Abstract Sarcomas are uncommon malignancies that represent more than 50 different tumor types. Surgery remains the mainstay of treating localised disease. Anthracycline and ifosfamide-based chemotherapy is an option for advanced disease; however, effective treatment of advanced soft tissue sarcoma remains a challenge. Advances in understanding the genetic nature of cancer have led to the development of new treatment options for sarcoma. Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor with antiangiogenic properties and promising activity in the treatment of GIST refractory to imatinib, however in either soft tissue sarcoma, experience with sunitinib is under development in different clinical trials. In this review we offer the experience with this small molecular target in non-GIST sarcomas.

Keywords Soft tissue sarcoma · TK inhibitors · Sunitinib malate

Introduction

Sarcomas are uncommon and heterogeneous malignancies that arise from mesenchymally derived connective tissues. Soft tissue sarcomas can occur in any site throughout the body. Forty-three percent are in the extremities, with two thirds of extremity lesions occurring in the lower limb, and 34% are intra-abdominal, divided between visceral (19%) and retroperitoneal (15%) lesions. They represent more than 50 different types that vary in their clinical presentation, histology grade, growth rate, disease evolution, and prognosis. Overall, the three most common histopathologic subtypes are malignant fibrous histiocytoma, liposarcoma and leiomyosarcoma.

Surgery remains the mainstay of treating localised disease and is able to achieve locoregional control in 80% of patients [1]. In some patients with unresectable disease or medical contraindications to operation, definitive radiation can be considered to achieve palliation. Patients with lesions >5 cm should be considered for adjuvant radiation therapy, a proven method of limiting local recurrence [2]. Half of all patients with adequate local disease control will develop distant metastases, usually to the lungs or liver, and overall survival (OS) is 50% at 5 years [3].

Multiple adjuvant chemotherapy trials have been performed, with difficulties in their interpretation because of their small size and absence of statistical power to detect small differences. Meta-analyses must also be examined with caution, because they combine studies with different designs, diverse criteria for enrolment, variation in pathologic assessment, different chemotherapeutic regimens and different end points. Data do not support the routine use of adjuvant chemotherapy for soft tissue sarcoma outside the setting of a clinical trial. However, extremity soft tissue sarcomas represent one situation in which adjuvant chemotherapy can be considered [4].

There is also relatively little evidence concerning the use of neoadjuvant chemotherapy in treating soft tissue sarcomas, and it should not be a therapeutic approach outside
of a clinical trial [5]. Nonetheless, preoperative chemotherapy is worth consideration during an attempt to maintain function of an extremity, and selected patients may have responses that allow for a more conservative resection or avoid the need for amputation.

Anthracyclines and ifosfamide-based chemotherapy is an option for advanced disease; however, effective treatment of advanced soft tissue sarcoma remains a challenge, and patients with metastatic disease at diagnosis have a 5-year OS of 25% [6]. Various combinations and dosages of conventional chemotherapeutic agents have not achieved significant improvements in OS. Doxorubicin cannot be favoured over ifosfamide, and combining both does not improve the time to progression or OS [7].

Surgical resection of metastases can provide selected patients with prolonged periods of freedom from disease, and radiation therapy provides palliation for individual patients who have localised symptomatic metastases.

Genetic alterations play a developmental role in the carcinogenesis of soft tissue sarcomas and include simple karyotypes, such as fusion genes due to reciprocal translocations and specific point mutations or nonspecific genetic alterations and typically complex unbalanced karyotypes, representing numerous genetic losses and gains [8]. Sarcomas with complex karyotypes have high frequencies of p53 and RB mutations as well as impairments in DNA repair and demonstrate severe chromosomal instability. This group includes some of the more commonly diagnosed sarcomas, such as leiomyosarcoma, rhabdomyosarcoma and osteosarcoma.

