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Current Perspective

Future treatment of soft tissue sarcomas will be driven by histological subtype and molecular abberations

Jaap Verweij [a,*], *Laurence H. Baker* [b]

[a] *Dept. of Medical Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands*
[b] *Departments of Internal Medicine and Pharmacology, University of Michigan, Ann Arbor, USA*

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ABSTRACT

Soft tissue sarcomas, although sharing a mesenchymal origin, are a heterogeneous group of diseases. Nevertheless they are studied and frequently treated as if they were all the same. Recent developments suggest that a different approach may be more adequate. Genetic profiling studies have indicated that some soft tissue sarcoma subtypes, despite a distinct histo-pathological difference, may be closely related. Molecular biology research in addition has identified several subtype-specific oncogenes and their protein products that could serve as treatment targets. Since many of the new molecularly targeted agents do not induce tumour regression, but mainly result in growth inhibition, it is therefore necessary also to change the study end-point in screening studies in the search for active treatments. In view of all these it is proposed to consider using alternative end-points such as progression-free rates at pre-set times, or progression arrest at first evaluation. By using databases from large cooperative groups it should be possible to identify progression arrest rates for each specific subtype, and these could serve as reference for future trial design. Soft tissue sarcoma treatment and research will require a change of approach and necessitate global cooperation.

1. Introduction

Soft tissue sarcomas are a rare group of diseases that all together comprise only 1% of all malignancies. Because of their relative rarity, soft tissue sarcomas have up to now been grouped certainly for the purpose of assessing treatment outcome in practice as well as in prospective clinical studies exploring drug treatment.

In the analyses of the large database of EORTC on sarcomas, histological subtype (with possible exception of very rare histological subtypes such as clear cell sarcoma and alveolar soft part sarcoma the numbers of which were extremely small in this large database) could not be identified as an important prognostic factor of response to either doxorubicin of ifosfamide-based cytotoxic therapy, independent of other clinical factors.[1,2] Yet the analysis of 3- and 6-month progression-free rates after first line drug treatment for metastatic disease from the EORTC database suggested differences in results between subtypes.[3] In addition to these data, increasing number of reports, not least related to our increasing knowledge of molecular biology of these diseases, have suggested that the various subtypes of soft tissue sarcomas should be approached individually.[4] While the latter may be an obvious thought for drugs targeted against specific molecular

* *Corresponding author:* Address: Dept. of Medical Oncology, Erasmus University Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. Tel.: +31 10 7034447; fax: +31 10 7034627.
E-mail address: j.verweij@erasmusmc.nl (J. Verweij).
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aberrations in cancer cells, it may be less obvious for cytotoxic drugs, which are commonly thought to be less cancer-specific. Yet the literature is filling up with evidence that even for cytotoxic drugs the assumption holds.

In this paper we will first review the data on increased sensitivity of specific subtypes of soft tissue sarcomas to specific cytotoxic agents, summarise in brief the current status for molecular targeted agents, and finally discuss the findings in light of the need for adapting our clinical trial designs.

2. Cytotoxic Agents

There are only two agents that have been considered active in soft tissue sarcomas in general, Doxorubicin and Ifosfamide.[1,2] In the above-mentioned analyses of the EORTC database on more than 2500 patients treated with doxorubicin[1] and over 1700 patients treated with ifosfamide-based therapy,[2] there was no distinct histological subtype that emerged as more sensitive to these agents. Currently, for the treatment of soft tissue sarcomas in general, doxorubicin cannot be favoured over ifosfamide or vice versa, and combining both does not improve the time to progression or overall survival.[5] A few very rare histological subtypes such as clear cell sarcoma and alveolar soft part sarcoma are commonly considered refractory to any type of chemotherapy, although the literature evidence is lacking due to the rareness of these subtypes.

Interestingly, however, for some drugs such as taxanes and others that are considered inactive in soft tissue sarcomas in general, activity in specific histological subtypes has been reported.

2.1. *Myxoid round cell liposarcoma*

Myxoid round cell liposarcomas are a subtype of liposarcomas characterised by a t(12;16)(q13;p11) and the more rare t(12;22)(q13;q12) chromosomal translocations, resulting in the FUS-CHOP and EWS-CHOP fusion proteins[6] that are believed to act as aberrant transcription factors. ET-743, or Trabectedin, a minor groove-binding agent that has reported activity in several soft tissue sarcomas, has been reported to yield extensive anti-tumour activity particularly in this liposarcoma subtype. There is now a growing support for the possibility that Trabectedin directly affects the ability of the fusion proteins to bind to promoters,[7] and is particularly active in states of nuclear excision repair proficient cells.[8] Others regard the mechanism as one of the general downregulation of transcription genes. In 51 patients with advanced pretreated myxoid liposarcoma Trabectedin was given either as a 24-hour continuous infusion or as a 3-hour infusion, every 21 days, at 1.1–1.5 mg^2.[7] After a median follow-up of 14 months two patients had complete responses (CRs) and 24 patients had partial responses (PRs); the overall response was 51% (95% CI 36–65). Median progression-free survival was 14 months, and progression-free survival at 6 months was 88%. This observation has meanwhile stimulated the initiation of two prospective studies to assess the role of trabectedin in the treatment of patients with myxoid liposarcoma in preoperative and metastatic settings. Furthermore, the selective mechanism of action for trabectedin in this translocation-related sarcoma is being studied, since the data suggest that specific changes in the sarcoma cells may sensitise to Trabectidin.

