Targeted Therapies for Sarcomas (Including Gastrointestinal Stromal Tumours)

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The management of sarcoma encompasses a broad range of malignancies, arising from bone, soft tissue and gastrointestinal sources, with unique pathologic and cellular pathways. Although sarcomas are rare – approximately 800 new sarcoma cases reported in Australia per year – the incidence has increased by 40% in 10 years.1 With an overall mortality of 50%, in a disease that predominantly affects the young, the community impact of this is significantly greater. It has been estimated that 17 years of life are lost per sarcoma patient, three times the rate of bowel or breast cancer.

In recent years, a number of critical biological and molecular factors driving the growth and progression of sarcomas have been identified. These insights have not only assisted in better characterising sarcoma subtypes, but have also helped identify potential therapeutic targets, enabling a rapid translation into proof of concept trials and effective new therapies. The impact of these breakthroughs has extended far beyond this smaller patient population, providing important insights into treating more common cancers with rationally developed molecularly targeted therapies.

This review will outline some of the advances in targeted therapies for sarcoma in recent years, as well as agents and therapies in development for treating this spectrum of diseases in the future.

Gastrointestinal stromal tumours

Gastrointestinal stromal tumours are the most common mesenchymal tumour of the gastrointestinal tract, most frequently arising in the stomach or small intestine.2 The incidence of gastrointestinal stromal tumours has been reported to be approximately 10-20 per million.3

The majority (around 80%) of gastrointestinal stromal tumours have a gain-of-function mutation in the proto-oncogene C-KIT, which renders KIT tyrosine kinase signalling constitutively active.4 Imatinib mesylate (Glivec®), a protein tyrosine kinase inhibitor (TKI) specifically developed to inhibit the BCR-ABL kinase in chronic myeloid leukaemia, also effectively inhibits the KIT and platelet derived growth factor receptor (PDGFR) tyrosine kinases. Insights into the understanding of the underlying molecular biology of gastrointestinal stromal tumours, first made in 1998, have been translated rapidly into the development of highly effective therapies for a disease that was essentially resistant to conventional cytotoxic chemotherapies.4 Imatinib was first used for gastrointestinal stromal tumours in 2000 and since then there have been multiple trials confirming its activity in metastatic gastrointestinal stromal tumour (figure 1).5-8

The exon at which the mutation occurs in KIT has been demonstrated to carry both prognostic and predictive significance (table 1).9 KIT mutational analysis can help predict response to imatinib; patients with an exon 11 mutation have a significantly better response than those with an exon 9 mutation or no detectable (wild-type) KIT mutation.19 Interestingly, in patients with exon 9 mutations, recent data has emerged suggesting imatinib dose can affect the quality of response. Those starting on a higher dose of imatinib (800mg/day) had significantly longer disease control than those starting on 400mg/day.9

Gastrointestinal stromal tumours can develop secondary resistance to imatinib therapy, most commonly due to the acquisition of a new mutation in the kinase domain of KIT.20 This changes the conformational state of the KIT protein, and thereby affects the ability of imatinib to bind to it and stop KIT-directed downstream signalling. Although less well understood, other mechanisms of resistance to imatinib and other kinase inhibitors can occur, including: KIT genomic amplification; activation of alternate signalling...
Figure 1: CT and FDG-PET scans of a patient with a metastatic GIST treated with imatinib mesylate.

1a: CT scan at baseline. Note large, heterogenous abdominal mass with areas of necrosis. Multiple liver metastases present.

1b: CT scan after four months of treatment. Note that although there has been no reduction in overall external tumour dimensions, there is a clear change in the characteristics of the tumour matrix, with a reduction in tumour density and more homogenous appearance. This is a classic response seen with treatment of GIST with imatinib and other kinase inhibitors.

1c: FDG-PET scan at baseline. Note the increased uptake of tracer in the sites of disease.

