Correlation between overall survival and growth modulation index in pre-treated sarcoma patients: a study from the French Sarcoma Group†

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Background: Growth modulation index (GMI), the ratio of two times to progression measured in patients receiving two successive treatments (GMI = TTP2/TTP1), has been proposed as a criterion of phase II clinical trials. Nevertheless, its use has been limited until now.

Patients and methods: We carried out a retrospective multicentre study in soft tissue sarcoma patients receiving a second-line treatment after doxorubicin-based regimens to evaluate the link between overall survival and GMI. Second-line treatments were classified as ‘active’ according to the EORTC-STBSG criteria (3-month progression-free rate >40% or 6-month PFR >14%). Comparisons used chi-squared and log-rank tests.

Results: The population consisted in 106 men and 121 women, 110 patients (48%) received ‘active drugs’. Median OS from the second-line start was 317 days. Sixty-nine patients experienced GMI >1.33 (30.4%). Treatments with ‘active drug’ were not associated with OS improvement: 490 versus 407 days (P = 0.524). Median OS was highly correlated with GMI: 324, 302 and 710 days with GMI <1, GMI = [1.00–1.33], and GMI >1.33, respectively (P < 0.0001). In logistic regression analysis, the sole predictive factor was the number of doxorubicin-based chemotherapy cycles.

Conclusion: GMI seems to be an interesting end point that provides additional information compared with classical criteria. GMI >1.33 is associated with significant OS improvement.

Key words: end point, growth modulation index, soft tissue sarcoma, time to progression

introduction

Soft tissue sarcomas (STS) are a heterogeneous group of tumours, accounting for 2% of adult cancers [1]. STS comprises more than 50 different histological subtypes. Despite an optimal local treatment (large en-bloc resection and adjuvant radiotherapy), more than 40% of patients experience metastatic recurrence [2]. Palliative chemotherapy based on doxorubicin represents the standard of care in these patients [3]. Doxorubicin provides a response rate of ~20% and a median overall survival (OS) time of ~12–18 months [4, 5]. Currently, there is no commonly accepted treatment after intolerance or failure of doxorubicin-based regimen. Nevertheless, several new drugs provide promising signs of activity: trabectedin [6], gemcitabine-docetaxel [7], pazopanib [8, 9], eribulin [10], brostacillin [11], and temozolomide [12].

The vast majority of literature data about the second-line treatment of advanced STS consists of a litany of phase II trials [13]. Confirmed phase III trials are rare [9]. In this context, it is important to note that the aim of phase II trials has been to screen out ineffective agents based on a pre-specified level of activity and to identify the most promising regimens for further randomised confirmatory phase III trials. The phase II trials constitute a crucial go/no go step for drug development [14, 15]. To select potentially active drugs, phase II trials require the use of standardised and rapidly available primary end points. RECIST remains the most frequent metric [16]. However, with the development of biochemically specific tumour growth inhibitors like the targeted therapies, the percentage of tumour shrinkage appears less relevant. Thus, other end points that take tumour growth dynamics into account could be considered, as for example, the rate of progression at fixed time points [17–20].
The use of inappropriate end points may lead to erroneous results and would thereby jeopardise the drug development process. On the retrospective analysis of several phase II trials, the Soft Tissue and Bone Sarcoma Group of EORTC have proposed 3-month progression-free rate as a primary activity end point, 20% being the level of insufficient activity (P0) and 40% the level of promising activity (P1) in sarcoma patients after failure or intolerance to doxorubicin [21]. Most of the recent phase II trials have been based on these statistical assumptions [8, 10, 13].

Many other activity end points have been proposed [20]. For example Von Hoff et al. [17] have proposed the Growth modulation index (GMI). GMI is the ratio of TTPs (time to progression) between two consecutive lines of therapy: TTPs with prior treatment (TTPn) and with subsequent experimental treatment (TTPn + 1). GMI (GMI = TTPn+1/TTPn) provides an attractive intra-patient comparison. Because the successive TTPs tend to be shorter in subsequent treatment lines in advanced forms of cancer, Von Hoff et al. [17] have suggested that GMI >1.33 is a non-ambiguous sign of drug activity. Until now, this criterion has been rarely used [22–27].

Based on these facts and because the choice of activity end point in phase II is crucial for improving the treatment of sarcoma patients, we conducted a multicentre study to (i) measure the GMI in patient with metastatic STS, (ii) measure the correlation between TTP1 and TTP2, and (iii) explore the link between GMI and other traditional activity end points.

**patients and methods**

**database**

We carried out a retrospective study in seven centres of the French Sarcoma Group (Lille, Lyon, Marseille, Dijon, Bordeaux, Nantes, and Besançon). The key-eligibility criteria were (i) patients with histologically proven metastatic STS, (ii) first-line treatment including doxorubicin, (iii) receipt and then receiving a second-line treatment, and (iv) available TTP1 and TTP2. All consecutive patients corresponding to those criteria were included. Patients received their first-line treatment between February 2000 and June 2011.

