NEW DRUGS IN THE MANAGEMENT OF SARCOMA

Maggie Moore and Jayesh Desai
Sarcoma Service, Peter MacCallum Cancer Centre, Victoria.
Email: jayesh.desai@ludwig.edu.au

Abstract

Sarcomas are a rare group of malignant mesenchymal tumours arising from bone and soft tissue. The diversity of this group of tumours and the rarity of each subtype poses significant challenges in the search for effective therapeutic agents. While recent advances in the molecular characterisation of these tumours has lead to the development of some promising agents targeting critical steps in the neoplastic process, it has also highlighted the true heterogeneity of sarcoma subtypes. These tumours can no longer be ‘lumped’ together for the purposes of research or treatment, but rather collaborative effort and novel clinical trial design are required to allow for accurate and timely assessment of emerging agents in specific sarcoma subtypes. New and emerging drugs and drug combinations for the treatment of advanced sarcoma will be discussed in this review.

Sarcomas are a rare group of malignant mesenchymal tumours arising from bone and soft tissue. Approximately 800 new cases of sarcoma are diagnosed in Australia each year, comprising <1% of cancer diagnoses overall, although a significantly greater proportion of those diagnosed in childhood and adolescence.1

There are more than 50 different histological subtypes of bone and soft tissue sarcoma (STS) and recent advances in molecular characterisation have brought with them with an increased understanding of the true heterogeneity of this group of neoplasms. Whereas previously these tumours were often ‘lumped’ together, both in the research and clinical context, modern practice dictates the tailoring of treatment strategies based not only on histology, but identified molecular mechanisms of tumourigenesis.

With rare exception, the prognosis of patients with unresectable metastatic sarcoma remains poor, however significant advances have been made over the last decade in the treatment of some sarcoma subtypes. This has been most notable in tumours where cell signalling pathways critical to the neoplastic process have been identified and specifically targeted by therapeutic agents. The most impressive example to date has been seen in the treatment of gastrointestinal stromal tumours (GIST) by imatinib, a protein tyrosine kinase inhibitor targeting c-KIT, a proto-oncogene mutated in the majority of these tumours.2,4

This review outlines the new drugs and drug combinations that have shown promise in the treatment of advanced sarcoma. A detailed description of the tumour biology and genetics that underlie the mechanism of action of many of these agents has not been undertaken, and can be found in the companion article “Importance of molecular genetics of sarcomas”.5

Trabectedin

Doxorubicin as a single agent or in combination with ifosfamide has been the standard of care for patients with advanced or metastatic STS for two decades. With objective response rates ranging from 9-34%,6-9 and no standard treatment option following failure of these two agents, it is clear that new active drugs are urgently required.

Trabectedin (ecteinascidin-743; ET-743) is a novel compound originally derived from the Caribbean tunicate ecteinascidia turbinate and now manufactured synthetically. Although the exact mechanism by which trabectedin exerts a cytotoxic effect is incompletely understood, it is known to bind to the minor groove of double stranded DNA, bending it towards the major groove.10 This interferes with the transcription coupled nucleotide excision repair pathway, inducing lethal DNA strand breaks.11 Trabectedin has also been shown to selectively inhibit activated gene transcription and lead to G2/M phase cell cycle arrest.12

Following promising pre-clinical data,13-15 phase I trials of trabectedin were undertaken, with tumour responses seen in a number of heavily pre-treated patients with advanced soft tissue sarcoma.16-19 This led to the initiation of three simultaneous phase II trials conducted in France, the United States and Europe assessing the efficacy and safety of trabectedin in this group of patients.20-22 A further phase II trial designed to compare two different schedules of administration was limited to pre-treated patients with advanced or metastatic leiomyosarcoma or liposarcoma.23 Trabectedin was subsequently assessed in the first-line setting.24 The results of these trials are summarised in table one.

