Soft tissue sarcoma: the clinically relevant basics and an update on systemic therapy options for patients with advanced disease

P. Schöffski, MD, MPH[1], D. Hompes, MD, PhD[2], A. Wozniak, PhD[1], H. Dumez, MD, PhD[1], I. Samson, MD[2], M. Stas, PhD[2], F. Sinnaeve[2], O. Bechter, MD, PhD[1], M. Debiec-Rychter, MD, PhD[3], E. Van Limbergen, MD, PhD[4], S. Pans, MD, PhD[5], R. Sciot, MD, PhD[6]

Sarcomas are a group of rare solid tumours arising from mesenchymal or connective tissue. This review focuses on soft tissue sarcoma and covers general topics such as the epidemiology, age distribution, site of disease, histogenesis, histological subtypes, prognosis and outcome of treatment. In more detail the article reviews current systemic treatment standards and selected adverse events of agents such as doxorubicin, ifosfamide, trabectedin and pazopanib, and briefly highlights some drugs that are used off-label in rare subtypes of sarcoma.

(Belg J Med Oncol 2013;7(3):80-88)

Introduction

Sarcomas are a group of rare solid tumours arising from mesenchymal or connective tissue. Collectively, sarcomas account for about 1% of all adult malignancies. Among the broader family of mesenchymal malignancies, soft tissue sarcomas are the most common tumours, as 80% of all sarcomas arise from soft tissue while only 20% of all sarcomas are bone sarcomas, including osteosarcomas, the Ewing family of tumours and chondrosarcomas. This review focuses on soft tissue sarcomas.

Histopathology

Soft tissue sarcoma consists of a group of rare tumours of mesenchymal origin. Of note, not all soft tissue tumours are malignant. The vast majority of mesenchymal laesions are benign entities; they are about a 100 times more frequent than malignant soft tissue sarcoma. The current version of the histopathological classification by the World Health Organization (WHO) is defining over 50 different histological subtypes of malignant soft tissue sarcoma.[1] The heterogeneity of this disease poses a challenge

University Hospitals Leuven, Leuven Cancer Institute, KU Leuven, Leuven, Belgium

[1]Department of General Medical Oncology and Laboratory of Experimental Oncology. [2]Department of Surgical Oncology. [3]Department of Human Genetics. [4]Department of Radiotherapy/Oncology. [5]Department of Radiology. [6]Department of Histopathology.

Please send all correspondence to: P. Schöffski, MD, MPH, University Hospitals Leuven, Department of General Medical Oncology and Laboratory of Experimental Oncology, Leuven Cancer Institute, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium, tel: +32 16 34 69 00, fax: +32 16 34 69 01, e-mail: patrick.schoffski@uzleuven.be.

Conflict of interest: The Department of General Medical Oncology has received funding for participation in multiple sarcoma trials led by different academic groups and pharmaceutical companies. P. Schöffski, MD, MPH has received honoraria from pharmaceutical companies (Pfizer, PharmaMar, Glaxo Smith Kline) for participation in advisory and educational events related to the treatment of soft tissue sarcoma. P. Schöffski, MD, MPH and A. Wozniak, PhD have received generous support from Fonds Wetenschappelijk Onderzoek - Vlaanderen (FWO Grants GA01311N, G081611N) and from Stichting tegen Kanker for basic and translational research in the field of soft tissue sarcoma.

Keywords: advanced disease, chemotherapy, metastasis, soft tissue sarcoma, targeted agents.

to the physician caring for patients with sarcoma, as the prognosis and potential response to treatment is difficult to predict given the very heterogeneous character of this family of malignancies.

Incidence and age distribution

In Europe the estimated incidence of soft tissue sarcoma ranges between 2-5/100,000/year.[2] A large number of sarcomas is misdiagnosed, so the incidence figures available in the literature probably represent an underestimation. The incidence of soft tissue sarcoma increases with higher age but sarcoma does occur in all age groups, both in female and in male patients. The highest incidence is observed between the age of 45 and 90 years. As compared to epithelial tumours, soft tissue sarcoma occurs relatively frequently in children, adolescents and young adults. Soft tissue sarcoma accounts for up to 10% of all paediatric malignancies and is an important cause of death in the group below 30 years of age. The predominant sarcoma subtype in children below the age of 15 years is rhabdomyosarcoma, which is very uncommon in adult patients. This review will focus on adult soft tissue sarcoma, with exclusion of gastrointestinal stromal tumours (GIST).

