Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years

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Background: The prognosis of advanced soft tissue sarcoma remains poor. Many phase II trials investigating new regimens have been published in the last 10 years.

Materials and methods: Full English-language reports of phase II clinical trials from January 1999 to October 2009 have been reviewed. We have defined those that provided 3- and 6-month progression-free survival rates (PFSR) >39% and 14%, respectively, as promising second-line regimens. For studies enrolling both chemotherapy and pretreated patients, we have compared the reported PFSR3 to the expected PFSR3 of an active treatment administered in the same proportions of pretreated and nonpretreated patients.

Results: Forty-nine trials were identified. Among the trials investigating new regimens in pretreated patients alone, the promising second-line regimens were ifosfamide, brostallicin, pazopanib (except in liposarcoma), temozolomide, trabectedin, dacarbazine–gemcitabine and docetaxel (Taxotere)–gemcitabine combinations (in uterine leiomyosarcoma). Among the trials enrolling both chemotherapy and pretreated patients, most regimens reached the level of efficacy; moreover, in three trials, the reported PFSR3 was particularly high: weekly paclitaxel (Taxol) in angiosarcoma, docetaxel–gemcitabine combination (in uterine leiomyosarcoma) and oral perifosine.

Conclusions: In the past 10 years, several drugs or combinations have demonstrated promising activity in exploratory phase II trials and warrant further investigation in appropriate phase III trials.

Key words: phase II trials, second-line regimens, soft tissue sarcoma

introduction

Adult soft tissue sarcomas are malignancies of connective tissue, accounting for ~1% of all human cancers [1]. While local control can be obtained through the use of surgery and radiotherapy, up to 40% of patients will eventually recur at distant sites, of whom >90% will ultimately die of this malignancy [1–3]. The most important predictor for distant metastases is the histological grade. Recent advances have refined our systemic treatment strategy for some relatively rare and unusual forms that are now best treated with (molecular)targeted therapies [such as imatinib mesylate for dermatofibrosarcoma or gastrointestinal stromal tumors (GIST)] [1]. In the vast majority of cases, however, both doxorubicin and ifosfamide remain the backbone of chemotherapy in patients with locally advanced or metastatic soft tissue sarcoma. They are the best single agents with proven activity and possibly dose–response curve. Combination chemotherapy regimens have not demonstrated improved survival compared with single agents [1]. Given that the primary aim is palliation, it is of major importance that drug side-effects do not outweigh the potential benefits of chemotherapy. For these reasons, doxorubicin remains the standard of care in this patient population in 2010. Overall survival is ~12 months [3]. Clearly, new agents with effects on soft tissue sarcoma need to be identified to improve treatment in these patients [4].

In the last 10 years, >50 phase II trials have been conducted to select drugs or combinations of drugs with potential activity as second-line regimens. Given that phase II trials are designed to detect ineffective treatments quickly, it is essential to analyze the statistical hypothesis presented in each trial carefully [5]. Van Oosterom et al. (3) and Van Glabbeke et al. [4] proposed progression-free survival rates (PFSR) at 3 and 6 months as end points for such trials. By comparing potentially active drugs (dacarbazine and ifosfamide) with ineffective drugs, the analysis
of trials conducted by European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) has made it possible to define levels of efficacy (P1) and levels of inefficacy (P0) for further phase II trials [4]. This study aims to classify the drugs investigated in the last 10 years according to prespecified levels of efficacy in order to distinguish between ineffective drugs and promising treatments warranting appropriate phase III trials.

**methods**

**publications**

Full English-language reports of phase II clinical trials (investigating classical agent or new agents or new combinations) from January 1999 to October 2009 have been considered for this study [6–57]. Bone sarcoma, rhabdomyosarcoma, GIST and primitive neuroectodermal tumors are not addressed here, as their treatment is different. We have separated studies investigating new regimens in pretreated patients alone from those combining chemonaive and pretreated patients in the same stratum.