2.2. *Angiosarcomas*

Angiosarcomas are of endothelial origin, and their growth seems to be depending on the presence of angiogenic growth factor autocrine loops.[9]

While taxanes are considered to be inactive agents in soft tissue sarcomas, in general,[10] they seem to yield activity against angiosarcomas. In the first report on activity in this subset for paclitaxel[11] 8 of 9 patients with angiosarcomas of the scalp responded to therapy. This unusual observation stimulated others also to retrospectively collect data or perform prospective studies. Recently EORTC reported a retrospective analysis on 32 patients also treated with paclitaxel,[12] of whom 8 had a primary localisation in the skin of the scalp. This study confirmed the sensitivity of scalp primary localisations (RR 75%), but also suggested relevant activity in metastases from other primary sites (RR 58%). Investigators at Fox Chase Cancer Center[13] found the same. And for docetaxel in cutaneous angiosarcomas[14] yet when taxol was studied prospectively in angiosarcomas[15] the French Sarcoma Group only noted 4 PRs in 23 evaluable patients (15%), as well as 14 SD. The latter study included 9 patients with radiation-induced sarcomas. Scalp angiosarcomas are often low-grade lesions while radiation-associated sarcomas are almost always high grade. Whether this explains the possibly lower observed activity is currently unknown.

An appropriate explanation for the activity of taxanes in this subtype of soft tissue sarcoma is still lacking. Angiosarcomas are tumours arising from the endothelial wall. It could be speculated that this pathogenesis and the suggested angiogenesis inhibition of taxanes are at least partly responsible for the reported drug activity. However, in vitro the respective formulation vehicles completely inactivated this angiogenic activity, suggesting that taxanes may need to be used at much higher doses than currently given for effective antiangiogenic effects.[16]

2.3. *Leiomyosarcomas*

While angiosarcomas are a relatively infrequent subtype of soft tissue sarcomas, leiomyosarcomas currently are among the most frequently reported subtype, the molecular causes of which remain unclear. Yet, for chemotherapy also in this subtype there are some remarkable observations. Trabectedin seems to have better activity not only in myxoid liposarcomas but also in leiomyosarcomas (progression arrest rates up to 56%),[17,18] dacarbazine's activity may be restricted to uterine leiomyosarcoma,[19] and more recently gemcitabine was suggested to be active in leiomyosarcoma.[20]

An appropriate explanation for the activity of trabectedin and dacarbazine in this subtype is not available.

For Gemcitabine numerous phase II studies had not shown major activity in general.[21–27] Collectively, however, some activity was seen in leiomyosarcomas. Yet, an initial non-randomised phase II study, combining gemcitabine with

docetaxel, so combining two agents thought to be inactive in soft tissue sarcoma,[28] yielded a surprisingly high response rate of 53% in leiomyosarcomas mostly of uterine origin. Part of the discrepancy between single agent data and these data from the combination could possibly be explained by gemcitabine pharmacology. The ability of cells to accumulate gemcitabine triphosphate is known to be saturable at gemcitabine dose rates that produce plasma gemcitabine levels of 10-25 μM.[29] Thus, pursuing a longer exposure to drug may be associated with greater anti-tumour effect. In addition data on synergy between gemcitabine and docetaxel suggested that drug administration sequence could be of importance.[30,31]

Given the fact that non-randomised studies on combinations of agents are inconclusive by definition, The Sarcoma Alliance for Research through Collaboration (SARC) performed a phase III randomised study to confirm the activity of gemcitabine + docetaxel.[20] The study did not restrict to leiomyosarcomas. The overall response rate was 9% for gemcitabine versus 16% for gemcitabine-docetaxel, and the latter also induced a statistically significant better time to treatment progression and overall survival. Interestingly, the response rate for patients with leiomyosarcoma was 11% for gemcitabine alone and 17% for the combination, so no different to other subtypes. This creates doubt again towards the suggested higher sensitivity of leiomyosarcomas for gemcitabine. In addition, a subsequent randomised study that was intended to confirm the activity in leiomyosarcoma was unable to do so.[32] Clearly, the chapter on this combination in leiomyosarcomas is far from closed.