Primary site of disease

Soft tissue sarcomas can develop at almost any anatomic site, such as the extremities (60%), the trunk or thorax, the retroperitoneum and the head and neck region. The more common soft tissue sarcomas originate from muscle, nerve tissue, fat or deep skin tissue. For a number of sarcomas the tissue of origin is not well characterised.

Histogenesis and histological subtype

The relative frequency of the different histological subtypes of soft tissue sarcoma has been described in a number of epidemiological studies, but there is a lot of variation in the available published series. The variation can in part be explained by the geographic region where the epidemiological study was performed. There is also a considerable rate of histological misclassification of sarcomas, which may contribute to the variable distribution in published series. The repeated revision of the histological classification also has to be accounted for. As an example, malignant fibrous histiocytoma has been a very common subtype in the past, but is virtually non-existent after the more recent revision of the WHO classification. A large proportion of these tumours is reclassified today as dedifferentiated liposarcomas, especially if they arise in the retroperitoneal area. Another issue making the interpretation of epidemiological data difficult is the fact that some sarcomas, e.g. the superficial skin sarcomas such as dermatofibrosarcoma protuberans or Kaposi sarcomas, are not accounted for in many series.

Prognostic factors and survival

The survival of patients with soft tissue sarcoma is far from satisfactory, even though the disease-free survival (DFS) has increased substantially in the past few decades due to the introduction of multidisciplinary approaches and with further standardisation of surgery, radiotherapy and the use of systemic therapy. The expected 5-year overall survival (OS) of soft tissue sarcoma across all subtypes and all disease stages is in the range of 50% according to North American series.[3] The prognosis of patients with inoperable, advanced or metastatic soft tissue sarcoma remains unsatisfactory and static over the past decades.

A number of prognostic factors for survival have been identified, including tumour stage, size, grade, histological subtype, age, presence or absence of metastasis, tumour site and margin of resection. Prognostic normograms have been developed, helping to predict the survival of patients with newly diagnosed soft tissue sarcoma, but in clinical practice such tools have limited value.[4] The 5-year survival of soft tissue sarcoma is generally dependent on tumour stage. While in early stage disease, 5-year OS rates of approximately 90% are reached, patients with more advanced stage at initial diagnosis have a 5-year survival rate of 50-60% only. Survival also depends on the histological subtype. The analysis of such data is difficult, as the histopathological classification of sarcomas has changed repeatedly, as described above. Furthermore, a number of sarcomas are still misclassified by pathologists, as these tumours are very rare and the morphological and genetic differentiation of the various subtypes requires expert skills and the availability of specific infrastructure, ranging from electron microscopy to modern molecular diagnostic tools.

Outcome of patients with local relapse or distant metastasis

The review focuses on patients with advanced disease. This includes sarcoma patients with local relapse after initial surgery (with or without radiotherapy), patients with distant metastasis or with both local relapse and metastasis. Patients with local tumour recurrence have a disease-specific survival of less than 50% at five years, and those with metastatic relapse have 5-year survival rates in the range of only 15%.[5] This figure has been disappointingly stable over the past decades. Thus, the major challenge is to achieve improvement of the outcome of patients with such advanced disease states.

