KEY ADVANCES IN THE SYSTEMIC THERAPY FOR SOFT TISSUE SARCOMAS: CURRENT STATUS AND FUTURE DIRECTIONS

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ABSTRACT

Soft tissue sarcomas (STS) represent a heterogeneous group of diverse neoplasms of mesenchymal origin. Once relapsed from standard therapy, STS patients have limited treatment options especially those that present with advanced or metastatic disease. In this review article, we highlight recent clinical data that led to the US Food and Drug Administration (FDA) approval of pazopanib (Votrient®) for STS and regorafenib (Stivarga®, BAY 73-4506) in gastrointestinal stromal tumours. We also review ongoing safety/efficacy data for trabectedin (Yondelis®, ET-743), and data from clinical studies of ridaforolimus (AP23573; MK-8669) and palifosfamide (ZIO-201). We provide a list of some promising ongoing trials in soft tissue sarcomas including first line studies of TH-302 and trabectedin. Finally, our article delves into recent advances in our understanding of the molecular pathogenesis of STS and novel therapies that might be explored as treatment options for specific STS histologies.

Keywords: Sarcoma, soft tissue sarcoma, gemcitabine, pazopanib, regorafenib.

INTRODUCTION

Soft tissue sarcomas (STS) represent a heterogenous group of diverse neoplasms of mesenchymal origin. According to recent Surveillance, Epidemiology, and End Results (SEER) database, approximately 11,000 men and women will be diagnosed with STS in 2013 accounting for <1% of all newly diagnosed cancers. Many patients with these tumours have distant metastases at presentation. It is estimated that around 4,000 patients with STS will die in 2013.[1] The major histologic subtypes include leiomyosarcoma (LMS), liposarcoma (LPS), synovial sarcomas, undifferentiated pleomorphic sarcomas, and malignant nerve sheath tumours. Historically, LMS, synovial, and undifferentiated pleomorphic sarcomas are considered chemosensitive, while the others are chemoresistant. Traditional cytotoxic drugs adriamycin (Rubex®) and ifosfamide (Mitoxana®) have been the mainstays of treatment in certain STS patients with advanced disease. The National Comprehensive Cancer Network (NCCN) Guidelines recommend anthracycline monotherapy, or combination with ifosfamide as the first line treatment for most histologic subtypes (category 2A and 2B evidence).[2] There has been a dearth of well-designed randomised trials in the area of metastatic STS, mostly due to the heterogeneity of the group and a lack of identification of specific dominant druggable molecular targets. Locally advanced and metastatic STS thus remain an area of significant unmet medical need. Results of recently published clinical studies in advanced or metastatic STS are described in the following sections.

Gemcitabine (Gemzar®) and Docetaxel (Taxotere®)

The gemcitabine and docetaxel combination is often used as a second line therapy in STS. This

combination is more active in uterine LMS and undifferentiated high-grade pleomorphic sarcoma than other subtypes. The possible synergistic effect of gemcitabine, a DNA synthesis inhibitor and docetaxel, a tubulin stabiliser that induces apoptosis, was explored in a Phase II trial of LMS patients in 2002. Out of 34 patients enrolled, complete response (CR) was observed in 3 patients, and partial response (PR) was observed in 15 patients for an overall response rate (ORR) of 53%.[3] A randomised Phase II study in 2007 showed an improvement in median progression-free survival (PFS) for the combination treatment (6 months) versus gemcitabine therapy alone (3 months). The objective response rate of 16% versus 8% and the median overall survival (OS) of 18 months versus 12 months in favour of the combination arm was demonstrated in a population that included several subtypes, but was especially pronounced in uterine LMS.[4] In this study, a fixed infusion rate of gemcitabine was used based on prior reports of a favourable pharmacokinetic profile and efficacy in STS.[5]

In a study of LMS patients, the French TAXOGEM study found no differences in treatment with single agent gemcitabine or the combination of gemcitabine and docetaxel. The objective response rates were 19% in the gemcitabine group, 24% in the gemcitabine plus docetaxel group for uterine LMS, and 14% and 5% for non-uterine LMS. The median progression-free survival times were not significantly different for either group: 5.5 months and 4.7 months for uterine LMS, and 6.3 months versus 3.8 months in non-uterine LMS.[6] Although the SARC and TAXOGEM studies differed in study design, patient selection, and slightly different dose intensities, and schedules of fixed dose gemcitabine, it is unclear whether any of these factors could explain the differences in outcome. Despite these differences, gemcitabine with or without docetaxel are preferred agents in first or second line treatment of a wide variety of STS subtypes, especially LMS.

