

Histology-driven chemotherapy of soft-tissue sarcoma

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Soft-tissue sarcomas are rare diseases with >50 subtypes. Surgery is the most important treatment in localized disease, sometimes combined with radiotherapy. Chemotherapy is used as palliation in advanced disease, sometimes also with a potential to decrease tumour size and eradicate micro-metastases, making meaningful surgery possible. The role of chemotherapy as adjuvant treatment in localized disease is not finally settled. Doxorubicin and ifosfamide are the two drugs with the best established response rates in soft-tissue sarcoma, and a combination of these drugs has been a 'gold standard' for several years. However, there is an emerging knowledge of the biology and sensitivity to treatment for different histological subtypes. New drugs such as gemcitabine, taxanes and trabectedin have been explored in several studies, showing promising results. Even if most studies have encompassed many different subtypes and were limited in size, knowledge related to specific treatment for different subtypes is emerging. Examples are trabectedin in liposarcoma and leiomyosarcoma, and taxanes in angiosarcoma.

Key words: chemotherapy, histological subtypes, soft-tissue sarcoma

background

Soft-tissue sarcomas (STS) are rare diseases encompassing <1% of all malignancies. More than 50 different histological subtypes of STS have been described, most of them very rare. Knowledge of the biological differences between subtypes, such as their genetics and natural history, has gradually increased over the years, and we also now understand more about the sensitivity to treatment of different subtypes. However, the heterogeneity of the subtypes has rarely been taken into account when performing clinical trials on treatment for STS. Our present knowledge is therefore mainly based on uncontrolled phase II studies or retrospective case series.

Most STS are localized in the extremities, especially in the legs, or on the trunk, but there are also STS localized in non-orthopaedic sites, e.g. uterus, retroperitoneum, thorax or head and neck. The most important treatment for all localized STS is radical surgery whenever possible. For orthopaedic sites, pre- or postoperative radiotherapy is demonstrated to decrease local recurrence [1, 2].

Chemotherapy has been widely used for decades in different situations in STS: (i) as palliative treatment in advanced cases; (ii) for down-staging, i.e. decreasing size to facilitate radical surgery of the primary tumour, lung metastases or, occasionally, metastases in other sites; and (iii) as adjuvant or neoadjuvant treatment in high-grade localized disease in combination with the local treatment of the primary tumour.

The most used chemotherapeutic drugs in all these situations, especially during later years, have been doxorubicin and ifosfamide, but especially in palliative situations many other drugs have been tested as second or further lines of

treatment. This has led to the observation of different sensitivities for different drugs or drug combinations between the more common subtypes. Formal evidence to guide first- or second-line treatment in different situations is, however, still awaited in most cases.

general sensitivity for chemotherapy

The most effective drugs, especially doxorubicin, have shown an ability to produce overall response (complete or partial) in advanced cases in the range of 20–30% [3], even if additional patients benefit minor responses or stable disease for a shorter or longer time. With the addition of more drugs, e.g. ifosfamide, in combinations, the overall response seems to be somewhat improved [4], but the effect on overall survival (OS) is uncertain, as discussed below.

In most cases the response is limited in time, but long-term survivors after only chemotherapy do exist, as shown in studies based on the EORTC database [5].

Some histotypes seem to be totally resistant, at least to the chemotherapeutic drugs available today, even if immunoactive drugs such as interferon or modern targeted drugs may have an effect in some cases. There is no evidence for the use of chemotherapy in, for example, gastrointestinal stromal tumours (GISTs) [6], extraskelatal myxoid chondrosarcoma [7, 8], clear cell sarcoma [9, 10] or alveolar soft part sarcoma [11].

Rather low sensitivity for chemotherapy is reported for, for example, epithelioid cell sarcoma, adult fibrosarcoma, haemangiopericytoma, and malignant peripheral nerve sheath tumour (MPNST), but that does not exclude that some patients with these variants may show response. This probability may increase by using drugs or combinations other than doxorubicin and ifosfamide.

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Intermediate sensitivity for chemotherapy seems to be present for most of the more common types of STS, such as liposarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma and angiosarcoma.