Role of perioperative (neo-adjuvant and/or adjuvant) treatment

There have been many attempts to improve the treatment outcome of locally advanced or locally relapsed disease by combining local treatment (surgery, radiotherapy) with systemic therapy, such as neo-adjuvant (preoperative) or adjuvant (post-operative) chemotherapy. There are only limited data supporting the use of such perioperative treatments in sarcoma. Preoperative treatment may be considered in patients for whom the feasibility of a wide oncological resection together with a good functional outcome is questionable.[6] The decision to use neo-adjuvant therapy has to take a number of factors into account, such as tumour histology, patient age, comorbidities and institutional experience. If the tumour proves to be radiotherapy- or chemotherapy-sensitive, neo-adjuvant therapy may render a tumour suitable for conservative rather than radical surgery. The role of post-operative or adjuvant chemotherapy remains even more controversial. Postoperative systemic therapy can improve progression-free survival (PFS) but there is conflicting evidence on improvements in OS from two large meta-analyses.[7] Adjuvant radiotherapy is frequently used in patients with poor surgical margins or after very complex surgical interventions, mainly in cases with a high risk of local recurrence. Such treatment is unlikely to improve OS.

Treatment intent in patients with advanced disease

In inoperable, advanced or metastatic soft tissue sarcoma the therapeutic goals are to achieve control over the disease, to stop or postpone disease progression and to achieve or maintain symptom control for prolonged periods of time. Chemotherapy is the most commonly used treatment for such patients and although response rates to chemotherapy are very low, about half of all treated patients are believed to derive some clinical benefit in advanced stages of the disease.[8]

Single-agent versus combination chemotherapy

If patients have recurrent or progressive soft tissue sarcoma after surgery or extensive synchronous metastasis at initial diagnosis the most commonly recommended treatment is chemotherapy. The first line chemotherapy for advanced, metastatic or non-resectable soft tissue sarcoma is typically based on anthracyclines, and the most frequently used compound is doxorubicin.[9] Such chemotherapy should routinely be used as single agent; only in exceptional circumstances a combination with a second drug such as ifosfamide can be recommended. The majority of clinical studies comparing single agents to combinations failed to show an OS advantage, but has consistently shown improvement in response rates and in PFS.[10] Virtually all of these studies demonstrated that combination chemotherapy is more toxic than single agent doxorubicin, which is the current standard of care for advanced metastatic soft tissue sarcoma.

While chemotherapy is the mainstay of palliative treatment for locally advanced or metastatic disease, surgery can be considered in selected cases as an adjunct to chemotherapy. A potentially curative approach, albeit efficient only in a small proportion of patients, is secondary resection of metastasis.[11]

Established agents

Doxorubicin and ifosfamide are routinely available and have a very broad label including sarcoma in most countries. Trabectedin is available in Europe. Apart from doxorubicin, ifosfamide and trabectedin a number of other chemotherapeutic drugs are used in selected subtypes of metastatic soft tissue sarcomas: dacarbacin, gemcitabine, doxetaxel and paclitaxel have some value in specific subsets of patients, even though not all of them are officially approved for sarcoma or have been adequately tested in this indication in larger randomised trials.[10,12-14] The

report focuses on approved, readily available agents with a proven track record in soft tissue sarcoma.

Doxorubicin

Doxorubicin is a cytotoxic anthracycline antibiotic which inhibits topoisomerase II, resulting in DNA-breakage.[15] The commonly used dose ranges from 60 to 75mg/m^2 once every three weeks. The drug is given by intravenous bolus infusion and is the standard of care in this disease. Response rates in clinical trials are ranging between 10 and 25%.[10,16] The dose-limiting toxicity of doxorubicin is cumulative cardiotoxicity, namely a decrease in left ventricular ejection function and other cardiac adverse events. There is also a high incidence of bone marrow depression and stomatitis. Doxorubicin has shown consistent efficacy in a number of sarcoma variants, nevertheless the results with single agent doxorubicin are far from being satisfactory. Across the broad range of histological subtypes of soft tissue sarcoma, the OS of patients treated with this drug is still approximately one year and the PFS is in the range of 2-5 months only.[16] The response rates to doxorubicin 75mg/m^2 in the most recent large randomised trial is below 15%.[17] On the other hand doxorubicin is easy to administer, can be given on an outpatient basis and patient's acceptance is quite high.

