Role of systemic treatment in adult soft tissue sarcomas

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Introduction

The treatment of soft tissue sarcomas is multidisciplinary and involves surgery, radiotherapy and chemotherapy [1–5]. With a multidisciplinary organisation, improved imaging, better surgical techniques and adjuvant treatment, the primary treatment is now less extensive [6]. The major treatment aim is to preserve as many organs and functions as possible and secondarily to achieve a good cosmetic result. For example, the amputation frequency has dropped from 30% to 15% in extremity sarcomas and, by use of adequate local treatment, local control can be achieved in 85–90% of patients [1–5]. In adults, the 5-year survival rate is about 60% according to Eurocare data, but the survival varies substantially from country to country [3]. Although there are multiple histological subtypes, for the purpose of treatment they are usually grouped under the heading of soft tissue sarcoma. However, some of the subtypes should probably be handled differently from other soft tissue sarcomas such as gastrointestinal stromal tumours (GIST), angiosarcomas and leiomyosarcomas [3].

At present, there is consensus that the standard treatment of low malignant as well as superficial cutaneous/subcutaneous soft tissue sarcomas independent of malignancy grade is surgery [1,2,6,7]. Similarly, there is consensus that the standard treatment of the majority of high malignant soft tissue sarcomas is surgery combined with adjuvant radiotherapy [6]. The radicality is assessed by the surgical margin and not whether organ-preserving surgery is performed or not. It should be carefully judged whether extremity-saving surgery will result in a functionally satisfying result. This judgement should take individual care into consideration. Currently, the effect of adjuvant chemotherapy has not been settled and awaits data from clinical trials before its adoption as a standard in clinical practice can be judged [8].

Retroperitoneal and intra-abdominal (visceral) sarcomas are often difficult to remove and need complicated surgery with involvement of various surgical specialities. For the retroperitoneal tumours, there is consensus that the standard treatment is surgery and if possible with free resection margins [9]. On the other hand, the effect of adjuvant radiotherapy and chemotherapy is not proven. Although there are no firm clinical data, it is recommended that the standard treatment of intra-abdominal sarcomas should be the same as that of the extra-abdominal sarcomas [1–3].

Despite an improved local treatment of the primary tumours, some of them are so locally advanced at the time of diagnosis that cure by use of local treatment modalities alone is not possible. Soft tissue sarcomas tend to spread early on, and metastatic disease will develop in about half of patients. A few of these patients with isolated metastases primarily to the lungs may be cured by a metastasectomy, but the majority will need systemic treatment [3,10,11]. Therefore, a large number of clinical trials have studied the effect of chemotherapy [3,11]. Improved outcome has been achieved in *children*, whereas the responsiveness of *adult* soft tissue sarcomas to chemotherapy has been disappointingly low. At present, the effect of systemic treatment of locally advanced or metastatic adult soft tissue sarcomas is unsatisfactory with few drugs being active [1–3]. In addition, the treatment is often toxic and is usually given with palliative intent in many of the patients. Thus, there is a need for new effective drugs for adult patients. Hopefully the increasing knowledge on molecular biology in soft tissue sarcomas will help in this development of new effective drugs — a development that is underway. In the present review, the treatment of adult soft tissue sarcomas will be reviewed with the primary emphasis on chemotherapy. In contrast, the treatment of extra-skeletal PNET and Ewing sarcomas as well as rhabdomyosarcomas will not be described in this paper. In Fig. 1 the overall treatment strategy of soft tissue sarcomas is summarised.

Operable local disease

As mentioned above, half of patients will develop metastatic disease, and the majority of these patients

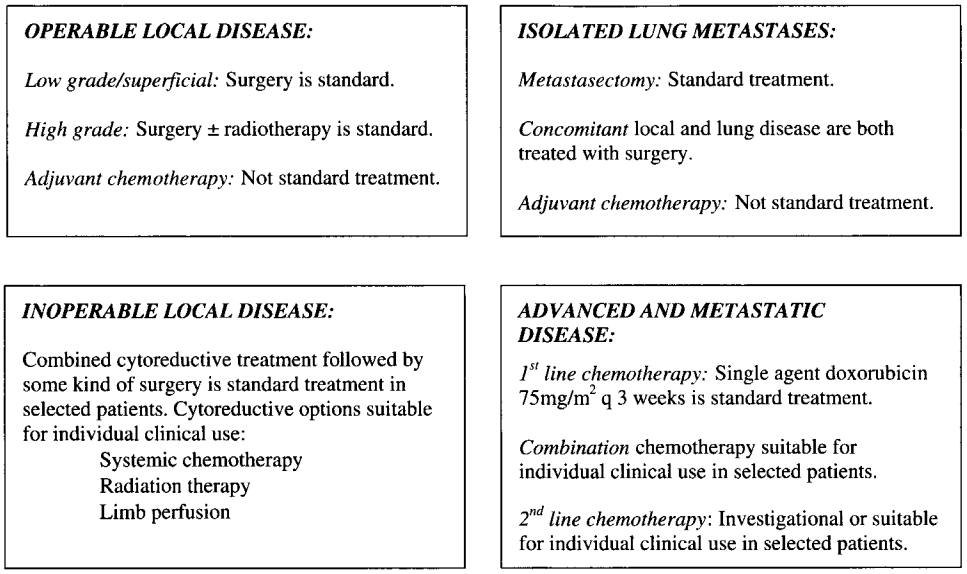

Fig. 1. Summary of treatment strategy of adult patients with soft tissue sarcomas.

will die, as chemotherapy will only cure a small number of them [1–3]. In an attempt to improve the survival of the patients with intermediate or high grade sarcomas, several groups have studied the use of chemotherapy in the primary treatment either prior to (neoadjuvant) or following (adjuvant) surgery.