1d: FDG-PET scan after four weeks of imatinib. Note the complete resolution of FDG-avid disease.

pathways independent of KIT; or increased action of drug efflux pumps such as MDR1. These molecular changes can lead to unique clinical changes in gastrointestinal stromal tumours, with the development of a resistant clonal nodule, an intra-tumoural nodule which grows despite clinical and radiologic control of the remainder of the disease. In the setting of imatinib failure or intolerance, sunitinib, an oral multi-TKI which inhibits KIT, PDGFB and vascular endothelial growth factor (VEGF) among others, has been shown in a Phase III study to increase time to progression and overall survival. Other KIT-directed TKIs including sorafenib, nilotinib and dasatinib, are currently undergoing clinical evaluation (table 2). Secondary mutations in the kinase domain in KIT have proven resistant to most KIT inhibitors. Alternate approaches to circumventing this, currently being assessed in clinical trials, include targeting kinases downstream of KIT (eg. mTOR), or with agents targeting the protein chaperones that are important in helping to stabilise the KIT-oncoprotein (eg. HSP90). For further reading, there are several recent excellent overviews of gastrointestinal stromal tumours and their management. 

Dermatofibrosarcoma protruberans

Dermatofibrosarcoma protruberans is a cutaneous fibroblast-derived soft tissue sarcoma. This rare tumour is an excellent example of the role of autocrine and paracrine loops involving growth factors – in this instance, PDGF – in driving malignancy and the ability to target the loop based on knowledge of this underlying biological mechanism.

The characteristic translocation seen in dermatofibrosarcoma protruberans is t(17;22) which leads to the formation of a fused proto-oncogene, resulting in upregulation of the the PDGFB gene. Mature PDGF production facilitates tumour growth by interacting in an autocrine fashion with PDGF receptor. This is the principal driving mechanism behind the tumour. Imatinib, with its ability to inhibit the PDGF receptor, has proven very effective in managing metastatic and locally advanced dermatofibrosarcoma protruberans that are not amenable to surgical resection. A number of published case reports and series have documented complete and partial responses to imatinib. Surgery for dermatofibrosarcoma protruberans can be particularly
challenging, with significant morbidity and high local recurrence rates, due to the highly infiltrative nature of this tumour. Neoadjuvant imatinib should therefore be considered in the multidisciplinary treatment of this disease. There has been a recent review on the management and background behind this effective treatment of dermatofibrosarcoma protuberans based on the sound understanding of its biology.52

Ewing’s family tumours (EFTs)

Ewing’s sarcomas are rare, highly malignant tumours, thought to derive from neural crest cells and most commonly originate in bone. The median age at diagnosis is only 15 years.52 Despite aggressive first line management with surgery, chemotherapy +/- radiotherapy, 30-40% of Ewing’s family tumours recur.

Translocations are common: t(11;22) and a related translocation occurs in over 80-90% of Ewing’s family tumours (table 3).53 This translocation creates a fusion protein (EWS-FL1), which acts as an aberrant transcription factor, hence driving the process of malignancy. EWS gene translocations are also seen (EWS-WT1) in desmoplastic small round cell tumours, a rare, aggressive, primitive sarcoma. The malignant growth of EFTs is reliant on the development of growth factor-mediated autocrine loops through which signalling occurs.54 These autocrine loops involve the insulin-like growth factor-1 (IGF-1) and its receptor. The IGF signalling pathway plays a key role in the pathogenesis of EFT and other tumours. The presence of the fusion gene results in a significant increase in secretion of IGF-1 or expression of its receptor.55 Autocrine IGF-1 signalling, increased significantly by these translocations, is known to contribute to tumour cell survival and maintenance of the malignant phenotype.56 Thus, there is compelling biologic rationale for targeting IGF-1 and its receptor.

