Soft-Tissue Sarcoma: Management of Metastatic Disease

Effective Date: March, 2017

The recommendations contained in this guideline are a consensus of the Alberta Provincial Sarcoma Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Sarcomas represent a rare and heterogeneous group of malignant tumors originating from mesenchymal cells, and comprise less than 1% of adult malignancies[1]. The majority of sarcomas originate from soft tissue (approximately 80%) with the remainder originating from bone. These tumors arise most frequently in the limbs, followed by the abdominal cavity/retroperitoneum, the trunk/thoracic region, and the head and neck.

Local complications from primary or recurrent soft-tissue sarcomas (STS) can cause significant morbidity and occasional mortality, however, the most life-threatening aspect of sarcomas are their propensity for hematogenous dissemination. For the majority of STS, the primary metastatic site is the lung[2], however, extrapulmonary metastases to the retroperitoneum, spine, and paraspinous soft tissues also predominate with myxoid/round cell liposarcomas, although typically lung metastases eventually develop in most of these cases[3]. With retroperitoneal and visceral sarcomas, the primary site of failure is local. Less commonly, these tumors can spread to the liver[2]. Spread to lymph nodes is rare except with clear cell and epithelioid sarcoma, angiosarcomas, synovial sarcomas and rhabdomyosarcomas[4].

The majority of patients who develop distant metastasis associated with STS are incurable if resection of pulmonary metastases is not feasible. The median survival after developing distant metastases is 11-15 months, with approximately 20-25% of patients still alive at 2 to 3 years[2,5]. For patients with metastatic unresectable disease, systemic therapy provides meaningful symptom palliation, by decreasing tumour bulk and diminishing symptoms, and may, in some cases, prolong survival.

GUIDELINE QUESTIONS

- What diagnostic, staging and risk factors should be considered when determining if a soft-tissue sarcoma patient should receive chemotherapy, and what type of chemotherapy should be used?
- What is the appropriate follow-up protocol for patients who have been treated with chemotherapy for soft-tissue sarcoma?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Sarcoma Tumour Team. Members of the Alberta Provincial Sarcoma Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Sarcoma Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in March, 2017.

TARGET POPULATION

Adult patients (18 years of age or older) who have been diagnosed with a soft-tissue sarcoma who are being considered for chemotherapy.

RECOMMENDATIONS

Patients with a diagnosis of gastrointestinal stromal tumor (GIST) are covered in a separate guideline available: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-sar002-gist.pdf

Diagnosis

1. For confirmation of diagnosis and biopsy of STS please refer to the Sarcoma Biopsy Guideline (Currently under development, will be available at: http://www.albertahealthservices.ca/info/cancerguidelines.aspx).

Staging

2. Available staging classifications have limited relevance and should be improved. The AJCC and UICC stage classification systems stress the important of the malignancy grade in sarcoma[6]. In general, other prognostic factors that may be useful are tumour site, resectability and presence of metastases. Also, for limb sarcomas, tumour size and depth are important. A chest spiral CT scan is mandatory for staging.

Table 1. American Joint Committee on Cancer (AJCC)/ International Union against Cancer (UICC) TNM staging system (Adapted from[6])

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour 5 cm or less in greatest dimension		
T1a	Superficial tumour		
T1b	Deep tumour		
T2	Tumour >5cm in greatest dimension[a]		
T2a	Superficial tumour[a]		
T2b	Deep tumour		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node involvement		
N1[b]	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage IA			
T1a	N0	M0	G1, GX
T1b	N0	M0	G1, GX
Stage IB			
T2a	N0	M0	G1, GX

T2b	N0	M0	G1, GX
Stage IIA			
T1a	N0	M0	G2, G3
T1b	N0	M0	G2, G3
Stage IIB			
T2a	N0	M0	G2, G3
T2b	N0	M0	G2, G3
Stage III			
T2a, T2b	N0	M0	G3
Any T	N1	M0	Any G
Stage IV			
Any T	Any N	M1	Any G

[a]Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.
[b]Presence of positive nodes (N1) in M0 tumours is considered stage III.

3. Regional lymph node metastases are rare, with the exception of some histologies (e.g. epithelioid sarcoma and clear cell sarcoma; for which regional assessment through CT/MRI may be added to the usual staging procedures).

4. Abdominal CT scan may be added for limb myxoid liposarcomas. Brain CT scan may be considered for alveolar soft part sarcoma, clear cell sarcoma and angiosarcoma.

