L'Institut Servier Annual Scientific Sessions

19th Colloquium 2019
Revolutions in cancer treatment:
how can they be integrated?

Malignant, locally aggressive connective tissue tumours

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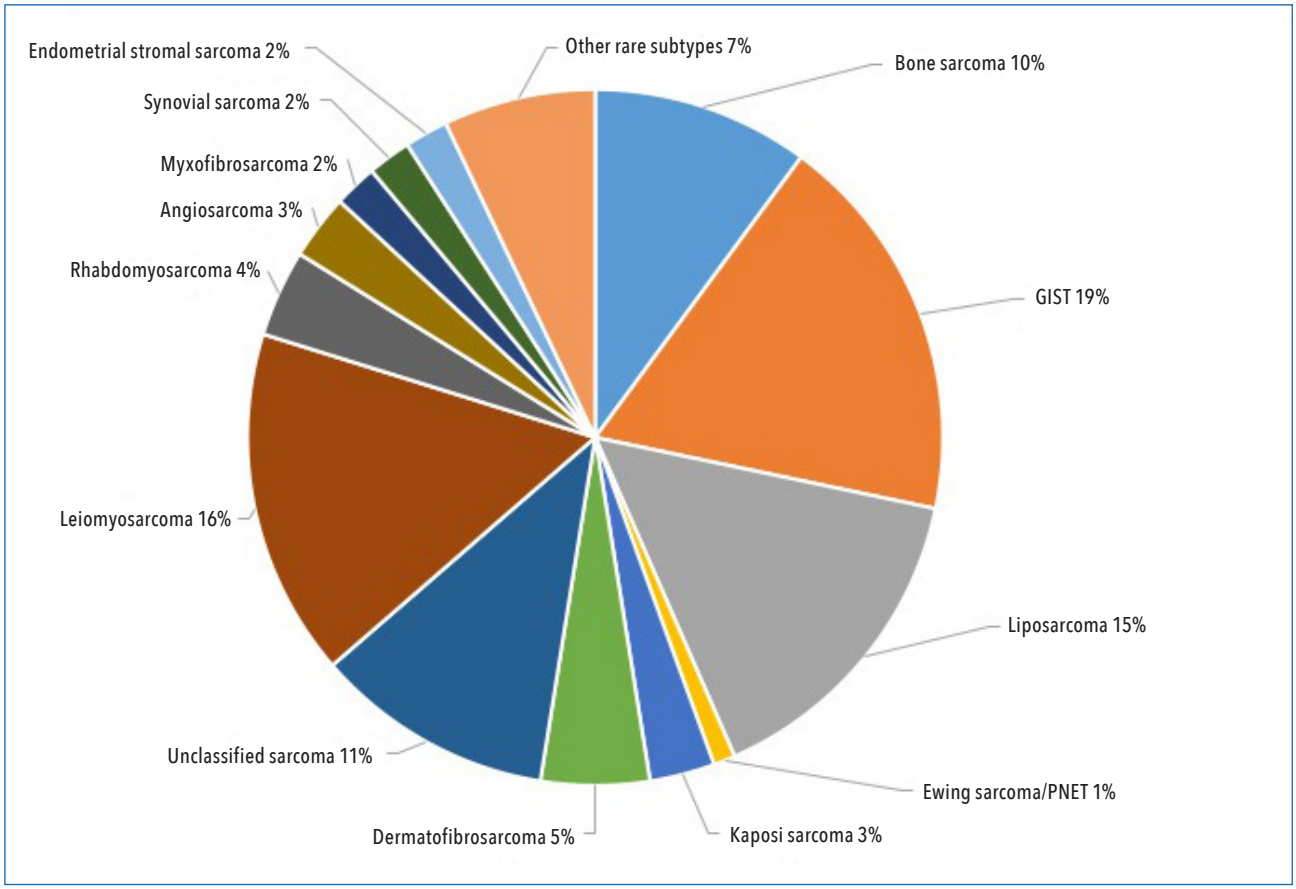
Springer Healthcare

Abstract

Progress in molecular biology has led to the characterisation of some specific molecular subtypes of malignant connective tissue tumours, and targeted therapeutic agents are being developed to correct these abnormalities. For example, the identification of mutations that activate KIT and PDGFRA, which are responsible for malignant transformation in gastrointestinal stromal tumours (GIST), has led to the development of a number of targeted molecules (imatinib, sunitinib, regorafenib, avrapritinib and repritinib). Imatinib is also used in treatment of dermatofibrosarcoma protuberans (also called Darier-Ferrand tumours), which is characterised by a translocation of the PDGF *gene, or in the treatment of pigmented villonodular synovitis, a locally aggressive soft tissue tumour, linked to an abnormality of the gene that codes for M-CSF. Over 20 years, molecular characterisation has resulted in spectacular progress in the effectiveness of treatment of certain soft tissue sarcomas (malignant connective tissue tumours) and some locally aggressive connective tissue tumours. Translational research is an essential tool for the development of future treatments, and identification of the response and resistance mechanisms used by these tumours.*

