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Controversies and consensus of neoadjuvant chemotherapy in soft-tissue sarcomas

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ABSTRACT

Together with surgery and radiotherapy, systemic treatment with cytotoxic chemotherapy and molecular targeted agents is one of the main therapeutic pillars in the treatment of soft-tissue sarcomas and is the mainstay of treatment in patients with advanced or metastatic disease. Unlike other more common malignancies such as breast and colorectal cancer, the role of chemotherapy when used in the adjuvant setting in soft-tissue sarcomas is less well defined. Results from prior studies have been conflicting, in part due to the heterogeneity and rarity of the disease, and large-scale meta-analysis has been performed to address this issue. Neoadjuvant chemotherapy, defined as the use of chemotherapy before definitive treatment with surgery or radiotherapy, has distinct theoretical and practical advantages, which can potentially be beneficial to the patient. However, the currently available evidence to support its use is even more scarce. In this review article, we describe the current established data behind the use of adjuvant chemotherapy in selected patients with localised soft-tissue sarcomas and, through extrapolation of available data, discuss the potential role of it when used in the upfront setting.

INTRODUCTION

Soft-tissue sarcomas (STSs) are a group of rare malignancies that make up only 1%–2% of all cancers in adults while accounting for a higher proportion of 7% of all malignancies in children. The challenges of treating STSs by far are due to the heterogenous nature of this group of diseases, which can arise from any extra-skeletal connective tissue, including the peripheral nervous system. Presently, there are more than 70 different histological types.[1] To complicate the matter even more, although STSs typically occur in the extremities and more commonly in the lower limbs, they can arise from any part of the body. This large permutation of tumour location and tumour histology creates a need for a multi-disciplinary approach in the treatment of STSs.

The major therapeutic objective for all patients with STS is to achieve (1) long-term survival and (2) avoidance of recurrence, while at the same time (3) maximising function and (4) minimising morbidity.

The standard of care for localised disease in adults has been wide surgical resection often combined with radiotherapy (RT), but the question of using adjuvant chemotherapy to improve survival rates in high-grade STS has been a subject of controversy. Moreover, while data to support the use of neoadjuvant chemotherapy before definitive surgery or neoadjuvant radiation are even more sparse, there remains a clear theoretical advantage of administration of a systemic treatment to eradicate possible distant micro-metastases before the definitive localised therapy, especially in high-risk patients, as evidenced by our routine use of neoadjuvant chemotherapy for locally advanced breast cancer as well as neoadjuvant concurrent chemo-radiation for rectal cancer. This review serves to discuss the controversies and possible consensus of this treatment approach.

ADJUVANT CHEMOTHERAPY IN ADVANCED STS OF ADULTS

While there is a clear role for adjuvant and neoadjuvant chemotherapy in paediatric and young adult patients with rhabdomyosarcomas (RMSs), Ewing's sarcomas (ESs) and osteosarcomas (OSs) and is now considered an inalienable part of the treatment paradigm of these diseases, the role of adjuvant chemotherapy in adults with non-RMS, non-ES and non-OS advanced STSs have been under scrutiny for generations of oncologists. Naturally, the clear improvements in disease-free and overall survival of patients with RMS, ES and OS who have received systemic chemotherapy are due to the 'double-edge sword' biology of these specific tumours, which renders them highly aggressive with a significant risk of metastases and yet exquisitely sensitive to multi-agent chemotherapy. As the efficacy of systemic chemotherapy in other high-grade sarcomas is less pronounced, as evidenced by lower response rates to treatment in the metastatic setting, it is not surprising that

data to support its use in the adjuvant setting are even less compelling.

Given the heterogenous nature of STS with differing tumour biologies, sensitivity to RT and chemotherapy and metastatic potential, the belief that adjuvant chemotherapy is effective for all STSs is an ineffectual approach. Throughout the years, specific enriched subgroups of patients with STS who are considered 'high-risk for recurrence' in terms of tumour size and histological grading, location of tumour and completeness of surgical resection have been selected and studied in over a dozen clinical trials with an aim to establish a survival advantage in patients who have been offered cytotoxic chemotherapy after surgery than those who have not. Most of the first-generation trials in the 1970s and 1980s involved the use of anthracyclines such as doxorubicin and epirubicin as a single agent or in combination with an alkylating agent such as dacarbazine. Results of these trials have been varied. Of the 14 trials published during that period, two trials showed a significant survival advantage in patients who have been treated with chemotherapy, whereas 3 trials showed the reverse, suggesting that the use of adjuvant chemotherapy could have been detrimental to patients' survival. The remainder showed no difference in outcomes between the treatment groups.

