The Role of Pathology in Treatment of Sarcomas: From Grading to Histotyping

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Key points

- Soft tissue sarcoma is a rare variant of cancer in which statistically powered clinical trials are difficult to be performed.
- The utility of adjuvant chemotherapy in soft tissue sarcomas is still debated.
- Specific histoypes have shown differential sensitivity to specific chemotherapeutic agents.
- The advent of molecular target therapy has further increased the importance of accurate morphologic subtyping of sarcomas.

Soft tissue sarcomas represent a distinctively heterogeneous group of rare malignancies, with an overall incidence, of around 5/100,000/year. From the clinical standpoint approximately 20 to 30% of cases recur locally and 30 to 50% of cases metastasize, most often to lungs. 5-year overall survival varies between 55% and 65%, regardless of stage and histology. Both rarity and heterogeneity represents main factors affecting on one hand diagnostic accuracy, and on the other the feasibility of statistically powered clinical trials.

In the past standard treatment was mainly represented by surgery, variably associated to radiotherapy in the attempt to improve local control (1,2). The use if chemotherapy in advanced disease as well as in the adjuvant setting has proved most fruitful in pediatric sarcomas (rhabdomyosarcoma, Ewing’s family of tumors, infantile fibrosarcoma), and osteosarcoma. On the other hand, the real efficacy of systemic treatment in adults’ soft tissue tumors is still source of debate (3). Two major issues which have been addressed by a number of clinical trials are the efficacy of adjuvant chemotherapy in the localized disease and whether a polychemotherapy with doxorubicin and ifosfamide is superior to doxorubicin alone in the advanced disease. By and large, the conclusion from these trials was that adjuvant chemotherapy is ineffective, or at best marginally effective, and that polychemotherapy is not superior to single agent chemotherapy. A meta-analysis was published in 1997, and it was unable to detect any statistically significant advantage in survival (4). However, trials included in this meta-
analysis had not used ifosfamide in addition to doxorubicin. Actually, a “second-
generation” study from the Italian Sarcoma Group (ISG) employing the combination of
doxorubicin and ifosfamide showed an improvement in survival (5). Interestingly,
chemotherapy did not affect the metastatic rate, indicating that chemotherapy most
likely delays rather than prevent systemic spread. Recently another meta-analysis was
preliminarily reported (6), showing the same degree of absolute benefit in relapse-free
survival and overall survival, but at least the difference in survival appeared now to be
significant. However, this study did not incorporate preliminary report from an EORTC Soft
Tissue and Bone Sarcoma Group clinical trial, which appears to be totally negative (7).
Disappointingly, after many years of such trials, the uncertainty regarding the utility of
adjuvant chemotherapy does not seem to be narrowed, and as a consequence the
community of sarcoma researchers remains divided on its efficacy. Patients all over the
world, especially if they are high-risk, are often offered adjuvant chemotherapy as an
option in conditions of uncertainty.

Whatever the treatment options, for years clinicians have not been showing much
interest into histotyping of soft tissue sarcomas. As matter of fact, most of decision making
was eventually made on grading (8-10). Certainly grading has proved to be one of the
most important tool in order to stratify patients into prognostically meaningful categories,
however certainly it was not meant for predicting response to adjuvant therapy. As
mentioned before adjuvant chemotherapy still does not represent a standard treatment.
Of course, in consideration of the rarity of soft tissue sarcomas, most clinical studies have
been performed on histologically heterogeneous series, assuming that all histotypes would
respond at the adjuvant treatment as a single disease. As a consequence, it seems likely
that two main problems have somewhat hampered the clinical studies investigating the
potential utility of adjuvant chemotherapy in soft tissue sarcoma: the use of a rather
restricted range of effective drugs (anthracyclins and ifosfamide), and their indiscriminate
use in a very heterogeneous collection of distinct tumor types. However, it is easy to
understand that clinical trials on very rare tumors are unfeasible by definition. As an
example, the incidence of angiosarcoma is in the order of 0.05/100,000/year. In a large
country (or area) of 100,000,000 people, one would find a few dozens new patients each
year. Even increasing the usual proportion of patients enrolled into clinical trials (hardly
exceeding 5%), it would be difficult to set up a clinical trial on hundreds such patients in a
reasonable number of years. Nonetheless, despite the impossibility to set up a randomized
clinical trial on angiosarcoma, angiosarcoma itself has contributed to prove that selected
groups of sarcomas may show specific sensitivity to different agents. In fact it has now become clear that angiosarcomas may respond to cytotoxic agents like taxanes, which are inactive in almost all other soft tissue sarcomas (11). It has been also very recently shown that antiangiogenic drugs seem also to work in angiosarcomas more than in most other sarcoma subtypes, further underlying the relationships between morphology and therapy (12). In general, it has become evident in recent years that some sarcoma subtypes may indeed show specific response patterns to medical therapy. Amongst adult soft tissue sarcomas, this has been the case for trabectedin (mainly active in leiomyosarcoma and myxoid liposarcoma) (13,14), gemcitabine (most active in leiomyosarcomas and undifferentiated high grade sarcomas) (15,16), not to mention imatinib that in addition too its stunning success in gastrointestinal stromal tumors (17-21), has also proved effective in dermatofibrosarcoma protuberans (DFSP) (22), chordoma (23), and desmoid fibromatosis (24). Therefore, even if one overlooks the peculiarities of the natural history of these subgroups, recent developments with chemotherapy, and even more with molecular targeted therapies, makes this split unavoidable.

The unveiling of the molecular mechanisms involved in the carcinogenesis of several subgroups of lesions and the possibility to utilize specific molecules targeting those mechanisms certainly represents the most important advance. In parallel with the well known application of tyrosine kinase inhibitors in GIST and DFSP, it has become evident that different non mutational alterations of targets such as PDGFRA and PGFRB may explain the clinical responses observed in patients affected by chordomas and desmoid fibromatosis (25,26). Of great interest is also the fact the myxoid liposarcoma, shown to be exquisitely sensitive to the marine derived alkaloid trabectidin (13,14), tend to exhibits differential sensitivity on the basis of the type of chimeric transcript derived from the fusion of the genes FUS and DDIT3 (27). This last observation not only further demonstrates the existence of histotype-related sensitivity, but also that within the same histotype specific molecular aberration may predict the chance of response.

The current evolution of therapeutic approach to soft tissue sarcoma certainly represent the offspring of the marriage between pathology and genetics. Both classic cytogenetics and molecular genetics has not only refined and validated classification schemes, but has also provided information that are being gradually incorporated in the clinics. A good example is certainly represented by the possibility to target well differentiated/dedifferentiated liposarcoma (know to be characterized by MDM2 gene
amplification and consequent MDM2 protein overexpression) with the MDM2 antagonist Nutlin-3a, capable of inducing apoptosis and growth arrest in neoplastic cells (28).

In conclusion, any attempt to identify effective systemic treatments for sarcomas must take into account not only the great morphologically heterogeneity that characterized this fascinating group of malignancies, but also the underlining molecular mechanisms. This seems to be crucial not only for molecular targeted therapies but, as appears to happen with trabectidin, also for agents exerting apparently less specific mechanisms of action. The main consequence is that accurate morphologic diagnosis will gain even greater importance, either as a direct tool to select the best therapeutic option, or as a crucial step to allow identification of the relevant molecular abnormalities to be targeted.

References