Cardiomyopathy is the major limitation. The risk of cardiomyopathy increases with the used cumulative dose. The maximum cumulative dose that should be administered should not exceed 550mg/m^2. The risk for cardiac toxicity increases in patients with a history of mediastinal irradiation or concomitant heart disease due to other conditions. Careful monitoring of the left ventricular ejection fraction prior and during treatment is mandatory. Treatment discontinuation must be considered at the first sign of impaired left ventricular ejection fraction or other clinically relevant cardiac events.

Ifosfamide

The second most commonly used drug in soft tissue sarcoma is ifosfamide, which is a cytotoxic alkalising agent belonging to the oxazaphosporine class of compounds. Drugs of this family induce DNA cross-links, which block tumour cells in late S-phase and early G2-phase of the cell cycle. As a single agent after failure of doxorubicin, ifosfamide is usually given at a dose of 8-12g/m^2 per cycle equally fractioned as single daily doses over three to five days. The most commonly used scheme is 3g/m^2 ifosfamide administered on day 1, 2 and 3, repeated every three weeks.[18] The drug is infused over 30 minutes but can also be given over 24 hours, and has been studied in a number of randomised phase III trials in sarcoma comparing this drug to other cytotoxic compounds or comparing different ifosfamide schedules to each other. Objective responses to ifosfamide in non-pretreated patients range between 10-25%. In the second line setting, where the drug is most commonly used, responses are in the range of 5-8%. The median survival of patients exposed to ifosfamide in second line after doxorubicin failure only varies between 35-45 weeks with a median time-to-progression of 6-14 weeks.[18] When compared to doxorubicin, ifosfamide achieves very similar results, therefore ifosfamide is a reasonable alternative if patients cannot be treated with an anthracyclin. Ifosfamide is associated with a number of adverse events including leukopenia, neutropenia, renal toxicity and encephalopathy. The urotoxicity of ifosfamide is related to a metabolite called acrolein, which affects the urinary tract and the bladder and can lead to haemorrhagic cystitis and dysuria. This must be managed by the concomitant administration of mesna. Another very characteristic adverse event of ifosfamide is encephalopathy, which is seen in up to 10% of all treated patients. The usual clinical signs are lethargy, hallucinations and other personality changes. This can be treated by the intravenous administration of methylene blue. A potentially irreversible adverse event is cumulative nephrotoxicity which can lead to renal insufficiency and even renal failure. This can in part be prevented by aggressive hydration of patients during administration of the anticancer agent. Apart from being the standard second line agent in soft tissue sarcoma, ifosfamide is also combined with doxorubicin in clinical situations where combination chemotherapy is regarded as a better alternative than single agent treatment.[10] The number of such indications is limited. Whenever administering doxorubicin in combination with ifosfamide the aim should be to give the highest single agent doses that can be administered, e.g. 75mg/m^2 of doxorubicin per cycle and approximately 9-10g/m^2 for ifosfamide with mesna uroprotection and haematopoietic growth factors.

EORTC trial 62012 confirms the current therapeutic standard

The most recent clinical trial comparing single agent doxorubicin to doxorubicin plus ifosfamide in non-pretreated advanced soft tissue sarcoma patients is EORTC 62012. This pivotal trial has failed to generate a statistically significant OS benefit but confirmed once again a significant PFS advantage of the combination over single agent treatment.[17] Response rates were 13.6% for single agent doxorubicin versus 26.5% for the combination. PFS increased from 4.6 months for single agent to 7.4 months for the combination. OS was 12.8 months for doxorubicin and 14.3 months for doxorubicin/ifosfamide, but this difference was non-significant according to the statistical plan of the trial. The survival at one year was 51% for patients receiving doxorubicin and 60% for doxorubicin plus ifosfamide.[17] This means that for all clinically relevant endpoints an advantage of combination chemotherapy was demonstrated in this well-powered study, but statistical significance was not reached for the chosen primary endpoint OS. Of note, there is not a single randomised phase III trial in metastatic soft tissue sarcoma that has been able to generate a clinically relevant and statistically significant OS benefit so far. The question remains whether OS is the ideal endpoint for such trials; some experts regard OS as a poor surrogate to assess the efficacy of drugs in such setting, as survival outcomes are confounded by second and third line treatments.