META-ANALYSES ADDRESSING THE ROLE OF ADJUVANT CHEMOTHERAPY IN STS

The Sarcoma Meta-Analysis Collaboration (SMAC) performed a quantitative meta-analysis of updated data from individual patients from available randomised trials to assess whether adjuvant chemotherapy could indeed improve survival and recurrence-free intervals and whether chemotherapy was differentially effective in different patients' demographics, histology of disease, extent of resection and use of RT .[2] At the time of initial reporting with a median follow-up of 9.4 years, 1568 patients from the 14 trials of doxorubicin-based adjuvant chemotherapy were included. Patients treated with chemotherapy had significantly better local recurrence-free survival (HR 0.73; 95% CI 0.56 to 0.94) and distant recurrence-free survival (HR 0.70, 95% CI 0.57 to 0.85). Overall recurrence-free survival was also significantly better, with HR for any recurrence at 0.75 (95% CI 0.64 to 0.87), translating to an absolute 6%–10% benefit of recurrence-free survival at 10 years. There was a trend toward improved overall survival that favoured chemotherapy, but it was not statistically significant (HR for death 0.89, 95% CI 0.76 to 1.03). There was no consistent evidence of any improvement according to age, sex, stage, site, grade, histology, extent of resection, tumour size or exposure to RT . There was a consistent evidence of a beneficial effect on survival in the subset of patients with extremity and truncal sarcomas. Among these patients who received adjuvant doxorubicin-containing chemotherapy, there was a statistically significant benefit for chemotherapy (HR for death 0.80, P=0.029), which translated into a 7% absolute benefit in overall survival at 10 years. Proponents applauded the individual patient data approach of this meta-analysis, which would remove any deficiencies of individual studies that had an inadequate sample size, heterogeneity of reported outcomes and variable exclusion of patients, although critics cautioned on the possible dilution of benefits of chemotherapy as tumours of other locations aside from extremities, as well as low-grade (5%) and unknown-grade (28%) tumours, were included in the analysis. More importantly, only one of the trials in the meta-analysis used ifosfamide, which was becoming an apparent important player in systemic therapies for advanced/metastatic STS, in combination with doxorubicin.

Second-generation randomised studies in the early 1990s incorporated ifosfamide in combination with anthracyclines in the adjuvant setting. Moreover, the use of granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis allowed for more intensive regimens. Prior suggestion of survival benefit for extremity and truncal STS has also led to the focus of studying the role of adjuvant chemotherapy in patients with tumours of these two locations. In total, four additional randomised trials were performed,[3–6] and two suggested possible survival benefit of adjuvant chemotherapy. An SMAC meta-analysis update was performed in 2008,[7] which now included a total of 18 randomised trials of 1953 patients with localised and resectable STS between 1973 and 2002. Five of these 18 trials used doxorubicin plus ifosfamide, while others employed an anthracycline alone or in combination with other agents. Compared with the original SMAC analysis, adjuvant chemotherapy continued to demonstrate a similar trend in RFS improvement. In terms of overall survival benefit, however, there was now evidence of significant improvement in overall survival in patients treated with ifosfamide and doxorubicin combination (OR for death 0.56; 95% CI 0.36 to 0.85), in contrary to patients treated with doxorubicin alone, which did not meet statistical significance (OR for death 0.84 (95% CI 0.68 to 1.03)). A caveat to this finding is the fact that over 340 patients of the EORTC 62931 study,[6] which was the largest single study of adjuvant chemotherapy in terms of number of patients enrolled to date and also failed to demonstrate a role for adjuvant chemotherapy, were not included. This trial did include a heterogenous group of high-risk and low-risk patients, as well as employed a relatively low dose of ifosfamide, which meant it could not have been fairly compared with other studies.

The current consensus among practising clinicians for adjuvant chemotherapy in STS is that patients should be discussed and assessed in a multi-disciplinary setting on a case-by-case basis. Patients' factors including, but not limited to, performance status and co-morbidities, as well as disease factors such as disease location, tumour size and histological subtype, should be considered and balanced with potential risks of treatment related toxicities, as well as possible quality-of-life impairments. For patients who elect to proceed with adjuvant chemotherapy, the

use of both ifosfamide and an anthracycline, in combination with MESNA, is recommended with a category 1 recommendation in the National Comprehensive Cancer Network guidelines.[8]

THEORETICAL AND PRACTICAL ADVANTAGES OF ADOPTING A NEOADJUVANT APPROACH

The use of chemotherapy prior to definitive surgical treatment has been studied and adopted most widely in the realm of loco-regionally advanced breast cancer. This was based on multiple prospective randomised clinical trials involving thousands of women that have clearly demonstrated that early systemic treatment of micro-metastatic breast cancer improves survival.[9] These data led several investigators to assess whether adjuvant systemic therapy might be even more effective if delivered before surgery.