5. Bone scan, whole-body MRI and PET scan are optional. Cost-effectiveness studies on their incorporation into the staging procedures are required. Whole spine MRI for the detection of bone metastases may be of particular utility in myxoid liposarcoma patients.

6. The surgical report should provide details on the preoperative and intraoperative diagnosis, the type of excision (wide excision versus marginal excision), the surgical margins obtained (eg. 2cm) and location of any close margins, and the intactness of the tumor during excision including any gross breaches of the tumor tissue or capsule. Completeness of resection describing whether any gross residual disease remains (R2 resection) should also be included, as well as multifocality of the tumor (especially for recurrent retroperitoneal/abdominal sarcomas). En bloc resected organs, nerves, and vessels should also be described especially as it impacts functional outcome.

General Considerations in treating stage IV/advanced Sarcoma (Adapted from [27])

Locally advanced primary and/or metastases
•We categorized clinical status as follows:
- •Locally advanced and inoperable
- •Locally advanced and metastatic
- •Locally operable and metastatic
- •Metastatic (inoperable)
- •Metastatic (potentially resectable)

•Palliative surgery for the primary tumour site may be appropriate in patients with locally operable disease and metastases, especially if the primary tumour is symptomatic or located in close proximity to vital anatomical structures[28].
•Surgery or radiotherapy of metastases may be options depending on patient symptoms, the sites of disease and number of metastases, especially in patients with a good general condition and indolent course[29,30].

Patient's general condition
•The general condition of a patient significantly influences treatment choice. Our model divides patients into three categories:
- •Highly symptomatic (Performance status (PS)≥2)
- •Mildly symptomatic (PS 1)
- •Asymptomatic (PS 0)

•Poor PS has been demonstrated to be a risk factor for early death[31,32], whereas good PS has been shown to be a favourable prognostic factor, associated with longer progression-free survival (PFS)[5].

Previous Chemotherapy
•This factor is important when considering treatment choice: for instance doxorubicin in the metastatic setting is not a viable option for a patient who has received the maximum cumulative life-time dose of anthracyclines in the adjuvant setting.
•The interval between chemotherapy regimens is also important, as a shorter interval (e.g. <3 months) may be associated with poorer outcome.

Shared Decision Making
•Once the characteristics of the tumour and the patient's clinical condition have been determined, the next step in the decision-making process is to assess the treatment goal. Shared decision making is extremely important and is highlighted in guidelines on the management of STS.

Treatment Goal
•Appropriate information on treatment goal is essential for adequate shared decision making.
•In general, palliative care is the primary intent of treatment for advanced STS, this should clearly be indicated to the patient (data suggests up to 81% of patients with advanced cancer receiving palliative chemotherapy did not understand that their treatment was not curative[33]).
•Even minor tumour shrinking can achieve symptom control and the onset of symptoms can likely be delayed by prolonging disease stabilization[29].
• Typically there are three different goals of care:
- •Symptom control/progression arrest (palliative aims)
- •Achievement of resectability
- •Cure

•Cure is included in the model as it is essentially the ultimate aim of treatment; however, cure is currently not possible for the great majority of patients with advanced STS.

Patient acceptance
•Some patients accept greater levels of toxicities and more aggressive treatment than others to reach their treatment goal, this can be described as 'patient acceptance'.

Treatment

First-Line

7. In general, advanced or metastatic patients are potential candidates for clinical trials, if available.

8. Metachronous resectable lung metastases without extrapulmonary disease are managed with surgery as standard treatment, if complete excision of all lesions is feasible[7]. Other appropriate local techniques can be resorted to, including sterotactic body radiotherapy (SBRT)[8,9], though surgery is the standard and more data are required on alternative less invasive options. When surgery of lung metastases is selected, a full staging work-up is required, to confirm that the lung metastases are isolated. Chemotherapy may be added to surgery as an option, taking into account the prognostic factors (a short previous recurrence-free interval and a high number of lesions are adverse factors, encouraging the addition of chemotherapy), although there is a lack of formal evidence that this improves outcomes. Chemotherapy is preferably given before surgery in order to assess tumour response and thus modulate treatment.

9. In cases where lung metastases are synchronous, in the absence of extrapulmonary disease by re-staging work-up, surgery of completely resectable residual lung metastases may be offered as an option, especially when a tumour response is achieved.

10. Best supportive care alone is an alternative for patients with advanced STS, patients with performance status $\geq$2, or patients with medical or psychiatric co-morbidities that will not allow safe administration of chemotherapy (see Table 2).