Although the objective response rates could be considered low for a cytotoxic agent (5-17%), it is widely acknowledged within the sarcoma community that duration of response and disease stabilisation in patients known to be progressing prior to study entry are also relevant when assessing the clinical activity of a new treatment. The European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue Bone and Sarcoma Group conducted a retrospective analysis of their database looking at the three and six
month progression free rates for chemotherapy in patients with STS. Active agents had progression free rates at six months of 30-56% in the first line setting and 14% in the second line setting.25 The six month progression free rate for trabectedin in the phase II first line trial was 24.4%, and between 20 and 35% in the four second line trials, indicating clinically relevant activity of this drug. Retrospective review and pooled analysis suggest that leiomyosarcoma and liposarcoma (especially the translocation related myxoid liposarcomas) may be particularly sensitive histological subtypes.26,27 In addition to being active, trabectedin appears to have an acceptable safety profile with the main toxicities being an asymptomatic transaminitis (grade 3-4 in 34-57% of patients) and neutropenia (grade 3-4 in 33-61% of patients), with the 0-7% rate of febrile neutropenia comparing favourably to that seen with doxorubicin and ifosfamide.20-24 Importantly, in contrast to the cardiac and renal toxicities that limit prolonged administration of doxorubicin and ifosfamide respectively, no cumulative dose limiting toxicities have been identified in studies of trabectedin allowing for prolonged treatment in responding patients.

Although not approved in Australia, the efficacy and tolerability of trabectedin in STS has led to the drug being approved in Europe and 21 other countries for the treatment of this group of tumours after failure of doxorubicin and ifosfamide. It currently holds orphan drug status in the United States for the treatment of STS and ovarian cancer, however is not FDA approved for either of these indications. Further clinical trials are currently underway assessing trabectedin in combination with other chemotherapeutic agents and in specific histological subtypes of STS, including a phase III trial comparing doxorubicin with trabectedin in the first-line treatment of patients with translocation related sarcomas. The results of these studies will further define the role of trabectedin in the treatment of this challenging group of tumours.

Table 1: Results of published Phase II trials of trabectedin in the treatment of soft-tissue sarcoma. (NR- not reported; PFS - progression free survival; OS - overall survival).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Number</th>
<th>Regime</th>
<th>Response rate</th>
<th>Median PFS (months)</th>
<th>Six-month PFS</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yovine et al 200422</td>
<td>Pre-treated soft tissue sarcoma</td>
<td>54</td>
<td>1.5mg/m2 24hr q3w</td>
<td>3.7%</td>
<td>1.9</td>
<td>24.1%</td>
<td>12.8</td>
</tr>
<tr>
<td>Garcia-Carbonero et al 200420</td>
<td>Pre-treated soft tissue sarcoma</td>
<td>36</td>
<td>1.5mg/m2 24hr q3w</td>
<td>8.0%</td>
<td>1.7</td>
<td>20.0%</td>
<td>12.1</td>
</tr>
<tr>
<td>Le Cesne et al 200521</td>
<td>Pre-treated soft tissue sarcoma</td>
<td>104</td>
<td>1.5mg/m2 24hr q3w</td>
<td>8.0%</td>
<td>3.4</td>
<td>29.0%</td>
<td>9.2</td>
</tr>
<tr>
<td>Demetri et al 200923</td>
<td>Pre-treated liposarcoma and leiomyosarcoma</td>
<td>136</td>
<td>1.5mg/m2 24hr q3w</td>
<td>5.6%</td>
<td>3.3</td>
<td>35.5%</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>134</td>
<td>0.58mg/m2 3hr qwk for 3 wk in 4wk cycle</td>
<td>1.6%</td>
<td>2.3</td>
<td>27.5%</td>
<td>11.8</td>
</tr>
<tr>
<td>Garcia-Carbonero et al 200524</td>
<td>Chemotherapy naive soft tissue sarcoma</td>
<td>36</td>
<td>1.5mg/m2 24hr q3w</td>
<td>17.1%</td>
<td>NR</td>
<td>24.4%</td>
<td>NR</td>
</tr>
</tbody>
</table>
Recent studies have explored the use of the cytotoxic agents gemcitabine and docetaxel in combination for the treatment of metastatic STS. Promising results have been seen in some sub-types, including leiomyosarcoma and undifferentiated high grade pleomorphic sarcoma (UPS).\textsuperscript{28-31}