Neoadjuvant chemotherapy

The concept of neoadjuvant chemotherapy is a topic for ongoing debate [1,8,12,13]. The aim of this treatment is to give the drugs preoperatively in an attempt to reduce tumour size and thereby improve operability and allowing a pathological response evaluation. In addition, this treatment has the theoretical advantage of treating possible micrometastases at an early stage and may establish the *in vivo* drug sensitivity of a tumour, thereby avoiding the toxicity of postoperative chemotherapy in non-responders. However, there may also be disadvantages, such as delayed surgery and compromised wound healing [13]. Although several modalities have been used to evaluate the effectiveness of neoadjuvant therapy, histopathological necrosis has been described as the most reliable method being an independent predictor of both local recurrence and overall survival [12,13]. However, due to a low number of patients included and too-short follow-up periods, these studies do generally not allow any definite statements on the importance of tumour necrosis [13].

The outcome of retrospective as well as non-randomised phase II studies of neoadjuvant chemotherapy suggests that chemotherapy given at this stage gives higher response rates than that of distant metastases [1,12,13], but otherwise these studies do not allow any firm conclusion. Most of the chemotherapy regimens tested have included not only doxorubicin, but also drugs like cyclophosphamide, cisplatin, etoposide, dacarbazine and especially ifosfamide [1]. The postoperative morbidity did not seem to be increased. Although not powered to draw definite conclusions on benefit, a recently published randomised phase II trial by the EORTC (European Organisation for Research and Treatment of Cancer) showed that it is less likely that major survival benefits will be achieved with this type of chemotherapy [12]. At present, neoadjuvant chemotherapy of patients with operable soft tissue sarcomas is not a standard treatment and should be considered as investigational. In patients in whom some surgical difficulties may be expected, it has been recommended that preoperative chemotherapy may be suitable for individual clinical use, but this will apply to very few patients. Further data on the effect of neoadjuvant chemotherapy are definitely needed, although the accrual problems of the recent EORTC study suggest that such data may be difficult to obtain.

Adjuvant chemotherapy

The effect of adjuvant chemotherapy after adequate surgery has been evaluated in at least 14 randomised trials [1,8,14,15] comparing doxorubicin-based chemotherapy with a no-treatment arm. Only two studies [8] have demonstrated a statistically significant improvement in overall and disease-free sur-

Table 1
Meta-analysis performed on 1568 individual patients in 14 randomised trials on the effect of adjuvant chemotherapy [14]

Outcome parameter [a]	Absolute benefit (10-year)	Hazard ratio	*P*-value
Local RFI	6% (75–>81%)	0.73	0.016
Distant RFI	10% (60–>70%)	0.70	0.0003
Overall RF survival	10% (45–>55%)	0.75	0.0001
Overall survival	4% (50–>54%)	0.89	0.12

[a] RFI = relapse-free interval.

vival. Although a trend towards improved prognosis in treated patients was demonstrated by several studies, most of them had a limited statistical power, and should be considered inconclusive rather than negative. There seemed to be a trend favouring combination chemotherapy over single agent doxorubicin. These inconclusive data led to a meta-analysis being performed on data from individual patients in all available randomised trials, with a total more than 1400 patients [14]. This analysis showed a reduction in both local and distance recurrence rates, but again, no significant improvement in overall survival (Table 1). A similar conclusion was obtained in a recent Cochrane analysis [15]. In both analyses, the strongest evidence of a beneficial effect on survival was shown in patients with sarcoma of the extremities. None of those trials, however, included ifosfamide, which is now recognised as one of the two most active drugs in soft tissue sarcomas. An Italian randomised trial compared a full-dose doxorubicin plus ifosfamide arm against a no-chemotherapy arm in very high-risk patients with "typical" limb soft tissue sarcomas [16]. The trial was stopped early as an interim analysis showed a significant advantage in favour of the chemotherapy group arm in terms of disease-free and overall survival.

All these data could suggest that adjuvant chemotherapy may be effective, especially in high-risk presentations, but currently there is no consensus on the adoption of adjuvant chemotherapy as standard practice in soft tissue sarcomas. As discussed by O'Byrne and Steward [8], there are major difficulties with trials of adjuvant chemotherapy, making the interpretation of their results difficult, i.e. enormous heterogeneity of the histological subtypes included as well as different sites of presentation, size of primary tumour, and histological grade. Confounding these problems is the relatively small size of the majority of the trials conducted.