There are hypothetical and practical reasons that neoadjuvant chemotherapy might be even more beneficial than conventional postsurgical adjuvant chemotherapy. First, the presumed mechanism of improved overall survival for adjuvant chemotherapy is avoidance of development of genetic heterogeneity and associated resistance, with progression of the cancer. Thus, one might hypothesise that avoiding the postoperative delay in initiation of therapy might even further improve overall survival in patients treated with neoadjuvant chemotherapy. Alternatively, surgery itself might promote local or distant relapse due to release of massive amounts of wound-healing cytokines, and therefore, neoadjuvant chemotherapy might serve to eliminate micro-metastatic deposits before exposure to this massive release of cytokines. Second, there may be a role for downstaging of tumours to facilitate and optimise the surgical approach with neoadjuvant chemotherapy. For example, patients with locally advanced 'inoperable' cancer might become surgical candidates. This is of importance in patients with tumours in the limbs in which an optimal control and shrinkage of the tumours can result in a limb-sparing surgery and can significantly improve patients' function and postoperative quality of life. This is already a well-adopted approach in the management of high-grade OSs.

Aside from the theoretical benefits highlighted above, neoadjuvant chemotherapy can also address practical considerations. In the era of custom-designed mega-prosthesis for limb-sparing surgery and complex conformal RT techniques being employed in RT to reduce treatment-related morbidities, the planning processes of these inalienable modalities of treatment are understandably prolonged. The planning process for neoadjuvant chemotherapy is relatively simple, and if the patient is of a good performance status, with satisfactory haematological and biochemical reserves, as well as normal baseline cardiac function (as there is a potential risk of anthracycline-induced cardiomyopathies), the use of neoadjuvant chemotherapy can be employed as a 'stop-gap measure' before or during the RT-planning or surgical-planning processes. Even without significant shrinkage of the tumours in question, patients often derive clinical benefit from neoadjuvant chemotherapy in terms of symptoms control, including pain relief. Improvement in symptoms prior to the start of the next treatment modality will likely improve treatment compliance. Performance status of patients may also be better in the preoperative than postoperative setting. Given the beneficial evidence of the ifosfamide and anthracycline combination over a single-agent approach, patients with better performance status will likely be more compliant to this more toxic treatment, and this indirectly can help ensure an adequate dose intensity of treatment. Giving chemotherapy before surgery also removes the risk of having postoperative perichemotherapy wound complications that could also negatively impact treatment intensity and compliance.

WHAT ARE THE AVAILABLE EVIDENCE FOR NEOADJUVANT CHEMOTHERAPY IN STS?

While there appears to be a list of compelling theoretical and practical advantages of neoadjuvant chemotherapy in STS, as opposed to in the postoperative setting, there is a surprising lack of evidence specifically addressing the role of chemotherapy when used in a neoadjuvant manner. Gortzak and colleagues[10] were the only group in recent literature that specifically studied the use of neoadjuvant chemotherapy. In this study, 150 patients, with high-risk patients with STS defined by having (a) primary tumours ≥8 cm of any grade or <8 cm but grades II–III, (b) grade II–III locally recurrent tumours after prior resection or (c) grade II–III tumours with inadequate prior surgeries performed, were randomised to either resection alone or be given three cycles of neoadjuvant doxorubicin (50 mg/m^2) and ifosfamide (5 g/m^2) before surgery. Unfortunately, this study was closed early due to slow accrual, and it was concluded that the 5-year disease-free survival (DFS) and overall survival was similar in both treatment groups (52% for no chemotherapy and 56% for chemotherapy arms, SE 7%; and 64% and 65% (SE 7%), respectively). The use of doxorubicin and ifosfamide at these doses, however, did not compromise subsequent treatment with surgery, with or without RT. The study confirmed the fact that complete and partial response rates to neoadjuvant chemotherapy is what is expected in the metastatic setting, with an objective response rate of 29% in the chemotherapy arm. Major criticisms of this study include: (1) the definition for high-risk patients in this study is not universally accepted; (2) patients with a large variety of histologies with varying chemo-sensitivities from fibrosarcomas to RMSs were included in the study; and (3) the dosage of doxorubicin and ifosfamide used in this study would in hindsight be considered underdosed, which may potentially have a negative impact on the possible magnitude of benefit of neoadjuvant chemotherapy.

