Soft tissue sarcomas: are all soft tissue sarcomas treated with the same drugs?

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The refinement of the histological classification and grading of sarcomas has enabled a large variety of nosological entities to be distinguished, while progress in the understanding of molecular alterations associated with sarcoma subtypes enabled the identification of early mutational events during tumour progression such as translocations and mutation of tyrosine kinases [1,2]. This knowledge is now guiding the development of novel agents in sarcomas.

Heterogeneous tumours, similar treatment?

Indeed, despite major progress in the classification of sarcomas, the treatment of these rare tumours has remained remarkably homogeneous both in localised and advanced settings. In the localised setting, primary biopsy followed by en bloc resection of the tumour, and adjuvant (sometimes neoadjuvant) radiotherapy represents the standard therapeutic approach for tumours >5cm, deeply seated and FNCLCC grade above 1. Chemotherapy is based on doxorubicin and ifosfamide, and can be delivered in the neoadjuvant setting when the tumour is not operable, aiming for tumour shrinkage and subsequent removal of the tumour (Casali 2010). Adjuvant treatment is recommended by some teams in specific cases without formal demonstration of an improvement in overall survival. Hyperthermia combined with chemotherapy has been shown to improve relapse-free survival in a single large randomised trial. In the advanced setting, doxorubicin, ifosfamide, DTIC and trabectedin remain the only registered cytotoxics for this indication, while imatinib in GIST and DFSP, and sunitinib, in second-line GIST are the only registered agents. Until recently, the homogeneity of clinical management contrasted, therefore, sharply with the heterogeneity of disease types that was being extensively characterised at the molecular level [3,4].

Histotype-adapted cytotoxic and targeted treatment

Recently some agents have been reported to exert specific activities in selected sarcoma subtypes: for cytotoxics, specific agents are now considered as particularly active in specific cell types, e.g. trabectedin in leiomyosarcomas and liposarcomas [5], taxanes and microtubule targeting agents in angiosarcomas [6], gemcitabine, and DTIC in leiomyosarcomas [7].

Molecular classification of sarcomas

In 2011, sarcomas can now be classified into distinct molecular and pathological entities: six molecular subgroups of connective tissue tumours may be distinguished as of now, keeping in mind that this is a rapidly evolving classification:

(1) Sarcoma with specific translocations generating a fusion gene whose protein products modulate transcription or may act as growth factors (e.g. EWS/Fli1 in Ewing sarcomas, PDGF-col1a1 in DFSP);
(2) Sarcomas with mutated activated kinases (*KIT* in GIST);
(3) Sarcomas with deletion of tumour suppressor genes such as *NF1* sarcomas;
(4) *MDM2* and *CDK4* amplification in WD/DD liposarcomas;
(5) Sarcomas with gross genetic alterations (e.g. leiomyosarcomas);
(6) Tumours with alterations of the intercellular adhesion pathways (aggressive fibromatosis with *APC* deletion or β catenin mutations) [8–16].

A rational approach to drug development in sarcoma

The new treatment approaches in these tumours are following the same refinements, targeting more ac-

curately specific molecular and histological subtypes, guided by the known molecular biology of these tumours. Importantly, the identification of a driver – or consistent – molecular alteration in a specific histotype has been more efficient to identifying active treatment, than the sole expression of a specific marker. We present below some examples of these approaches.

Specific therapeutic for molecular subtypes of GIST

Targeting of KIT with specific tyrosine kinase inhibitors imatinib, then sunitinib (and more recently in clinical trials everolimus, nilotinib, sorafenib, dasatinib, HSP90 inhibitors, regorafenib), has led to major improvement in the survival of these patients affected with an otherwise chemo- and radio-resistant disease [3]. While molecular characterisation of GIST and identification of *KIT* mutations and then PDGFR mutations were first reported in 1998, it is now clear that many different molecular subtypes of GIST can be identified, with specific clinical presentation, prognosis, outcome and treatment. GIST with mutations of *KIT* on exon 11, on exon 9, more rarely on exons 13, 14, 17, mutations of *PDGFRA* on exon 18 D842V, other mutations on exons 18, 12, 14, mutation of *BRAF*, loss of *NF1*, and mutations on succinyl deshydrogenase enzyme complexes are characterised by specific clinical presentations, outcomes, and response to treatment. They now should be treated with different strategies, both in metastatic and adjuvant phases. Tumours with mutations on exon 9 should receive 800 mg/day of imatinib in the advanced phase, while this treatment is not active in *PDGFRA* D842V mutations, poorly active in *SDH* mutations, and tumours with *NF1* loss. Specific agents, such as crenolanib are starting to be developed in the specific molecular subtype of PDGFRA D842V mutation.