The present data indicate that the possible effect of adjuvant chemotherapy in soft tissue sarcomas is at most small — an effect that should be balanced against the toxicity reported for most of chemotherapy regimens. This toxicity may explain that many of the patients did not complete the planned chemotherapy [8]. Consequently, in many countries adjuvant chemotherapy is not standard treatment in the primary treatment of soft tissue sarcomas and is only used within the framework of clinical trials. However, in a number of countries adjuvant chemotherapy is considered suitable for individual clinical use in selected patients (type 2 level of evidence), i.e. in those with poor prognostic factors (high grade, tumour diameter 5–10 cm, deep location), but the treatment is only given after shared decision-making between the fully informed patient and the clinician. If a benefit from adjuvant chemotherapy should be expected in the future, new treatment approaches need to be developed for soft tissue sarcomas. An ongoing randomised EORTC study is currently evaluating the effect of adjuvant high dose intensity chemotherapy with combined doxorubicin and ifosfamide with haematopoietic growth factor support and these data should be awaited.

Inoperable local disease

Inoperable local disease has a very poor prognosis. Therefore, in these cases it is reasonable to look for any available treatment option that could give a partial response and thereby hopefully convert inoperable into operable disease [1,2]. Even a marginal excision could be regarded as a goal in such cases, especially if it could be followed by radiotherapy. In some cases, in particular low grade sarcomas, even debulking surgery may be useful in the individual patient at least as far as quality of life is concerned. Available therapeutic options are cytoreductive chemotherapy, irradiation, or newer loco-regional approaches such as isolated limb perfusion. Radiotherapy can be combined with chemotherapy. Chemotherapy may be given intravenously or as an intra-arterial infusion, where both therapeutic and toxic systemic effects will be seen. Otherwise, chemotherapy can be given as a regional intra-arterial perfusion, often without major systemic effects. However, isolated regional perfusion can be combined with intravenous chemotherapy. Isolated hyperthermic limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma may be used [1].

No controlled evidence has been obtained so far that demonstrates superiority of any of these approaches. The limb perfusion techniques have been demonstrated to be relatively well tolerated. Reported complete response rates are in the range of 30%,

and partial remission rates in the range of 50% [1]. The limb-salvage rate may be increased and rates above 80% have been described, although it is difficult to assess this benefit properly from uncontrolled studies. Overall, it has been recommended that a combined approach with a cytoreductive treatment modality, followed by some kind of surgery, if at least marginally feasible, may be regarded as standard treatment in selected patients. With regard to the choice of the cytoreductive treatment modality, each of the available options, such as systemic chemotherapy, radiation therapy, limb perfusion, may be considered as suitable for individual clinical use (type 3 level of evidence).

Isolated metastases

Many of the patients with high-grade sarcomas develop lung metastases as their first sign of disseminated disease. A number of retrospective studies have indicated that at least a fifth of these patients achieve long-term disease-free survival after complete removal of the lung metastases [1–3,10]. Thus, there is consensus that the standard treatment of isolated lung metastases is metastasectomy. In patients with concomitant local and lung disease, it is recommended that adequate surgery of the primary tumour and surgery of the lung metastases is standard treatment, and that the surgery should be done according to the same criteria as that applied for each of the two settings individually.

The studies have also demonstrated a number of prognostic factors in these patients, with the number of metastases (≤ 4) and the disease free interval (>1–2 year) being the most important [1–3,10]. However, at present, none of those have been of value in selecting patients for pulmonary metastasectomy. Postoperative treatment with either radiotherapy or chemotherapy has as yet no proven effect [1,10]. When lung lesions are inoperable, an attempt has been described in converting them to a resectable status by the use of neoadjuvant chemotherapy, but this has only proven feasible in few cases. Surgical removal of further operable and isolated lung relapses is suitable for individual clinical use in selected patients (type 3 evidence).

Resection of isolated metastases in other organs and especially in the liver has also been described, but currently it is not standard treatment and should primarily be used as part of clinical trials.

Metastatic disease

Despite optimal primary therapy, approximately half of patients with soft tissue sarcomas will develop distant metastases. Consequently, chemotherapy has been extensively studied in soft tissue sarcomas. Unfortunately, the responsiveness to chemotherapy has been disappointingly low [3,11]. Median survival is generally less than 12 months, although long-term survival has been described in a limited number of patients [3]. However, chemotherapy is widely used in these patients, basically with a palliative intent, but is clearly inadequate. The chance of a partial response does not exceed 20–40%. At present, no study has been initiated comparing chemotherapy with best supportive care, and indeed best supportive care without chemotherapy may be a reasonable option at least in a subset of advanced sarcoma patients. There is consensus that an attempt with a first-line chemotherapy regimen may be considered a standard option at least for good performance status patients and/or patients in whom some clinical benefit is reasonably expected if a partial response does occur. Currently, there is no recognised standard second-line chemotherapy regimen and it should preferably be given within clinical trials. The effect of single as well as combination chemotherapy is summarised below.

Single agent chemotherapy

Doxorubicin appears to be the most active drug in the treatment of soft tissue sarcomas. During the last decade more than a thousand patients have been treated with the drug in connection with several reported studies. The cumulative response rate in non-pretreated patients was about 25% [1–3,11,17,18]. Doxorubicin treatment is limited because of cumulative cardiotoxicity, but unfortunately, none of the tested anthracycline analogues has shown superiority or comparability to doxorubicin in terms of therapeutic activity and toxicity such as epirubicin, carminomycin and mitoxantrone [3,17]. A few studies have indicated that epirubicin may be active as part of combination chemotherapy regimens, but whether it is a better alternative than doxorubicin has not been demonstrated in these studies [3,17].

