

Advances in treating soft tissue sarcoma

The Sarcoma Unit at The Royal Marsden is one of largest of its kind in Europe. It is recognised worldwide for its strength in diagnosing and treating sarcoma.

There is no doubt that the current interest in developing new anticancer agents for the group of rare cancers called sarcomas began with the introduction of imatinib for the treatment of a sarcoma that occurs in the bowel wall, called gastrointestinal stromal tumour (GIST). GISTs, although rare, are the commonest sarcomas to arise in the gut and the majority occur in the stomach.

Imatinib is an orally administered tyrosine kinase inhibitor which was known to inhibit a signalling protein called KIT. It was in clinical development when activating mutations in KIT and the importance of KIT protein in the diagnosis of GIST were first identified.

Imatinib has proved to be highly effective against GIST. It has hugely improved the outlook for patients with advanced stages of this disease and proved to be a paradigm for the molecularly targeted therapy of cancer. Another example of the rational targeted use of imatinib is for dermatofibrosarcoma protuberans (DFSP), a disease that is driven by a translocation involving the *COL1A1* and *PDGFB* genes. This results in overexpression of platelet derived growth factor beta (PDGFB). Imatinib

is also effective against locally advanced or metastatic DFSP by virtue of its ability to inhibit platelet derived growth factor receptor beta (PDGFRB). We are now beginning to see the treatment of other sarcomas yield to the same application of knowledge concerning the underlying biology of the disease.

CLINICAL SARCOMA RESEARCH AT THE ROYAL MARSDEN HOSPITAL

New developments in GIST

The Sarcoma Unit at The Royal Marsden has been actively involved in research into GIST since trials with imatinib began. It became clear within the first few years that although a striking breakthrough, imatinib was not a cure. Some tumours possess mutations that make the tumours relatively unresponsive to treatment and secondary mutations may arise that confer drug resistance. In some cases, the use of a higher dose of the drug may be effective such as when the mutation is in exon 9 of the *KIT* gene.

Sunitinib

New agents have also been developed, such as sunitinib. This agent has a somewhat different spectrum of activity in terms of growth factor inhibition, since it also inhibits the growth of new

blood vessels in tumours (angiogenesis). Sunitinib has been shown to be effective in patients with imatinib resistant disease.

We will be studying sunitinib in a new second line therapy study compared with high dose imatinib and will also be investigating its activity first line. Given what we have learnt about its superior activity against GIST and both exon 9 and so-called “wild-type” disease (ie, no detectable activating mutations), together with the retention of activity against certain secondary mutations, it will be interesting to discover whether these features translate into improved or prolonged disease control, especially in these unfavourable subtypes.

Cediranib

We recently completed a clinical trial with another tyrosine kinase inhibitor called cediranib (AZD2171) together with colleagues at the Christie Hospital. The study used ¹⁸Fluorodeoxyglucose positron emission tomography (FDG PET) to define the response of imatinib-refractory GIST. This demonstrated activity in refractory GIST, but also, in treating a small group of patients with other sarcomas, we demonstrated activity against a very rare tumour called alveolar soft part sarcoma (ASPS) (Figure 1).



“We are working to improve treatment options for sarcoma through the application of knowledge concerning the underlying biology of the disease.”

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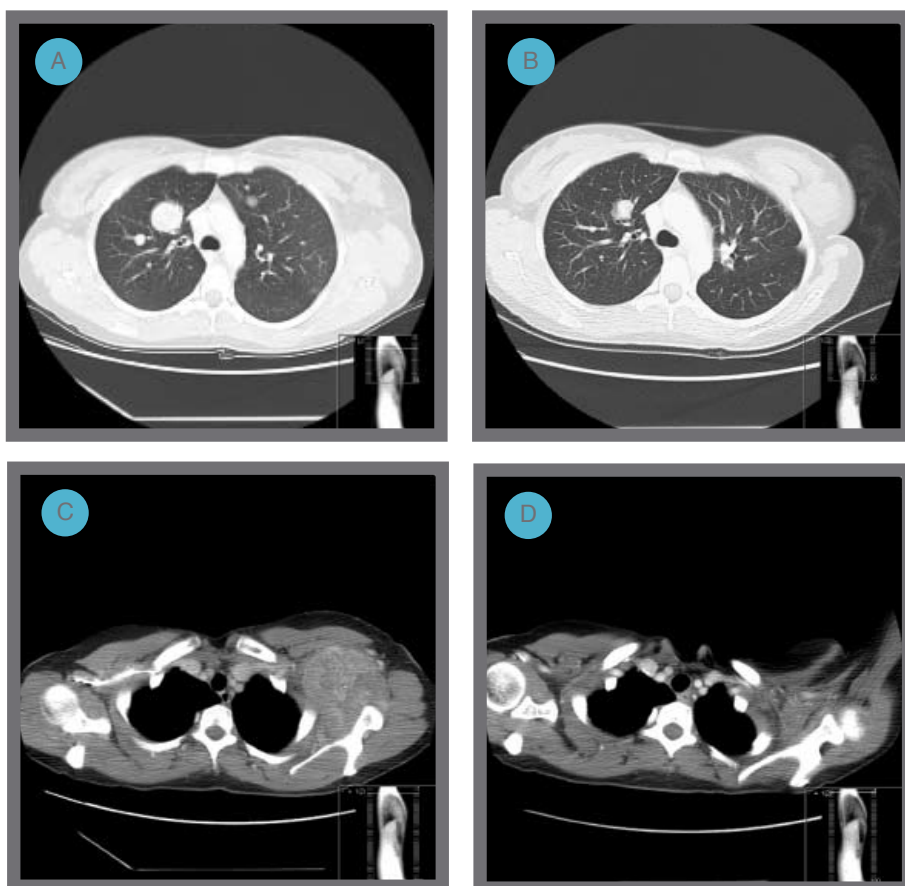


