Retroperitoneal sarcomas: patterns of care in advanced stages, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group


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Background: Retroperitoneal sarcomas (RPS) are heterogeneous. Advanced stages include unresectable locoregional (LR) disease, abdominal sarcomatosis and distant metastasis. There is no available report assessing palliative chemotherapy in advanced RPS. This study analyzes management and outcome in a large cohort of patients with advanced RPS, considering main histological subtypes separately.

Patients and methods: We conducted a retrospective analysis of adult patients diagnosed with a RPS between 1 January 1988 and 31 December 2008 across 12 centers of the French Sarcoma Group. All cases were centrally reviewed by an expert pathologist.

Results: Five-hundred eighty-six patients were included, 299 patients received palliative chemotherapy, with a median of two lines (range 0–8). Fifty patients underwent palliative surgery. Two hundred fifty-five patients (85%) were assessable for response after first line of chemotherapy. Among them, 69 patients (27%) had progressive disease, 145 (57%) had stable disease, 37 (14.5%) had partial response and 4 (1.5%) complete response. Median time from first line of palliative chemotherapy to progression was 5.9 months [4.9–7.3] and median overall survival (OS), 15.8 months [13–18]. In multivariate analysis, prognosis factors independently associated with poor OS were male gender, performance status (PS) >1 and grade >1. There was no difference according to stage of disease. Palliative surgery did not appear to add any survival benefit.

Conclusion: These results emphasize the scarcity of available options for RPS in the advanced setting and the urgent need to develop new strategies. Patients with good PS should be included in clinical trials and best supportive care should be considered in those with poor PS.

Key words: retroperitoneal sarcoma, palliative, chemotherapy, prognosis

Introduction

Retroperitoneal sarcomas (RPS) are a rare and heterogeneous group of tumors mainly made up of three histological subtypes [1]. well-differentiated liposarcomas (WDLPS) that are low-grade tumors with locoregional (LR) malignancy, dedifferentiated liposarcomas (DDLPS) with relatively low risk of metastasis [2, 3] and leiomyosarcomas (LMS) with relatively high metastatic potential.

Despite complete initial resection, more than 50% of patients treated for a RPS will relapse locally [4]. At relapse, surgery may offer a second chance of complete remission for some selected
patients [5]. However, complete resection rates decrease gradually with relapses [6, 7], and a significant proportion of patients will present with incompletely resected or nonresectable disease.

Palliative stage is defined as the impossibility to obtain complete resection of the disease. Because distinct histological subtypes in RPS have different evolution modalities, palliative stage includes nonresectable LR disease, nonresectable abdominal sarcomatosis, defined as involvement of the peritoneum irrespectively of the number of foci [8, 9], and distant metastasis. This diversity of presentations makes assessment of treatments difficult.

The role of palliative surgery in RPS is not clear. Most existing studies have retrospectively assessed the impact of partial reductive surgery on survival. Some studies reported a survival advantage with this strategy [6, 10] whereas others did not [7, 11].

The two major drugs used in advanced STS are doxorubicin and ifosfamide. Trabectedine has also shown activity, especially in LPS and LMS [12]. However, apart from these drugs, options are limited and inclusion in a clinical trial is the best choice [13]. Until recently, very few phase II clinical trials for new drugs in advanced STS have focused on specific histological subtypes [14] and retrospective studies on this topic are rare and small [15, 16]. Moreover, there is no dedicated publication assessing palliative chemotherapy in RPS specifically.

The main aim of this study was to give a description of patterns of care of RPS in the palliative setting and to detail palliative chemotherapy used in first line. Secondary objectives were to define prognostic factors for time to progression (TTP) and OS from first-line palliative chemotherapy and to consider main histological subtypes separately.