Trabectedin

Trabectedin is an anticancer agent of marine origin acting as a DNA minor-groove binder. The cytotoxic alkaloid was isolated from the Caribbean marine tunicate called Ecteinascidia turbinate.[19] The drug is a DNA guanine-specific minor groove-binding agent blocking the cell cycle in late S- and G-phase. Trabectedin is given as a 24-hour infusion at a dose of 1.5mg/m^2 every three weeks; this can be done during a short hospitalisation or in the outpatient setting through disposable elastomeric pumps.[20] The drug is usually combined with steroids which have a beneficial effect on the safety profile of this compound. The DNA repair profile of sarcoma cells predicts the outcome of treatment with trabectedin.[21] Trabectedin is approved in Europe after failure of anthracyclines and ifosfamide in soft tissue sarcoma or in patients who are unsuited to receive these agents. Trabectedin is not approved in the United States for sarcoma. Dose-limiting toxicities include neutropenia and thrombocytopenia but the drug can also cause liver function abnormalities, liver failure, rhabdomyolysis and other severe complications.

A critical factor to prevent acute toxicities is to ensure that patients have normal alkaline phosphatase values, which must be checked prior to each administration of the drug in addition to routine blood counts. Trabectedin is showing the best efficacy in the so-called "L"-sarcomas, meaning in leiomyo- and liposarcoma. Within the family of adipocytic tumours the drug has exquisite activity in the subtype of myxoid/round cell liposarcoma. This tumour type is one of the most chemotherapy-sensitive sarcoma subtypes anyhow, independent of the drug that is given.

Trabectedin has not yet been studied in a completed randomised phase III trial. Its approval is based on a randomised phase II study comparing two different schedules of administration of the agent resulting in a clinical efficacy advantage in terms of time to progression for the 24-hour 3-weekly schedule over a weekly 3-hour infusion schedule.[22]

Off-label cytotoxic treatments

There is increasing evidence regarding the off-label use of other drugs in the field of sarcoma that will not be discussed in detail in this review. Gemcitabine with or without docetaxel is commonly used in some specific sarcoma subsets, even though they are not approved for this indication. There is considerable doubt whether gemcitabine actually has to be combined with docetaxel. A recent, not yet fully published French meta-analysis of clinical trials indicated that single agent gemcitabine may be as efficient as the combination while being less toxic. The most relevant trial in this field has compared gemcitabine with and without docetaxel in patients with advanced soft tissue sarcomas.[23] The trial suggested a PFS benefit for the combination and even an advantage in terms of OS. There has been a lot of criticism regarding the Bayesian statistical design of this trial, nevertheless the study forms the basis for the use of this combination in a number of sarcoma settings. There is increasing interest in using gemcitabine as single agent or in

combination also in adjuvant settings as in the case of uterine sarcomas, but there is no scientific evidence for such a concept. Hence, such treatments should not be given outside clinical studies. Another drug that is frequently used in the field of sarcoma is paclitaxel, which shows exquisite activity in smaller series of patients with advanced vascular tumours, especially angiosarcomas. Paclitaxel has not been studied in large scale, randomised, multi-centric trials so the evidence level is still low.[14]

Adverse events observed with common cytotoxic agents for treatment of sarcoma

Every cytotoxic compound used for the treatment of soft tissue sarcoma has specific adverse events. All these drugs are relatively non-specific and interact not only with the malignant cells but also with normal tissue, especially in cells with a high proliferation rate. Doxorubicin is associated with cardiomyopathy. Ifosfamide gives uro- and nephrotoxicity and encephalopathy.[24] Trabectedin can cause haematological events, gastrointestinal side-effects and rhabdomyolysis.[25] Gemcitabine is associated with myelosuppression, docetaxel gives dose-dependent sensory neuropathy and paclitaxel is associated with haematological events, neurotoxicity and arthralgia, to mention a few typical events.