Some sarcomas more common in childhood and adolescence are in most cases clearly sensitive to multiagent combinations of drugs. This is true for extraskeletal Ewing sarcoma, rhabdomyosarcoma of embryonal and alveolar types, and desmoplastic small round cell tumour; the last of these has, nevertheless, a very poor prognosis. This group of tumours will not be discussed further in this review.

standard chemotherapy

Many chemotherapeutic drugs have been tested in STS with best single-agent response of ~20–30% demonstrated for doxorubicin [3]. A dose–response relationship has been demonstrated, with optimal response rates at dose levels between 75 and 90 mg/m² [12]. Epirubicin is an anthracycline analogue of doxorubicin, with supposed lower cardiotoxicity, but high-dose epirubicin has not been shown to be a useful alternative to standard dose doxorubicin in STS [13]. Another way to reduce the potential risk of cardiotoxicity using anthracyclines may be the use of pegylated doxorubicin, but since the effect of this preparation seems to be inferior to that of standard doxorubicin [14] this option may be reserved for patients with pre-existing cardiac disease who are otherwise excluded from anthracyclines or in specific situations as discussed below.

The only other drug with single-agent activity at the same magnitude is ifosfamide at doses of 9–11 g/m² [15]. Even if cardiac toxicity is absent with this drug, it may pose other problems such as renal or central nervous system (CNS) toxicity.

Many studies have investigated combination therapies, including doxorubicin and ifosfamide and/or other drugs, as reviewed recently [16]. In this review, three phase III studies were included comparing single-agent doxorubicin [17, 18], or doxorubicin + dacarbazine [19], with combinations including ifosfamide [18, 19] or the related drug cyclofosfamide [17]. A meta-analysis of these three studies showed that the combinations including ifosfamide/cyclofosfamide produced a significantly increased tumour response rate of 50% ($P = 0.009$), but there was no difference in OS after 1 year ($P = 0.76$). The toxicity was significantly increased in the combination arm, however. In the choice between alkylating agents, ifosfamide has been shown to be the more effective [20].

Based on these findings, the combination of doxorubicin and ifosfamide is recommended as standard therapy, especially when a good response would increase the possibility of surgery with curative intent, or when a good response is considered to benefit the individual patient, e.g. by decreasing disturbing symptoms. In other cases, doxorubicin alone is preferred if no other tumour-specific factors favour the combination. Such a factor could be the histological subtype as discussed further on.

To explore further factors identifying patients who may benefit from the addition of ifosfamide in first-line treatment, a retrospective analysis was recently performed on the large patient series from EORTC-STBSG [21]. In this analysis, the increased response rate but equal OS for regimens containing ifosfamide was confirmed. Predictive factor analysis showed

that patients with leiomyosarcoma did not benefit from ifosfamide, with a decreased OS ($P = 0.0247$). A trend towards better survival was seen for patients with liver metastases ($P = 0.0712$). Regarding response, a decrease was seen for both liposarcoma (significant) and leiomyosarcoma (non-significant), but an increase (non-significant) was demonstrated for synovial sarcoma when ifosfamide was added.

High-dose ifosfamide (9–12 g/m²) as single treatment may be effective as second-line treatment, even in patients initially treated with doxorubicin and ifosfamide in lower doses (~5 g/m²) [22–24].

Adjuvant treatment with doxorubicin with or without ifosfamide has been explored in many randomized studies, most of them small, and the results have been conflicting. In brief, the largest studies, performed by the EORTC soft-tissue and bone sarcoma group, have been negative [25, 26]. On the other hand, a large meta-analysis with the last published update including 1953 patients from 18 adjuvant trials demonstrated that the combination of doxorubicin and ifosfamide gave an absolute risk reduction for death of 11% [27]. Furthermore, another meta-analysis including one of the EORTC studies also showed a significant benefit for doxorubicin-containing adjuvant treatment for both 5-year disease-free survival (DFS) and OS [28]. Thus, it is still unclear whether to treat or not in the adjuvant setting. The answer may be to select patients with identified increased risk for metastatic disease based on biological tumour-related criteria; an option currently being investigated by the Scandinavian Sarcoma Group.

other drugs and combinations

dacarbazine and temozolomide

Dacarbazine is an old alkylating agent approved for use in STS in many countries. It has a modest activity as a single agent, with a response rate of 17% [29, 30], and has mostly been used in multidrug combinations as MAID (mesna, doxorubicin, ifosfamide and dacarbazine) or CyVADIC (cyclofosfamide, vincristine, doxorubicin and dacarbazine). Its role in this context is not proven, but when single-agent doxorubicin was compared with CyVADIC an increased response for the combination was shown, where dacarbazine may have contributed [17]. Dacarbazine has also been used as second- or further line therapy with some effect [31].

