Abstract

Despite extensive research efforts over the past two decades to identify effective agents for the treatment of soft tissue sarcomas, few agents are available, and with modest utility. There is a high unmet medical need to develop novel therapies for the treatment of patients with soft tissue sarcomas. Clinical trials for soft tissue sarcomas should be optimally designed, and it is crucial that they identify and define the desired clinical outcome. Survival is often the ultimate endpoint; however, physiological and biological markers are often used to predict the potential therapeutic benefit of a new agent. These endpoints can be easily measured, but can lead to false-positive results and do not take into account the complicated nature of soft tissue sarcomas. Alternative endpoints that are currently being evaluated include the progression-free survival rate, time to progression, tumor growth rate, and progression arrest rate. This article discusses some of the limitations of current endpoint criteria and potential endpoint criteria that could be used to evaluate treatment options for patients with soft tissue sarcomas. The Oncologist 2008;13 (suppl 2):27–31

Introduction

Soft tissue sarcomas are malignant tumors that may arise in the mesenchymal tissues of the extremities, trunk, retroperitoneum, head and neck, and, more rarely, the gastrointestinal tract or gastrointestinal stroma. The American Cancer Society estimates that about 9,220 new soft tissue sarcomas will be diagnosed in the U.S. in 2007; 1,840 male and 1,720 female patients are expected to die from the disease [1]. Despite an extensive research effort in the past two decades to identify effective agents for the treatment of soft tissue sarcoma, few have been identified. Only three cytotoxic drugs have demonstrated activity in soft tissue sarcoma: doxorubicin, ifosfamide, and, to a lesser extent, dacarbazine, although even these agents are associated with relatively low objective response rates (RRs). Doxorubicin and ifosfamide, which either alone or together compose the standard chemotherapy regimens for soft tissue sarcoma, have consistent RRs of only 10%–25% as single agents [2–5]. Novel therapies for the treatment of soft tissue sarcoma are therefore urgently needed.

Phase II clinical trials are essentially evaluating data designed to assess whether a new agent is worthy of further investigation in phase III trials. In designing phase II clinical trials to identify viable agents for the treatment of soft tissue sarcoma, it is important to properly define the desired clinical outcome. Survival is the ultimate, definitive endpoint for evaluating the efficacy of an oncology drug. However, survival data take a relatively long time to mature, and they may be confounded by subsequent therapies. Therefore, surrogate endpoints, which are physiological or biochemical markers that are thought to be predictive of clinical outcome, are often used to predict potential therapeutic benefit. One benefit of surrogate endpoints is that they are relatively quickly and easily measured. However, the use of surrogate markers can lead to the production of false-positive results. For example, although a therapy may influence levels of one or more surrogate markers, this does not necessarily translate to any effect on the disease process. Thus, additional criteria for identifying agents with activity in soft tissue sarcoma should be established.
ISSUES WITH CURRENT ENDPOINTS IN SARCOMA
Several issues make traditional phase II trial designs unsuitable for screening new soft tissue sarcoma agents. First, objective response may not be an appropriate surrogate marker for therapeutic activity in soft tissue sarcoma. The widely used Response Evaluation Criteria in Solid Tumors (RECIST) define response in terms of the degree of target lesion reduction. However, a few limitations exist for the evaluation of tumor response by volume reduction in soft tissue sarcoma. Accurate measurement of tumor dimensions can be challenging in non–well-defined lesions, such as peritoneal metastases or lesions found in the gastrointestinal tract. In addition, because tumor tissue may be replaced by necrotic or fibrotic tissue, a substantial reduction in viable tumor cell volume may not result in a marked decrease in overall tumor volume. Finally, the sarcoma might be completely removable by surgery even after minor but clinically relevant tumor reduction.

Another issue with assessing response in soft tissue sarcomas is that many of the new agents being investigated are cytostatic. In contrast to cytotoxic agents, which more often reduce tumor size, cytostatic agents (e.g., antiangiogenic agents) modulate tumor environments and/or cellular targets, thereby delaying tumor growth. Such agents are therefore not expected to result in a decreased tumor volume, which makes traditional response criteria irrelevant in this setting.

Finally, objective response does not encompass duration of response, quality of response, or disease stabilization. Disease stabilization is particularly relevant to soft tissue sarcoma, as patients who exhibit prolonged stable disease (SD) in the absence of tumor volume changes sufficient to be classified as complete response (CR), partial response (PR), or progressive disease (PD) often have similar clinical outcomes as those patients who experience a PR [6–8]. As an example, Figure 1 compares the hypothetical tumor evolution of two soft tissue sarcoma patients during treatment with dacarbazine. One patient achieved a PR that lasted 4 weeks and then progressed, while the other patient never achieved a PR, but disease stabilization effectively postponed progression. In such patients, progression may be a more valid primary endpoint than objective response.