3. Cancer (cell)-specific agents

3.1. *Gastrointestinal stroma tumours (GISTs)*

The development of Imatinib for GIST serves as an example for the development of treatment based on cancer (cell)-specific molecular changes. Overexpression of the oncogene product receptor c-KIT (CD117) is a frequent, albeit not specific, characteristic of GIST. Importantly, this receptor is known to frequently harbour activating mutations in GIST.[33,34] The activity of the KIT-tyrosine kinase inhibitor imatinib was clearly shown.[35–38] Detailed analysis has now revealed that Exon 9 mutations in KIT are somewhat less sensitive to Imatinib than other mutations.[39,40] KIT-negative GISTs may still be sensitive to Imatinib if there is a PDGFR imatinib sensitive mutation. One mutation at exon 18, D842 V, and possible other mutations at that exon are resistant to imatinib. The data indicate not only that the disease may be drug sensitive due to specific molecular changes, but also that the required drug dose may be depending on specific changes within these molecular changes.[39,40] This in itself is a historical finding.

3.2. *Synovial sarcomas*

Nielsen et al[41] have analysed gene expression pattern in a small series of soft tissue tumours. A distinct gene-expression pattern for synovial sarcomas (SS) was identified. They were differentiated by a unique pattern of expression of 104 genes, among others including the epidermal growth factor receptor (EGFR1). A screening phase II study of the EORTC Soft Tissue and Sarcoma Group performed a study on Iressa (Gefitinib) in EGFR expressing synovial sarcomas failing previous chemotherapy, unfortunately did not lead to any anti-tumour activity.[42] This suggests that the receptor may not be functional in SS, which is still not known. An important lesson learned from this and other studies is that expression of a receptor itself may not be a sufficient reason to target it clinically. The important lesson is that we will need data on target functionality in vivo, prior to starting clinical studies with cancer (cell)-specific agents, not just target expression or even target mutation.

3.3. *Dermatofibrosarcoma protuberans (DFSP)*

Dermatofibrosarcoma protuberans is a rare cutaneous spindle cell neoplasm characterised by rare metastatic spreading and yet a high frequency of locoregional recurrence due to an indolent subcuticular tissue spread after inadequate primary treatment. Dermatofibrosarcoma protuberans can be distinguished from other mesenchymal neoplasms based on the immunohistochemical expression of CD34 antigen and the genetic presence of specific chromosomal translocations.[43] It is associated with the chromosomal translocation, t(17:22), which fuses the COL1A1 and PDGFbeta genes.[44] Autocrine /paracrine PDGFB-mediated activation of PDGFRB drives DFSP proliferation. Given the fact that Imatinib also targeted PDGF-related mutations, DFSP was part of a 'basket-protocol' phase II study on Imatinib in a variety of diseases.[45] Activity was noted and the data were considered sufficient to register the agent for this rare indication. This rendered it difficult to perform the subsequently required formal phase II studies to confirm activity. Recently EORTC and SWOG presented their pooled data from 2 phase II studies.[46] Of 24 patients 11 patients (46%) had partial response, 9 had stable disease and only 4 had progressive disease as best response. The median time to progression was 1.7 years. Another small study using the drug prior to surgery yielded similar activity.[47]

3.4. *Haemangioendotheliomas*

The role of angiogenesis also suggested for the proliferation of haemangioendotheliomas has now also stimulated a phase II study of bevacizumab in this disease.[48] The patients were treated with high 15 mg/kg IV dose of bevacizumab every 3 weeks. Of 26 patients, 3 (12%) achieved a PR and 13 an SD, several of which were durable. Clearly interesting, but early observations.

3.5. *Various sarcomas*

The above-noted activity of specific inhibitors of angiogenesis, however, was not the first observation in soft tissue sarcomas. The thrombospondin-mimetic ABT-510 had previously shown some activity in a variety of soft tissues.[49–51] Unfortunately, development of this agent was not pursued. However, very recently, Pazopanib,[52] Sorafenib[53] and Sunitinib[54] have all shown modest activity in phase II trials in soft tissue sarcomas, with an interesting subtle difference in potentially sensitive histological subtypes. Taking the 40% PFR at

3 months to identify a drug with potential activity,[3] sorafenib might have activity in angiosarcoma (3-month PFR 64%), and high-grade undifferentiated pleomorphic sarcoma (42%), both sorafenib and pazopanib in leiomyosarcoma (54% and 44%), synovial sarcoma (42% and 49%) and 'other' histologies. And taking the 6-month PFR, there is a striking dissimilarity for synovial sarcomas, where Sorafenib did not yield a 6-month PFR, while for Pazopanib it was 30% and well above the 20% threshold. This could point to a possible true difference between agents that have minor differences in TK inhibitory profiles. On the other hand we cannot yet exclude that the observation differences are simply due to study population characteristics.