**studies investigating regimens in pretreated patients**

The primary end points were reported 3- and 6-month PFSR in each stratum. We have collated the number of patients treated, the major characteristics of the study population (histological subtypes or tumor locations), and the 3- and 6-month PFSR. We recalculated 95% confidence intervals (95% CI) for each PFSR. Based on the EORTC experiment (380 patients), Van Glabekke et al. have previously reported that 3- and 6-month PFSR are 39% and 14%, respectively, with active drugs (dacarbazine or ifosfamide, 146 patients). Three- and six-month PFSR are 21% and 8%, respectively with inactive drugs such as mitozolomide, nimustine, fotemustine, liposome-encapsulated activating agent muramyl tripeptide phosphatidylethanolamine, etoposide, etc. In this study, we have defined the drugs yielding a 3-month PFSR ≥40% and a 6-month PFSR ≥14% as ‘potentially active’ and the drugs yielding a PFSR ≤20% or a 6-month PFSR ≤8% as ‘inactive’. All other possibilities have been classified as ‘equivocal results’.

**studies enrolling both pretreated and nonpretreated patients**

We have extracted the reported 3-month PFSR and 95% CI. We have collated the proportion of chemonaive patients, pretreated patients and reported 3-month PFSR. According to the EORTC experiment (1215 patients), the 3-month PFSR under active first-line treatment is 62% [4]. Taking into account the proportions of pretreated and nonpretreated patients for each study, we have estimated the 3-month PFSR (ideal PFSR) of an active treatment as follows: = (proportion of chemonaive patients × 0.62) + (proportion of pretreated patients × 0.39). We have identified ineffective drugs as those that did not reach this ideal PFSR (i.e. over 95% CI of reported PFSR below ‘ideal PFSR’).

**results**

**studies, drugs and regimens**

Fifty-two full reports of phase II trials in pretreated patients were published from January 1999 to October 2009 [6–57].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Investigated treatments</th>
<th>Subtypes</th>
<th>n</th>
<th>Three-month PFSR % (95% CI)</th>
<th>Six-month PFSR % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[20]</td>
<td>Brostallicin, 10 mg/m² d1 (21-day cycle)</td>
<td>All</td>
<td>43</td>
<td>45 (29–60)</td>
<td>22 (9–34)</td>
</tr>
<tr>
<td>[23]</td>
<td>DTIC, 500 mg/m² and gemcitabine 1800 mg/m² every fortnight</td>
<td>All</td>
<td>26</td>
<td>46 (27–65)</td>
<td>27 (10–44)</td>
</tr>
<tr>
<td>[15]</td>
<td>Gemcitabine, 900 mg/m² d1 and d8 every 21 days plus docetaxel 100 mg/m² d8 (21-day cycle)</td>
<td>Uterus LMS</td>
<td>51</td>
<td>72 (60–84)</td>
<td>51 (32–64)</td>
</tr>
<tr>
<td>[33]</td>
<td>Ifosfamide, 3 g/m² d1–d3 (21-day cycle)</td>
<td>All</td>
<td>40</td>
<td>65 (50–79)</td>
<td>20 (7–32)</td>
</tr>
<tr>
<td>[28]</td>
<td>Pazopanib, 800 mg/d</td>
<td>LMS</td>
<td>42</td>
<td>44 (28–59)</td>
<td>&gt;33 (–)</td>
</tr>
<tr>
<td>[28]</td>
<td>Pazopanib, 800 mg/d</td>
<td>S</td>
<td>39</td>
<td>48 (28–59)</td>
<td>&gt;33 (–)</td>
</tr>
<tr>
<td>[28]</td>
<td>Pazopanib, 800 mg/d</td>
<td>Non-Lipo</td>
<td>43</td>
<td>40 (24–54)</td>
<td>&gt;33 (–)</td>
</tr>
<tr>
<td>[38]</td>
<td>TMZ, 75–100 mg/m²/d (42-day cycle)</td>
<td>All</td>
<td>43</td>
<td>42 (27–56)</td>
<td>25 (12–38)</td>
</tr>
<tr>
<td>[9]</td>
<td>T, 0.58 mg/m²/week, 3-h infusion</td>
<td>LMS and Lipo</td>
<td>134</td>
<td>47 (39–56)</td>
<td>16 (21–36)</td>
</tr>
<tr>
<td>[37]</td>
<td>T, 1.5 mg/m²/3 weeks, 24 h infusion</td>
<td>All</td>
<td>54</td>
<td>40 (25–51)</td>
<td>24 (12–34)</td>
</tr>
<tr>
<td>[9]</td>
<td>T, 1.5 mg/m²/3 weeks, 24 h infusion</td>
<td>LMS and Lipo</td>
<td>136</td>
<td>56 (48–65)</td>
<td>44 (35–52)</td>
</tr>
<tr>
<td>[11]</td>
<td>T, 1.5 mg/m²/3 weeks, 24 h infusion</td>
<td>All</td>
<td>36</td>
<td>47 (31–63)</td>
<td>22 (8–35)</td>
</tr>
<tr>
<td>[21]</td>
<td>T, 1.5 mg/m²/3 weeks, 24 h infusion</td>
<td>All</td>
<td>99</td>
<td>52 (42–62)</td>
<td>29 (20–38)</td>
</tr>
</tbody>
</table>