**calculation of growth modulation index**

TTP1 was the TTP observed with doxorubicin-based regimen as first line. TTP2 was the TTP observed with the second-line regimen. In both cases, TTP was measured according to RECIST 1.0. GMI was the ratio of both TTPs: GMI = TTP2/TTP1 [17–19]. In all cases, GMI was calculated; there was no censored data.

**definition of active drugs**

These patients received different second-line regimens. According to a critical review of the published trials [13], we considered the following regimens to be active drugs: ifosfamide in all histological subtypes, gemcitabine and docetaxel in all histological subtypes, paclitaxel in angiosarcoma, and trabectedin in all histological subtypes.

**statistical analysis**

The description of patients was based on classical descriptive statistics: number of cases, percentages, mean and standard deviation, median, and extreme values. We estimated the correlation coefficient between TTP1 and TTP2. OS was calculated from the day 1 of the second-line treatment to the day of the patient’s death. The exploration of the link between GMI and OS was carried out using Log-rank test. The associations between GMI and other classical activity end points (best objective RECIST 1.0 response, response at 3 months and response at 6 months) were analysed using $\chi^2$ tests. The identification of predictive factors for GMI >1.33 was carried out using univariate logistic regression analysis.

**results**

**general**

The study population consisted of 227 patients (121 women and 106 men). The median age was 57 (range, 1–82). The most common primary sites were limbs ($n$ = 90), retropertitoneum ($n$ = 45), and uterus ($n$ = 36). The most common histological subtypes were: leiomyosarcoma ($n$ = 87), liposarcoma ($n$ = 35), synovial sarcoma ($n$ = 17), and undifferentiated spindle cell sarcoma ($n$ = 30). FNCLCC grade was known in 175 cases. Plus doxorubicin, the first-line treatment also included ifosfamide in 116 cases and dacarbazine in 31 cases. One hundred and ten patients received an active regimen as a second-line treatment (Table 1).

**growth modulation index**

The median TTP1 was 197 days (range, 17–2191 days). The median TTP2 was 134 days (range, 2–1616 days). The correlation coefficient between TTP1 and TTP2 was $R^2 = 0.07$ ($P = 0.147; S1$). The median GMI was 0.75 (range, 0.01–27.5). Sixty-nine (30.4%) patients experimented a GMI >1.33, of whom 30 had received an inactive drug.

**GMI and overall survival**

The median OS was 317 days (range, 2–3259 days). There was a strong correlation between GMI measured as a continuous variable and OS: hazard ratio = 0.842 ([0.746–0.924], $P < 0.001$). We then partitioned the patients according to three values of GMI: GMI <1, 1 <GMI <1.33, and GMI >1.33. The median respective OS of each partition was 324, 302, and 710 days ($P = 0.0001; S2$). GMI >1.33 was associated with a significant improvement of OS (Figure 1).

**predictors for GMI >1.33**

None of the tested clinical and pathological risk factors was predictive for GMI >1.33 (Table 1). Patients who received six cycles of doxorubicin corresponding to the cumulative dose had a lower probability of GMI >1.33. The number of cases was too limited to explore the role of each drug. Patients who received active or inactive drugs according to classical definitions as a second-line regimen experienced the same range of GMI >1.33.

Furthermore, we classified the patients into four groups according to their GMI and which drug they received as second line (active or inactive): GMI >1.33/active drug, GMI >1.33/inactive drug, GMI <1.33/active drug, and GMI < 1.33/inactive drug. The median respective OS of each group was 680, 710, 324, and 324 days, respectively, ($P < 0.0001$), suggested that GMI was predictive of OS, but not the use of active/inactive drug according to the classical definition (S3).
GMI and other activity end points
There were strong correlations between GMI and parameters of response to second-line regimens: best objective response, response at 3 months and response at 6 months (Table 2).

discussion
The present study suggests a correlation between GMI and OS in patients with advanced STS treated with different second-line chemotherapy regimens. GMI > 1.33 was associated with a significant improvement of OS (710 days, *P* < 0.001). Furthermore, the GMI was related to other classical activity end points such as the objective response according to RECIST, or the non-progression rate at fixed time points, which is the common assessment method used as the EORTC-STBSG criteria for defining an active drug [21]. The GMI seems to be useful in a heterogeneous population such as STS patients. Easily calculated and feasible [22, 23], GMI eliminates inter-patient variability by providing an intra-patient comparison of

<table>
<thead>
<tr>
<th>Total n (%)</th>
<th>GM1 &gt;1.33, n</th>
<th>GM1 ≤1.33, n</th>
<th>Odd ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>121 (53.3)</td>
<td>36</td>
<td>85</td>
</tr>
<tr>
<td>Men</td>
<td>1064 (46.7)</td>
<td>33</td>
<td>73</td>
</tr>
<tr>
<td>Limb</td>
<td>90 (39.6)</td>
<td>23</td>
<td>67</td>
</tr>
<tr>
<td>Uterus</td>
<td>36 (145.9)</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Retropertoneum</td>
<td>45 (19.8)</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>Other primaries</td>
<td>56 (24.7)</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Age &lt; 25 years</td>
<td>11 (4.8)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Age = [25–60] years</td>
<td>134 (59)</td>
<td>42</td>
<td>92</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>82 (36.1)</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>87 (38.3)</td>
<td>23</td>
<td>64</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>35 (15.4)</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>30 (13.2)</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>17 (7.5)</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Other subtypes</td>
<td>58 (25.6)</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Grade 1</td>
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<tr>
<td>Unknown grade</td>
<td>52 (22.9)</td>
<td>18</td>
<td>34</td>
</tr>
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</table>