**patients and methods**

We retrospectively analyzed medical charts of patients older than 18, treated for a primary RPS between 01 January 1988 and 31 December 2008 and referred to one of the 12 participating centers of the French Sarcoma Group (GSF-GETO). The list of patients originated from the GSF database (Conticabase). Inclusion criteria were (i) data available on initial treatment and follow-up and (ii) no concomitant uncontrolled other tumor. All histological diagnoses were systematically reviewed by an expert pathologist member of the French Sarcoma Group (GSF-GETO). Patients with fibrous solitary tumors and other tumors of uncertain malignancy were excluded from the analysis. In all cases, radiological, surgical and pathological reports were analyzed.

Patients’ characteristics at the time of first-line palliative chemotherapy included age, gender and performance status (PS). Tumor characteristics included histology, grade according to the FNCLCC, and stage (unresectable LR disease, unresectable sarcomatosis (defined as intraoperative involvement [9, 17]) and distant metastasis). In order to minimize the misclassification of WDLPs due to subsequent dedifferentiation, we considered the latest available histology for LPS whenever it was available.

Characteristics of treatment included type of chemotherapy (monochemotherapy/polychemotherapy), use of anthracyclines, ‘closing’ treatment after first line (maintenance chemotherapy, palliative reductive surgery or radiotherapy) and palliative surgery, defined as surgery only carried out with a clear symptomatic/partial reductive intent. Follow-up generally consisted of a CT scan every two or three cycles of chemotherapy and evaluation of response was done according to Response Evaluation Criteria in Solid Tumours [18]. This retrospective study was approved by institutional ethics review boards.

**statistical methods**

Median follow-up was calculated based on Shuster’s method [19]. Between-group differences were evaluated with $\chi^2$ test or Fisher’s exact test for categorical variables and Student’s $t$-test for continuous variables.

(i) Time to progression (TTP) and (ii) OS was defined from the date of the first cycle of first-line palliative chemotherapy to (i) progression or death or (ii) death or last patient contact. Survival rates were estimated with the Kaplan–Meier method [20]. Prognostic factors for TTP and OS from first line were selected with the log-rank test in the population of patients who received at least one cycle of chemotherapy [21].

**results**

**patterns of care in advanced stage**

Among the 586 patients with an initial diagnosis of primary RPS included in the study, 299 (51%) and 50 (8.5%) eventually received palliative chemotherapy or underwent surgery with a palliative intent, respectively. Palliative chemotherapy was initiated for metastatic disease (± associated LR relapse) in 176 patients (59%) and for isolated LR evolution in 123 patients (41%) (supplementary Figure S1, available at Annals of Oncology online). Patient characteristics at first-line chemotherapy are provided in supplementary Table S1, available at Annals of Oncology online.

First line was a monochemotherapy for 146 patients (49%) and contained anthracyclines for 224 patients (75%). Drugs are detailed in supplementary Table S2, available at Annals of Oncology online. Overall 30 patients received ‘maintenance’ chemotherapy after first line, mainly based on cyclophosphamide given orally on a metronomic schedule. ‘Closing’ palliative surgery or radiotherapy was done after first line in 29 patients and 17 patients, respectively.

Two hundred fifty-five patients (85%) were assessable for response. Among them, 69 patients (27%) had progressive disease, 145 (57%) had stable disease, 37 (14.5%) had partial response (PR), and 4 (1.5%) complete response (CR). Global response rate (PR + CR) was 16% (Table 1). It was higher with polychemotherapy (20.8% versus 12.8% with monochemotherapy, $P = 0.02$) but not statistically different with or without anthracyclines (17.7% versus 10.5% respectively, $P = 0.2$). Response rates considering histology are given in Table 1.

Median TTP from first line was 5.9 months [4.9–7.3]. Median OS from first line was 15.8 months [13–18]. TTP and OS from first line considering histology are given in Table 2. Patients received a median of two lines (1–8), and 33% received ≥3 lines of palliative chemotherapy.