Although the study design has been criticised, it has been indicated that a dose–response relationship may exist for doxorubicin [3]. Currently, single agent chemotherapy with doxorubicin at a dose of 75 mg/m^2 q 3 weeks is the standard treatment for metastatic soft tissue sarcomas (type 1 level of evidence). If a partial response represents a goal on clinical grounds, combination chemotherapy may

give higher response rates and may be considered suitable for individual clinical use in selected patients. The possibility of ameliorating anthracycline cardiotoxicity by use of compounds like dexrazoxane is presently under investigation [3]. At present, it can only be speculated why so many patients with soft tissue sarcomas do not respond to anthracyclines and further data are certainly needed. Overexpression of p-glycoprotein in association with the multidrug-resistant phenotype has been described as one of the possible explanations [3].

Liposomal entrapped doxorubicin (*Caelyx*, Doxil) represents a novel formulation to deliver doxorubicin, which may increase the tumour effect with less toxicity. Caelyx is effective in soft tissue sarcomas [3,11,19], and in a recent randomised phase II study comparing Caelyx 50 mg/m^2/1 hour intravenous q 4 weeks to standard dose doxorubicin 75 mg/m^{2}q 3 weeks, the response rates to both drugs were similar, while Caelyx was considerably less myelotoxic [19]. This may imply that caelyx could be an alternative to doxorubicin and the drug may well be easier to combine with agents such as ifosfamide given its lack of myelotoxicity. A phase I EORTC study testing combined Caelyx and ifosfamide in advanced soft tissue sarcomas is ongoing.

A second active drug in the treatment of soft tissue sarcomas is *ifosfamide*, with a response rate of around 25% [1–3,11]. Ifosfamide given at a standard dose has also demonstrated activity as second-line chemotherapy, although the activity is definitely lower than that observed in first-line treatment. The use of mesna has allowed studies on dose intensity and novel schedules with ifosfamide, and they have indicated that there may be a dose–response effect of ifosfamide [3]. However, at present the optimal dose and scheduling of ifosfamide administration have not been settled. In general, it seems that ifosfamide is more toxic than doxorubicin and is therefore the second choice in most patients. With the present knowledge, it seems that a regimen in which ifosfamide is given in bolus on 3 or 4 subsequent days in a total dose of about 9 g/m^2, may lead to an optimal balance between effectivity and toxicity.

Ecteinascidin (ET743) is a new drug that has recently been tested in phase I and II trials at doses up to 1650 μg/m^2 every 3 weeks [3,20]. It seems to have an unusual toxicity profile with limited haematological toxicity and alopecia, but frequent fatigue and occasional severe hepatic and general toxicity [3,20]. ET743 has been reported to induce objective responses when given as both first- and second-line treatment, with response rates ranging from 7% to 18% [3]. However, data from larger phase III studies are needed before we know if ET743 has a role in the treatment of soft tissue sarcomas.

Table 2
Single agents tested in phase II trials in advanced and metastatic soft tissue sarcomas

Agents tested as 1st- and 2nd-line chemotherapy	
ACNU [a]	MGBG [a]
Caelyx	Miltefosine [a]
Chlorozotocin [a]	Mitomycin [a]
Cisplatin [a]	Mitixantrone [a]
Dacarbazine	Mitozolomide [a]
Docetaxel	MT-PPE [a]
Doxorubicin	MZPES [a]
Ellipticinium [a]	Paclitaxel [a]
Epirubicin	PALA [a]
Etoposide [a]	Piperazinedione [a]
Fotemustine [a]	Piritrexin [a]
Gemcitabine [a]	Raltitrexed [a]
Ifosfamide	Temozolomide [a]
Imatinib mesylate	TGU [a]
Lomidamine [a]	Tomudex [a]
MDS [a]	Ecteinascidin-743
Methyl-GAG [a]	Vinblastine [a]
Methotrexate [a]	Vindesine [a]

[a] Minor effect. References in [2,3].

In addition to these drugs, several *other drugs* have been tested both as first- and second-line chemotherapies (Table 2), but unfortunately, very few of these drugs have shown any meaningful activity [1–3,11]. Dacarbazine is a well-known drug showing some activity in soft tissue sarcomas, but is rarely used in clinical practice. Thus, there is an urgent need for new and more active drugs. Examples of agents presently being tested include trofosfamide, exatecan, brostallicin, iressa (in HER1/EGFR1-positive synovial sarcomas) and paclitaxel (in angiosarcomas and leiomyosarcomas).