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase. Pharmacodynamic studies performed in patients with sarcoma and pancreatic cancer have shown improved clinical efficacy of the drug when administered as a fixed dose infusion (FDI) compared with bolus dosing, thought to be due to optimisation of intracellular accumulation of the drug.\textsuperscript{32-33} Phase II trials of single agent gemcitabine for first or subsequent line treatment of metastatic soft tissue sarcoma have yielded response rates of 3-18\% (median 6.5\%), with many of these studies identifying leiomyosarcoma as a histological subtype associated with a better response.\textsuperscript{33-39}

Docetaxel is a taxane drug which promotes microtubule assembly and stabilisation in the cell leading to inhibition of DNA, RNA and protein synthesis. Despite an initial phase II trial conducted by the EORTC reporting a 17\% (five of 29 patients) response rate to docetaxel as second line therapy in patients with advanced soft tissue sarcoma, a subsequent larger phase II trial by the same group, comparing sequential therapy with doxorubicin then docetaxel on progression or the reverse, showed a 0\% response rate to docetaxel in both lines of treatment.\textsuperscript{41}

Although the findings of pre-clinical studies evaluating potential synergy between gemcitabine and taxanes have been inconsistent,\textsuperscript{29,42,44} the results of four clinical trials assessing the activity of gemcitabine and docetaxel in advanced sarcoma have been promising.\textsuperscript{28-31} Hensley et al evaluated docetaxel and gemcitabine (as a FDI) in a phase II trial of 34 patients with leiomyosarcoma, the majority of which (29 patients) were of uterine origin.\textsuperscript{31} They reported a response rate of 53\% (including three complete responses), time to progression of 5.6 months and a median overall survival of 17.6 months in a population where 47\% (16 patients) had received prior treatment with a doxorubicin based regime.

Two subsequent retrospective reviews support the activity of this combination in a broader spectrum of sarcoma histologies. In a study from the University of Michigan, an overall response rate of 43\% was reported in 35 patients with a variety of advanced bone and soft tissue sarcomas, including 7/12 (58\%) of patients with leiomyosarcoma.\textsuperscript{29} A French study assessing 133 patients with advanced soft tissue sarcoma treated with docetaxel/gemcitabine found an overall response rate of 18.4\%, with a higher response rate for patients with leiomyosarcoma than other histological subtypes (24.2\% v10.4\%; p = 0.06).\textsuperscript{30}

The activity of the docetaxel/gemcitabine combination was then compared to gemcitabine alone in a multicentre randomised phase II clinical trial conducted by the Sarcoma Alliance for Research.\textsuperscript{28} In this study, 122 patients with metastatic soft tissue sarcoma were adaptively randomised to receive gemcitabine alone (1200mg/m2 by FDI D1, D8 every 21 days) or a reduced dose of gemcitabine (900mg/m2 by FDI D1, D8 every 21 days) in combination with docetaxel (100mg/m2 D8 every 21 days). The response rate was 8\% for single agent gemcitabine and 16\% for the combination. The response rate for the 29 patients with leiomyosarcoma treated with docetaxel/gemcitabine in this study was 17\% (compared with 11\% for gemcitabine alone). Notably, amongst the 11 patients with UPS enrolled on this trial, four patients (36\%) responded to combination treatment including one complete response. Response for this histology in the single agent arm was also higher (25\%) than the average suggesting a particular sensitivity of UPS to gemcitabine alone and in combination with docetaxel.

It should be noted that patients receiving treatment on the combination arm in this trial experienced significantly more toxicity than those on the gemcitabine alone arm, with more than 40\% of patients discontinuing therapy due to non-hematologic toxicities. These were predominantly constitutional symptoms such as myalgias and fatigue. The authors acknowledge that the dose and scheduling used in the study is probably too high for long-term use and this should be borne in mind when considering this combination in routine practice.

**Denosumab**

Denosumab is a fully human monoclonal antibody that specifically inhibits Receptor Activator of Nuclear Factor Kappa B ligand (RANKL), an important mediator of osteoclast activation. Under normal conditions RANKL is expressed on a number of different cell types including lymphocytes and stromal cells.

