Phase II Studies in Soft Tissue Sarcoma: Time for Reappraisal

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Soft tissue sarcoma (STS) is a very heterogeneous group of tumors, in which >50 different entities are discerned. Despite this heterogeneity among the different entities, all advanced STS subtypes have been treated similarly, with doxorubicin and ifosfamide as the most commonly applied agents. This changed approximately a decade ago when the importance of STS subtyping was shown by the success obtained with imatinib for gastrointestinal stromal tumors (GISTs). Since then, STS research has focused more on subtype-specific treatments, which resulted in the identification of new treatments for several STS entities, including taxanes for angiosarcoma, trabectedin for liposarcoma and leiomyosarcoma, imatinib for dermatofibrosarcoma protuberans, and gemcitabine and the combination of gemcitabine and docetaxel for leiomyosarcoma [1]. However, despite these additional treatment options, the prognosis for patients with advanced STS has roughly remained the same over the last decades, stressing the high need for novel agents.

In the search for novel treatment options, phase II studies play a crucial role. Phase II studies are screening studies in which it is determined, mainly on the basis of predefined criteria for antitumor activity, whether or not a regimen for a particular tumor type is worth investigating further. If a phase II study fails to identify an inactive regimen as inactive, patients participating in the subsequent phase III studies will be exposed to unnecessary side effects while precious time and money will be wasted and the development of other potential active regimens will be hindered. On the other hand, the development of true active drugs should not be halted during phase II studies, emphasizing the need for correct design and execution of phase II studies.

In the article accompanying this commentary [2], the French Sarcoma Group describes a phase II study with sorafenib in patients with angiosarcomas. Sorafenib is a tyrosine kinase inhibitor targeting several factors, including BRAF and vascular endothelial growth factor receptor

(VEGFR). The progression-free rate (PFR) at 9 months served as the primary endpoint and a two-stage design according to Simon was applied. Two different tumor strata were studied: patients with superficial angiosarcoma and those with visceral angiosarcoma. Both strata were stopped after the first stage because of insufficient antitumor activity. The PFRs at 9 months were 3.8% and 0% for the two strata, respectively, which led the authors to conclude that sorafenib has only limited activity against this tumor type. There are several elements of this study that merit further attention because these are generally applicable to most phase II studies in STS.

The first issue concerns which drugs should be investigated in what population. Unfortunately, sorafenib's exact mechanism of action is not known, but it is thought to be through antiangiogenic effects. In recent years, much effort has been put into studies exploring antiangiogenic drugs, including sunitinib, bevacizumab, and also sorafenib. Until now, only pazopanib had been explored in a phase III study, which was presented at the latest American Society of Clinical Oncology Annual Meeting [3]. The threefold longer progression-free survival (PFS) interval with pazopanib than with placebo in patients with advanced nonadipocytic STS failing doxorubicin- or ifosfamide-based regimens shows the potential of antiangiogenic drugs in STS treatment. But, importantly, the antitumor activity was still relatively modest, with a median PFS duration of 4.5 months in pazopanib-treated patients [3]. This underlines the importance of finding the most appropriate populations that could benefit from such therapies. To study a specific STS histological subtype, such as was done in the study accompanying this commentary, is a good initiative, but probably not enough. Indications that the VEGF-VEGFR pathway is important in the tumor biology of angiosarcomas and hints of antitumor activity with sorafenib for vascular tumors in a previous phase II trial [4] formed the rationale to explore sorafenib for angiosarcoma treatment, but the exact

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factors that drive the tumor biology of angiosarcoma and whether or not these can adequately be inhibited by sorafenib are unknown. In an attempt to identify a subgroup of angiosarcoma patients who may benefit from sorafenib, the mutational status of *VEGFR-2* was assessed. It was previously reported that ~10% of angiosarcoma patients have tumors harboring mutated *VEGFR-2* and that *VEGFR-2* phosphorylation of cells carrying this gene variant could be easily inhibited by sorafenib [5]. Unfortunately, none of the patients included in this trial had a tumor carrying this gene variant.