The type 1 IGF receptor (IGF-1R) is a receptor tyrosine kinase which activates the PI3K/AKT/mTOR, Ras/MAP kinase and JAK/STAT signalling pathways. Either IGF-1 itself or its receptor can be targeted by monoclonal antibodies, or small molecule tyrosine kinase inhibitors. Pre-clinical studies of small molecule inhibitors of antibodies to the IGF-1 receptor have demonstrated inhibition of Ewing tumour cell proliferation.57-59 Phase II trials are currently underway investigating the activity of monoclonal antibodies to IGF-1 receptor, based both on a strong pre-clinical rationale, and on promising results from Phase I studies, where a number of sustained responses have been seen, particularly in patients with Ewing’s sarcoma.52

It is also known from preclinical studies that Ewing’s sarcoma cell lines carrying the EWS-FL1 fusion protein express varying levels of mTOR cell signalling protein. mTOR is a downstream signalling pathway of the IGF-1 receptor and PI3K/AKT pathways, which are activated in numerous cancers.60 Dysregulation of the mTOR pathway can result from numerous alterations, both

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
<th>Consequence</th>
<th>Targeted agent</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT exon 11 (juxtamembrane domain)</td>
<td>57-70%</td>
<td>Constitutively active KIT TK signalling</td>
<td>Single best predictor for favourable response to imatinib. Higher RR and PFS on imatinib than exon 9.</td>
<td>More likely to develop 2nd mutations (compared with exon 9 mutations).</td>
<td>4,9,10,19</td>
</tr>
<tr>
<td>KIT exon 9 (extracellular domain)</td>
<td>5-18%</td>
<td>Intermediate response to imatinib. Better outcomes with high dose (800mg) than low dose (400mg). Appear sensitive to sunitinib.</td>
<td>Uncommon to develop 2nd mutations.</td>
<td></td>
<td>9,11</td>
</tr>
<tr>
<td>KIT exon 13,14, 17 (exon 17 = activation loop)</td>
<td>0.6-1.4%</td>
<td>Imatinib less effective in most exon 17 mutations. Sunitinib: lower efficacy for 2nd KIT mutations in exon 17/18 compared with exon 13/14.</td>
<td>2nd mutations can cause imatinib resistance.</td>
<td></td>
<td>11-13</td>
</tr>
<tr>
<td>PDGFRA Exon 12 (juxtamembrane or 18 (activation loop)</td>
<td>5-10%</td>
<td>Constitutively active PDGFRA TK signalling</td>
<td>Less responsive to imatinib.</td>
<td></td>
<td>14,15</td>
</tr>
<tr>
<td>Wild type</td>
<td>10-15%</td>
<td>Mechanisms unclear</td>
<td>Less responsive to imatinib. Appear sensitive to sunitinib. Tumours express cKIT with IHC but no mutations.</td>
<td>Majority of GISTs in children/adolescents.</td>
<td>16-18</td>
</tr>
</tbody>
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TK= tyrosine kinase     IHC = immunohistochemistry     RR= response rate     PFS = progression-free survival
upstream and downstream from mTOR itself. As potential therapeutic agents, mTOR inhibitors such as rapamycin, temsirolimus (CCI-779), everolimus (RAD-001) and deforolimus (AP23573) are being evaluated in various clinical trials. A pre-clinical study demonstrated that rapamycin blocked the proliferation of Ewing's sarcoma cell lines, indicating that mTOR signalling is central to the biologic mechanisms of Ewing's sarcoma growth. Early clinical studies have demonstrated promising results in refractory sarcomas (table 2). There has been a recent comprehensive review about mTOR inhibition in sarcoma. Plans are also underway to evaluate the efficacy of combining an mTOR and IGF1 receptor inhibitor in refractory EFT.

Rhabdomyosarcoma

Rhabdomyosarcomas, thought to be derived from primitive skeletal mesenchymal cells, are the most common soft tissue sarcomas in children. Subtypes include embryonal (60%, better prognosis) and alveolar (20%, worse prognosis). IGF-2 is known to be overexpressed in rhabdomyosarcomas; this autocrine IGF-2 loop involves mTOR as a downstream signalling pathway. A rhabdomyosarcoma xenograft model has demonstrated anti-tumour activity by the inhibition of the IGF-1R signalling pathway using the mTOR inhibitor temsirolimus. The effect of monoclonal antibodies to IGF1R on the growth of rhabdomyosarcomas will be evaluated in a current international Phase II co-operative group trial being co-ordinated by the Sarcoma Alliance for Research through Collaboration.