Giant cell tumour (GCT) of the bone is a rare osteolytic bone tumour seen predominantly in young adults. Although it is considered benign, GCT can be locally aggressive and in rare cases metastasise to the lung.\textsuperscript{45} Surgery forms the mainstay of treatment, however there are limited options for patients with unresectable primary or recurrent disease.

It has been suggested that the RANKL expression, observed in the mononuclear stromal cells of GCTs in several studies,\textsuperscript{46-48} stimulates the recruitment of osteoclast-like giant cells from their normal monocytic precursors.\textsuperscript{49} This overpopulation of giant cells then causes the osteolysis associated with these tumours. In an open label phase II study, 37 patients with recurrent or unresectable GCT were treated with subcutaneous denosumab 120mg every 28 days after three initial weekly loading doses.\textsuperscript{50} In this trial 30 of the 35 assessable patients (86\%; 95\% CI 70-95\%) had a tumour response including all of the 20 patients who were assessed by histology, with response defined as elimination of at least 90\% of the giant cells on repeat biopsy.
In view of these very promising results, further investigation of denosumab as a treatment for GCT is justified, with specific attention to the optimal duration of treatment with this agent and the safety profile of denosumab required. An international open label phase II study is currently underway in an attempt to address the latter point and is recruiting at sites within Australia.

mTOR Inhibitors

The phosphotidylinositol 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) pathway is a cell signalling pathway which plays a central role in the control of cell proliferation, survival, mobility and angiogenesis. This pathway is abnormally activated in a range of cancers, including sarcomas, which has led to its evaluation as a therapeutic target.

A number of mTOR inhibitors are being assessed in clinical trials against a variety of tumour types. Of these, the most data concerning activity against non-GIST sarcomas has been reported for ridaforolimus. In a phase I dose escalation trial of ridaforolimus administered to patients with advanced malignancies, all seven patients with sarcoma were noted to have a partial response (two patients), minor response or stable disease for more than three months. This led to a phase II study of ridaforolimus in patients with advanced soft tissue or bone sarcoma with a primary endpoint of clinical benefit response, defined as complete or partial response or stable disease for ≥16 weeks. The results were presented in abstract form at the American Society of Clinical Oncology Annual Meeting in 2006 and updated in 2007. Of the 212 patients enrolled on this trial, 61 patients (29%) had a clinical benefit response, including five partial responses. The most frequent toxicities were mucositis, fatigue, rash, thrombocytopenia and hyperlipidemia, most of which were mild to moderate in severity.

In light of this promising clinical activity and acceptable safety profile, this agent is now being evaluated in the phase III clinical trial ‘Ridaforolimus in Treatment of Sarcoma-SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus)’. This study is a randomised double-blind placebo-controlled trial assessing the safety and efficacy of ridaforolimus administered as maintenance therapy to patients with metastatic sarcoma who have achieved a favourable response to chemotherapy. The study has completed enrolment, with results expected in early 2011.

Insulin-like growth factor-1 receptor (IGF-1R) inhibitors

The insulin-like growth factor (IGF) signalling pathway is another potential therapeutic target currently being explored. This pathway is involved in the regulation of cell growth and survival, with preclinical data suggesting it plays an important role in tumourigenesis. A number of monoclonal antibodies targeting the IGF-1R are currently being evaluated in clinical trials in sarcoma AMG 479, R1507 and figitumumab (CP-751,871). Results have been reported for a phase I trial of figitumumab and in abstract form for Phase II trials of AMG 479 and R 1507. These are summarised in table two.

Future trials of these agents in the treatment of the Ewings family of tumours and other sarcomas are likely to be in combination with chemotherapy and other targeted therapies, with a strong rationale for this approach. One effect of IGF-1R signalling is to protect the cell from apoptosis, so inhibiting this pathway may sensitise the cells to the effects of anti-cancer drugs, a theory that has been borne out in several pre-clinical models. The lack of overlapping toxicities with conventional cytotoxic agents used to treat sarcoma adds further merit to this approach.