Chemotherapy with any of these agents can have a severe negative impact on the quality of life of the patients during the actual treatment period, while the quantity, quality and duration of responses achieved are very unsatisfactory in the majority of cases. Whenever considering chemotherapy in the palliative setting of metastatic soft tissue sarcoma, quality of life and other patient-related factors have to be taken into account when making definitive decisions. The key problem in soft tissue sarcoma remains primary resistance to chemotherapy as illustrated by the low response rates and the rapid occurrence of secondary resistance during or after initial treatment. The results of second and third line chemotherapies in sarcoma are usually much worse than the outcome of first line treatment with an anthracycline.

New cytotoxic agents in late stages of clinical development

A number of innovative agents with promising anti-tumour activity in soft tissue sarcoma in earlier studies are currently being tested in international randomised phase III trials. These include drugs of the oxazaphosphorine family such as palifosfamide, a DNA-alkylating metabolite of ifosfamide, and TH-302, a hypoxia-activated prodrug selectively targeting hypoxic regions of solid tumours.[26,27] Both agents are developed in the first line setting of metastatic soft tissue sarcoma. According to a recent press release, the pivotal trial with palifosfamide added to doxorubicine did meet its primary endpoint. Development of the compound in this indication is terminated. Furthermore, eribulin mesylate, a synthetic analogue of halichondrin B, a compound originally isolated from marine sponges, is currently compared to dacarbacine in a pivotal trial in previously treated L-sarcomas.[28] Accrual to this trial has now been completed.

Pazopanib

Pazopanib is the first non-chemotherapeutic anti-cancer agent approved by regulatory authorities for soft tissue sarcoma. Pazopanib interferes with the VEGF and PDGF-pathways. The approval of this oral antiangiogenic agent is based on the largest trial that has ever been performed in patients with this disease, EORTC 62072 (PALETTE). Pazopanib is an orally bioavailable tyrosine kinase inhibitor (TKI) which already showed evidence of efficacy in mesenchymal diseases during a dose-finding phase I study, and in a phase II study performed by EORTC (trial 62043).[29,30] The latter revealed promising PFS rates. In the following pivotal multinational phase III trial EORTC 62072, pazopanib was compared at the standard dose of 800mg daily per os to a matching placebo.[31] This study confirmed the efficacy of the angiogenesis inhibitor in heavily pre-treated patients with soft tissue sarcoma previously exposed to more than two lines of systemic therapy. The median PFS in patients treated with pazopanib was 20 weeks as compared to 7 weeks with placebo, which was significant. The benefit of pazopanib was independent of the number of prior lines of systemic therapy, the performance status at baseline or the type of soft tissue sarcoma. Survival curve suggested a benefit of pazopanib over placebo (12.6 versus 10.7 month median OS), but this difference was not statistically significant. This can in part be explained by imbalanced post-study treatments, the OS analysis was confounded by various factors.

Seventy-five percent of the placebo-treated group in the registration trial received further treatments and the anticancer follow-up therapy included chemotherapies, targeted therapies, radiotherapy, surgery or other interventions.[31] Pazopanib is a drug that induces disease stabilisation: partial responses are rare (4%), but stable disease is achieved in about half of all patients. In Europe, pazopanib is approved for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy or for patients who are unsuited for such therapy.

Guidelines

A number of academic organisations have published guidelines for the treatment of inoperable, advanced, metastatic sarcoma. The ESMO-guidelines recommend as first line treatment anthracyclines as single agent or in combination with ifosfamide or single agent ifosfamide if there are specific contra-indications.[32] Second line treatments include ifosfamide at standard doses if patients have not previously been treated with this agent during first line treatment. A high dose ifosfamide schedule is recommended by ESMO if the drug had been previously used at a lower dose. Trabectedin is recommended especially for L-sarcomas. Best supportive care is considered a reasonable option for a number of patients instead of continued chemotherapy.