Combination chemotherapy

Combination chemotherapy will generally give higher response rates than that of single drugs. Many uncontrolled studies have evaluated combination chemotherapy and response rates of 50–60% have been described for various combined doxorubicin and ifosfamide regimens [3,11,18], and the data suggest that selected patients with advanced or metastatic soft tissue sarcomas may have a relatively high chance of response to combination chemotherapy. However, complete responses are rare, even with the most intensive regimens. Lower response rates have usually been reported in randomised studies and with no survival benefit of combined compared with single drug chemotherapy (Table 3). Three randomised tri-

Table 3
Randomised studies comparing single dose doxorubicin with combination chemotherapy in advanced and metastatic soft tissue sarcomas

Study group[a]	Treatment regimen[b]	Number of patients	Overall response (%)[c]
ECOG 1982	D	71	27
	D + C + V	80	19
GOG 1983	D	155	16
	D + DT	160	24
GOG 1985	D	66	19
	D + C	66	19
ECOG 1987	D	123	18
	D + DT	119	30
ECOG 1990	D	176	17
	D + VI	171	18
ECOG 1993	D	95	20
	D + I	94	34
	D + M + CP	90	32
EORTC 1995	D	263	23
	D + I	142	28
	D + V + C + DT	258	28

[a] References in [3,11,18].
[b] D = doxorubicin; C = cyclophosphamide; V = vincristine; DT = dacarbazine; VI = vindesine; I = ifosfamide; M = mitomycin; CP = cisplatin.
[c] No survival differences.

als have compared doxorubicin or doxorubicin-based chemotherapy with doxorubicin plus ifosfamide. Two of them from ECOG (Eastern Cooperative Oncology Group) [3,18] showed a statistically significant higher response rate for the doxorubicin plus ifosfamide arm, whereas the third from the EORTC did not show a benefit [21]. None of the studies demonstrated a survival benefit. It remains unclear whether this approach has any impact on survival in the majority of cases.

There remains some controversy between those who advocate the use of single agent doxorubicin and those who believe that a more aggressive approach using drug combinations is justified. A prospective randomised trial was performed by the EORTC that compared single agent doxorubicin with a combination of doxorubicin and ifosfamide and also the four drugs CYVADIC combination [21]. Although the combination treatments gave slightly higher response rates, there was no improvement in progression-free or overall survival and they were significantly more toxic. Despite the fact that these data were published in 1995, it has become common practice to use high doses of ifosfamide together with doxorubicin in the treatment of younger patients with aggressive tumours, especially if there is the possibility of subsequent surgical resection of pulmonary metastases. It seems at least feasible that the high response rates reported in single arm combination chemotherapy phase II studies are due to case selection, with younger patients and those with more rapidly progressive disease being more responsive.

The justification for re-visiting the issue of single agent versus combination treatment lies in the fact that many people now believe the dose of ifosfamide used in the Santoro study was too low. Attempts were made in the early 1990s to intensify sarcoma treatment by increasing the dose of doxorubicin in combination with ifosfamide, using haematopoietic growth factors [3]. Although the results of a phase II study were promising, no benefit was seen in a randomised trial compared with the standard dose [3]. Patel et al. [22] achieved a 66% response rate using doxorubicin 75 mg/m^2 plus ifosfamide 10 g/m^2. Reichardt et al. first reported a response rate of 52%, including 22% complete remissions, using epirubicin 90 mg/m^2, ifosfamide 12.5 g/m^2 and G-CSF [23]. Leyvraz et al. also published similar results using doxorubicin 90 mg/m^2 plus ifosfamide 10 g/m^2 with GM-CSF [24]. The consistency of these data suggests that selected patients may have a high likelihood of response to intensive treatment.

Combination treatment could be the indicated treatment given prior to pulmonary metastasectomy. Assessing the response to pre-operative chemotherapy enables one to determine the chemosensitivity of the disease and limits exposure to ineffective treatment. A patient with rapidly progressive, life-threatening disease should perhaps receive combination treatment since there is insufficient time to try individual single agents sequentially. It would be useful to know in these settings whether there is a significant advantage for combination therapy. For this reason, a randomised multicentre phase III trial will soon be initiated by the EORTC, comparing standard dose single agent doxorubicin with doxorubicin 75 mg/m^2/d1 + ifosfamide 3 g/m^2/d1–3 given each 3 weeks. Clearly, if an advantage can be demonstrated in terms of response rate and progression-free survival for the more intensive treatment, it would be worth looking subsequently for a survival difference. Presently, it is only a minority of patients with advanced and metastatic soft tissue sarcomas who should be treated with combination chemotherapy outside clinical trials.

Treatment intensification

In advanced soft tissue sarcomas, both doxorubicin and ifosfamide have shown a dose–response relationship [1–3]. Patients with advanced or metastatic soft tissue sarcomas progressing after standard-dose ifosfamide may obtain an objective response after

high-dose ifosfamide at doses above 9 g/m^2 given at an interval of 3–4 weeks [3]. However, none of the tested dose intensive regimens have shown a survival advantage compared with single agent doxorubicin. Currently, there are only a few studies that have looked at the effect of high-dose chemotherapy with haematopoietic stem cell support in sarcomas, most of which have focused on Ewing's sarcomas and rhabdomyosarcomas [3,25]. In addition, most of the studies on high-dose chemotherapy are hampered by the inclusion of a limited number of patients. When high-dose chemotherapy is given to patients responding to conventional chemotherapy it seems that a single course of high-dose chemotherapy is capable to induce relatively high response rates and a number of those patients will be long-term survivors [3,25]. Nonetheless, these data have been obtained from uncontrolled studies with selected patient populations; data from phase III trials are needed. Thus at present, treatment intensification is still an experimental strategy.

