival between the two arms, even if there is a trend in favor of CT arm at 3 years (81% in arm A and 69% in arm B; P = 0.41; Figure 2).

discussion
We have shown for the first time a statistical impact of adjuvant chemotherapy on DFS in this population of 81 patients without impact on OS yet. However, API association was toxic, with two deaths among 39 patients. Those two deaths added to one death from pulmonary embolism in arm A would probably impact the OS. If we analyze the time of relapse, those three deaths have to be censored at the time of relapse, those three deaths have to be censored at the time of relapse, and none in arm B.

Table 2. Grade 3–4 toxic effects (WHO scale) in 138 cycles of chemotherapy

<table>
<thead>
<tr>
<th>Toxicity (cycles)</th>
<th>Grade 3–4 (cycles) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (128)</td>
<td>30 [23%]</td>
</tr>
<tr>
<td>Neutropenia (129)</td>
<td>41 [32%]</td>
</tr>
<tr>
<td>Febrile neutropenia (129)</td>
<td>11 [9%]</td>
</tr>
<tr>
<td>Thrombocytopenia (130)</td>
<td>57 [44%]</td>
</tr>
<tr>
<td>Toxicity (38 patients)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>22 [58%]</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 [58%]</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9 [24%]</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>29 [76%]</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>8 [21%]</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>1 [3%]</td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>2</td>
</tr>
</tbody>
</table>
death, and we declare 15 events in arm A and 26 events in arm B. Then, there is a statistical difference on interval-free of relapse in favor of chemotherapy ($P = 0.013$), but it was not initially our judgment criterion.

USs are characterized by a high relapse rate, even when localized, and show a dismal survival rate when metastatic [1, 2]. Although adjuvant pelvic RT has not shown a significant gain in survival, it has however improved local control in the pelvis. Pelvic radiation has no clear impact on survival due to abdominal recurrences above the pelvic fields of radiation, or to distant metastases. An EORTC phase III study comparing pelvic RT versus no adjuvant therapy in US showed a reduction in local relapse, but no effect on OS [1]. Within such a context of metastatic risk, adjuvant CT appears to be a relevant question. For patients with soft tissue sarcoma (STS) too, the impact of adjuvant CT on the survival remains a topic of debate [7, 8]. Some studies or metaanalyses demonstrated a significant benefit of adjuvant CT in terms of OS; a recent analysis of a large cohort-based study with long-term follow-up indicates that patients with high-grade STS (FNCLCC grade 3) may benefit from adjuvant chemotherapy [9]. But those results contradicted other reports that have failed to prove any benefit of adjuvant CT. In USs, histological grade has no prognostic impact [2] and cannot be used for the indication of an adjuvant therapy. The diagnosis of US is in itself a poor prognostic factor and may justify a more aggressive adjuvant therapy in a prospective manner.

In the adjuvant setting, Omura et al. [3] reported the only randomized published study of adjuvant CT in early-stage (stage I and II) USs ($n = 156$). Patients were randomized to receive either doxorubicin (60 mg/m² every 3 weeks in eight courses) or no chemotherapy at all. The decision to give adjuvant RT in both arms was at the discretion of the investigators. No significant advantage was noted for OS nor for PFS between the two groups, even though a trend emerged in favor of chemotherapy, particularly for LMS (44% versus 61% of relapse rate with and without adriamycine, respectively). A chemotherapy protocol that produces better results than doxorubicin alone in sarcomas has not been defined yet. In metastatic and/or loco-regional advanced USs, the most active drugs remain doxorubicin, ifosfamide, cisplatin with response rates (RR) ranging from 17% to 42% [10–15]. Combinations of drugs avoiding cross-resistance were first evaluated in STS during the 1980s. There are only few published studies on multiagent regimens in metastatic USs [10, 16–18]. Until recently, the most active multiagent chemotherapy regimen combined doxorubicin and ifosfamide [17], and yields RR about 30% in LMS. Lately, a phase II study of gemcitabine plus docetaxel in uterine LMS showed a 36% RR [19]. We published a multidrug regimen designated as DECAV, combining dacarbazine, cyclophosphamide or ifosfamide, cisplatin, adriamycin, and vindesine [20]. This regimen was notable for that it combined drugs usually used to treat USs with high dose intensity for each drug, added to cisplatin. The objective RR of the 54% achieved in this series is high, but the median duration of responses is low. It is notable that responses occur even in LMS, which is in contrast with reported data on STS [21, 22].

### Table 3. Results

<table>
<thead>
<tr>
<th></th>
<th>Arm A CT + RT</th>
<th>Arm B RT</th>
<th>Total</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up</td>
<td>4.3 years (0.5–8.7)</td>
<td>4.3 years (0.3–7.9)</td>
<td>4.3 years (0.3–8.7)</td>
<td></td>
</tr>
<tr>
<td>Relapse (patients)</td>
<td>15 (38.5%)</td>
<td>26 (62%)</td>
<td>41 (51%)</td>
<td></td>
</tr>
<tr>
<td>3-year DFS (95% CI)</td>
<td>55% (40% to 70%)</td>
<td>41% (27% to 57%)</td>
<td>41% (27% to 57%)</td>
<td>0.048</td>
</tr>
<tr>
<td>3-year OS (95% CI)</td>
<td>81% (66% to 91%)</td>
<td>69% (52% to 82%)</td>
<td>69% (52% to 82%)</td>
<td>NS</td>
</tr>
<tr>
<td>5-year OS (95% CI)</td>
<td>72% (53% to 85%)</td>
<td>55% (37% to 72%)</td>
<td>55% (37% to 72%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival; CI, confident interval.

