Targeted therapies in soft tissue sarcomas

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Soft tissue sarcomas are rare cancers but because of their association with characteristic chromosomal translocations and activating mutations they may be particularly susceptible to molecularly targeted therapies. Gastrointestinal stromal tumour (GIST) became the paradigm for targeted therapy in solid tumours owing to the success of imatinib, which has transformed the prognosis in this disease. Translocation-driven tumours have proved harder to target, but the impact of fusion proteins on gene expression is beginning to be understood and may also reveal new targets for therapy, such as insulin-like growth factor 1 receptor, now that effective inhibitors have been discovered. Angiogenesis inhibition also appears to be a promising area for research in sarcomas and many new targets are emerging at the same time as agents capable of investigating them in the clinic are being developed. It is not unrealistic to hope that targeted therapies will play an increasing role in the management of sarcomas in the near future.

Key words: angiogenesis, GIST, IGF-1R, molecularly targeted therapy, mTOR

introduction

Soft tissue sarcomas are mesenchymal neoplasms divided into ~50 distinct diagnoses that occur across the age spectrum and can occur in any part of the body. In many cases they are characterized by specific molecular abnormalities, often in the form of balanced chromosomal translocations that generate unique fusion proteins. Most commonly these have the effect of activating a transcription factor, which can then exert an impact on a number of different genes. It is frustrating that in spite of the fact that one of the defining translocations in a sarcoma was characterized >20 years ago, in this case the t(X;18) translocation in synovial sarcoma [1], this has not, at least until recently, resulted in the identification of a suitable target for therapy.

gastrointestinal stromal tumour

It was a sarcoma that became the solid tumour paradigm for the molecularly targeted therapy of cancer, i.e. gastrointestinal stromal tumour (GIST). Activating mutations of the KIT gene were first reported >10 years ago [2], at about the same time that expression of KIT was recognized as a key diagnostic parameter for this disease [3]. The orally administered experimental drug STI571, a tyrosine kinase inhibitor now known as imatinib, was in the process of being developed for the treatment of chronic myeloid leukaemia, owing to its ability to inhibit ABL, which is activated in this disease by the t(9;22) translocation resulting in the formation of a BCR–ABL fusion protein. It was known that imatinib was also an inhibitor of KIT and the first patient with GIST was treated in early 2000. The remarkable success of imatinib in this case [4] led rapidly to clinical trials in Europe and North America that confirmed the activity of the drug in advanced GIST [5, 6]. Studies carried out to determine the most appropriate dose of imatinib randomized patients to either 400 or 800 mg daily, the European phase I/II trial having established 800 mg as the maximum tolerated dose [6]. Ultimately >1600 patients were randomized in trials in Europe/Australasia and North America confirming that 400 mg daily is the appropriate dose except for patients with mutations in exon 9 of KIT, who have a worse prognosis and benefit from treatment with the larger dose, at least in terms of progression-free survival [7].

The use of imatinib in GIST has not only taught us about the utility of small molecule tyrosine kinase inhibitors in the treatment of cancer, but has helped unlock more precisely the molecular mechanisms underlying growth stimulation and inhibition of cell death in this disease. We now have some insight into the complexity of signalling in terms of the prognostic impact of different mutations in KIT [8], the existence of rarer, but similar, mutations in PDGFRA [9], the types of secondary mutation that confer resistance to imatinib [10] and alternative signalling pathways that may drive the disease in the absence of activating mutations in these genes. The so-called ‘wild-type’ GISTs may be associated with germ-line mutations in other genes, e.g. the NF1 gene in neurofibromatosis type 1, or are currently of unknown aetiology, such as paediatric GIST. The phenotype of paediatric GIST, now recognized to occur in young adults at least up to age 30 years, is generally that of gastric GIST, presenting with anaemia, with a female predominance and a rather indolent disease course. The benefit of imatinib is not striking and other agents that are more effective at inhibiting the wild-type receptor may be more effective, although this has not been proved clinically [11]. In these, there is some evidence for increased signalling via the insulin-like growth factor
Angiogenesis inhibitors

A number of agents that inhibit molecular targets involved in new blood vessel growth have been reported to show efficacy against soft tissue sarcomas [16–18]. Of these the most extensively studied is the tyrosine kinase inhibitor pazopanib. In a phase II study conducted by the EORTC, pazopanib produced a rate of progression arrest at 3 months sufficient to justify cohort expansion in patients with synovial sarcoma, leiomyosarcoma and a group of other tumours including those of vascular origin, but was relatively inactive against adipocytic tumours [19]. This promising result led to a large, placebo-controlled randomized clinical trial with survival as the primary end point (the PALETTE study) that recently closed to accrual.

A number of individual sarcoma subtypes have been shown to respond to tyrosine kinase inhibitors that inhibit both VEGFR and platelet-derived growth factor receptor (PDGFR), in addition to other targets. Alveolar soft part sarcoma has been shown to respond to both sunitinib [20] and cediranib [21], the latter drug producing a number of objective remissions in this rare disease, known to be totally refractory to conventional cytotoxic chemotherapy. What was particularly striking about the cediranib responses was their durability, which has led to a single-arm phase II study and plans for a randomized phase II study in order to confirm this original observation. The anti-VEGF antibody bevacizumab has been reported to be active against angiosarcoma, with a 12% objective response rate and 62% disease stabilization rate [22]. There is also a report of bevacizumab combined with temozolomide having activity against solitary fibrous tumour [23].

