Editorial

Relapse in synovial sarcoma: what can be done for poor outcomes?

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Improving patients' chances of cure after their tumors have relapsed is one of the greatest challenges oncologists face, especially when it comes to patients whose front-line treatment had already included both chemotherapy and radiotherapy. It is almost as if oncologists had just one shot to fire in their battle against cancer, no second chances. Once standard chemotherapy has failed, cancer clone cells are likely to develop multidrug resistance, becoming insensitive to any further systemic therapy. Likewise, reirradiation after local relapse within previous radiation fields is rarely feasible and, even when it can be attempted, it is usually to no effect.

Synovial sarcoma is a good example to discuss in this scenario. It is a typical tumor spanning the pediatric and adult age groups [1]. This high-grade soft tissue sarcoma carries a good overall prognosis – approximately three in four patients are cured nowadays – generally depending on the feasibility of surgical resection, the tumor's size and site, and any presence of metastases [1–4]. As in other tumor types however, studies on synovial sarcoma have reported a narrow 'salvage gap', definable as the difference between event-free survival and overall survival. This is tantamount to saying that the chances of further treatments curing patients who progress or relapse are decidedly slim.

A recent Italian pediatric study described the pattern of synovial sarcoma recurrence and the prognostic variables influencing survival with a view of finding a risk-adapted stratification procedure that could facilitate the planning of second-line therapies [5]. If we could distinguish between patients who have realistic prospects of cure with currently available treatment options and those unlikely to benefit from them, then the latter might, in principle, be offered experimental therapies. Most of the relapses in the pediatric sample considered were metastatic (particularly to the lung), and 10-year survival after relapsing was 21% [5]. The final outcome was influenced

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by the time to relapse and the type of recurrence (i.e., patients whose disease recurred locally more than 18 months after their first diagnosis had a reasonable chance of cure), while the prognosis was dismal for patients with early, metastatic relapse. The likelihood of secondary remission also depended on a good response to second-line chemotherapy and/or the feasibility of complete surgical resection (at both local and distant sites) [5]. The study's findings support the value of intensive chemotherapy, since fairly satisfactory responses were reported (e.g., after using high-dose ifosfamide, even as a rechallenge). They also indicate that aggressive surgery may be justified; while amputation may not be recommended when the disease first develops, it might be seen as a practicable option for locally relapsing synovial sarcoma of the limbs.

Even after we have clarified the clinical variables that can predict the outcome, formulated a risk-based algorithm and optimized our use of currently-available therapeutic weapons (high-dose ifosfamide and aggressive surgery), survival after recurrence will probably still be largely unsatisfactory for most synovial sarcoma patients. New approaches are clearly needed to really improve their outcome, meaning new comprehensive strategies for treating relapsing patients, new forms of cooperation among oncologists, new insight from biologists, new validated biomarkers for patient selection and effective new drugs with novel mechanisms of action.

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While front-line treatments are generally based on standardized, shared guidelines or cooperative protocols, patients who relapse are often treated individually. All too often, such patients are an oncologist's 'first case', and nothing is gained from other colleagues' experience in similar situations. Every effort should be made to involve relapsing patients in prospective clinical trials, just like newly diagnosed cases. Pediatric oncologists are well aware that their knowledge has improved in recent years, with a positive fallout on the outcome of pediatric tumors, partly thanks to their successful national and international networking. Implicit in the goal of treating patients who relapse within prospective cooperative protocols lies the need for numerous cultural and practical changes: we have to develop a new working model and this entails a complicated system of cooperative relations and new infrastructure. Synovial sarcomas are rare, and relapsing cases are fortunately even more so – and the same can be said of many other tumors, and pediatric cancers in particular – that is why a global-scale international cooperation is so essential. Pediatric oncologists dealing with synovial sarcomas must learn to do several things:

- They need to work closely with adult medical oncologists;
- They must reinforce their collaboration with biologists to really improve their understanding of tumorigenesis and identify targets/pathways relevant to tumor growth;
- They need to establish broad multilevel forms of cooperation with national and international disease-specific groups (e.g., the European Pediatric Soft Tissue Sarcoma Study Group) [6], and with networks focusing on the development of new drugs (in Europe, the integrated research consortium called Innovative Therapies for Children with Cancer) [7];
- They should strive to create new partnerships with pharmaceutical industries and the regulatory authorities [8].

While partnerships with industry and the authorities may be more of a logistic issue than anything else, cooperation between pediatric and adult medical oncologists (even when they are dealing with the same diseases) sometimes seems to encounter cultural obstacles relating to a mutual diffidence, and both parties' inclination to defend their own strategies. Such issues simply have to be forgotten because pooling their resources and expertise would generate synergistic effects [9]. For example, in the case of relapsing synovial sarcoma, adult oncologists have considerable experience of developing novel therapies that could help pediatric oncologists to improve their participation in Phase I/II trials.

Close cooperation may also be fundamental for the purpose of identifying new biological markers for patient selection in relation to their prognosis and the efficacy of therapy. A recent French study reported that a 67-gene signature related to chromosome integrity, mitotic control and genome complexity, called complexity index in sarcoma (CINSARC) could predict the risk of metastatic spread and possibly a synovial sarcoma's response to chemotherapy too [10]. There is evidence of differences in genome instability between adult and pediatric cases [10], suggesting a potential role for this biomarker in explaining

why children reportedly fare better than adults sometimes [1]. Broader forms of cooperation may generate enough tumor samples to enable this impression to be confirmed and lead to age-related biological studies. Identifying molecular targets is fundamental to the development of therapies with novel mechanisms of action. Specific t(X;18)(p11.2;q11.2) chromosomal translocations and the SYT-SSX transcript (in its various forms), as well as the proteins overexpressed by the tumor cells (EGF receptor, HER-2/neu and Bcl-2) [11–13] make synovial sarcoma potentially interesting for histology-driven targeted therapy [14]. Just to give an example, pazopanib is a multikinase angiogenesis inhibitor that has proved rather effective in adult patients with relapsing or refractory advanced soft tissue sarcoma, and synovial sarcoma in particular [15]. Other promising drugs for synovial sarcoma that are being tested are trabectidine, Bcl-2 antisense oligonucleotide and monoclonal antibody against FZD10, a cell surface receptor in the Wnt pathway [16–19]. Adoptive immunotherapy using tumor-infiltrating lymphocytes against NY-ESO-1 cancer/testis antigen (expressed in 80% of synovial sarcoma) is another alternative therapy that may be worth investigating [20]. It is hard to say as yet whether any of these new therapies will really improve the outcome of patients with recurrent or refractory synovial sarcoma, but we are firmly convinced of the need for more patients with relapsing synovial sarcoma to be included in a shared and structured approach, and involved in dedicated clinical trials on relevant biomarker-directed, targeted therapy.

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