Pazopanib (Votrient®)

Agents against the vascular endothelial growth factor (VEGF) axis have been well-studied in STS. Sorafenib (Nexavar®), a tyrosine kinase inhibitor of platelet-derived growth factor receptors (PDGFR), VEGFR-1, VEGFR-2, and VEGFR3, was shown to be minimally active in high-grade STS patients who had 0-1 prior therapies. Response rates of less than 5% were noted, but PFS at 3 months and 6 months were 53% and 22%, respectively. 61% of patients required dose reductions due mostly to dermatologic toxicities.[7] The highest response rates in this study were in angiosarcoma patients (14% PR). Sunitinib (Sutent®), another multi-targeted TKI was tested in STS patients who had received 0 to 3 prior therapies. There was one response in 48 patients and the 4-month progression-free survival was 22%. This study included patients with rare sarcomas such as giant cell tumours, alveolar soft part sarcoma, chordoma, and desmoplastic small round blue cell tumours.[8] Thus, other than angiosarcoma and other less common subtypes, VEGF-TKI's have not been shown to be highly active in patients with STS.

Pazopanib however, is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR-1, 2 and 3), platelet derived growth factor receptor (PDGFR-A and B), and v-kit Hardy Zuckerman 4 feline sarcoma viral oncogene homolog (c-kit) that demonstrated activity in Phase II studies in non-adipocytic sarcomas. It was initially US Food and Drug Administration (FDA)-approved for advanced renal cell carcinoma in 2009. Recently, pazopanib received approval by the FDA in patients with advanced soft tissue sarcoma (except adipocytic STS or gastro-intestinal stromal tumours) who have received prior chemotherapy. The approval was based on a randomised double blind placebo-controlled multicenter trial of patients with metastatic STS who had received an anthracycline containing regimen or were ineligible for it. Patients were randomised 2:1 to either pazopanib (800 mg PO QD) or placebo. The median overall survival was 12.6 months in the pazopanib arm and 10.7 months in the placebo arm (HR 0.87, 95% CI 0.67-1.12). Overall progression-free survival (PFS) in the intent to treat population was 4.6 months in the pazopanib group versus 1.6 months in the placebo group. The OS benefit correlates well with the PFS benefit of 3 months. Unfortunately, the trial was not powered to detect a statistically significant 3-month OS difference in the two arms. The OS data could also be confounded by the fact that patients received post-study therapy with trabectedin (25% versus 32%), gemcitabine (17% versus 23%) taxane (10% versus 18%) and ifosfamide (10% versus 17%). Nevertheless, the PFS benefit was seen across the pre-specified

subgroup analyses, and was independent of the number of prior chemotherapy agents and tumour bulk. The most common Grade 3/4 adverse events experienced by ≥5% of patients on pazopanib were fatigue, diarrhoea, hypertension, and decrease in appetite. The most common (≥20%) observed adverse events (all grades) were fatigue, diarrhoea, nausea, decreased appetite, vomiting, tumour pain, hair colour changes, musculoskeletal pain, headache, dysgeusia, dyspnoea, and skin hypopigmentation.[9] The demonstration that the VEGF pathway could be exploited for therapeutic benefit in the majority of STS has opened the future for combined treatments with targeted and non-targeted agents.

Regorafenib (Stivarga®, BAY 73-4506)