Second-line chemotherapy

As indicated in the above sections, there are presently no recognised standard second-line chemotherapy regimen. A recurrence after standard doxorubicin is frequently treated with ifosfamide in standard doses or even higher [1–3,11]. However, at present it is recommended that second-line chemotherapy should be regarded only as investigational or suitable for individual clinical use in selected patients. If available, the patients should be offered participation in phase II studies testing new drugs. When the progression-free interval has been long (i.e. >12 months), the clinician could (if possible) revert to the same chemotherapy already used in the first-line.

GIST and other subtypes

There are multiple histological subtypes, but as mentioned earlier these are usually grouped under the heading of soft tissue sarcoma for the purpose of treatment. However, the improved outcome of gastrointestinal stromal tumours (GIST) treated with a specific drug (imatinib mesylate) may indicate that some of the subtypes should be handled differently from other soft tissue sarcomas [3]. An example is leiomyosarcomas being more resistant to chemotherapy than many other histological subtypes, and therefore a new treatment strategy is needed for these sarcomas. If all the histologies are analysed together, neither topotecan nor gemcitabine showed any relevant activity, but in leiomyosarcomas, some activity was noted [3] — indicating that these drugs should be further evaluated in this histology. Angiosarcomas may be another subtype that should be treated differentially as recent data have indicated that taxanes may be effective in this rare subtype [3]. But further studies are needed and a number of cooperative groups have taken such an initiative.

It is hoped that the increasing knowledge on the molecular biology of soft tissue sarcomas will help in the development of new effective drugs that can be used as a subtype-specific treatment of soft tissue sarcomas. The effect of the new drug imatinib mesylate in *GIST* is a very good example of this development. GIST is the most common sarcoma arising in the gut and represents a very rare group of mesenchymal tumours that arise from the connective tissues of the gastrointestinal tract. Previously, these tumours were classified as leiomyosarcoma, but they are now accepted as a distinct entity and are characterised by expression of CD34 and CD117 [3]. GISTs commonly have gain of function mutations in the *c-Kit* gene that codes for the KIT receptor tyrosine kinase, making the signalling pathway independent of external influence [3]. KIT ("CD117") is the receptor for the stem cell factor and appears to be responsible for promotion of tumour growth and prevention of cell death in many of these tumours (Fig. 2).

For patients with surgically resectable tumours, the standard treatment is surgery according to the same primary treatment strategy as that of other soft tissue sarcomas [3]. On the other hand, patients with unresectable, metastatic and advanced GISTs have a poor prognosis, with a median survival of about 12 months, and unfortunately these tumours do respond poorly to radiotherapy and chemotherapy. As GIST is likely controlled by a single gene, theoretically one should be able to control the disease by inhibiting this gene — a theory that has become practice with the new drug imatinib. It was developed as an inhibitor of BCR–ABL, the tyrosine kinase that is activated by chromosomal translocation and gene fusion in chronic myeloid leukaemias [3,26,27]. It was recognised that overexpression of KIT in GIST, often due to mutations in *c-Kit*, might make imatinib mesylate a useful drug in this setting, since this was another target tyrosine kinase inhibited by the drug (Fig. 2). In a very short time phase I, II and III studies have been performed showing that imatinib mesylate is indeed very active drug in GIST [3,26,27]. Although further data are still needed it is clear from these studies that median survival of patients with GIST has been increased by treatment with imatinib mesylate and that symptomatic benefit will be obtained

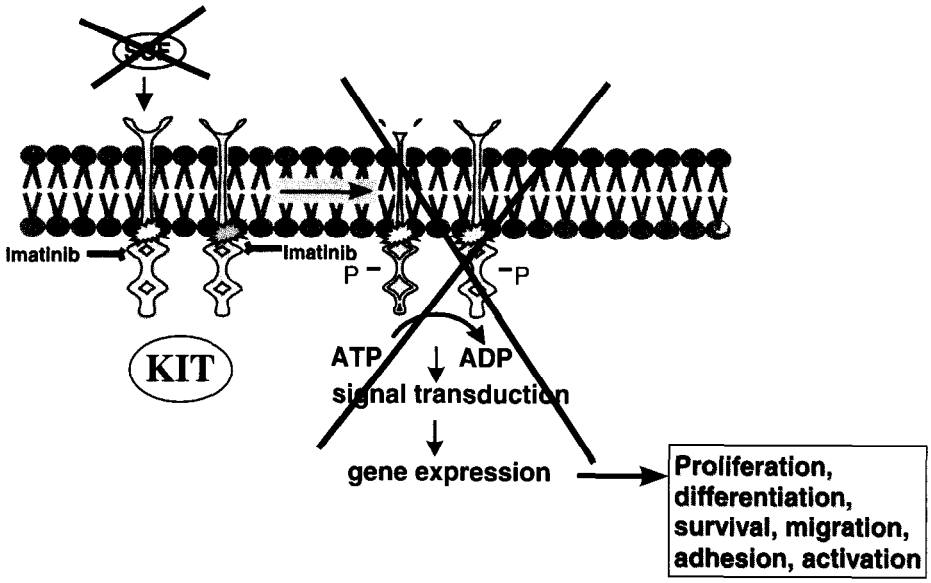

Fig. 2. The inhibition of KIT by imatinib mesylate thereby inhibiting cell proliferation and differentiation of the GIST.