Figure 1: Response of alveolar soft part sarcoma (ASPS) to treatment with cediranib (AZD2171). (A) Lungs before treatment, (B) Lungs after 15 months of treatment with cediranib, (C) Left axilla mass before treatment and (D) Left axilla mass after 15 months of treatment with cediranib.

ASPS is characterised by indolent growth of secondary tumours (metastases) that sometimes reach a certain size and become dormant, raising the possibility that growth is restricted by angiogenesis. Like sunitinib, cediranib is also an inhibitor of angiogenesis. ASPS does not respond

to conventional chemotherapy hence the interest in this result which we hope to build on by performing further studies in this disease.

Imatinib and disease recurrence

There is a great deal of interest in the use of imatinib to try and prevent disease

recurrence in patients at significant risk of relapse after removal of a high risk GIST. A study comparing 12 months of imatinib versus placebo has demonstrated a significant improvement in time to disease recurrence (progression-free survival), especially in patients with large tumours.

Ongoing studies are examining the benefit of treating for two or three years. The Royal Marsden is participating in a large European study, being conducted by the EORTC Sarcoma Group (STBSG), which hopes to answer the question as to whether such treatment could improve survival.

OTHER SOFT TISSUE SARCOMAS AS DISTINCT DISEASES

Although doxorubicin and ifosfamide have formed the basis of the drug treatment of sarcoma for many years, it is now recognised that certain sarcomas respond to other chemotherapy agents. For example, angiosarcoma can be treated effectively with paclitaxel. The combination of gemcitabine and docetaxel was shown to be active against leiomyosarcoma of the uterus. A subsequent randomised trial demonstrated that the combination was superior to gemcitabine alone

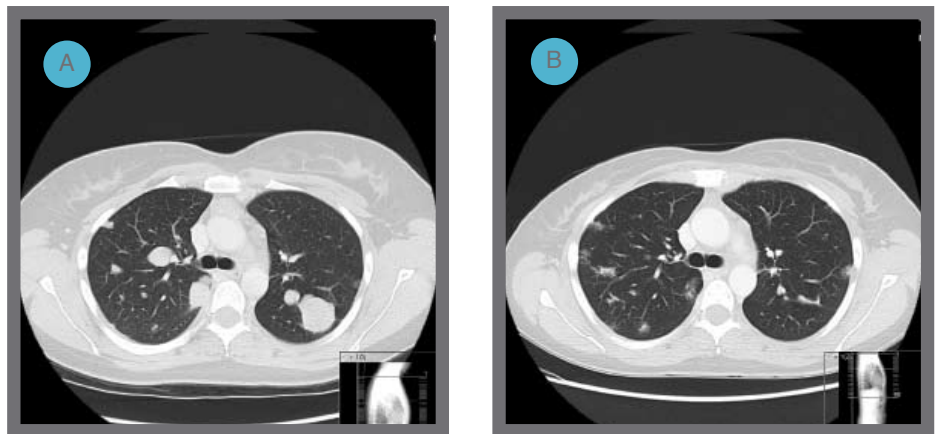


Figure 2: Patient with synovial sarcoma (A) before treatment and (B) following nearly a year of pazopanib treatment.

and produced a survival advantage. Median survival was 17.9 months for the combination therapy but only 11.5 months for gemcitabine alone.

We recently completed the first study of gemcitabine plus docetaxel as first line therapy for patients with advanced leiomyosarcoma, both of uterine origin and elsewhere, together with colleagues at University College Hospital. The activity of the combination has been confirmed in this setting and a comparative Phase III trial is being planned.