Imatinib in pigmented villonodular synoviti/ -tenosynovial giant cell tumour

Pigmented villonodular synovitis (PVNS), also known as tenosynovial giant cell tumour (TGCT), is a rare pathological entity affecting the synovium in young adults. It is a locally aggressive neoplastic process with specific genetic alterations (92–95), a specific t(1;2) translocation, involving the collagen 6A3 gene (on 2q35), and the M-CSF (a.k.a CSF1) gene (on 1p13), is present in a fraction of tumour cells in PVNS/TGCT. This fusion gene expressed by a fraction of the cells encodes for a fusion protein that attracts non-neoplastic cells expressing M-CSFR, through a paracrine ("landscape") effect. PVNS/TGCT is generally treated by surgery alone. However, relapses may occur, and re-excision may be needed, with possible important functional impairment [17]. Imatinib has been reported to block M-CSFR activation at therapeutic concentration. These observations prompted us to evaluate imatinib in a patient with recurrent and symptomatic PVNS/TGCT following surgery: a complete remission was observed in the first patient. A subsequent retrospective study confirmed the activity of this agent in a larger retrospective cohort and two prospective clinical trials are currently testing nilotinib in this tumour with a rapid inclusion rate [18].

IGF1R in Ewing sarcomas and other sarcomas

Ewing sarcomas are characterised by fusion genes that encode for transcription factors regulating a number of genes; among these the IGFBP3 gene has been found down-regulated by the fusion protein. IGFBP3 regulates the IGF1/IGF1R pathway, by interacting with IGF1 and recombinant IGFBP3 inhibits the proliferation of ES cells and promotes apoptosis in Ewing sarcoma cell lines [8]. With this strong biological rationale, phase I and II trials of IGF1R Ab were conducted. The current results suggest a 30% rate of tumour control in patients with refractory disease, with some long-lasting responses in patients with single-agent therapy. It will be important to identify additional predictive markers for these treatments in these diseases.

MDM2 amplification in well-differentiated and dedifferentiated liposarcomas

The constant amplification of the *MDM2* gene and less consistently of the *CDK4* gene in well-differentiated and dedifferentiated liposarcomas suggests that inhibitors of these proteins might have therapeutic value [11]. Phase I trials of CDK4 inhibitors are currently being performed. Phase I trials testing inhibitors of MDM2/p53 interactions (nutlin, RG7112) have been conducted and reported at ASCO 2011 (Ray-Coquard and colleagues, Proc ASCO 2011) showing major signs of pharmacodynamic response in these tumours, with an induction of p53, p21, cell cycle arrest, apoptosis, systemic induction of MIC1, as early as eight days after exposure to the agent.

Molecular targeted agents: empirical approaches

Although a growing numbers of sarcomas exhibit molecular alterations on proteins whose function can be modulated, still the majority of subsets do not yet have a druggable "driver" molecular alteration. In

these cases, targeting a biological pathway shared by different histotypes can still be a proposed strategy. Trials exploring inhibitors of mTOR, of VEGFR, and modulators of heat shock proteins can be grouped within such an empirical approach.

Inhibitors of mTOR

The most documented mTOR inhibitor for the treatment of sarcomas is ridaforolimus, for which the initial results of a large phase II trial showed clinical benefit (i.e. CR+PR+SD by RECIST criteria for more than four months) in 28% of patients (Chawla and colleagues, Proc ASCO 2006). This molecule has been tested in a phase III trial (SUCCEED) testing maintenance following response or stable disease in the first to third line of treatment including 711 patients. Reported at ASCO 20111, ridaforolimus very significantly improved PFS in this series (RR, 0.71, $P < 0.0001$) (Chawla et al, Proc ASCO 2011).