The British Sarcoma Group recommends single agent doxorubicin or ifosfamide or doxorubicin and ifosfamide in the first line setting.[32] These guidelines were published before the results of EORTC 62012 had been presented, which failed to generate an OS benefit for the combination of doxorubicin plus ifosfamide. The British Sarcoma Group recommends second line treatments with either ifosfamide, trabectedin, gemcitabine and docetaxel or the older drug dacarbacin.[32]

The National Comprehensive Cancer Network (NCCN) has published more detailed North American guidelines, and the list of drugs considered for treatment of sarcoma reflects the common practice of off-label use in the United States, which may not be applicable to the European situation, due to reimbursement limitations.[6]

Conclusion

Soft tissue sarcoma is a very heterogeneous and rare family of malignancies that can occur in all age groups and all anatomical sites. Treatment outcomes are far from being satisfactory, especially in the subset of patients with inoperable, locally advanced and/or metastatic disease. The diagnosis of soft tissue sarcoma poses a significant challenge to all involved disciplines, including radiologists and pathologists. The classification of soft tissue sarcoma is undergoing continuous evolution, and a number of subtypes can only be diagnosed correctly when sophisticated molecular diagnostic tests are applied and results are interpreted by expert geneticists and pathologists. Treatment planning requires close interaction between all involved disciplines represented within an expert sarcoma team that is meeting on a regular basis and is updating institutional treatment standards based on growing scientific evidence.

To achieve optimal treatment results patients with presumed, newly diagnosed or progressive soft tissue sarcoma should be transferred to reference sites. These reference institutions should have a track record of multidisciplinary sarcoma care and ongoing surgical, radiotherapeutic and/or chemotherapy trials in soft tissue sarcoma (see also http://www.uzleuven.be/nl/ig-algemeen-medische-oncologie/klinische-studies for a list of ongoing studies in our centre).[32] Ideally, such institutions should be embedded in multinational sarcoma research initiatives and have strong links with patient advocacy groups with a specific interest in sarcoma. Reference sites should also have a tradition of performing basic or translational research in the field of sarcoma and have access to comprehensive diagnostic tools including but not limited to imaging (CT, MRI, FDG-PET), histopathology (conventional staining, immunohistochemistry, electron microscopy) and genetic testing (cytogenetics, FISH, array- CGH, and -omics).

References

1. Fletcher C, Unni KK, Mertens F. Pathology and Genetics of Tumours of Soft Tissue and Bone. World Health Organization Classification of Tumours 2002.

2. Casali PG, Blay JY; ESMO/CONTICANET/EUROBONET consensus panel of experts. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v198-203

3. Ries LA, Ward KC, Young JL jr. Sarcomas. In: National Cancer Institute: SEER Survival Monograph. Ries LA, Young JL jr, Keel GE, et al. (eds); 2007, pp. 89–92.

4. Eilber FC, Brennan MF, Eilber FR, et al. Validation of the postoperative nomogram for 12-year sarcoma-specific mortality. Cancer 2004;101(10): 2270-5.

Key messages for clinical practice

1. Standardisation of treatment for soft tissue sarcoma poses a significant challenge due to the heterogeneity of this orphan family of diseases and the rarity of the individual histological subtypes of adult soft tissue sarcoma.
2. Soft tissue sarcoma should preferably be diagnosed, treated and followed-up in reference sites with a true multidisciplinary setup and a track record of ongoing research activities in the field of mesenchymal malignancies.
3. Standard of care for patients with treatment-naïve advanced, inoperable or metastatic soft tissue sarcoma is in most cases single agent doxorubicin; ifosfamide, trabectecin and pazopanib are established agents for single agent treatment of adult sarcoma after failure of anthracyclins or in case of specific contra-indications.
4. Chemotherapy combinations, the off-label use of selected other agents in specific histological subtypes of adult sarcoma or selected clinical settings, and the treatment with truly experimental agents in the context of clinical studies should be restricted to reference sites.
5. In a number of clinical settings of advanced soft tissue sarcoma, participation in clinical trials is the preferable option for patients, given the poor treatment outcome associated with routinely available standards of care.

5. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for disease-specific survival after first relapse of soft-tissue sarcoma: analysis of 402 patients with disease relapse after initial conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys 2003;57(3):739-47.

6. NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma, v.1. 2012. http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf [accessed January 2013].

7. Tierney JF, Mosseri V, Stewart LA, et al. Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials. Br J Cancer 1995;72(2):469-75.