CI, confidence interval; LMS, leiomyosarcoma; PFSR, progression-free survival rates; S, synovial sarcoma; Lipo, liposarcoma; DTIC, dacarbazine; TMZ, temozolomide; T, trabectedin.
From 33 reports, 40 different strata have been retained and analyzed (Tables 1–3) [6–38]. Nineteen studies enrolling chemonaive and pretreated patients in the same stratum have been analyzed separately (Table 4, [3, 9, 57]); three were excluded because of missing data (Figure 1, [44, 47, 53]).

**studies investigating new regimens in pretreated patients**

**potentially active drugs.** Table 1 shows the treatments warranting further explorations. The following regimens administered in all histological subtypes reached both prespecified levels of efficacy: trabectedin (21-day cycle) [11, 21, 37], brostallicin [20], gemcitabine and dacarbazine combination [23], long-course temozolomide [38] and ifosfamide 3 g [33]. Some regimens appeared to be potentially active for particular subtypes of sarcoma: trabectedin (weekly regimen) for liposarcoma and leiomyosarcoma [9], gemcitabine–docetaxel combination for uterine leiomyosarcoma [15] and pazopanib for the following histological subtypes: leiomyosarcoma, synovial sarcoma and nonliposarcomas [28] (Table 1).

**inactive drugs.** Most of the investigated drugs or combinations of drugs failed to reach both prespecified levels of efficacy: short-course temozolomide [36], doxorubicin associated with a multi-drug resistance inhibitor [7], docetaxel [34], raltitrexed [6], topotecan [27], bryostatin [8], TZT-1027 [26], SU416 [19], semaxanib [16], gefitinib in HER-1-expressing synovial sarcoma [26], pazopanib in liposarcoma [28] and imatinib in non-GIST [35] (Table 2). We observed that six phase II studies explored the efficacy of gemcitabine (five different schedules/145 patients) in soft tissue sarcoma [10, 12, 25, 29] or in uterine leiomyosarcoma [12]. In five cases, the study failed to reach both levels of efficacy [10, 12, 25, 29, 32].

**equivocal results.** In 10 cases (Table 3), we could not classify the drugs as potentially effective or inactive because of incomplete data [17, 30] or discrepancies at the two end points (3 and 6 months, see Table 4) [12–14, 18, 24, 31, 33].

**studies investigating new regimens in both nonpretreated and pretreated patients**

Four regimens did not reach the ideal PFSR: imatinib [41], O6-benzylguanine and carmustine combination [54], O6-benzylguanine and dacarbazine [22], and the ifosfamide combination [24]. Table 2. Inactive drugs or regimens