Specific translocation targets

Imatinib has been demonstrated to have efficacy against the skin sarcoma dermatofibrosarcoma protuberans (DFSP). DFSP is driven by a t(17;22) translocation resulting in the fusion of the COL1A1 and PDGF-B genes, resulting in overexpression of PDGF-B. Imatinib is thought to work in this disease via inhibition of PDGFRB and can be useful in controlling locally advanced inoperable tumours with a response rate of ~50% [24, 25].

Pigmented villonodular synovitis (PVNS) is generally a relatively benign disease but it can cause bone erosion and significant local damage. It is characterized by a t(1;2) translocation involving a collagen gene and CSF1, the gene for macrophage colony-stimulating factor (M-CSF). In addition to inhibiting KIT, ABL and PDGFR, imatinib also inhibits the M-CSF receptor and appears to have activity against PVNS [26].

A number of chromosomal translocations result in activation of MET, the receptor for hepatocyte growth factor, involved in invasion and angiogenesis. In alveolar soft part sarcoma the characteristic translocation is t(X;17)(p11.2;q25) resulting in a chimeric transcription factor ASPSCR1–TFE3. Gene expression array studies have revealed activation of MET and phosphorylation, i.e. activation of, downstream effectors [27]. In clear cell sarcoma the usual translocation, t(12;22)(q13;q12) gives rise to a EWSR1–ATF1 gene fusion, less commonly t(2;22)(q34;q12) resulting in a EWSR1–CREB1 gene fusion [28], which also results in upregulation of MET [29]. A response has been reported in clear cell sarcoma in a phase II study of the MET inhibitor ARQ197 [30].

The IGF signalling pathway

Although an association between IGF signalling and certain sarcomas has been known for many years [31, 32] the precise mechanisms underlying these were unknown and it seemed unlikely that the pathway could be inhibited safely in a selective fashion owing to the close homology between the IGF receptors and the insulin receptor and the fact that IGF and insulin receptors form heterodimers, increasing the degree of cross-talk between the two pathways. However, developments have been rapid in recent years and this is now regarded as a very important target for anticancer therapy. A mechanism has been proposed linking the t(11;22) translocation associated with Ewing sarcoma and enhanced signalling. It has been shown that the EWS–FLI1 fusion protein binds to the IGF binding protein 3 (IGFBP3) promoter, reducing production of IGFBP3 and effectively upregulating IGF1 [33]. In rhabdomyosarcomas, loss of heterozygosity and loss of imprinting have been implicated as means of upregulating the IGF pathway [34, 35]. The advent of selective monoclonal antibodies (mAbs) that inhibit the IGF1 receptor (IGF-1R) has made clinical exploration of pathway inhibition possible. Eight different mAbs have been...
tested in clinical trials to date. Activity against Ewing sarcoma was first reported in a phase I trial of R1507 [36] and subsequently in an expanded phase I cohort with figitumumab [37]. A large phase II trial with R1507 in sarcomas, including Ewing, synovial, rhabdomyosarcoma, osteosarcoma and a number of other subtypes, closed early owing to a decision not to continue with the clinical development of the agent, but hopefully the results of this study will still be reported once the data are mature. Small molecule inhibitors of IGF-1R that also inhibit the insulin receptor to some degree are also now in clinical trial and clearly a great deal of research will be required to determine which is the most effective way of interfering with this important pathway.

mTOR signalling

The mammalian target of rapamycin, mTOR, is an important signalling protein that coordinates responses from a number of oncogenic receptor tyrosine kinases that signal through PI3 kinase and AKT. Rapamycin itself, now known as sirolimus, has produced clinical benefit in patients with malignant perivascular epithelial cell tumours (PEComas) [38]. In this group of diseases mutations in genes of the tuberous sclerosis complex, TSC1 and TSC2, result in upregulation of mTOR with resultant effects on protein synthesis and proliferation. The mTOR inhibitor ridaforolimus (previously known as deforolimus) was tested in a large phase II study of bone and soft tissue sarcomas [39]. Although the objective response rate was low, there was a high incidence of apparent disease stabilization leading to a phase III trial in which patients were randomized to ridaforolimus or placebo following a response or disease stabilization after chemotherapy for advanced soft tissue or bone sarcoma (the SUCCEED trial) with progression-free survival as the primary end point.

possible new targets

As new potent signalling inhibitors become available it is possible to envisage targeting signalling pathways that have hitherto been resistant to intervention. For example, malignant peripheral nerve sheath tumours developing in the context of neurofibromatosis, i.e. in the presence of a germ-line mutation in NF1 causing loss of function of neurofibromin, resulting in stimulation of RAS signalling. More potent inhibitors of intermediate signalling proteins downstream of RAS, such as MEK, are being developed raising hopes that it may become possible to inhibit this pathway effectively. A protein called anaplastic lymphoma kinase (ALK) is reported to be upregulated in inflammatory myofibroblastic tumour [40]. However, things may not be so straightforward since a recent publication reported that patients without ALK-1 expression were more likely to experience recurrence or metastasis [41]. It is known that in many sarcomas there is loss of the tumour suppressor PTEN, leading to upregulation of the PI3 kinase/AKT/mTOR pathway. A number of PI3K and AKT inhibitors are currently in phase I clinical trial, again raising hopes that targeted agents are going to be valuable in treating sarcomas.

conclusions

In conclusion, molecularly targeted therapies are increasingly being tested against sarcomas owing to their frequent association with a relatively restricted oncogenic genetic event, such as KIT mutation in GIST. In a number of these diseases the translocation or mutation appears to continue to drive the disease even when other genetic events have taken place. Owing to the rapid advances being made in the development of new targeted agents there is reason to hope that more sarcomas will become amenable to effective molecularly targeted therapy in the near future.

disclosures

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references

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