Advances in understanding the genetic nature of cancer have led to the development of new treatment options for sarcoma. Mutations and overexpression of tyrosine kinase (TK) receptors or receptor ligands activate oncogenic signal transduction and are responsible for a variety of cellular processes, including cell-cycle regulation, proliferation, adhesion, migration, invasion, transcription and survival. TKs make up the majority of defective signalling pathways in sarcomas, including mutations in the platelet-derived growth factor receptor (PDGFR), c-Kit, vascular endothelial growth factor receptor (VEGFR) and insulin-like growth factor-1 receptor (IGF1-R) signalling pathways [9]. Antagonists of TK receptors may be antibodies that bind to the extracellular binding domain of the receptor or small molecule inhibitors that act by competing for the adenosine triphosphatase (ATP)-binding domain in the catalytic site of the enzyme [9].

Imatinib mesylate constitutes the classic example of targeted therapy in mutation activating c-Kit gastrointestinal stromal tumours (GISTs) [10]. The activity of the KIT-tyrosine kinase inhibitor imatinib in GIST has been shown to depend on possible mutations in Kit exons [11]. Imatinib has also shown some activity in dermatofibrosarcoma protuberans (DFSP), which is associated with a specific chromosomal translocation that activates PDGFR-mediated proliferation [12]. Kaposi’s sarcoma has been shown to express high levels of both c-Kit and PDGFR, and imatinib has shown potential effectiveness as a treatment option [13].

Although gefitinib and erlotinib, both EGFR inhibitors, had shown potential antitumor effects in early reports, phase II studies demonstrated no clinical activity in treating synovial sarcoma and malignant nerve-sheath tumours, respectively [14]. The monoclonal antibody that inhibits the human epidermal growth factor receptor-2 (HER-2) trastuzumab (Herceptin®) has been evaluated in Ewing’s sarcoma alone and in combination with chemotherapy, without therapeutic benefit [15].

Several VEGFR inhibitors have shown preclinical activity in patients with soft tissue sarcoma and are undergoing clinical trials [16]. IGF-1R is of great importance in the development of sarcomas, because when activated, it is implicated in cellular proliferation, differentiation and prevention of apoptosis. Elevated expression of IGF-1R has been shown to correlate with a favourable prognosis. There are promising preclinical data to encourage further evaluation of IGF-1R inhibitors in both bone and soft tissue sarcoma [17].

Other potential therapeutic targets in sarcoma management are those dependent on Src signalling, the inhibition of which has been associated with blockade of cell migration and invasion. Therefore, inhibitors of Src kinase activity, such as dasatinib, are under evaluation [18]. In vitro studies have revealed that epithelioid sarcomas expressing EGFR-1 respond to EGFR1-antibody treatment [19]. Clear-cell sarcoma (CCS) is characterised by production of a chimeric transcription factor, Ewing’s sarcoma – activating transcription factor1 (EWS-ATF1), which is formed as the result of a disease-specific chromosomal translocation. EWS-ATF1 activates the microphthalmia-associated transcription factor (MITF), which activates c-Met transcription. This TK receptor has recently shown to be activated in CCS [20, 21]. Also, c-Met expression is critical for CCS invasion, chemotaxis and survival and therefore a candidate therapeutic target to improve clinical management of CCS.

Sunitinib maleate is an oral multitargeted tyrosine kinase inhibitor with antiangiogenic and antitumor activity. It potently inhibits VEGFR, PDGF, c-Kit receptor kinases, Fms-like TK 3 receptor (FLT3) and the receptor encoded by the RET protooncogene [22]. Sunitinib is now approved as first-line treatment in metastatic renal-cell carcinoma [23] and is recommended for treating imatinib-refractory GIST.

The approval basis for treating imatinib-resistant GIST was an international, randomised, double-blind, placebo-controlled trial of sunitinib in patients with GIST who had disease progression during prior imatinib mesylate treatment or who were intolerant of imatinib. The primary objective was to evaluate time to tumour progression [24]. A prespecified interim efficacy analysis showed improvement in time to progression in the sunitinib-treated patients with a time to tumour progression of 27 weeks compared with 6 weeks in the placebo group. It is thought