**Table 1.** Patient characteristics and predictors for GMI >1.33

**Table 2.** Predictors for GMI >1.33 and OS. **Table 2.** Predictors for GMI >1.33 and OS.

**Table 3.** Predictors for OS and active drugs.

**Table 4.** Predictors for OS and active drugs.
progression-free survival (PFS), such that each patient/tumour couple becomes its own control [28]. Unlike an isolated PFS, the GMI measures the impact of successive treatments on the natural history of the disease with the hypothesis that TTP becomes shorter as the disease progresses [17]. Nevertheless, until now, clinical reports on the use of GMI have remained rare in the literature [22, 23, 25, 26].

Interestingly, we found that the OS was not significantly different in patients who had received an ‘active drug’ as a second-line regimen compared with the others even if patients who had received an active drug experienced a longer PFS (153 days versus 111 days, \( P = 0.042 \)). This observation confirms the recently observed limitations of the EORTC-STBSG criteria, with a lack of confirmed phase III trials despite promising drug activity found in phase II trials [13].

Von Hoff had arbitrarily proposed the GMI >1.33 cut-off as a definition of an active drug [17]. He suggested that this threshold provides a meaningful benefit and avoids hazardous fluctuations. In our study, the 1.33 cut-off appears to be more relevant than 1.00 (Table 2). Similar results have been found in STS patients who received trabectedin as salvage therapy [27], which justified the use of this cut-off in STS.

Interestingly, the classical parameters used for describing STS (histological subtypes, grade, locations of metastasis) are not predictive of having a GMI >1.33. This finding suggests that GMI is the marker of the tumour growth inhibition; this time-dependent dynamic phenomenon seems to not be dependent on these classical descriptive parameters. This result indicates that GMI measures, at an individual level, the contrast between the tumour control obtained with second-line treatment and the tumour control obtained with classical first-line treatment. However, we observed that patients who received the cumulative dose of doxorubicin were most likely those achieving a GMI < 1.33. In these cases, doxorubicin was administrated for as long as possible, most likely without severe toxic effect or disease progression. This finding may be related to the aggressiveness of the tumour, resulting in a good initial response to the first treatment, but with a rapid relapse with the subsequent treatments. However, GMI’s value depends on the response to the first line. A patient with a good response for both first-line and second-line will experiment worst GMI.

There are some limitations to this study. First, GMI is not a validated end point, and there are some methodological limitations for its use. The main methodological difficulties are related to two factors: (i) GMI requires a good estimate of correlation between TTP1 and TTP2 [18, 19], and (ii) GMI is highly exposed to time-assessment bias [19–26, 28]. In the present study, the GMI was evaluated retrospectively. There is no doubt that the time of tumour assessment was not uniform for each patient. Thus, the GMI results must have been influenced by the frequency of the tumour evaluation, which may have been different among the participating centres or if the patient was included in a clinical trial. As TTP is a time-dependent criterion, the visit schedule and data collection procedures should be standardised to avoid ascertainment bias [23]. Furthermore, using the GMI as end point requires the inclusion of pre-treated patients who have undergone a previous treatment failure, with the risk of loss of information and a hazardous evaluation schedule during the first line of chemotherapy.

Another major methodological for the use of GMI, which corresponds to a paired failure time, is that this criterion requires, in theory, a strong correlation between TTP1 and TTP2 [18, 28]. In our study, this correlation was low \( (R^2 = 0.07; P = 0.147) \). Nevertheless, a strong correlation seems to be rarely found in the literature [18, 22, 26]. This correlation is an important parameter for sample calculations in future clinical trials based on GMI [18]. Another challenge with using GMI is represented by slow-growing tumours, for which a long period of time is needed to distinguish the absence of progression due to treatment effect from the natural history of disease. An increased follow-up may be responsible for loss of participants and may increase the need for enrolment of more patients.
leading to increases in the duration and the cost of the trial. Nevertheless, the use of classical end points such as PFS is prone to the same issue for slow-growing tumours.

Finally, the improvement of the OS with a GMI >1.33 was high in our study (710 days versus 324 days). Since now, no data have proved a link between GMI >1.33 and the tested treatment. Thus, the GMI needs to be evaluated in prospective trials.

This study suggests that GMI could be an interesting exploratory end point in future prospective early trials investigating new drugs in sarcoma patients. This study raises new questions that will require additional studies, including: (i) what are the biological mechanisms that explain and drive the increase of GMI? (ii) what is the optimal proportion of patients with GMI >1.33 that would define a promising drug? and (iii) are we sure that a drug that provides a sufficient proportion of GMI >1.33 responses will be effective in adjuvant or neoadjuvant therapy?

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disclosure

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references