Agents targeting angiogenesis

A phase II trial with the VEGFR2 tyrosine kinase inhibitor pazopanib (in four strata: leiomyosarcoma, liposarcomas, synovial sarcomas and others) had shown antitumor activity with a median PFS beyond that of active agents according to the EORTC model [19] for all subtypes, but liposarcomas, with responses in synovial sarcomas, and leiomyosarcomas, and four months PFS >40% for all subgroups but LPS; some patients (135) are still experiencing prolonged progression-free survival 60 months after initiation of the treatment. This study was followed by a prospective randomised phase III study vs. placebo (PALETTE, EORTC 62072) showing a very significant improvement in progression-free survival in a series of 369 patients (HR, 0.31, $P < 0.0001$) (Van der Graf et al Proc ASCO 2011).

Conclusions

Research on soft tissue, visceral, and bone sarcoma is a very active area of both clinical and biological research. Dramatic progress has been made through the understanding of the biology of these tumours, and has allowed the development of targeted therapies, cytotoxics, focussing specifically on given histological subtypes and leading to improvements in disease control rate and survival.

Conflict of interest statement

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References

1 Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. *N Engl J Med* 2005;**353**:701–11.
2 Helman LJ, Meltzer P. Mechanisms of sarcoma development. *Nat Rev Cancer* 2003;**3**:685–94.
3 Casali PG, Blay JY; ESMO/CONTICANET/EUROBONET Consensus Panel of experts. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010 May;**21**(Suppl 5):v198–203.
4 Casali PG, Blay JY; ESMO/CONTICANET/EUROBONET Consensus Panel of Experts. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010 May;**21**(Suppl 5):v98–102.
5 Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol* 2009 Sep 1;**27**(25):4188–96.
6 Penel N, Bui BN, Bay JO, et al. Weekly paclitaxel for metastatic or unresectable angiosarcoma. Results of a FNCLCC–French Sarcoma Group Phase II trial, the ANGIOTAX Study. *J Clin Oncol* 2008;**26**:5269–74.
7 Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of Sarcoma Alliance for Research through Collaboration study 002. *J Clin Oncol* 2007;**25**:2755–63.
8 Prieur A, Tirode F, Cohen P, Delattre O. EWS/FLI-1 silencing and gene profiling of Ewing cells reveal downstream oncogenic pathways and a crucial role for repression of insulin-like growth factor binding protein 3. *Mol Cell Biol* 2004;**24**:7275–83.
9 McArthur G. Dermatofibrosarcoma protuberans: recent clinical progress. *Ann Surg Oncol* 2007;**14**:2876–86.
10 Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998;**279**:577–80.
11 Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003;**299**:708–10.
12 Korf BR. Diagnosis and management of neurofibromatosis type 1. *Curr Neurol Neurosci Rep* 2001;**1**:162–7.
13 Sirvent N, Coindre JM, Maire G, et al. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. *Am J Surg Pathol* 2007;**31**:1476–89.
14 Idbaih A, Coindre JM, Derré J, et al. Myxoid malignant fibrous histiocytoma and pleomorphic liposarcoma share very similar genomic imbalances. *Lab Invest* 2005;**85**:176–81.
15 Kotiligam D, Lazar AJ, Pollock RE, Lev D. Desmoid tumor: a disease opportune for molecular insights. *Histol Histopathol* 2008;**23**:117–26.
16 Dômont J, Salas S, Lacroix L, et al. High frequency of beta-catenin heterozygous mutations in extra-abdominal fibromatosis:

a potential molecular tool for disease management. *Br J Cancer* 2010;**102**:1032–6.

17 West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *Proc Natl Acad Sci USA* 2006;**103**:690–5.

18 Blay JY, El Sayadi H, Thiesse P, Garret J, Ray-Coquard I. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). *Ann Oncol* 2008;**19**:821–2.

19 Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer – Soft Tissue and Bone Sarcoma Group (EORTC Study 62043). *J Clin Oncol* 2009;**27**:3126–32.