A NEW AGENT FOR LEIOMYOSARCOMA, LIPOSARCOMA AND OTHER SUBTYPES

Although the drug now known as trabectedin (previously ET-743) has been studied for a number of years, including trials at The Royal Marsden, it was only recently licensed in Europe for the treatment of refractory sarcoma. Previous Phase II trials had demonstrated its utility against soft tissue sarcomas. A randomised Phase II trial in patients with leiomyosarcoma and liposarcoma demonstrated that a 24-hour infusion of the drug given every three weeks was superior to weekly infusions. Trabectedin binds to DNA in a unique fashion, resulting

in abnormalities (adducts) which cancer cells are unable to repair, while attempts to do so result in increased cancer cell killing.

Understanding these processes may in the future enable us to select patients who are most likely to benefit from this drug. Together with colleagues in Italy and elsewhere, we helped to demonstrate that it may also be particularly useful in the treatment of a disease called myxoid liposarcoma.

ANGIOGENESIS INHIBITION

The pioneering work of Judah Folkman established angiogenesis as a crucial property of growing solid tumours. Recently, a multicentre EORTC Phase II study, in which The Royal Marsden participated, has demonstrated that another VEGFR inhibitor called pazopanib has significant activity against most types of soft tissue sarcoma, other than liposarcoma (Figure 2). These results require confirmation in Phase III trials.

LABORATORY RESEARCH

We are playing a major collaborative role in a European Union sponsored Network of Excellence project designed to facilitate translational work on soft tissue sarcomas. One of

the key features of the collaboration (designated CONTICANET) will be sharing tissue samples with which to validate previously published studies such as the gene expression profile associated with metastatic behaviour in leiomyosarcoma, and the observed overexpression of the transcription factor E2F3 in synovial sarcoma. A number of other sarcoma translational research projects are also underway.

FUTURE NEW DEVELOPMENTS

Insulin-like growth factor-1 receptor

It has been known for some years that insulin-like growth factors could play an important role in regulating the growth of certain diseases such as Ewing's sarcoma. However, until recently this knowledge could not be exploited for therapeutic purposes. Now a number of monoclonal antibodies have been developed against the insulin-like growth factor-1 receptor (IGF-1R). One of these, R1507, has demonstrated activity against Ewing's sarcoma. Gene expression studies and other evidence suggest that such agents may be of value in other sarcomas, including rhabdomyosarcoma and synovial sarcoma.

We will shortly be joining a multinational study of R1507

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in Ewing's and other sarcomas and are also studying another monoclonal antibody against IGF-1R called CP751,871 as a single agent and in combination.

Chaperone inhibition in GIST

An alternative approach to inhibiting receptor proteins such as KIT is to affect their production. Proteins require careful folding in order for them to work properly and are helped to adopt their proper shape by protein complexes called chaperones, which include the heat shock proteins such as HSP90. Mutated proteins appear to require the attention of chaperones more than ordinary proteins and KIT is one such protein that is a so-called client of HSP90.

Inhibitors of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17-AAG) which we studied on the Drug Development Unit at The Royal Marsden, can result in the destruction of proteins such as the mutant form of KIT, causing inhibition of the growth signal. An analogue of 17-AAG, IPI-504, has been tested in patients with imatinib-resistant GIST with promising results. We will be involved in a Phase III clinical trial with IPI-504 that is due to commence during 2008.

Mammalian target of rapamycin, mTOR

A rapamycin analogue, AP23573, has been shown to result in disease stabilisation in patients with bone and soft tissue sarcomas. We will be joining a Phase III trial shortly to investigate whether mTOR inhibition is capable of prolonging response duration in patients with sarcoma. Patients who have had stable disease or objective remission on conventional chemotherapy will be randomised to AP23575 or placebo.

Another potential new target

As new agents enter clinical trial, new opportunities open up based on our ever-growing knowledge of the fundamental biology of sarcomas. Many sarcomas are characterised by chromosomal translocations, as discussed above in relation to DFSP. In many cases the precise consequences of such translocations are unclear but in others a clear target has emerged which we may soon be able to exploit.

One such example is the rare disease alveolar soft part sarcoma, mentioned above in relation to cediranib. The translocation between chromosomes X and 17, (t(X;17)(p11;q25)) results in the fusion protein ASPL-TFE3. This has been shown to upregulate the promoter of the *MET* gene. MET is the

receptor for hepatocyte growth factor and is involved in cancer cell survival, invasion, and angiogenesis.

Inhibitors of MET are now in early clinical trial, raising the prospect for studies of MET inhibition in those diseases where MET is known to be important, including alveolar soft part sarcoma (ASPS), a disease for which there is currently no proven active therapy. A Phase II study is planned that will include patients with ASPS using a MET inhibitor currently in Phase I trial on the Drug Development Unit.

CONCLUSIONS

For many years in spite of being able to distinguish different types of sarcoma on the basis of genetic abnormalities, this did not lead to improvements in therapy. Recently the tide appears to have turned, starting with the identification of *KIT* mutations in GIST, and the unique defining features of sarcomas are beginning to be addressed by selective therapeutic approaches. Hopefully, it will not be too long before other sarcomas apart from GIST and DFSP will be treated routinely using disease-tailored, molecularly targeted therapy.