11. Surgical resection of extrapulmonary metastatic disease may be an option (with or without chemotherapy) in highly selected cases following a multidisciplinary evaluation, taking into consideration their site and the natural history of the disease in the individual patient.

12. Radiation therapy (Stereotactic body radiotherapy) of pulmonary oligometastses or ablation of extrapulmonary metastases may also be considered as alternative to surgery in highly selected patients[8].

13. For patients with unresectable disease, systemic therapy should be considered taking into account histology and biologic behavior of the disease as well as health status and patient preferences. Enrollment in a clinical trial should be considered if available. Standard chemotherapy is based on anthracyclines as the first-line treatment. There is no formal demonstrations that multi-agent chemotherapy is superior to single agent chemotherapy with doxorubicin alone in terms of overall survival, however, a higher response rate can be expected, in particular in a number of sensitive histological types, according to several, although not all, randomized clinical trials[10]. Therefore, multi-agent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumour response is felt to be potentially advantageous and patient performance status is good. Olaratumab plus doxorubincin has demonstrated overall survival superiority over doxorubicin alone ($p<0.001$) in a phase II randomized trial, however, phase III study has finished accrual and results are pending, and the drug is not, at the time of publishing this guideline, Health Canada approved[11].

14. One trial demonstrated that gemcitabine + docetaxel is more effective than gemcitabine alone as second-line chemotherapy[19], with special reference to leiomyosarcoma and undifferentiated pleomorphic sarcoma, but data are conflicting as gemcitabine + docetaxel failed to demonstrate any advantage over gemcidabine alone in leiomyosarcoma patients in the phase II French study, while being more toxic[21].

Gemcitabine was shown to have anti-tumour activity in leiomyosarcoma and angiosarcoma also as a single agent[34]. In 2015, the UK group reported the phase 3 study of gemcitabine/docetaxel versus doxorubicin in treatment naïve metastatic sarcoma of all subtypes, with 27% of 257 patients enrolled with uterine leiomyosarcoma. This study failed to show an improvement in the primary endpoint of progression-free rate at 24 weeks (46% versus 46.1%; HR=1.28, p=0.07) and secondary endpoints including median progression-free survival (5.5 versus 5.4 months; HR= 1.28, p=0.07) and overall survival rate at 24 weeks (82.5% versus 86.7%; HR=1.07, p=0.67) [34]. In addition, there is increased toxicity in the gemcitabine/docetaxel arm.

15. In patients with angiosarcoma and cutaneous angiosarcomas, taxanes are an alternative option in the first or second line, given their high antitumour activity in this specific histological type[12], liposomal doxorubicin has also been shown to be effective in small studies[13-15]. An alternative option is gemcitabine +/- docetaxel[16].

Second-line (or beyond)

16. Best supportive care can be an option in patients by which further-line therapies have already been used in the patient or performance status <u>>2 or who wish for no further treatment.</u>

17. Patients who have already received chemotherapy may be treated with ifosfamide, if they did not progress on it previously. High-dose (~14g/m^2) may be an option for patients who have already received standard-dose ifosfamide[17,18].

18. Although an overall survival benefit was not achieved, Trabectedin has proven activity in patients with metastatic leiomyosarcoma and liposarcoma who have received at least two cytotoxic therapies including an anthracycline[19,20]. Benefit was seen in progression free survival and clinical benefit as compared to single agent darcarbazine. Trabectedin is Health Canada approved for patients with metastatic liposarcoma or leiomyosarcoma who have failed after treatment with a previous anthracycline and ifosfamide, but is not provincially funded, however, it is an option for those patients willing to pay or whom have private insurance covered.

19. Dacarbazine has some activity as a second-line therapy (mostly in leiomyosarcoma and solitary fibrous tumour). The Phase II trial of the combination of dacarbazine and gemcitabine was shown to improve the OS and PFS over dacarbazine in a randomized trial[22]. Phase III data comparing eribulin versus dacarbazine in advanced liposarcoma or leiomyosarcoma demonstrated superior overall survival with eribulin (p=0.0169), however, increased grade 3 or higher adverse events were higher in the eribulin group, and one treatment-related death was reported (226 patients in the eribulin arm)[23]. Submission to Health Canada and Funding Board are pending.

