The introduction of targeted therapies, along with the recognition of the importance of histology-driven chemotherapy, has led to a re-evaluation of the importance of histological subgroups, in a family of tumours comprising dozens of them. This is paralleled by a re-evaluation of the importance of histological subgroups, in a family of tumours comprising dozens of them. Histology is now felt to be relevant not only for target therapies, but also for chemotherapy, as long as other cytotoxics in addition to doxorubicin and ifosfamide were shown to be active when challenged in selected subgroups.

**doxorubicin and ifosfamide**

Doxorubicin and ifosfamide are wide-spectrum agents in sarcomas. Indeed, there is some evidence that ifosfamide may have low activity in leiomyosarcoma [1]. In this subgroup, on the other hand, dacarbazine, a drug included in old combination regimens, and the related agent temozolomide seem especially active [2], so that doxorubicin–dacarbazine might serve as a multi-drug option. Actually, published randomized trials did not show any survival advantage for combinations over single-agent doxorubicin [3–5]. However, they suggest that there may be a higher response rate when multi-agent chemotherapy is used. For this reason, this is often selected when one wants to maximize the activity of chemotherapy, as in the adjuvant or pre-operative setting or when it is felt that tumour response would improve, or prevent, symptoms. Patient’s willingness, performance status and age are factored in the decision as well.

Results are awaited of a large EORTC randomized trial which compared full-dose doxorubicin–ifosfamide versus doxorubicin. However, there are limitations in trials pooling all histologies and disease extents, all the more at a time when single subtypes are finding different histology-driven best options. Thus, the results of this trial will need to be put into the context of currently available medical treatment of adult soft tissue sarcomas.

Ifosfamide is often used in the second-line chemotherapy setting at ‘high-doses’, in the range of 14 g/m$^2$ [6]. At these dose levels, ifosfamide may be active also in patients already exposed to standard doses. The toxicity profile is significant, while it may be substantially lower by giving it as a prolonged infusion in 14 days [7]. Synovial sarcomas and de-differentiated liposarcomas may be amongst the histologies more likely to take benefit.

**histology-driven chemotherapy**

Taxanes are inactive in sarcomas. However, there is evidence that they are active in angiosarcoma, a highly aggressive histological subtype [8].
Indeed, docetaxel was combined with gemcitabine, trying to exploit a synergism between the two drugs. However, there are conflicting reports about the value of the combination in comparison to gemcitabine alone [9, 10]. In addition, this regimen seems to be mainly active in leiomyosarcomas and possibly pleomorphic sarcomas (which, by the way, may have a myogenic differentiation). Thus, gemcitabine-docetaxel, or even gemcitabine alone, has become a convincing choice in leiomyosarcomas, including uterine leiomyosarcomas. Of course, the tolerability of single-agent gemcitabine is much higher than the combination, so that its use may be all the more interesting in the palliative setting. Gemcitabine alone is active in angiosarcoma as well [11].

Leiomyosarcomas, including uterine leiomyosarcomas, are sensitive to the marine-derived agent trabectedin. The other histologies in which trabectedin is active are liposarcoma and, to some extent, synovial sarcoma [12, 13]. However, liposarcomas are a variegated family in which well- and dedifferentiated liposarcomas are a completely different entity from myxoid/round cell liposarcomas. These are marked by a chromosomal translocation. It appears that trabectedin displaces the fusion protein from selected genes, thus ‘targeting’ the pathogenetic mechanism of the disease [14]. This is paralleled by an anti-tumour activity whose spectrum is qualitatively superior to the average anti-tumour activity of the drug in other soft tissue sarcomas [15].

**histology-driven target therapy**

Randomized trials were recently reported about two target agents in adult soft tissue sarcomas, respectively, pazopanib and ridaforolimus [16, 17]. Pazopanib was tried in advanced, pre-treated adult soft tissue sarcomas, excluding liposarcomas, with a median progression-free survival advantage of about 3 months over placebo. Ridaforolimus was tried in sarcomas as a kind of maintenance therapy following best response to chemotherapy, showing a benefit on progression-free survival, which, however, was short. Also pazopanib seems to work better in selected histologies, i.e. leiomyosarcoma and synovial sarcoma, although studies are ongoing to further elucidate its differential efficacy across histologies [18].

Both drugs, in fact, were challenged within trials across several histologies. Ridaforolimus, for example, is an inhibitor of mammalian target of rapamycin (mTOR). In this regard, there is evidence that mTOR inhibitors have a special activity in PEComas (perivascular epithelioid cell tumours) [19, 20]. These tumours, in fact, are marked by a disruption of the mTOR pathway.

In addition to pazopanib, other antiangiogenic agents tested in soft tissue sarcomas were sunitinib and sorafenib. Phase 2 studies are available across histologies, but again it is apparent that their value is different depending on the sub-type [21, 22]. Sorafenib seems to be active in angiosarcoma. The anti-tumour activity of sunitinib was showed in alveolar soft part sarcoma, solitary fibrous tumours and clear cell sarcoma [23 –25]. Intriguingly, patterns of tumour response to sunitinib, for example, were different between alveolar soft part sarcoma and solitary fibrous tumour, being dimensional in the former and non-dimensional (‘GIST-like’) in the latter. It is left to understand whether this may have to do with a different mechanism of action. Indeed, the antiangiogenic mechanism may not be critical, and platelet-derived growth factor receptor (PDGFR) was shown to be involved. Also cediranib was shown to be active in alveolar soft part sarcoma [26]. The combination of temozolomide and bevacizumab was shown to be active in solitary fibrous tumour as well [27].

There is one histological type which has paradigmatically found its targeted therapy: dermatofibrosarcoma protuberans [28]. This is marked by a chromosomal translocation which leads to over-stimulation of platelet-derived growth factor receptor beta (PDGFRB), effectively targeted by imatinib. The disease is a surgical one, so that medical therapy is seldom required. However, it may be clinically useful for challenging local presentations, and metastases develop in some cases. These are marked by a fibrosarcomatous component, which is sensitive, though with the limiting factor of early secondary resistance [29].

Crizotinib was shown to be active, as expected, in ALK-rearranged myofibroblastic inflammatory tumours [30].

**conclusions**

Clearly, the number of agents available today for adult soft tissue sarcomas is incomparable even to a few years ago. Virtually all the new agents have a spectrum of anti-tumour activity which is confined to some histologies. With regard to targeted therapies, it is also obvious that biomolecular predictors need to be found in order to further ‘target’ the medical treatment within the sensitive histological subtypes. It follows from all this that evidence needs to be built in small subsets within a family of tumours which are rare overall. Thus the quality of evidence available at the moment on several of these agents is limited, often anecdotal. Nonetheless, the results have been clinically striking in several cases, although the mechanism of action has been elucidated only in some sarcomas.

This brings about problems in current clinical practice, inasmuch as regulatory and reimbursement issues obviously arise from a lack of high-quality evidence. Then, future clinical research is in acute need for new methodological solutions, able to cope with the challenges posed by small populations [31]. The sarcoma community is part of the efforts ongoing in the field of rare cancers to work out new methods for clinical trials in the age of molecularly targeted therapies.

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