<table>
<thead>
<tr>
<th>Reference</th>
<th>Investigated treatments</th>
<th>Subtypes</th>
<th>n</th>
<th>Three-month PFSR (95% CI)</th>
<th>Six-month PFSR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[36]</td>
<td>TMZ, 150 mg/m² d1–d5</td>
<td>All</td>
<td>32</td>
<td>ND</td>
<td>3 (0–9)</td>
</tr>
<tr>
<td>[7]</td>
<td>Doxo + VX710 (120 mg/m²/h, 72 h CIV)</td>
<td>All</td>
<td>15</td>
<td>53 (28–78)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>[34]</td>
<td>Docetaxel, 100 mg/m² d1 (21-day cycle)</td>
<td>All</td>
<td>16</td>
<td>31 (8–59)</td>
<td>ND (–)</td>
</tr>
<tr>
<td>[29]</td>
<td>G, 250 mg/m² d1, d8, d15 (28-day cycle)</td>
<td>All</td>
<td>18</td>
<td>ND (–)</td>
<td>5 (0–16)</td>
</tr>
<tr>
<td>[32]</td>
<td>G, 1250 mg/m² d1 and d8 (21-day cycle)</td>
<td>All</td>
<td>32</td>
<td>ND (–)</td>
<td>3 (0–9)</td>
</tr>
<tr>
<td>[10]</td>
<td>G, 1000 mg/m² d1, d8, d15 (21-day cycle)</td>
<td>All</td>
<td>14</td>
<td>33 (12–48)</td>
<td>28 (16–40)</td>
</tr>
<tr>
<td>[22]</td>
<td>G, 1000 mg/m² d1, d8, d15 (28-day cycle)</td>
<td>Uterus Le</td>
<td>42</td>
<td>&gt;38 (–)</td>
<td>ND (–)</td>
</tr>
<tr>
<td>[25]</td>
<td>G, 1000 mg/m² for seven consecutive weeks followed by a 1-week rest</td>
<td>All</td>
<td>8</td>
<td>25 (3–46)</td>
<td>22 (3–41)</td>
</tr>
<tr>
<td>[6]</td>
<td>Raltitrexed, 3 mg/m² d1 (21-day cycle)</td>
<td>All</td>
<td>23</td>
<td>17 (14–20)</td>
<td>ND (–)</td>
</tr>
<tr>
<td>[27]</td>
<td>Topotecan, 1.5 mg/m² d1–d5 (21-day cycle)</td>
<td>All</td>
<td>15</td>
<td>ND (–)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>[8]</td>
<td>Bryostatin, 120 mg/m²/72 h (14-day cycle)</td>
<td>All</td>
<td>12</td>
<td>ND (–)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>[26]</td>
<td>TGT-1027, 2.4 mg/m² d1 and d8 (21-day cycle)</td>
<td>All</td>
<td>29</td>
<td>ND</td>
<td>3 (0–11)</td>
</tr>
<tr>
<td>[19]</td>
<td>SU416, 145 mg/m² twice weekly (28-day cycle)</td>
<td>All</td>
<td>26</td>
<td>27 (9–43)</td>
<td>11 (0–23)</td>
</tr>
<tr>
<td>[16]</td>
<td>Semaxanib, 145 mg/m² twice weekly</td>
<td>All</td>
<td>13</td>
<td>7 (0–22)</td>
<td>0 (–)</td>
</tr>
<tr>
<td>[26]</td>
<td>Gefitinib, 500 mg/d</td>
<td>HER-1-expressing S</td>
<td>46</td>
<td>ND (–)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>[28]</td>
<td>Pazopanib, 800 mg/d</td>
<td>Lipo</td>
<td>19</td>
<td>26 (6–46)</td>
<td>&gt;5 (–)</td>
</tr>
<tr>
<td>[35]</td>
<td>Imatinib, 400 mg/d</td>
<td>All</td>
<td>24</td>
<td>29 (11–47)</td>
<td>ND</td>
</tr>
</tbody>
</table>

CI, confidence interval; CIV, continuous intravenous; DTIC, dacarbazine; G, gemcitabine; Le, leiomyosarcoma; Lipo, liposarcoma ND, not done; PFSR, progression-free survival rates; S, synovial sarcoma; TMZ, temozolomide.
temozolomide [55, 56] and dolastatin [57]. All other regimens reached the ideal PFSR. Three seemed to provide a better outcome than ideal PFSR: weekly paclitaxel in angiosarcomas [52], gemcitabine and docetaxel combination in uterine leiomyosarcoma [45] and oral perifosine [40] (Table 4).

**discussion**

We observed that reviewing phase II clinical trials in patients with advanced soft tissue sarcoma is simple and straightforward. From the 52 remaining studies, only 10 (20%) were focused on specific histological subtypes (mainly uterine leiomyosarcoma). Only five studies (10%) were stratified. The stratified phase II trials are particularly suitable for assessing the drugs used in soft tissue sarcomas forming a heterogeneous disease group. In view of the increasing complexity of the histological classification of soft tissue sarcomas, however, this type of histology-based stratified phase II trial requires a rapid central pathological review [28]. Only three studies were randomized (7.5%). Randomized phase II trials allow the concurrent evaluation of drugs or combinations of drugs in the same timeframe and population [9, 33, 34]. The advantages of a randomized study over separate studies include decreasing the effects of patient selection bias, population drift and stage migration and the ability to ensure that uniform criteria are used [5]. Nevertheless, there are not adequately powered for formal comparisons [5]. Nineteen trials enrolled both chemonaive and pretreated patients in the same stratum, making it necessary to calculate an ideal 3-month PFSR reflecting the respective proportions of both patient categories.