20. A randomized trial showed a benefit in PFS averaging 3 months for pazopanib given up to progression to advanced, previously treated, STS patients (excluding liposarcoma)[24]. Thus, it is an option in non-adipocytic STS. Pazopanib is Health Canada approved but not provincially funded. However, it may be an option for those patients willing to pay or whom have private insurance coverage.

21. Radiation therapy or other local management strategies (surgery, ablation) should be used as a palliative resource in all cases as appropriate to the clinical need (e.g. bone lesion at risk of fracture). Pain and symptom management support services should also be used as a palliative resource as clinically needed.

Special Consideration of Rare Subtypes

22. Alveolar soft part sarcoma is a slow growing soft tissue sarcoma presented commonly in the extremities. Often times, patients remain asymptomatic, even in the presence of metastatic disease. Phase 2 studies of single agent sunitinib and cedrianib in previously treated and untreated alveolar soft part sarcoma, with ORR 5/9 and 35-67%, respectively[16,25,26]. Even more impressive the median progression-free survival was 17 months in the sunitinib trial while the 6-month progression-free rate in the cedrianib treated patients was 84%. Currently, a sequential randomized phase II trial comparing cedrianib followed by sunitinib and suntinib followed by cedrianib coordinated by the NCI is ongoing. Either cedrianib or sunitinib has not received regulatory approval in this indication.

Table 2. Contraindications and comorbidities effecting treatment choice in advanced soft tissue sarcoma[a] (Adapted from [27])

Treatment	Contraindication	Precautionary comorbidity
Doxorubicin	Overt heart failure	Decreased cardiac function
	Severe hyperbilirubinemia (≥4 mg/dL)	Poor Bone marrow reserve
		Increased bleeding tendency
		Infection
Ifosfamide	Severe renal impairment	Elevated serum creatinine/renal impairment
		Inability to tolerate fluid challenges/Decreased cardiac fucntions.
		Age (elderly)
		Known urothelial injury
		Diabetes mellitus
		Infection
		Poor bone marrow reserve
		Neurological disorders
Dacarbazine	Severe renal impairment	Hepatic impairment
		Poor bone marrow reserve
Trabectedin[b]	Significant hepatic impairment (ALKP>2.5 ULN, AST/ALT >3x ULN, Bil >1.5x ULN)	Poor bone marrow reserve
	Combination with Yellow Fever vaccine	Alcohol use (due to hepatotoxicity of product)
	Concomitant use with alcohol	Infection
	Cardiac failure	Combination with live, attenuated vaccines
	Renal impairment	
Pazopanib[b]		Severe hepatic impairment
		Severe renal impairment
		Uncontrolled hypertension
		Cardiac dysfunction
		History of bleeding diathesis
		Pre-existing risk of bowel perforation
		Risk or history of pneumothorax

Treatment	Contraindication	Precautionary comorbidity
Gemcitabine	Thrombocytopenia	Impaired hepatic or renal function Yellow Fever vaccine administration (or live attenuated vaccines)
Paclitaxel	Insufficient or low platelet count/white blood cell count Serious, uncontrolled infection Severe hepatic impairment	
Docetaxel	Insufficient or low white blood cell count Severe hepatic impairment	

[a]Treatments described here are those most commonly used in advanced STS
[b]Health Canada approved, however, it is not currently funded in Alberta
[c]Contraindication dependent on agent used

SEARCH STRATEGY

Search: Soft tissue sarcoma chemotherapy
Date: 1-JUL-14 to 1-JUL-16
Detailed search: (("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields] OR ("soft"[All Fields] AND "tissue"[All Fields] AND "sarcoma"[All Fields]) OR "soft tissue sarcoma"[All Fields]) AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields])) AND (Clinical Trial[ptyp] AND ("2014/06/01"[PDAT] : "3000/12/31"[PDAT]))
Results: 143
Included: 31
Inclusion criteria: Greater than 50% adult patient cohort, phase II/III clinical trial, soft tissue sarcoma (Elastofibromas, Fibromas, Fibrous histiocytomas, Glomus, Granular cell, hemangiomas, Hibernomas, Lipomas, Leiomyomas, Lipoblastomas, Lipoblastomas, Lymphangiomas, Myxoma, Neurofibromas, Neuromas, Pecoma, Rhabdomyomas, Schwannomas, Tenosynovial giant cell), English abstract available

GLOSSARY OF ABBREVIATIONS

Acronym	Description
PFS	Progression-free survival
PS	Performance status
STS	Soft tissue sarcoma

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2017. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Sarcoma Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Sarcoma Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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