The disappointing results from this trial show that, before commencing trials with drugs in certain populations, an adequate understanding of which factors are important in the tumor biology of the investigated tumor type and whether or not the drug of interest can block the function of these particular factors is crucial. Furthermore, with respect to antiangiogenic drug for STS, we have to go back to the results from previous trials of sorafenib and other antiangiogenic drugs for STS and to determine retrospectively whether or not we can find factors associated with outcome. This may lie in a particular profile of soluble angiogenic blood factors or in tumor characteristics that go beyond histopathological subtyping. Only by such efforts can the right patients for the right drug be identified, thereby increasing the likelihood of success using these agents for STS treatment.

Another important issue coming forth from this study by the French Sarcoma Group [2] is how to assess antitumor activity in an STS phase II trial. The most traditional endpoint in phase II studies is the response rate (RR). Assessment of responses is relatively easy, and because spontaneous tumor shrinkage is extremely rare, a drug that induces responses is certainly doing something. But in cases when a drug yields responses that are only short lived, it is questionable whether or not such a drug provides clinical benefit. Moreover, there are several drugs that induce a low RR but lead to a better overall survival outcome, including sorafenib for hepatocellular carcinoma, which, in a placebo-controlled phase III trial showed an RR of 2% but resulted in a median survival time that was 2.8 months longer [6]. Additionally, the finding that patients with GISTs who experience stable disease with imatinib have an overall survival outcome similar to that of patients with a response to imatinib and fare much better than patients with progression clearly indicates that prolonged disease stabilization can also benefit patients [7]. In order to not miss drugs yielding a low RR but inducing prolonged disease stabilization, the PFR at a certain time point after treatment initiation has been proposed as an endpoint in phase II studies [8]. For that purpose, the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC-STBSG) established PFRs at 3 and 6 months for regimens considered “active” and “nonactive” when given as second-

line therapy [8]. These thresholds to identify active and non-active treatments were subsequently used in several trials and their relevance was recently shown. On the basis of a PFR at 3 months that was higher than the PFR at 3 months for second-line therapies for STS as established by the EORTC-STBSG [8], pazopanib explored in a phase II study was considered active, warranting further investigation in patients with relapsed nonadipocytic STS [9]. And in a recent, placebo-controlled phase III trial, the activity of pazopanib in this setting was confirmed [3]. In the study discussed herein, the PFR was also chosen as the primary endpoint. If the PFR at a certain time point is the primary endpoint, it is essential that there is objective progression before study entry within the same period in which the PFR is determined after treatment initiation. Otherwise, in the case of an indolently progressing tumor, no progression at a certain time point may only reflect the natural course of the disease and the drug may not impact tumor growth. Remarkably, in the study by the French Sarcoma Group, it was not mandatory that patients had objective progression at study entry. At first glance, the investigators circumvented this prerequisite by taking the PFR at a remarkably late time point, namely, 9 months. It is unlikely that an aggressive tumor type such as angiosarcoma would not show progression at such a late time point. The PFR at 9 months in this study was <5%; however, if a high PFR at 9 months would have been found, meeting the predefined criteria for further evaluation of sorafenib, it could not have been ruled out that a substantial number of patients had slowly growing tumors, thereby rendering the study impossible to interpret.

How should we proceed? As already mentioned, better insight into the mechanisms of action of investigated agents and into the tumor biology of the different STS entities is pivotal for selecting the right patient population for the drug of interest, thereby increasing the chance for successful trials. Furthermore, for agents that are not expected to induce tumor shrinkage, the PFR at a certain time point is a valuable endpoint provided that patients have objective progression before inclusion. In addition, the exercise previously done by the EORTC-STBSG should be repeated and new PFR thresholds for active and inactive agents should be established. This should be done by grouping the data from all phase II STS trials that have been performed recently and then specifying the diverse major STS subtypes, taking into account that this also does not capture the whole spectrum of heterogeneity within STS. By doing so, we will hopefully get an international consensus on when to consider the antitumor activity of drugs explored in phase II trials worthwhile enough for further investigation. Research in STS is already featured by intense worldwide collaboration, but for further progress this collaboration should be intensified even more.

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