As opposed to the recent approval of anti-VEGF agents in non-GIST STS, gastrointestinal stromal tumours (GISTs) are especially responsive to the VEGF-TKI, Sunitinib (Sutent®). The activity of sunitinib as second line therapy in GIST is well-established. The use of sequential anti-VEGF strategies has been effective in improving progression-free survival in renal cell carcinoma, and this approach is now promising in treating unresectable advanced or metastatic GIST. Regorafenib is an oral multi-tyrosine kinase inhibitor of VEGFRs 2 and 3, and RET, Kit, PDGFR and Raf kinases. In 2013, the FDA expanded the use of regorafenib to treat patients with advanced inoperable GIST unresponsive to imatinib (Gleevec®) or sunitinib. The approval was based on an international randomised double blind, placebo controlled trial of 199 patients with histologically confirmed metastatic or unresectable GIST who experienced disease progression while on sunitinib. The primary endpoint of median PFS was significantly better for the regorafenib group at 4.8 months compared to 0.9 months for patients receiving placebo (HR 0.27, 95% CI 0.19-0.39, p<0.0001). The most common drug-related adverse events (Grade 3 or higher) were hypertension, hand-foot skin reaction, and diarrhoea. Serious adverse events (SAEs) occurred infrequently (<1%) and included liver damage, severe bleeding, blistering and peeling of the skin, very high blood pressure, heart attack, and perforations in the intestine.[10]

Gemcitabine Plus Dacarbazine (DTIC)

A Phase II study of dacarbazine (DTIC) with or without gemcitabine in soft tissue sarcomas showed a PFS of 4.2 months in the gemcitabine plus DTIC arm (n=57) compared to 2 months in the DTIC alone (n=52) arm (HR 0.58, 95% CI 0.39-0.86, p=0.005). Median overall survival was 16.8 months in the gemcitabine plus DTIC arm versus 8.2 months in the DTIC arm (HR 0.56, 95% CI 0.36 to 0.90, p=0.014). Overall response rate was 12 months in the combination arm versus 4% for the DTIC arm (p=0.16). A Cox regression analysis of prognostic factors for survival in the study population identified histology (LMS versus others) as significant prognostic factor for PFS and OS. Median PFS and OS were 4.9 and 18.3 months respectively for the LMS subtype in the gemcitabine and DTIC group versus 2.1 months and 7.8 months for those with non-leiomyosarcomatous subtypes. The combination of DTIC and gemcitabine was generally well-tolerated. Granulocytopenia was the most common Grade 3/4 haematologic toxicity. Febrile neutropenia was observed in 9% patients in the combination arm versus 6% in the DTIC arm.[11]

Trabectedin (ET-743, Yondelis®)

Trabectedin is a novel marine antineoplastic alkaloid with a unique mechanism of action. It binds to the DNA minor groove and interferes with transcription-coupled nucleotide excision repair thereby inducing lethal DNA strand breaks, a mechanism that lends itself to increased activity in translocation-related sarcomas including myxoid LPS.[12,13]

It was approved in the European Union as an orphan drug for the treatment of advanced soft tissue sarcoma in patients who have failed therapy with anthracycline and ifosfamide. The approval was based on a Phase II study in LMS and LPS patients who had failed anthracycline plus ifosfamide therapy and multiple other supporting studies.[14] The primary endpoint, time to progression (TTP) was 2.3 months in the qwk 3-hour group (N=134) versus 3.7 months in the q3wk 24-hour group (N=132). This compared well with the 3.4 month TTP in the initial 24-hour group (from 3 other Phase II studies). The PFS was 2.1 (95% CI 1.9-3.4) months in the qwk 3-hour group versus 3.5 (95% CI 2.0-4.5) months in the q3wk 24-hour group and 2.7 (95% CI 1.7 – 3.7) months in the Initial 24-hour group. The most common grade 3-4 adverse events (AEs) in the q3wk 24-hour group were increased alanine aminotransferase, (ALT) (12%), neutropenia (12%), increased aspartate aminotransferase (AST)

(8%), and dyspnoea, fatigue, nausea, and vomiting (7% each). In addition, rhabdomyolysis leading to death was seen in five patients (0.5%) in the integrated safety database.[8] The recent data from the expanded access program of trabectedin in patients with incurable soft tissue sarcoma demonstrated longer overall survival in patients with LPS (median of 16.2 months, 95% CI 14.1 – 19.5) versus other histologies (median 8.4 months, 95% CI 7.1-10.7) for the 903 patients evaluable for OS. More importantly, out of 1,895 total patients enrolled, grade 3 or 4 AEs exhibited by ≥5% of patients included nausea, increased ALT, neutropenia, anaemia, thrombocytopenia, and fatigue. These were consistent with previous studies.[15] The results of first line trabectedin versus doxorubicin-based treatment in translocation-related sarcomas are expected soon. In addition, a large multi-institutional international Phase III study comparing trabectedin versus dacarbazine has recently reached its accrual goals for LPS that have failed two prior therapies (NCT01343277).