8. Karavasilis V, Seddon BM, Ashley S, et al. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. Cancer 2008;112(7):1585-91.

9. Grimer R, Judson I, Peake D, et al. Guidelines for the management of soft tissue sarcomas. Sarcoma 2010:506182.

10. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 1995;13(7):1537-45.

11. Kim S, Ott HC, Wright CD, et al. Pulmonary resection of metastatic sarcoma: prognostic factors associated with improved outcomes. Ann Thorac Surg 2011;92(5):1780-6.

12. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist 2012;17(9):1213-20.

13. Bramwell V, Blackstein M, Belanger K, et al. A Phase II study of docetaxel in chemotherapy-naïve patients with recurrent or metastatic adult soft tissue sarcoma. Sarcoma 1998;2(1):29-33.

14. Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer 2008;44(16):2433-6.

15. Riggs CE. Antitumor antibiotics. In: Perry MC (Ed.) The chemotherapy sourcebook. Lippincott Williams & Wilkins 2001, pp 231-4.

16. Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 2007;25(21):3144-50.

17. Judson I, Verweij J, Gelderblom H, et al.Results of a randomised phase III trial (EORTC 62012) of single agent doxorubicin versus doxorubicin plus ifosfamide as first line chemotherapy for patients with advanced, high grade soft tissue sarcoma: a survival study by the EORTC Soft Tissue and Bone Sarcoma Group. ESMO Congress 2012, Vienna.

18. Van Oosterom AT, Mouridsen HT, Nielsen OS, et al. EORTC Soft Tissue

and Bone Sarcoma Group. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur J Cancer 2002;38(18):2397-406.

19. Schöffski P, Dumez H, Wolter P, et al. Clinical impact of trabectedin (ecteinascidin-743) in advanced/metastatic soft tissue sarcoma. Expert Opin Pharmacother 2008;9(9):1609-18.

20. Schöffski P, Cerbone L, Wolter P, et al. Administration of 24-h intravenous infusions of trabectedin in ambulatory patients with mesenchymal tumors via disposable elastomeric pumps: an effective and patient-friendly palliative treatment option. Onkologie 2012;35(1-2):14-7.

21. Schöffski P, Taron M, Jimeno J, et al. Predictive impact of DNA repair functionality on clinical outcome of advanced sarcoma patients treated with trabectedin: a retrospective multicentric study. Eur J Cancer. 2011;47(7):1006-12.

22. Demetri GD, Chawla SP, Von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol 2009;27(25):4188-96.

23. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol 2007;25(19):2755-63. Erratum in: J Clin Oncol. 2007 Aug 20;25(24):3790.

24. Grochow LB. Covalent DNA-binding Drugs. In: Perry MC (Ed.) The chemotherapy sourcebook. Lippincott Williams & Wilkins 2001, pp 196-7.

25. Schöffski P, Wolter P, Clement P, et al. Trabectedin (ET-743): evaluation of its use in advanced soft-tissue sarcoma. Future Oncol 2007;3(4):381-92.

26. Jones B, Komarnitsky P, Miller GT, et al. Anticancer activity of stabilized palifosfamide in vivo: schedule effects, oral bioavailability, and enhanced activity with docetaxel and doxorubicin. Anticancer Drugs 2012;23(2):173-84.

27. Liu Q, Sun JD, Wang J, Ahluwalia D, et al. TH-302, a hypoxia-activated prodrug with broad in vivo preclinical combination therapy efficacy: optimization of dosing regimens and schedules. Cancer Chemother Pharmacol 2012;69(6):1487-98.

28. Schöffski P, Ray-Coquard IL, Cioffi A, et al; European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG). Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol 2011;12(11):1045-52.

29. Hurwitz HI, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res 2009;15(12):4220-7.

30. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer- Soft Tissue and Bone Sarcoma Group (EORTC study 62043). J Clin Oncol 2009;27(19):3126-32.

31. Van der Graaf WT, Blay JY, Chawla SP, et al.; EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012 19;379(9829):1879-86.

32. The ESMO / European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 (suppl 7): vii92-9.