Way forward

In clinical practice there has been an escalation of the use of targeted agents in trials and routine practice in the 21st century. Many new drugs are promiscuous in that they inhibit multiple kinase pathways, rather than specifically blocking a particular biological pathway. Some agents which are currently undergoing clinical trials for sarcoma therapy are outlined in table 2. However, outcomes as impressive as those seen for gastrointestinal stromal tumours and dermatofibrosarcoma protuberans are not always seen, often
because in most solid tumours, multiple pathways involved in tumour growth are likely to exist. The inhibition of only one of these pathways may therefore not be adequate in stopping that tumour’s most critical mechanisms for growth. Perhaps this is because in some circumstances we are yet to find the unique ‘switch’ that is the key driver of the oncogenic process. Alternatively, the stroma or micro-environment of the tumour may also need to be considered, given the important role they play, as the milieu that tumour cells exist within; targeting these as well may prove to be particularly important.

It can be particularly difficult when pre-clinical evidence demonstrates the likely utility of targeting a particular pathway, to move to ‘proof-of-concept’ trials where a tumour is rare. Although the Phase III clinical trial remains the ‘gold standard’ for proving efficacy, this may be difficult to perform for tumours such as rhabdomyosarcoma or desmoplastic small blue round cell tumours, where the incidence is low. More realistically, the efficacy of targeted agents for these tumours may need to be shown in carefully selected cohorts of patients from international collaborations. This highlights the need for collaboration between expert centres in the development of novel agents for many sarcoma subtypes.

Since imatinib was first used on compassionate grounds in 2000, the potential for developing effective new targeted therapies for other sarcoma subtypes has been successful. Further progress will now largely depend on ongoing collaborative efforts to better define sarcomas based on their molecular subtypes, with clinical trials adapted to deal with both the complexities and subtleties of assessing responses to modern biological therapies.

**Conflict of interest statement:** Jayesh Desai is on the advisory boards for Novartis, Pfizer and Infinity Pharmaceuticals and receives research support from Novartis.

### Table 3: Selected chromosomal translocations in sarcomas

<table>
<thead>
<tr>
<th>Sarcoma type</th>
<th>Translocation</th>
<th>Effect of translocation</th>
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<tbody>
<tr>
<td>Ewing’s/PNET</td>
<td>t(11;22) (80-85%)</td>
<td>EWS-FL1 translocation: some variants associated with more favourable prognosis. FL1 acts as transcription factor.</td>
</tr>
<tr>
<td></td>
<td>t(21;22)</td>
<td></td>
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<tr>
<td></td>
<td>t(7;22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(17;22)</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma (alveolar)</td>
<td>t(2;13)</td>
<td>PAX-FOX01a gene fusion. Encodes chimeric transcription factor. Fusion status correlates with clinical outcome.</td>
</tr>
<tr>
<td></td>
<td>t(1;13)</td>
<td></td>
</tr>
<tr>
<td>DFSP</td>
<td>t(17;22)</td>
<td>Fusion of collagen 1 type 1a and PDGFb.</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(X;18)</td>
<td>Biology of fusion product not well known – transcription co-factor.</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)</td>
<td>EWS-ATF1</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>t(12;16)</td>
<td>CHOP-EWS/CHOP-TLS fusion product.</td>
</tr>
<tr>
<td>Desmoplastic small round-cell tumour</td>
<td>t(11;22)</td>
<td>EWS-WT1</td>
</tr>
</tbody>
</table>

### References


64. Wan X, Shen N, Mendoza A, Khanna C, Helman LJ. CCI-779 inhibits rhabdomyosarcoma xenograft growth by an antiangiogenic mechanism linked to the targeting of mTOR/HIF-1alpha/VEGF signaling. Neoplasia. 2006;8:394-401.