Using the levels of efficacy/inefficacy defined by Van Glabbeke et al., we have classified the drugs investigated in pretreated patients with advanced soft tissue sarcoma during the last 10 years (Tables 1–3). The consistency between 3- and 6-month PFSR was ~62%. Therefore, we strongly recommend monitoring both end points in further studies. In 13 of 40 trials enrolling only pretreated patients, the investigated drug or combination of drugs yielded a 3-month PFSR ≥40% and a
6-month PFSR ≥14% (Table 1). These drugs and combinations could be considered as potentially active and require further confirmatory phase III clinical trials. These promising drugs or combinations are trabectedin, brostallicin, dacarbazine and gemcitabine combination, docetaxel and gemcitabine combination, pazopanib (in nonliposarcoma) and long-course temozolomide. It is noteworthy that the five published phase II trials investigating trabectedin reached both levels of efficacy (in terms of progression-free survival).

In contrast, numerous drugs are clearly ineffective (Table 2). In the six studies investigating the efficacy of gemcitabine alone, we observed that five did not reach any level of efficacy. In the sixth, the 3-month PFSR was 46% and the 6-month PFSR was 13%. Nevertheless, the small sample size (15 patients) implied large CI (21%–72% and 0%–30%, respectively). In view of these data, we cannot retain gemcitabine alone as a promising drug [10, 22, 25, 29, 32], even in patients with uterine leiomyosarcoma [22].

The trials enrolling both chemonaive and pretreated patients have proven imatinib, O6-benzylguanine and carmustine–dolastatin-10 combination to be ineffective regimens. Weekly paclitaxel in angiosarcomas, gemcitabine–docetaxel combination in uterine leiomyosarcomas and oral perifostine are promising regimens, providing 3-month PFSR largely superior to the ideal PFSR.

There are some limitations to this study. Firstly, we selected full English-language reports; there is no doubt that publication biases restricted the distribution of other ‘negative studies’ [58]. Some drugs or combinations are still under investigation at the time of this review and so no definitive conclusion could be made for the newest drugs or combination, for example a stratified phase II trials investigating more precisely the activity of Brostacillin in the different histological subtypes, soft tissue sarcomas. We conducted a retrospective study on published data with these limitations: across the phase II trials, the methods of tumor assessment or inclusion criteria (e.g. histological subtypes) are not homogeneous. The results of these studies could not be formally compared. We have simply presented the results in the same way, using the same metric of efficacy. This analysis is based on the PFSR and not other end points, such as toxicity profile, tolerability and complexity of administration, which could affect drug development. The choice of PFSR could be debated and some may argue that response rate is the gold standard for the assessment of new cytotoxic agents. Nevertheless, given that palliation is the primary aim of chemotherapy in patients with locally advanced or metastatic soft tissue sarcoma, from physician and patient perspectives maintaining quality of life and limiting the tumor burden with manageable drug toxicity for as long as possible, is more important than obtaining an objective response [59–61].

By nature, phase II clinical trials do not provide a definitive answer as to the activity of an investigational drug or combination of drugs. Phase II clinical trials are screening studies that aim to estimate whether a drug warrants further evaluation in a particular patient population as quickly as possible. The sample size and decision-making criteria of phase II clinical trials depend on statistical assumptions, anchored by the expected level of efficacy (P1) and of inefficacy (P0). If the investigational drug or combination achieves P1, the investigational regimen deserves further investigation. If the results of the phase II clinical trial yield the level of activity expected from an inactive drug or combination, however, the investigational treatment is rejected from further testing. Moreover, the sample size is calculated to ensure that these two criteria are mutually exclusive [4, 5]. It is of major importance, therefore, that the values of P0 and P1 are objectively justified. The thresholds proposed by the EORTC-STBSG provide a rationale for rejecting ineffective drugs or selecting promising drugs.

The aim of the present study was not to provide a daily guidance for daily practice because the promising activity of some drugs or combinations had not been confirmed by appropriate phase III trials (e.g. efficacy of docetaxel–gemcitabine combination in patients with metastatic uterine leiomyosarcoma). The primary aim of the present study is to generate hypothesis for further clinical trials, if possible appropriate phase III clinical trials, which analyze other end points, such as overall survival, toxicity profile and possibly quality of life. A ‘positive’ result from a phase II trial is not usually considered sufficient to justify the routine administration of the drug. Today, there are at least 10 potentially active drugs or combinations that warrant sufficiently resourced phase III trials.

**disclosure**

The authors declare no conflict of interest.

**references**