Ridaforolimus (AP23573; MK-8669)

The dysregulation of mammalian target of rapamycin (mTOR) pathway has been observed in many tumour types.[16] Ridaforolimus, a mTOR inhibitor, was found to show activity in advanced sarcomas in a Phase II study of 193 patients with 3% partial responses and 25% stable disease response.[17] Ridaforolimus was not approved by the FDA as maintenance therapy, in patients with either soft tissue or bone sarcomas who had achieved at least a stable disease (SD) with prior chemotherapy, primarily because a minimal 3 week difference in PFS and significant toxicity including pneumonitis. A pivotal trial comparing ridaforolimus or placebo maintenance for patients with soft tissue sarcoma or bone sarcomas who had achieved SD, partial response (PR) or complete remission (CR) with prior chemotherapy showed a median PFS of 17.7 weeks in the ridaforolimus arm versus 14.6 weeks in the placebo arm (HR 0.69, p<0.0001). The median OS in the ridaforolimus arm was 90.6 weeks versus 85.3 weeks in the placebo arm (HR 0.93, p=0.46). Significant adverse events including pneumonitis (10% versus 0.6%), renal failure (10% versus 1%) and hypersensitivity reaction (10% versus 2%) were reported more often in the ridaforolimus arm.[18]

Palifosfamide (ZIO-201)

The neurotoxicity and nephrotoxicity of ifosfamide are primarily thought to result from the toxic metabolites of ifosfamide, chloroacetaldehyde and acrolein. Palifosfamide is a tris formulation of the functional active metabolite of ifosfamide, isophosphoramide mustard.[19] The PICASSO-3 study investigating the combination of palifosfamide and doxorubicin versus doxorubicin alone in metastatic STS, was halted by the sponsor due to lack of PFS benefit. Median PFS was 5.98 months in the combination arm versus 5.23 months in the doxorubicin arm.[20] Even though the Data Monitoring Committee recommended following the patients for the secondary endpoint of assessing overall survival, the sponsor statement indicates otherwise.[21]

ONGOING STUDIES

Table 1 lists some important ongoing studies in soft tissue sarcoma. A Phase IIb/III study comparing the efficacy of trabectedin administered as a 3-hour or 24-hour infusion to doxorubicin in patients with advanced or metastatic soft tissue sarcoma (EORTC, NCT01189253) is currently enrolling patients. A study investigating trabectedin or dacarbazine for patients with advanced LPS or LMS who have been previously treated with an anthracycline containing regimen is currently underway (NCT01343277). An expanded access program for non-L-type sarcomas is also open in the US (NCT00210665), which will allow evaluation of adverse events.

TH-302 is a pro-drug that is activated in the hypoxic tumour environment to its active form bromo-isophosphoramide mustard (Br-IPM), a potent DNA alkylating agent. The Phase III trial comparing the combination of TH-302 and doxorubicin versus doxorubicin alone (NCT01440088) was initiated based on favourable Phase II data showing a median PFS 6.7 (95% CI 6.2 to 8.1) months for the combination arm compared to median PFS of 21.5 (95% CI 16.0 to 27.6) months for the doxorubicin arm. Dose limiting toxicities were Grade 4 thrombocytopenia and Grade 3 infection with Grade 4 neutropenia.[22]

Based on the regorafenib data in GIST, a randomised, double-blind, placebo-controlled, Phase II study evaluating the efficacy and safety of regorafenib in patients with histologically

Table 1. Important ongoing clinical studies in soft tissue sarcoma.