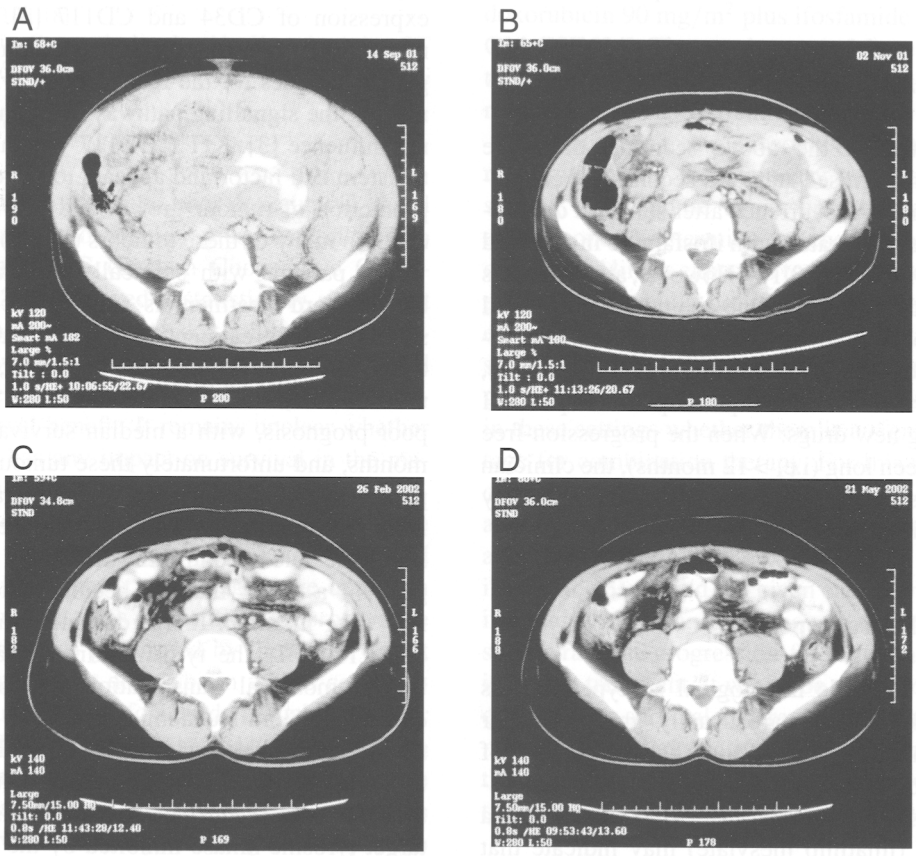

Fig. 3. Example of a patient with a very large GIST tumour treated successfully with imatinib mesylate. CT scans prior to treatment (A), and 7 weeks (B), 5 months (C) and 7 months (D) after treatment.

with little toxicity in more than three quarters of the patients with surgically unresectable, metastatic and advanced GISTs [3,26,27]. A quite dramatic effect has been described in some patients (Fig. 3).

At present, imatinib mesylate is the standard treatment for advanced or metastatic GIST. The optimal dose of imatinib mesylate has not yet been defined and awaits data from a large phase III study compar-

ing 400 mg and 800 mg. It is well known that the optimal dose will vary from patient to patient, and while we are waiting for further data, imatinib mesylate is given orally in a start dose of 400 mg daily. In patients with progression the dose is increased to a daily dose of 600–800 mg [3]. The treatment duration of imatinib mesylate has yet not been settled and the patients should continue the treatment as long as there is no disease progression. In the latest update of the ongoing studies, about 75% of patients are still on treatment with a minimum follow-up of 16 months [3]. At present, further studies are planned to determine the role of imatinib mesylate in the adjuvant or neoadjuvant settings. Soon a multicentre randomised phase III study will start in intermediate- and high-risk patients, comparing 400 mg daily of imatinib mesylate for 2 years with no adjuvant treatment.

Prognostic factors and treatment outcome

Many studies have tried to identify prognostic factors that would help in selecting the best treatment for subgroups of patients with soft tissue sarcomas [1–3]. In locally resectable tumours, the prognostic factors described as independent predictors of disease-specific survival are histological grade, tumour size and completeness of resection, and in some studies, also tumour depth and local recurrence (Table 4). Grade is likely the most important factor, although its importance diminishes with time, whereas the resection margins seem to influence late outcome of patients (>5 years), at least with extremity and retroperitoneal soft tissue sarcomas [1–3].