**prognostic analysis**

The only factor significantly associated with TTP from first line in univariate analysis was PS (PS = 1, HR = 1.6 [1.2–2], $P = 0.002$; PS ≥ 2, HR = 1.8 [1.2–2.8], $P = 0.007$).
Factors significantly associated with OS from first line in univariate analysis were gender, PS, histology and grade. There was no difference in terms of survival according to the stage of the disease. Median OS was 13 months [11.1–17.1] for patients with advanced LR disease, 15.5 months [11.7–19.6] for sarcomatosis and 21 months [15.9–28.1] for distant metastasis (P = 0.15).

Palliative surgery did not appear to add any significant survival benefit. Median OS was 16 months [13–24.9] for patients receiving palliative surgery versus 15.6 months [12.3–17.5] for those who did not (P = 0.83).

In multivariate analysis, factors that remained independently associated with OS were gender, PS and grade (Table 3). Median OS was 21.6 months [17.2–26.8] for patients with PS = 0, 11.9 months [9.5–14.5] for PS = 1 and 8.3 months [3.4–13.3] for PS ≥ 2 (P < 0.0001). It was 24.2 months [16.1–not reached] for grade 1, 17 months [13–24.3] for grade 2 and 11.8 months [9.3–13.9] for grade 3 tumors, respectively (P < 0.0001) (Figure 1A and B).

Table 1. Response rates to first line of palliative chemotherapy in all patients assessable for response (n = 255), and across histological subtypes: DDLPS (n = 102), WDLPS (n = 35), LMS (n = 65), US (n = 26) and other (n = 27)

<table>
<thead>
<tr>
<th>Progression</th>
<th>Stable disease</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>All patients</td>
<td>69</td>
<td>27</td>
</tr>
<tr>
<td>DDLPS</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>WDLPS</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>LMS</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>US</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 2. Time to progression and overall survival from first line of palliative chemotherapy of all patients (n = 299) and across histological subtypes: DDLPS (n = 124), WDLPS (n = 38), LMS (n = 73), US (n = 30) and other (n = 34)

<table>
<thead>
<tr>
<th>Time to progression (months) [95% CI]</th>
<th>Overall survival (months) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>5.9 [4.9–7.3]</td>
</tr>
<tr>
<td>DDLPS</td>
<td>5.8 [3.9–8.3]</td>
</tr>
<tr>
<td>WDLPS</td>
<td>5.0 [2.2–13.2]</td>
</tr>
<tr>
<td>LMS</td>
<td>7.0 [5.0–9.2]</td>
</tr>
<tr>
<td>Other</td>
<td>5.4 [1.9–8.2]</td>
</tr>
</tbody>
</table>

TTP, time to progression; DDLPS, dedifferentiated liposarcoma; WDLPS, well-differentiated liposarcoma; LMS, leiomyosarcoma; US, unclassified sarcoma.

Table 3. Multivariate analysis of factors associated with overall survival after first line of palliative chemotherapy, in all patients overall (n = 299), in patients with DDLPS (n = 124) and LMS (n = 73), respectively (reference)

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>HR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>1.5 [1.1–1.9]</td>
<td>0.009</td>
</tr>
<tr>
<td>PS (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.7 [1.2–2.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2</td>
<td>3 [1.9–4.8]</td>
<td></td>
</tr>
<tr>
<td>Grade (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.7 [1.1–2.7]</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>2.3 [1.5–3.7]</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDLPS</td>
<td>Not retained</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.6 [1–2.5]</td>
<td>0.017</td>
</tr>
<tr>
<td>3</td>
<td>3 [1.3–6.9]</td>
<td></td>
</tr>
<tr>
<td>Stage (LR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcomatosis</td>
<td>0.8 [0.3–2]</td>
<td>0.01</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0.4 [0.2–0.7]</td>
<td></td>
</tr>
</tbody>
</table>

HR: hazard ratio; CI: confidence interval; DDLPS: dedifferentiated liposarcoma; PS: performance status; LMS: leiomyosarcoma; LR: locoregional.

HR: hazard ratio; CI: confidence interval; DDLPS: dedifferentiated liposarcoma; PS: performance status; LMS: leiomyosarcoma; LR: locoregional.