Investigation	STS type	Primary End-point	Line of therapy	NCI clinicaltrials.gov #
TH-302 and doxorubicin versus doxorubicin	STS excluding GIST	OS	First	NCT01440088
Trabectedin versus doxorubicin	Chemosensitive STS subtypes	PFS	First	EORTC NCT01189253
Trabectedin versus dacarbazine	Liposarcoma and leiomyosarcoma	OS	Second	NCT01343277
Gemcitabine + Pazopanib versus Gemcitabine + docetaxel	STS excluding LPS, bone sarcoma and GIST	PFS	Second	NCT01593748
Cabazitaxel versus prolonged infusional ifosfamide	Dedifferentiated LPS	PFS	Second	EORTC NCT01913652
Regorafenib versus placebo	LPS, LMS, synovial sarcoma	PFS	Second	NCT01900743
Eribulin versus dacarbazine	LMS and adipocytic sarcoma	OS	Third	NCT01327885
Trabectedin (open access)	Non L-type STS	Adverse events	After standard therapy	NCT00210665

proven metastatic and/or unresectable soft tissue sarcoma (STS) after failure or intolerance to doxorubicin (or other anthracycline) is currently recruiting patients (NCT01900743).

Previous studies indicate that the incidence of somatic p53 gene mutation is low in most sarcomas (<20%).[23] Mouse double minute 2 homolog (MDM2) binds and inactivates p53 thereby promoting the ubiquitination and proteasomal degradation. The Phase II study evaluating the MDM2 inhibitor from Roche in soft tissue sarcomas (NCT01605526) was recently completed, with data from the study expected to be released in the near future. Another approach to inhibit the export of p53 and other tumour suppressor proteins could involve the use of nuclear export inhibitors. KPT330, an inhibitor of nuclear export is currently undergoing Phase I testing in soft tissue sarcomas (NCT01896505).

The FDA approval of sipuleucel-T (PROVENGE®) and CTLA-4 antibody ipilimumab (YERVOY™) for metastatic castration resistant prostate cancer and late-stage melanoma respectively has renewed interest in exploring immunomodulatory therapy for the treatment of STS. In addition, there has been a renaissance in the immunotherapy trials with programmed death 1 (PD-1) protein, a T cell co-inhibitory receptor, and one of its ligands, PD-L1 and the promising data in melanoma and non-small cell lung cancer.[24,25] Since the clinical trial of inhaled GM-CSF for osteosarcoma patients with recurrent lung metastasis showed no significant clinical benefit or even an immune response,[26] there are not many investigations of immunotherapies in STS. A current ongoing study from the University of Miami is investigating the use of adjuvant vaccination with autologous dendritic cells with our without gemcitabine (to inhibit myeloid derived suppressor cells) is currently recruiting patients (NCT01803152). In addition, a clinical trial using autologous, activated dendritic cells for intra-tumoural injection for all solid tumours has been initiated across multiples sites in the US that is open to STS patients as well (NCT01882946).

Mifamurtide (Mepact), also known as liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE), is an activator of macrophages and monocytes and has been approved for the treatment of osteosarcoma in Europe but not in the USA. The clinical trials in patients with osteosarcomaresulted in 8% and 13% improvement in 6 and 5-year overall survivals, when added to chemotherapy in non-metastatic and metastatic patients with osteosarcoma, respectively.[27]

Recent advances in the understanding of molecular pathways underlying the pathogenesis of soft tissue sarcomas have identified various genes that are overexpressed in different STS subtypes. These include MDM2 gene amplification in well-differentiated and de-differentiated LPS,[28] NAB2-STAT6 translocation in solitary fibrous tumour,[29] angiopoietin-TIE pathway in angiosarcoma,[30] BCL-2 overexpression in synovial sarcoma,[31] CDK-4 amplification in alveolar rhabdomyosarcoma,[32] ALK aberrations in rhabdomyosarcoma,[33] and lack of arginosuccinate synthase in various sarcomas.[34]

CONCLUSION

The tremendous advances in our understanding of tumour biology at the 'multi-omic' level that includes the genomic, proteomic, transcriptomic, and the post-transcriptomic levels has brought to forefront novel cellular pathways, aberrations and targets for therapeutic intervention across multiple adult tumour types. However, the wide-ranging diversity of STS subtypes, both from a histologic as well as a molecular perspective and the rarity has hindered our understanding of the disease and the ability to develop more effective therapies. Doxorubicin held the distinction of being the only FDA-approved drug in STS for over two decades. The approval of pazopanib is a significant incremental advance, and provides an important treatment option for patients who progress on doxorubicin (with or without ifosfamide). Soft tissue sarcomas still represent a significant unmet medical need. Ongoing clinical studies along with advances in immunotherapy and targeted therapies offer the potential for more effective treatment strategies in the future.

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