Temozolomide is an oral analogue of dacarbazine, mainly used in brain tumours, which also has been explored in STS with somewhat conflicting results. A study from EORTC did not find a meaningful effect as second-line treatment [32], whereas other studies have shown some responses and disease stabilization in leiomyosarcoma especially of uterine origin [33–36]. Another possible use for this drug could be in combination with bevacizumab in haemangiopericytoma/solitary fibrous tumour [37].

gemcitabine

Gemcitabine is a pyrimidine antimetabolite characterized by a favourable toxicity profile and used for several malignancies, such as carcinoma in the pancreas and bladder. Its effect in STS was initially investigated ~10 years ago in several small phase II

studies, showing only modest activity with partial remissions (PRs) in single patients, mostly those with leiomyosarcomas [38–40]. A somewhat larger study from the M.D. Anderson Cancer Center comprised 17 patients with gastrointestinal (GI) leiomyosarcomas and 39 other STS patients [41]. In the GI group no responses were found; these cases were probably all GISTs. In the other group, however, seven PRs were observed and, interestingly, among them there were four out of 10 leiomyosarcomas. The three remaining PRs occurred in one angiosarcoma, one malignant fibrous histiocytoma (MFH) and one unspecified sarcoma.

Apart from the verified responses, disease stabilization for a shorter period has also been demonstrated in some of these studies, also confirmed by later reports [42, 43]. One study explored gemcitabine as first-line therapy in advanced STS with rather disappointing results; 7% PR and 20% stable disease (SD) [44].

The promising effect of gemcitabine in some studies, especially with regard to leiomyosarcomas, has prompted studies with combinations including this drug. This has led to the development of the now very common combination of gemcitabine and docetaxel described below.

taxanes

Paclitaxel has shown a convincing activity in human immunodeficiency virus (HIV)-associated Kaposi's sarcoma [45, 46]. Several reports have also demonstrated that classical Kaposi's sarcoma responds to the taxanes docetaxel [47] or paclitaxel [48–50].

A high response rate for paclitaxel in angiosarcoma of the scalp or face [51] has shown this treatment to be a reasonable first-line option, and a later study showed that a similar effect is achieved by docetaxel [52]. Other angiosarcomas also respond well to paclitaxel [53] or docetaxel [54, 55]. Radiation-induced angiosarcomas most often occur in the breast, and in advanced cases good treatment options seem to be offered by docetaxel [56] or paclitaxel [57].

Paclitaxel has also been explored for other STS with some activity demonstrated in first-line treatment [58], but without a clear effect in pre-treated patients [59, 60]. In previously treated leiomyosarcoma of the uterus a moderate efficacy has been shown [61].

gemcitabine and docetaxel

The combination of gemcitabine and docetaxel, both with modest activity in STS, has been investigated in different STS, and promising effects have been found, especially for leiomyosarcoma, but to a certain extent also for other histiotypes [62–64].

A randomized trial compared single-agent gemcitabine in fixed dose with a lower fixed dose gemcitabine combined with docetaxel [65]. The combination produced better progression-free survival (PFS) and OS compared with gemcitabine alone. In the combination arm, response or disease stabilization for at least 24 weeks was observed in eight out of 29 patients with leiomyosarcoma, in seven out of 11 patients with a high-grade pleomorphic sarcoma and in two out of 3 patients with pleomorphic liposarcoma, whereas other histiotypes responded less well.

The potential specific sensitivity for gemcitabine in leiomyosarcomas has led to investigations limited to such tumours of uterine origin, and very promising results have been achieved both in first-line [66] and in second-line treatment [67]. Furthermore, an adjuvant phase II study with the same combination indicated an improved 2-year PFS superior to historical rates [68].

Vinca alkaloids

This family of antimetabolic drugs has also been explored in STS, vincristine as early as in the 1960s. As a single agent its activity seems to be very limited, with a possible exception for paediatric rhabdomyosarcoma [69]. Nevertheless, its use in combinations as CyVADIC was established as a standard in the late 1970s following US studies with very promising responses [70]. Later on, the efficacy of vincristine in adult STS was questioned, and its use has been abandoned. However, some studies indicate effects in some patients treated with other *Vinca* alkaloids such as vindesine [71] or vinorelbine [72]. Vinorelbine in combination with gemcitabine has been associated with meaningful disease control, also including one patient with a high-grade pleomorphic sarcoma achieving a complete remission lasting for >1 year [73].