Table 2: Results of phase I and II trials of IGF1-R inhibitors in the treatment of advanced sarcoma (DSRCT- desmoplastic small round cell tumours; CBR- clinical benefit rate; MOS- median overall survival; PFR- progression free rate).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Population</th>
<th>Number of patients</th>
<th>Efficacy</th>
<th>Grade 3/4 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG 479</td>
<td>II</td>
<td>Pre-treated EFT and DSRCT</td>
<td>35</td>
<td>RR 6%</td>
<td>37% (thrombocytopenia, neutropenia, hyperglycemia)</td>
</tr>
<tr>
<td>R 1507</td>
<td>II</td>
<td>Pre-treated EFT</td>
<td>125</td>
<td>RR 14%</td>
<td>13% (diarrhoea, anaemia, thrombocytopenia)</td>
</tr>
<tr>
<td>Figitumumab</td>
<td>I</td>
<td>Pre-treated EFT and other sarcoma</td>
<td>29</td>
<td>RR 7% 6M PFR 28% (6M PFR 40% EFT)</td>
<td>17% (deep venous thrombosis, back pain, vomiting, abnormal liver function tests, raised uric acid)</td>
</tr>
</tbody>
</table>
Multi-targeted Kinase Inhibitors and c-MET Inhibition

Sunitinib and cediranib are multi-targeted kinase inhibitors which have shown promising signs of activity in the treatment of metastatic alveolar soft part sarcoma (ASPS). ASPS is a rare sarcoma, characteristically affecting the soft tissues of the extremities in young patients. It has a relatively prolonged natural history, however the presence of metastatic disease dictates a poor prognosis. No chemotherapeutic agents have demonstrated activity in the treatment of this disease. ASPS is characterised by an unbalanced translocation t(X;17)(p11.2;p25), which leads to dysregulated expression of the transcription factor TFE3. This activates MiT (Microphthalmic transcription factor) and results in the overexpression of the c-met receptor tyrosine kinase. In tumour cells, c-met activation is known to promote tumour growth, angiogenesis and metastasis.

Sunitinib is an orally administered tyrosine kinase inhibitor, with activity against a range of targets including VEGFR, PDGFR, c-KIT and RET. It is currently licensed for the treatment of renal cell carcinoma and imatinib resistant gastrointestinal stromal tumour. In a case series of 10 patients with unresectable progressive ASPS, treated with sunitinib 37.5mg daily continuously via a compassionate access scheme, five of eight (63%) assessable patients demonstrated a partial response by RECIST criteria with a further patient exhibiting stable disease for >6 months. No grade 3-4 toxicity was seen.

Cediranib is a once daily oral tyrosine kinase inhibitor, with activity against a range of targets including VEGFR, PDGFR and c-KIT, has shown promising activity in a large randomised phase II trial of soft tissue sarcomas conducted by the EORTC. In an effort to differentiate activity across a spectrum of STS, this trial stratified patients into four different arms, with activity (defined as progression free rate at 12 weeks) seen in three (leiomyosarcoma, synovial sarcoma, other STS subtypes) of the groups; but not in the adipocytic group. These results have lead to the conduct of an international randomised phase III trial (the PALLEtte study) in patients with STS refractory to conventional chemotherapy. In this trial patients are randomised to pazopanib 800mg/day or placebo, with a primary endpoint of progression free survival. Enrolment has recently been completed with results expected in early 2011.

Conclusion

An improved knowledge of the molecular alterations driving specific subtypes of sarcoma has lead to the rational development of a number of promising therapeutic agents in bone and soft tissue sarcomas. However, developing these relatively small proof-of-concept studies into the larger randomised trials that are usually required by regulatory and funding agencies to demonstrate efficacy against current standards of care remains a significant challenge.

It is vital that the sarcoma research community works closely with the pharmaceutical industry and regulatory agencies to develop new, more efficient trial designs which allow accurate and timely assessment of the benefit of an intervention for specific patient groups even if the tumour subtype is very rare. The formation of sarcoma specific collaborative international networks (such as the World Sarcoma Network) has been an important step in enabling such trials.

Finally, with the majority of recent advances in the treatment of sarcoma patients stemming from progress in the understanding of important molecular mechanisms driving these cancers, a continued focus on basic research and the integration of molecular pathology into sarcoma trial design is essential to improving outcomes for patients with bone and soft tissue tumours.

References