Furthermore in vitro studies indicated that Epithelioid sarcomas expressing EGFR-1 respond to EGFR1-antibody treatment.[55] This suggests that the receptor may be functional for this sarcoma subtype and provide a basis for a clinical study.

Enhanced hepatocyte growth factor (HGF) receptor (Met) signalling has been suggested to play a role in the development and progression of clear cell sarcoma of tendons, synovial sarcomas, malignant primitive neuroectodermal tumour, dermatofibrosarcoma protuberans and epithelioid sarcoma,[56–59] but proper functionality studies for these receptors have not yet been performed and the drugs targeting these receptors have only recently entered clinical studies' agents.

Farnesyl Transferase Inhibitors (FTIs) can inhibit the trafficking of ras protein to the cell membrane.[60] This oncogene has been suggested to be related to the NF1 gene, overexpressed in the neurofibromatosis type 1 syndrome, which can predispose to malignant peripheral nerve sheath tumours. As indicated, whether this overexpression is sufficient evidence to chase this target in this disease remains doubtful. Finally the overexpression of IGF-1R in rhabdomyosarcoma[61] (and the Ewing Sarcoma Family of Tumours) has already led to the assessment of the IGFR-1 inhibitor R1507 in a recently completed (for accrual) phase II study in 320 patients involving multiple histologies.

4. Study design

Collectively these data suggest that soft tissue sarcomas should preferably no longer simply be pooled together in clinical studies. Not from a pathology point of view, and not from a molecular abnormality point of view. For instance, Chugh et al[62] performed an interesting phase II study on imatinib in 190 soft tissue sarcomas. They used a Bayesian Hierarchical Statistical Model (BHM), and borrowed information across sarcoma subtypes assuming that they were interrelated in expression of molecular targets. Cohort expansions and early stopping rules were pre-defined, allowing outcomes in one subtype to influence the decision making in others. The wrong assumption of interrelated molecular targets explains why the study outcome was negative. No explanation could be offered for the suggested clinical benefit of some of the 50 patients treated with aggressive fibromatosis on this trial. Despite the assumption issues, the design possibly remains a powerful clinical trial methodology, in circumstances where functionality of the molecular target for tumour growth in the studied sarcomas is granted beyond doubt.

While the design was different from the design of the trial reported by Chugh et al,[62] the studies on both Pazopanib[52] and Sorafenib[53] acknowledged the relevance of disease subtypes. Both included strata defined based upon specific histology, and also an 'other' soft tissue sarcoma cohort. Such 'other sarcoma' cohorts basically still ignore the above-described differences in drug sensitivity of subtypes of soft tissue sarcomas but were included since some subtypes are so rare, it will hardly be possible to perform formal screening phase II studies in each of these subsets. In all 3 studies[52,53,62] for each of the cohorts a Simon optimal two-stage design was used. As a consequence these became large phase II trials. With some minor modifications this trial design is now adopted in currently ongoing studies. Interestingly, the two angiogenesis (multi tyrosine kinase) inhibitor studies resulted in different histology subtype profiles for sensitivity, suggesting that different tyrosine kinase inhibition profiles may even be important for different histologies.

In line with the growth inhibitory effect of the agents tested, the activity was best described as prolonged absence of progression, and thus expressed in Progression-Free Rates or Progression-Free Survival. Assessing these parameters adequately without randomisation is clearly not easy and will always be subject to selection bias. One also has to realise that using the rates from large databases to some extent is making use of historical controls, which are subject to evident criticism. But even randomisation per se will not mean that the obtained data can simply be projected to the common population. This adds another element to the required change in soft tissue sarcoma trial design[4] but is beyond the scope of this paper. Whether or not prolonged absence of progression or progression-free interval prolongation will be as indicative of clinical benefit as response by RECIST or other criteria remains to be proven by subsequent randomised phase III studies.

5. Conclusion

The development of Imatinib for GIST has clearly the hallmark of molecular-change-specific treatment in sarcomas. However, our experience with inhibiting KIT has also taught us that simply chasing a target without fully understanding its functionality for tumour growth will lead to disappointment.

Positively, recent research on the molecular biology of soft tissue sarcomas has identified several possible targets for drug development in specific sarcoma subtypes or even shared among various subtypes.

Although none of the reviewed data may be considered as final proof, all of them at least suggest that there may be subtype specificity in drug sensitivity. This calls for a change in soft tissue sarcoma clinical trial design towards subtype-specific studies, in order to find out if subtype-specific treatment is indicated. It also calls for close collaborations between investigators and investigator groups, even on a global level, since the low incidence of subtypes of soft tissue sarcomas prevents single institutions from doing the appropriate studies within reasonable limits of time.

Conflict of Interest

No Conflict of Interest.

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