Connective tissue tumours are mesenchymal tumours with a malignancy equivalent to that of soft tissue sarcomas. They are very rare (1% of adult cancers). These tumours make up a very heterogeneous group of diseases, comprising at least 50 different histological subtypes[1] (**Figure 1**). Some sarcomas present a specific molecular abnormality: thus gastrointestinal stromal tumours (GISTs) are characterised by kinase mutations; translocations adjacent to fusion genes are seen in dermatofibrosarcoma protuberans (DFSP); and *MDM2* or *CDK4* oncogene amplifications are typical in well-differentiated or undifferentiated liposarcomas. Inactivation of certain genes has also been seen, such as *INI1* in epithelioid sarcomas.[2]

Figure 1. Connective tissue tumours are a very heterogeneous group of diseases, with numerous histological subtypes. Based on reference [1], Ducimetière et al. PLoS One 2011;6:e20294.



GASTROINTESTINAL STROMAL TUMOURS (GISTS)

GISTs are the commonest type of soft-tissue sarcoma (18% of sarcomas). These tumours show molecular abnormalities affecting tyrosine kinase receptors such as KIT and platelet-derived growth factor receptor-α (PDGFRA). More than 90% of GISTs are characterised by a causal oncogenic mutation in *KIT* (80%) or *PDGFRA* (10%).[3-6] The commonest mutations of *KIT* are mutations in (juxtamembrane) exons 11 and 9; the commonest mutations of *PDGFRA* affect exons 12 and 18.[7] In addition to mutations of *KIT* or *PDGFRA*, other research has focused on mutations, inhibitors or deficiencies of succinate dehydrogenase (SDH; ≈10%), type I neurofibromatosis mutations (*NF1*) or *BRAF*, or fusions involving NTRK (<2%).

Imatinib is a powerful inhibitor of *KIT*, *PDGFRA* and the CSF receptor, which was approved in 2002 for treatment of metastatic GISTs. This targeted therapy is very effective; when used as a first-line treatment, it has led to a tenfold increase in overall survival (median of 52 months) for patients with metastatic GISTs whose median survival was previously barely 6 months.[8] Patients with a mutation in exon 11 of *KIT* were most sensitive to imatinib (median overall survival of 66 months), while patients with a mutation in exon 9 or wildtypes had an overall survival that was not quite as long (median of 38 to 40 months).[9] Although spectacular progress has been made in the treatment

of these patients, they often presented with resistance to imatinib, with secondary mutations occurring in *KIT* exons 17 and 18. Other targeted therapies with much wider activity spectra have therefore been developed: sunitinib and regorafenib. The efficacy of sunitinib versus placebo has been demonstrated in patients who had GISTs resistant to imatinib, or who were intolerant of imatinib.[10] Sunitinib has significantly improved progression-free survival (PFS) in these patients (median PFS of 27 weeks with sunitinib as compared with 6 weeks in the placebo group). The efficacy of regorafenib has also been demonstrated versus placebo in patients with imatinib- and sunitinib-resistant GISTs.[11] Regorafenib has significantly improved PFS for patients (median of 4.8 months) in comparison with patients given a placebo (median < 1 month).

Forms of resistance to these treatments have, however, appeared, with patients presenting with mutations in exon 17 of *KIT* or exon 18 of *PDGFRA*. Other targeted therapies that are even more effective and also very selective for *KIT* and *PDGFRA* are being developed. Examples include BLU 185 or avapritinib,[12] which will act on these "tertiary" resistance mutations. Based on initial data, the efficacy of this treatment appears very promising:[13] in patients with an intestinal tumour with a D842 V mutation in exon 18 of *PDGFRA*, who are therefore resistant to imatinib and the other targeted therapies, researchers reported that avapritinib permitted them to achieve a median PFS of almost 23 months. A phase III study evaluating avapritinib versus regorafenib is being conducted as a third-line treatment for patients with metastatic GISTs who have progressed on imatinib and sunitinib.

Another tyrosine kinase inhibitor that is very effective against *KIT* and *PDGFRA* is ripretinib (DCC-2618). In a phase I study conducted in patients receiving at least 100 mg of ripretinib daily, patients receiving it as second-line treatment had a median PFS of 42 weeks; those receiving it as third-line treatment had a median PFS of 40 weeks (versus 20 weeks on regorafenib), and for fourth-line and subsequent treatments the median PFS was 24 weeks (as compared with less than 8 weeks on imatinib as the fourth line of treatment).[14] A phase III study (INVICTUS, NCT03353753) comparing patients treated with ripretinib as a fourth or subsequent line of treatment versus placebo showed a median PFS of 6.3 months in the ripretinib arm (versus 1 month in the placebo arm), with overall survival of 15.1 months in the ripretinib arm (versus less than 6.6 months in the placebo arm).[15, 16]

In 20 years, some amazing results have thus been achieved for patients with rare diseases like GISTs, with at least three targeted lines of treatment approved and two others showing very promising results.