trabectedin

Binding of the DNA minor groove is the mechanism of action for the marine-derived drug trabectedin, making it the first compound in a new class of chemotherapeutic drugs. Intensively explored in many malignant diseases, it was initially considered of specific interest in STS based on promising results in phase II studies in pre-treated patients showing rather low response rates, but stabilization of disease in several patients and an OS of ~1 year [74–76]. Since a somewhat superior efficacy was indicated for liposarcomas and leiomyosarcomas in these studies, a randomized multicentre phase II study including these histiotypes was performed comparing two dose schedules: 1.5 mg/m² in 24 h every third week and 0.58 mg/m² in 3 h every week for three weeks out of four. A statistically significant benefit was demonstrated for the schedule with 24 h infusion every third week, with a median time to progression of 3.7 versus 2.3 months, and a median PFS at 6 months of 35.5% versus 27.5% [77]. Based on these results, trabectedin was approved in Europe as second-line monotherapy for STS in 2007.

Tumour response has been noted in several different histological subtypes, but the most marked sensitivity has been seen in liposarcoma and leiomyosarcoma, followed by synovial sarcoma. Myxoid liposarcoma seems to be especially sensitive to trabectedin, which recently was verified in a single-institution series from Milan with a response rate of 50% and a median PFS of 17 months [78].

The combination of trabectedin and doxorubicin has been explored in a dose-finding phase I study in 41 patients [79]. Five patients (12%) achieved a PR (two myxoid liposarcoma, one other liposarcoma, one leiomyosarcoma and one with sarcomatoid carcinoma) and 37% maintained stable disease for >6 months. Median PFS was 9.2 months.

etoposide

The topoisomerase II inhibitor etoposide in short-duration infusions has not shown convincing activity in studies in STS, either as a single drug [80] or in combination with ifosfamide [81, 82]. However, a randomized study in small cell lung cancer has shown a dramatic schedule dependency of this drug, favouring long-duration continuous infusions [83]. Based on that observation, the Scandinavian Sarcoma Group has treated advanced STS with 600 mg/m² given continuously for 72 h followed by ifosfamide 1.5 g/m² per day for 3 days, supported by granulocyte colony-stimulating factor (G-CSF); both drugs were dose escalated if haematological toxicity so permitted [84]. In spite of a relatively low dose of ifosfamide, an overall response of 42% (11% CR, 31% PR) was noted in this group of untreated patients with metastatic or locally advanced disease. A marked dose–response association was observed.

The combination of etoposide with carboplatin induced remissions in one study of MPNST refractory against first-line treatment [85]. Pre-clinical data indicate elevated levels of topoisomerase IIa in MPNST, and it is possible that etoposide is especially useful in this histiotype.

This concept is further investigated in an ongoing trial of the US group SARC (Sarcoma Alliance for Research through Collaboration). Early results speak in favour of a possible effect of the combination of ifosfamide and etoposide in MPNST.

Etoposide has also been given in tablet form, but as a single drug at doses of 50 mg/m² daily it has shown no or low efficacy [86, 87]. In per oral combinations, e.g. with trofosfamide, it may be more active, as discussed below.

trofosfamide

Trofosfamide is an oxazaphosphorine with ifosfamide as the main metabolite, and with generally low toxicity. It is given as tablets, continuously or over longer periods, so-called metronomic use, which is shown to sharply reduce endothelial progenitor cells that may participate in tumour angiogenesis [88]. Some phase II studies have shown activity in heavily pre-treated patients with advanced STS, predominantly disease stabilization but also some formal responses [89–91]. Another trial used the drug as maintenance after partial remission or disease stabilization and seemed to demonstrate a prolonged PFS and OS compared with patients without maintenance [92]. An ongoing German randomized phase II trial is comparing oral trofosfamide with intravenous doxorubicin in metastatic STS.

Furthermore, the German Cooperative STS study (CWS) recommended trofosfamide as maintenance therapy in combination with oral etoposide and idarubicin after aggressive chemotherapy in children with STS. The combination of etoposide and trofosfamide has been used in Scandinavia as palliation for patients failing single-agent trofosfamide. Results are often encouraging, but have not yet been published.

drug choice per histopathological subtype

The evidence-based knowledge of the optimal chemotherapeutic drugs to use in specific STS histiotypes is

hampered by the rarity of all these variants, and the following recommendations must therefore be interpreted with caution. However, in spite of lacking randomized trials for most situations, there is now good reason for not always using ‘the golden standard’ of doxorubicin ± ifosfamide in STS.