PROGRESSION AS AN ENDPOINT
Classical phase II clinical trial designs aim to characterize the activity of a new agent as either a success or a failure in each patient. If trial results are consistent with the level of activity expected from an active agent (P1), the new agent deserves further testing. Likewise, if the results are consistent with the level of activity expected from an inactive agent (P0), the new agent is rejected from further testing. A phase II trial is considered to be positive when the level of activity of the new agent is consistent with that of an established active agent, with a confidence level (β) as low as 5% or 10% [9].

Progression-Free Rate
To create a standard reference to guide the choice of the active and inactive parameters of statistical designs for phase II soft tissue sarcoma trials, van Glabbeke et al. (2002) [10] explored data on 1,154 patients from the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group database. The aim of that study was to estimate the progression-free rates (PFRs) that can be reasonably expected from an active agent (or combination) and from an inactive agent in soft tissue sarcoma. All patients entered in the studies used had to have proven progression prior to entry. The study investigators examined PFRs at 3 months and 6 months in both previously treated and untreated patients with a variety of soft tissue sarcomas who received 11 different agents according to 13 therapeutic regimens. Only two of these agents, doxorubicin and ifosfamide, demonstrated significant antitumor activity and were thus considered to be active drugs. The decision to assess 3- and 6-month PFRs was a compromise between the need to avoid false-positive results and the practical complications that can be associated with long observation periods. Importantly, in this analysis by the EORTC, progression was still defined according to the World Health Organization (WHO) criteria. However, based on the original publication of the RECIST, there was hardly any difference in progression rates if assessed by the WHO criteria or the RECIST [11]. In later work the EORTC also confirmed this in a prospective study on ecteinascidin (ET)-743, directly comparing the WHO criteria with the RECIST [12]. In 146 pretreated patients who received an active agent, the PFRs were estimated to be 39% and 14% at 3 and 6 months, respectively, while the PFRs in 234 patients treated with inactive regimens were 21% and 8%, respective

![Figure 1](http://theoncologist.alphamedpress.org/)  
**Figure 1.** Hypothetical tumor evolution in two soft tissue sarcoma patients during treatment.  
Abbreviations: PR, partial response; SD, stable disease.
tively (Fig. 2). These results suggest that for the second-line treatment of soft tissue sarcoma, a 3-month PFR ≥ 39% may be representative of an active agent, while a 3-month PFR ≤ 21% may be representative of an inactive agent. Likewise, 6-month PFRs ≥ 14% and ≤ 8% suggest active and inactive agents, respectively. PFRs that fall between these values may not be as useful and necessitate analysis of other parameters to determine whether a drug should be advanced to phase III trials. The EORTC concluded that these estimates are sufficiently reliable to be used in phase II trials as reference values for the P0 and P1 parameters of the statistical design in future phase II trials and suggested that parameters estimated from clinical trial data with an error rate of 5% can be used as a guide to proceed with the clinical development program of a new agent but not to prove the therapeutic value of the drug.

**Time to Progression Ratio**

Another manner of evaluating progression is to examine time to progression (TTP), which is defined as the time from initiation of therapy to first documentation of disease progression or worsening of disease-related symptoms [13]. Mick et al. [13] examined a phase II clinical trial design that evaluates the clinical benefit of cytostatic agents by comparing the most recent TTP before study entry (TTP1), that is, on a previous drug, with the TTP on study drug (TTP2). The study authors concluded that if the ratio of the two sequentially measured failure times (TTP2/TTP1), called the “growth modulation index,” exceeds 1.33, then the drug is potentially active and should be investigated in phase III trials. While this method is theoretically attractive, it is applicable only to patients for whom the time to previous progression has been accurately documented.

The growth modulation index was put into use in a study that investigated the outcome of patients with advanced gastrointestinal stromal tumors (GISTs) who crossed over to high-dose imatinib mesylate (800 mg) after progression on low-dose (400 mg) imatinib [14]. GISTs represent a subset of sarcomas that develop in the gastrointestinal tract and often spread within the abdomen. While GISTs account for only 0.2% of all gastrointestinal tumors, 80% of all gastrointestinal sarcomas are GISTs [15]. Imatinib mesylate is a small-molecule inhibitor of at least three human receptor tyrosine kinases, including Kit, which is mutated in the majority of GIST patients [16]. Imatinib has demonstrated efficacy in this disease state [17] and is indicated for the treatment of Kit-positive GISTs. In the imatinib dose crossover study, only 2.5% of patients who crossed over from 400 mg of imatinib to 800 mg of imatinib had a PR as defined by the RECIST [14]. However, calculation of the growth modulation index revealed that 24.5% of patients had a TTP2/TTP1 > 1.33, suggesting that 800 mg of imatinib has specific activity in a proportion of patients who progress on the 400-mg dose. This value was closer to that (32.8%) for overall response (PR + SD), which further indicates that disease stabilization can have a substantial impact on progression.