DERMATOFIBROSARCOMA PROTUBERANS (DFSP)

DFSP or Darier-Ferrand tumours are rare sarcomas (5% of sarcomas), which in more than 90% of cases are characterised by a chromosomal translocation t(17,22) resulting in fusion of the PDGFbeta1 and *COL1A1* genes. This translocation causes overexpression of *PDGFbeta,* which activates the PDGF receptor. The usual treatment for these tumours is surgery, but patients may relapse with forms that are often very aggressive, locally advanced and often inoperable because the surgery would be too destructive.

Studies in a small number of patients have described the value of targeted treatment with imatinib to reduce the volume of these tumours. A grouped analysis of two phase II clinical studies (EORTC and SWOG) including a limited number of patients (N=24) with locally advanced disease showed that the patients with DFSP with a t(17,22) translocation responded to imatinib.[17] In all, 30% of the patients showed an objective response and their median PFS was 1.7 years. With two phase II studies and no randomised study, imatinib has been approved as a treatment for patients with locally advanced DFSP.

PIGMENTED VILLONODULAR SYNOVITIS (PVNS)

PVNS is a connective tissue tumour of tendon sheaths, characterised by uncontrolled proliferation of the synovial membrane, resulting in increases in the volume of joints, deformation and severe pain; it is extremely disabling for patients. PVNS is not malignant and can be treated by surgical synovectomy but the recurrence rate is 25 to 90%.

It has been shown, however, that PVNS is characterised by a t(1, 2) chromosomal translocation, leading to a fusion between the *CSF1* gene (CSF1R ligand) and the *COL16A3* gene. This translocation leads to overexpression of CSF1, which stimulates and recruits neoplastic inflammatory cells, thereby creating a paracrine feedback loop. Once again, imatinib, which blocks the CSF1 receptor, has been found to be a useful treatment. A phase II study including 29 patients[18] has shown partial responses to imatinib in 15% of patients, with a median PFS of 20.9 months and stabilisation of their condition in 74% of cases, with 72% of patients showing a symptomatic response. This targeted treatment has not yet been approved for PVNS, but this treatment option is recommended by the European Society for Medical Oncology (ESMO).[19]

Studies have been carried out very recently with pexidartinib (PLX3397), a selective inhibitor of the CSF1 receptor, *KIT* and FLT3-ITD, which acts on both cancer cells that express CSF1 and on inflammatory cells. A phase I study in 20 patients showed that 20% of them had a partial response and 35% were stabilised.[20] A phase III study versus placebo showed that PLX3397 was effective in terms of response at 25 weeks.[21] According to the results, 15% of patients showed a 15% response, while 25% saw a partial response and 39% were stabilised.

Fusion events involving the *NTRK1*, *NTRK2* and *NTRK3* genes, which code for the three types of neurotrophin receptors TRKA, TRKB and TRKC, respectively, are extremely powerful oncogenic drivers.[22, 23] These fusions are found in fewer than 1% of sarcomas but they are very often seen in childhood fibrosarcomas (90 to 100% of cases), and in some other solid tumors. *NTRK* inhibitors such as entrectinib and larotrectinib have been developed in NTRK fusion tumors. A compilation of 70 patients with soft-tissue sarcomas with NTRK rearrangement, based on three studies, has shown that larotrectinib was very effective with a response rate of 87% and median progression-free survival (PFS) and overall survival (OS) of 28 and 44 months, respectively.[24] Entrectinib in patients with tumours with NTRK rearrangement (54 patients, 13 of whom had sarcomas) has also been found to be very effective, with median duration of response, PFS and OS of 12.9, 11.8 and 23.9 months, respectively.[25]

PROSPECTS FOR THE FUTURE

Clinical trials are being carried out in chondrosarcomas in which IDH1 and IDH2 mutations have been identified, but the results so far have not been very satisfactory. New targets are being considered, particularly among the many genes involved in DNA repair mechanisms. Treatment combinations involving different mechanisms of action are under consideration.

So far 15% of sarcomas are still unclassified and, although important oncogenic drivers have been identified, this is still only true for a small number of sarcomas. For example, there is still no targeted treatment for Ewing sarcomas. Nevertheless, there are grounds for optimism since amazing progress has been made in the past two decades with the emergence of targeted therapies. Most sarcomas have extremely complex genomic alterations and translational research is an essential tool for developing future treatments and identifying the response and resistance mechanisms developed by these tumours. Clearly, therapeutic progress in the near future will rely on close collaboration between clinicians and fundamental researchers.

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