**Figure 1.** Disease-free survival according to adjuvant therapy group. Vertical line at 3 years: 95% confident interval; Rothman’s method.

**Figure 2.** Overall survival according to adjuvant therapy group. Vertical line at 3 years: 95% confident interval; Rothman’s method.
In the adjuvant setting though, there are few prospective phase-II multi-agent adjuvant studies. Hempling et al. [23] reported results with the CYVADIC regimen (cyclophosphamide, vincristine, doxorubicin, and dacarbazine) in stage I USs. Patients did not receive postoperative RT nor brachytherapy. Seven patients of 20 (35%) developed a recurrent disease, and the 5-year PFS rate was 65%. The VAC regimen (vincristine, actinomycin D, and cyclophosphamide), tested by others in retrospective studies [24–26], yielded roughly the same results. Those multigent trials showed encouraging results, but were not randomized, first because those tumors are rare, and second since most of the teams do not consider surveillance alone (without adjuvant therapy) as an adequate option in high-risk localized US.

DECAV is an active regimen in US with encouraging results in an adjuvant setting too, but is still very toxic to be used routinely [20]. We thus excluded then vindesine and dacarbazine from our second-generation regimen, rather than reducing the dose intensity of each drug. The rational was first that vindesine had not been explored alone in phase II for sarcomas, and then that dacarbazine is usually considered less active than doxorubicin, ifosfamide, and cisplatin in the three histological subtypes. We then reported the results of a feasibility study of an adjuvant therapy with API regimen followed by RT in localized USs (excluding low-grade ESS). Results were encouraging when overall survival and relapse free survival were compared with those of the 18 patients—matched on stage, age, histology and surgical procedure—who had received adjuvant RT alone.

A phase II prospective study—including 23 patients with stages I to IV high-grade uterine LMS combining gemcitabine plus docetaxel for completely resected—has been published with a median follow-up of 49 months. Results for PFS at 2 years in the 18 stage I and II patients are encouraging; unfortunately, the study was not randomized and was restricted to high-grade LMS [27].

We conducted the SARCGYN randomized study to answer to this debated and major question considering US. Unfortunately, inclusions were difficult due to the rarity of the disease, an important rate of patients’ refusal or exclusion criteria (patients with microscopic pulmonary nodes evocating possible lung metastasis). Finally, study had to be stopped before the end of recruitment.

One of the issues about the SARCGYN study regards the inclusion of CS, but according to classification systems used in 2001, US included CS. Recently, they have been reclassified as a dedifferentiated or metaplastic form of endometrial carcinomas. The most important particularity is the possible difference in chemosensitivity among histopathological subtypes. The interest of the API regimen was the association of drugs active in LMS (doxorubicine and ifosfamide), high grade ESS (doxorubicine cisplatine) and CS (cisplatine and ifosfamide). Moreover, CS were stratified in the SARCGYN study. If we exclude CS from the survival analysis and retain 53 LMS and 9 US, we then have 30 patients in arm A and 32 patients in arm B. The disease-free survival (DFS) at 3 years is 51% (95% CI 34% to 69%) in arm A and 40% (95% CI 25% to 58%) in arm B, respectively (NS), and DFS at 5 years is 51% (95% CI 34% to 69%) in arm A versus 29% (95% CI 16% to 47%) in arm B respectively (P = 0.098). But the study, though stratified, was not built to analyze subgroups.

conclusions
This study, added to the other randomized study reported by Omura et al. [3], shows that addition of four cycles of API chemotherapy prior adjuvant pelvic RT increases slightly the DFS. Those results have to be confirmed with a longer follow-up, but the two toxic deaths may impact the global prognosis. A less toxic chemotherapy is debatable, but could be less effective; besides, and according to the latest histological classification, carcinosarcomas will have to be excluded from the future trials. There is, at the moment, no other prognostic factor (in particular grade) that can be used to select patients in prospective trials for USs.

acknowledgement
Gilles Charrot for editing the manuscript.

fundings
With the support of Association pour la Recherche contre le Cancer and Chugaï Pharma (no grant number).

disclosure
The authors have declared no conflicts of interest.

references
Phase I/IIa trial of the mammalian target of rapamycin inhibitor ridaforolimus (AP23573; MK-8669) administered orally in patients with refractory or advanced malignancies and sarcoma†

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Received 22 June 2012; revised 12 October 2012; accepted 15 October 2012

Background: Ridaforolimus is an inhibitor of mTOR with evidence of antitumor activity in an I.V. formulation. This multicenter, open-label, 3 + 3 design nonrandomized, dose-escalation, phase I/IIa trial was conducted to determine the

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