Alveolar Soft Part Sarcoma: Should We Be Targeting the Tumor or Targeting the Vasculature?

Jaap Verweij

Department of Medical Oncology, Erasmus University Medical Center – Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

Soft tissue sarcomas constitute a heterogeneous group of tumors that, due to their rare occurrence, used to be pooled for treatment assessment purposes. With the improvement in diagnostics and the development of molecularly targeted agents one has become increasingly aware that it is important, however, to differentiate the various subtypes from one another [1]. The development of imatinib for gastrointestinal stromal tumors (GIST) [2] can serve as an example. Alveolar soft part sarcoma (ASPS) is an extremely rare subtype of soft tissue sarcoma. It is characterized by translocation t(X:17)(p11;p25) on one hand, and a usually indolent growth pattern on the other [3]. Similar to GIST, it is quite insensitive to the commonly used cytotoxic drugs [4].

Trabectedin (ET-743; Yondelis®, PharmaMar SA, Madrid, Spain), an agent isolated from the Caribbean tunicate Ecteinascidia turbinata. Trabectedin is a cytotoxic drug that binds to the minor groove of DNA [5], and induces double-stranded DNA breaks [6] and G2-M cell cycle arrest [7]. Trabectedin is registered for use in soft tissue sarcomas in the EU and several other countries. While in general the response rates observed with its use are low, the level of progression arrest achieved is considerable [8]. However, studies on the activity of the agent in ASPS are lacking. In this issue of ONKOLOGIE, Pink et al. [9] present a retrospective analysis on a collected case series of 7 patients with ASPS treated with trabectedin. The retrospective collection and analysis of the series is hampered by the inevitable limitations of each retrospective analysis, for instance the impossibility to exclude an unintended patient selection bias. This in itself calls for major caution in trying to interpret the data of any case report based series.

Five of the 7 patients were treated with the registered dose for trabectedin, which is 1.5 mg/m² as a 24-h continuous intravenous infusion, repeated every 21 days. 2 patients were given a reduced dose. A clear dose-response relationship for trabectedin in soft tissue sarcoma has not been described yet, but if there is one, it is unlikely this will have negatively influenced the outcome interpretation of the treatment in the current series. On the other hand 1 or 2 of the patients had not been pretreated with chemotherapy. This aspect can be of influence since there are data to suggest differences in the outcome of trabectedin treatment, depending on the level of pretreatment with cytotoxics [8].

However, all of these are minor issues to put the observations into context. The most important issue is the absence of formal response evaluation criteria in solid tumors (RECIST)-based tumor regressions in the patients treated. This renders it important to try and assess the relevance of stable disease (SD). Acknowledging the potential relevance of SD in patients with soft tissue sarcomas the European Organization for Treatment and Research of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group has propagated the use of progression free rates (PFR) as a tool for clinical trial purposes in screening studies to assess the potential activity of the drug under study [10]. The 6-month PFR of 57% reported by Pink et al. [9] is clearly higher than the 40% 6-month PFR indicated by the EORTC to suggest an agent may be active. However, ASPS patients were not included in the EORTC studies that were used to create the reference. Due to the indolent behavior of this subtype it is quite likely that the PFR boundaries indicated by the EORTC cannot be applied to ASPS, since they would lead to overestimation of actual drug activity. So how can we be sure that the suggested activity is relevant? The other way to assess this would be by use of the growth modulation index (GMI) [11], as the investigators have done, comparing the time to progression (TTP) on the current treatment to the TTP on the previous treatment. This can only be done in patients that have been pretreated. In this respect there seems to be a possible inconsistency in the paper concerning patient F that in table 1 is listed as pretreated and in table 2 as non-pretreated. If the latter where correct, the GMI cannot be calculated and thus not reported in table 3 for patient F. However, even when excluding this patient, in all pretreated patients the GMI this seems to favor the trabectedin use. Again, a word of caution is indicated, since one has to realize the data on TTP on the prior therapy, due to the retro-
spective nature of the analysis, could not be collected in a standardized way. Therefore, even with the details provided in the table in the paper of Pink et al. [9], it remains impossible for the reader to fully assess the relevance. One may state that for ASPS the TTP of 2–5 months on previous therapy in the reported patients is relatively short for an indolent disease such as ASPS. This could reflect a relatively aggressive behavior of the disease in the patients treated, but could also reflect ineffectiveness of the prior treatment used. Most importantly, without seeing actual measurement data, an interpretation of the observed GMI remains difficult.

If we take the disease stabilization rate reported by the authors as 86%, it is important to realize that the 95% confidence limits of the observation still vary from 42 to 99% and that the chance of a false positive observation remains 7–58%.

This is one of the two reasons why one has to remain careful in taking the statements of the authors that ‘trabectedin can be considered the only currently registered drug with clinical activity in this disease’ and ‘...trabectedin can be considered as a fairly well tolerated therapy option to achieve disease stabilization in patients who had experienced disease progression’. The second reason is that there may be other and possibly better options for these patients, as partly correctly referred to by Pink et al. [9] as well. In general the vascular endothelial growth factor (VEGF)-based multi-tyrosine kinase inhibitors seem to exert important activity in ASPS [12–14]. Initially similar collected case series as the one from Pink et al. [9] suggested activity including a relevant number of RECIST based partial remissions with cediranib [12] and sunitinib [13]. The latter drug is commercially available and could thus be considered a treatment option. Importantly the case report observations have been confirmed in a formal phase II study on cediranib [14]. Kummar et al. [14] studied 36 patients, and at the time of reporting could evaluate 28 for response. 12 of these patients achieved a RECIST PR (43%), had > 20% reduction in lesion size, and 6 additional ones were stable for at least 6 months. This represents a disease control rate at 6 months of 78%. Importantly many of these disease controls were already known to last much longer than 6 months. While cediranib is no longer available, these data seem to suggest that VEGFR inhibitors may have major activity in ASPS. While study treatment still would be preferred and direct comparison between agents is lacking, consideration of this class of agents for patients with ASPS would be worthwhile.

The observations from Pink et al. [9] are certainly interesting, but should be viewed with caution and should be placed into appropriate perspective.

Disclosure Statement

The author declares no conflict of interest.

References


238

Onkologie 2012:35:237–238

Verweij