Certainly, issues other than histology also influence our choice of treatment. Age, co-morbidity and expected tolerance of side effects may all be of importance, with less toxic regimens to be preferred for more vulnerable patients. The purpose of the treatment is also of importance, and in patients where surgery with curative intent may be possible later, the regimen with best possible response should be used. Furthermore, for some patients, options other than conventional chemotherapy may be available. Such options may be chemotherapy with hyperthermia, showing impressive results in a randomized study [93], isolated limb perfusion [94, 95] or targeted drug therapy. In the following recommendations, none of these factors has been taken into account.

The following recommendations only include specific options and advice for some of the more common histiotypes, and do not exclude the use of the other options mentioned above.

leiomyosarcoma

non-uterine. No drug has been shown to be superior to doxorubicin in this common entity, but ifosfamide should probably be avoided as discussed above [21]. As second line, there are two good alternatives: (i) gemcitabine + docetaxel [62–65]; and (ii) trabectedin [77].

uterine. Gemcitabine + docetaxel seems to be the most effective option in this entity [86, 87] and may be regarded as first-line treatment. As further line treatments doxorubicin and trabectedin may be used, and temozolomide may also be worth trying.

liposarcoma

Doxorubicin is regarded as first-line treatment. Whether to add ifosfamide or not is an open question in the light of the recent EORTC survey indicating a somewhat lower response rate for the combination [21]. Since the main reason to add ifosfamide in the treatment of STS in general is the possibility of achieving a better response, liposarcoma may be an entity favourably treated with doxorubicin only, as described for leiomyosarcoma. Trabectedin seems to be a reasonable second-line choice [77]; in myxoid liposarcomas it may even be more effective than doxorubicin for many patients [78].

synovial sarcoma

Doxorubicin + ifosfamide is strongly recommended for this entity, which seems to be the histiotype which benefits most from ifosfamide [21]. The concept of using high-dose ifosfamide as a single drug even after resistance to the combination, which has been successful in several studies [22–24], may be especially well suited for this entity. Some patients with synovial sarcoma also seem to benefit from trabectedin [76, 96].

angiosarcoma

Taxanes (paclitaxel or docetaxel) seem to be the drugs of first-line choice [51–57], reserving doxorubicin + ifosfamide for second-line treatment.

undifferentiated pleomorphic sarcoma/MFH

Doxorubicin + ifosfamide is the main alternative, assuming that the findings of the superiority of this combination for STS in general is also true for this common entity. If the impressive effect of gemcitabine + docetaxel found in one study [65] is verified, this could be an alternative.

MPNST

Doxorubicin + ifosfamide is regarded as the standard option even if this histiotype probably has a rather low sensitivity for this combination. Ongoing and further studies will define the potential role of etoposide.

haemangiopericytoma/solitary fibrous tumour

This entity seems to respond poorly to chemotherapy in general. A promising effect, however, has been noted for the combination of temozolamide and bevacizumab [37].

Kaposi's sarcoma

Taxanes and pegylated doxorubicin have both shown remarkable effects in HIV-associated and classical Kaposi's sarcoma, and should be used as first- and second-line treatments when systemic therapy is needed.

other types

Infrequent or no responses to chemotherapy are reported for several rare histiotypes, e.g. alveolar soft part sarcomas [11], extraskeletal myxoid chondrosarcoma [7, 8] and clear cell sarcoma [9, 10], even if divergent good results have been reported in rare case reports [97]. Other variants not specifically mentioned here, e.g., fibrosarcoma, myxofibrosarcoma, and pleomorphic rhabdomyosarcoma, may be sensitive to chemotherapy, and no drugs have been demonstrated superior to doxorubicin + ifosfamide for these entities.

future development

More controlled randomized trials are needed to tailor therapy for patients with different STS subtypes in the future. In parallel, we may well obtain tools other than the histiotype, such as molecular markers or other biological or patient-related predictors, to lead us in this tailoring. Furthermore, new drugs, new combinations and new dose schedules must be explored to optimize therapy and, of course, this is a process without an end. One interesting field where very little has been done so far is the option of combining classical chemotherapeutic drugs with modern targeted therapy.

conclusions

Even if doxorubicin, with or without ifosfamide, still must be regarded as the main chemotherapeutic drug in most cases of

STS, emerging knowledge indicates that other drugs may be defined as the first- or second-line choice for certain histiotypes. The most important of these drugs seem to be trabectedin, gemcitabine and taxanes, but others, such as etoposide, dacarbazine and temozolamide, may play an important role. Collaborative efforts with preferably randomized trials are needed to increase our knowledge of the best available treatment for these rare tumours.

disclosure

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