On the other hand, only a few studies on prognostic factors have been performed in patients with metastatic disease, except for patients undergoing pulmonary metastasectomy. Therefore, the EORTC sarcoma group [28] have analysed their sarcoma database with information on several thousand patients with inoperable advanced and metastatic disease, treated with chemotherapy (Table 4). The final multivariate analysis showed that low age and the histology liposarcoma were favourable factors for response. Presence of liver lesions had a very significant unfavourable prognostic value, both for survival and response to therapy. This might reflect the fact that either liver lesions are less chemosensitive than other types of lesions, or that the presence of liver metastases are a sign of advanced disease. Other unfavourable factors for survival included advanced age, poor performance status at treatment, recent diagnosis and high histopathological grade [3]. However, it is important to notice that the histological entity of GIST had not been identified at the time of diagnosis for most of the included patients. A more recent study [29] on patients with distant metastases arising from primary extremities sarcoma has confirmed the prognostic value of age and duration of previous progression-free survival, but did not find any impact of histopathological grade. They also found that resection of metastatic disease and presence of a preceding local recurrence may independently influence survival.

Table 4

Prognostic factors for outcome of soft tissue sarcoma patients with either local disease treated with surgery ± radiotherapy or metastatic disease treated with chemotherapy

Prognostic factors	Operable local disease		Metastatic disease	
	Local recurrence	Survival	Response	Survival
Patient age		+	+	+
Performance status				+
Histological grade	+	+	+	+
Tumour size		+		
Tumour depth		+		
Anatomical location		+		
Surgical margin	+	+		
Local recurrence		+		+
Relapse-free interval				+
Liver metastases			+	+
Liposarcoma			+	

During the last years, a number of new molecular prognostic markers have been studied, such as Ki-67, P53, MDR1, MRP, Rb, ras, myc, MDM2, CDK4, GLI, etc. [30]. Although studies have described a correlation of these factors with the prognosis of soft tissue sarcomas, their prognostic value has not been clearly defined. Further data are needed to define whether they may replace some of the traditional prognostic factors. In the design of future clinical studies, these new prognostic markers should be taken into consideration.

The treatment of patients with advanced and metastatic soft tissue sarcomas is generally considered as palliative. However, 10–30% of patients achieving a complete response with surgery, chemotherapy, or both will be alive and disease-free at 5 years [3]. A 5-year survival of 8% of patients treated with doxorubicin-containing regimens has recently been described, and the majority of these patients experienced long-term survival afterwards [3]. Clinical response to first-line chemotherapy was the most significant parameter correlated to 5-year survival [3]. Consequently, the treatment of advanced soft tissue sarcomas cannot always be considered as consistently palliative, and the goal of future experimental

protocols could be to improve the *complete* response rate to chemotherapy or to treatment strategies with combined chemotherapy and surgery.

Conclusions

The treatment of soft tissue sarcomas is multidisciplinary and involves surgery, radiotherapy and chemotherapy. With a multidisciplinary organisation, improved imaging, better surgical techniques and adjuvant treatment, the primary treatment is now less extensive. Although there are multiple histological subtypes, for the purpose of treatment they are usually grouped under the heading of soft tissue sarcoma. However, an increasing number of the subtypes are likely to be handled differently from other soft tissue sarcomas such as GIST.

At present, there is consensus that the standard treatment of low malignant as well as superficial cutaneous/subcutaneous soft tissue sarcomas independent of malignancy grade is surgery. Similarly, there is consensus that the standard treatment of the major part of the high malignant soft tissue sarcomas is surgery combined with adjuvant radiotherapy. Currently, the effect of neoadjuvant and adjuvant chemotherapy has not been settled and awaits data from clinical trials before its adoption as a standard in clinical practice can be judged. However, in a number of centres, adjuvant chemotherapy is considered suitable for individual clinical use in selected patients with very poor prognostic factors. However, it is clear that if a benefit from adjuvant chemotherapy should be expected in the future, new treatment approaches should be developed for soft tissue sarcomas.

For the retroperitoneal tumours, there is consensus that the standard treatment is surgery and if possible with free resection margins. On the other hand, the effect of adjuvant radiotherapy and chemotherapy is not proven. It is also recommended that the standard treatment of intra-abdominal sarcomas should be the same as that of the extra-abdominal sarcomas. For patients with isolated lung metastases, it is recommended that the standard treatment is metastasectomy. In patients with concomitant local and lung disease, it is recommended that both the primary tumour and the metastases should undergo surgery according to the same criteria as that applied for each of the two individual settings. Resection of isolated metastases in other organs is currently not standard treatment and should primarily be used as part of clinical trials.

At present, the effect of systemic treatment of locally advanced or metastatic soft tissue sarcoma in *adult* patients is unsatisfactory, with few drugs being active. In addition, the treatment is often toxic and is usually given with palliative intent in many of the patients. At present, no drug combinations have demonstrated any clear advantage when compared with single agent doxorubicin. Therefore, single agent doxorubicin is considered the standard treatment for advanced soft tissue sarcomas. However, this strategy may change, and it is likely that some subgroups of patients should be treated with combination chemotherapy. Second-line chemotherapy should be regarded as investigational or suitable for individual clinical use in selected patients, and, if available, the patients should be offered participation in phase II studies testing new drugs.

There is a desperate need for new effective drugs for adult patients. It is hoped that the increasing knowledge on molecular biology in soft tissue sarcomas will help in this development of new effective drugs — a development that is underway. The effective treatment of GIST with imatinib mesylate is a good example that should be followed for other histological subtypes.

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