**Tumor Growth Rate**

Progression may also be assessed by comparing variations in tumor growth rate (TGR) before and after treatment initiation. Lopez-Martin et al. (2003) [18] analyzed the effects of ET-743, a novel tetrahydroisoquinoline compound that has been shown to block cell cycle progression in a number of preclinical sarcoma models [19], as a third-line agent in pretreated, advanced soft tissue sarcoma patients [18]. TGR was defined as the relative variation in tumor measurements per unit of time (months). For each patient, TGR was calculated before and after treatment initiation. As shown in Figure 3A, these patients experienced true tumor progression, with growth rates as high as 40% in the 5 months prior to treatment. Following initiation of ET-743 therapy, patients experienced a significant decrease in TGR. Interestingly, 25% of patients who did not achieve a formal regression (Fig. 3B) did experience long-lasting SD that lasted an average of 17 months, which is relatively long for soft tissue sarcoma, particularly with first-line treatment.

**Progression Arrest Rate**

A fourth method of evaluating progression is to establish a PD threshold, which involves setting a maximum PD rate above which an agent will be rejected [20]. Table 1 shows a
comparison between RR data and PD rate data from phase II studies in various solid tumor types. Setting a PD threshold of 50% for soft tissue sarcomas may be a useful method for assessing the activity of therapies in screening trials. An example of the progression arrest rates (PARs) from a number of agents investigated in phase II trials for the treatment of soft tissue sarcomas is shown in Figure 4. Four agents—doxorubicin, trofosfamide, ET-743, and ifosfamide—have mean PARs >50% and therefore fall above the PD threshold of 50%. These results indicate that PARs may be useful, early signs for assessing whether a drug may be active in soft tissue sarcoma.

**Symptom Palliation**

An alternative, although somewhat less effective, endpoint for predicting progression is symptom palliation. The symptom improvement rate can be a very easy instrument to assess the clinical benefit of an agent—in many cases, symptom evaluation does not even require radiographic assessment. The epidermal growth factor receptor tyrosine kinase inhibitor gefitinib is an example of an agent that has a relatively low response rate (18.4%–19.0%) but a much larger symptom benefit rate (37.0%–40.3%) [21]. While a demonstrable overall clinical benefit based on symptom relief can be part of the U.S. Food and Drug Administration approval for a drug, this was not the case for gefitinib, because of various methodologic issues in the symptom relief analysis [22]. However, in a phase II trial of imatinib in GIST patients, tumor-related symptoms were relieved in 24 of 27 (89%) patients, often within a week after initiating therapy (Fig. 5) [23]. Seventy-three percent of patients remained progression-free at 1 year, suggesting that symptom palliation may actually be predictive of disease progression.

![Figure 3](http://theoncologist.alphamedpress.org/)

**Figure 3.** Variation in tumor growth rate estimates in pre-treated patients with advanced soft tissue sarcoma who experienced clinical benefit with ecteinascidin-743. (A): Total population. (B): Patients without tumor regression but who experienced long-lasting stable disease. Abbreviation: IC₉₅, 95% inhibitory concentration.

### Table 1. Response rates versus progressive disease rates in various tumor types

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Response rate</th>
<th>Progressive disease</th>
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<tr>
<td>Breast&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;30%</td>
<td>&lt;20%</td>
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<td>Non-small cell lung carcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Glioma&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;10%</td>
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<tr>
<td>Soft tissue sarcoma</td>
<td>&gt;10%</td>
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<sup>a</sup>Data from the National Cancer Institute of Canada database [19].

<sup>b</sup>Theoretical.

![Figure 4](http://theoncologist.alphamedpress.org/)

**Figure 4.** Progression arrest rates in phase II clinical trials of various agents being investigated for the treatment of soft tissue sarcomas. Abbreviations: ESO, esorubicine; ET-743, ecteinascidin-743; IFN, interferon.

![Figure 5](http://theoncologist.alphamedpress.org/)

**Figure 5.** Response versus symptom improvement rate for imatinib in gastrointestinal stromal tumor patients.
CONCLUSIONS
Phase II studies do not provide a definitive answer regarding the activity of an investigational agent. Phase II studies are truly screening studies, and their aim is to estimate as quickly as possible whether a drug may be useful in a certain patient population. Response is not always the best endpoint for phase II clinical studies, particularly for a complex family of diseases such as soft tissue sarcomas. Alternative endpoints that are currently being evaluated and show some potential in this setting include the PFR, TTP ratio, TGR, and PAR.

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