Analysis of prognostic factors for OS from first line was possible in the two main histological subtypes of RPS that are DDLPS and LMS. Results of these subgroup analyses are presented in Table 3.

discussion

In this study, the most common first line of palliative chemotherapy consisted of anthracyclines, known to be the most active drugs in STS [23]. However, response rates were remarkably low. Response rate with anthracyclines was only 15% for LPS, and only one response was observed for DDLPS without anthracyclines. These results are concordant with two smaller studies which evaluated chemotherapy for advanced WD/DDLPS [15, 16] and support the poor sensitivity of LPS to conventional chemotherapy—apart from myxoid LPS, which are very rare in the retroperitoneum. Unclassified sarcomas had a response rate of only 4% which illustrates the chemoresistance of these tumors of poor prognosis.

Fifty-nine percent of the patients included in this study received first-line palliative polychemotherapy, which was associated with a better response rate but did not affect TTP or
survival compared with monochemo therapy. These results confirm current recommendations for use of monochemo therapy apart from situations where optimizing chances of response may benefit to the patients, such as for symptomatic disease [24].

The median OS was 16 months, and this is explained by the enrichment in WDLPS in the retroperitoneal localization. Indeed, OS was about two times longer for WDLPS than for DDLPS. Notably, these two histological subtypes have generally been considered as one in previous studies despite their different behavior. In fact, OS of DDLPS in the advanced setting seems as poor as that of unclassified sarcomas. On the other hand, despite a higher initial response rate, the subgroup ‘other’ had the worst OS. This result demonstrates that response to chemotherapy is not necessarily associated with survival and clinical benefit is often of short duration in these tumors.

In this study, prognostic factors associated with OS from first line of palliative chemotherapy were female gender, PS and grade. In a large study on STS, van Glabbeke et al. also found that PS and grade were significant factors associated with OS in this setting, as well as age, liver involvement and time lapse since initial diagnosis [25]. Karavasilis et al. did not take PS into account because of missing data [26]. In our study, PS was the most significant factor associated with OS, overall and more specifically in DDLPS. This study also emphasizes the importance of grade on prognosis in the palliative setting, for LMS as well as for DDLPS. The interest of grading DDLPS is still a subject of debate and our results promote grading of these tumors.

We isolated the event ‘abdominal sarcomatosis’ to allow analysis of its own prognostic value but did not show any difference according to stage. This indicates that unresectable LR disease and sarcomatosis are at least as pejorative as distant metastasis for most of these patients. van Glabbeke et al. considered liver metastasis as an independent pejorative prognostic factor for survival in advanced STS [25]. Surprisingly, unresectable LR disease and sarcomatosis were associated with a worse outcome compared with distant metastasis for LMS. The hypothesis we propose is that unresectable abdominal involvement can be more rapidly life-threatening than systemic localization in LMS of retroperitoneal localization.

We did not find any benefit in survival for palliative surgery. However, we cannot exclude that this treatment may have a symptomatic role and therefore an impact on quality of life, notwithstanding its potential morbidity [27, 28]. Further studies should address this specific point.

This retrospective study has several limits such as selection bias, or its multicenter nature that can be associated with heterogeneity, especially in assessment of response, but reflects treatment decisions made in everyday clinical practice. Due to the little number of events in rare histological subgroups, several prognostic subgroup analyses were not carried out.

This study is the first to specifically assess patterns of care in the palliative setting for patients with RPS. Overall, these results highlight the poverty of available options and the urgent need to develop new strategies for advanced RPS, taking specific biology of tumor subtypes into account. Future clinical trials will hopefully rely on pathway-specific rationales, as illustrated by recent trials testing MDM2 antagonists or CDK4 inhibitors in WDLPS/DDLPS [29]. Our data could serve as a reference for assessment of response and outcome with these investigational drugs. Patients with good PS should be offered to participate to clinical trials. Given the moderate benefit expected with standard chemotherapy and the absence of survival benefit demonstrated with palliative surgery, best supportive care should be considered in patients with poor PS.

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disclosure

The authors have declared no conflicts of interest.
references