EXTRAPOLATING FROM OTHER RELEVANT CLINICAL TRIALS

Without more recent and robust neoadjuvant chemotherapy data, we can extrapolate from findings obtained by the Italian and Spanish Sarcoma Groups' clinical trial that addressed the issue of perioperative chemotherapy. Between January 2002 and April 2007, Gronchi and colleagues[11] studied over 300 high-risk patients with STS to show that three cycles of preoperative chemotherapy were not inferior to five cycles of perioperative chemotherapy (three cycles of preoperative followed by two cycles of postoperative) in terms of patients' survival. The overall survival of patients within this study also compared favourably with predicted data based on the Memorial-Sloan Kettering and Milan prognostic nomograms. The chemotherapy used is what we would now consider an adequate dose with epirubicin at 120 mg/m^2 and ifosfamide at 9 g/m^2 on 3-weekly cycle with growth factor support. This non-inferiority stood the test of time as confirmed by updated results from a 10-year follow-up published more recently.[12] The objective response rate to chemotherapy was 25%, but minor responses that would otherwise have not satisfied as a response as per Response Evaluation Criteria In Solid Tumors (RECIST) or Choi Criteria were seen in an additional 41%. It can be argued that these minor responses can have a significant impact on the ability to perform limb-sparing surgery, and this is evidenced by <10% of patients with high-risk extremity tumours requiring primary amputations in both study arms. From these results, it is safe to say that it is indeed feasible to give chemotherapy before surgery, which can result in an improvement in survival compared with historical series, and that in the setting of preoperative neoadjuvant and postoperative adjuvant chemotherapy, the latter's influence on survival is trumped by the former.

Histology was shown to be a significant prognostic factor for overall survival, with patients with undifferentiated pleomorphic sarcomas (UPSs) having the most favourable outcome and leiomyosarcoma (LMS) portending the worst. This trend was observed, although not statistically significant, also for PFS. UPS consistently demonstrated a higher response rate by both RECIST and Choi Criteria than LMS, which suggests that there is indeed a possible benefit of adjuvant chemotherapy in some histologies. On the other hand, benefit for histology-tailored versus standard neoadjuvant chemotherapy could not be shown in the ISG-STS-1001 international, open-label, randomised, phase III, multi-centre trial conducted in 287 patients with high-risk (deep seated, high grade or ≥5 cm) extremity or truncal STS. Patients with five different histological subtypes of STS were randomised 1:1 to standard chemotherapy of full-dose epirubicin and ifosfamide or histology-tailored therapy (trabectedin for high-grade myxoid liposarcomas (MLPSs) (n=64), high-dose ifosfamide alone for synovial sarcoma (n=70), etoposide plus ifosfamide for malignant peripheral nerve sheath tumour (n=27), gemcitabine plus dacarbazine for leiomyosarcoma (LMS) (n=28) and gemcitabine plus docetaxel for UPS (n=97) (table 1)). In an interim analysis at a median follow-up of 12.3 months, the projected DFS at 46 months was 62% for standard chemotherapy and 38% for histology-specific therapy (HR for DFS 1.95, 95% CI 1.12 to 3.19). In exploratory subset analysis, the difference in DFS favouring standard therapy was seen in all histological subtypes, with the exception high-grade MLPS, in which DFS was similar (HR 1.03, 95% CI 0.24 to 4.39). A more worrying finding was the fact that distant metastases accounted for a large proportion of DFS failures, which is in contradiction to the initial purpose of prescribing chemotherapy for these individuals in the first place. The design of this trial has been called into question, as the choice of the varying histology-specific regimens used in trial was based on regimens from prior reports that were described as showing promising activity in these specific histologies. There was no conformity as to which setting these histology-specific regimens were used previously. The variety of situations included neoadjuvant, inoperable/metastatic and based on historical data and subsequent modelling and nomogram analysis.[13–17] The choice of three cycles of neoadjuvant epirubicin and ifosfamide was based on the prior short, full-dose adjuvant chemotherapy trial as described earlier, but there are no studies that addressed whether three cycles of the histology-tailored chemotherapies that consisted of different cytotoxic agents may have equivalent pharmacokinetics or pharmacodynamic effect. The overall duration of treatment of only three cycles of chemotherapy, as opposed to the completion of more cycles in patients with responding or stable disease in patients treated in the inoperable or metastatic setting, may also affect the magnitude of any survival impact. To date, a histology-driven approach to neoadjuvant chemotherapy can only be considered as experimental, and until further data become available, the standard approach of full-dose ifosfamide and an anthracycline is advised across various histological subtypes.

OUR APPROACH TOWARDS THE USE OF NEOADJUVANT CHEMOTHERAPY IN STS

A multi-disciplinary team discussion is essential for all patients embarking on neoadjuvant treatment. Without clear evidence to support the widespread use of neoadjuvant chemotherapy in patients with STS, we believe that presently, neoadjuvant chemotherapy can be considered in selected patients on a case-by-case basis. Our current practice is to consider neoadjuvant chemotherapy in patients who have high-risk tumours, as defined as large, high grade and deep seated to deep fascia, with relatively chemo-sensitive histologies, who are (a) presently symptomatic and can benefit from a rapid relief of symptoms and/or (b) whom we would consider giving adjuvant chemotherapy to postoperatively anyway. In this situation, we feel that we are bringing a preplanned treatment option earlier and in doing so can hopefully allow subsequent treatment modalities to also reap from the benefits

Table 1 Distribution of histologies and treatment regimens in ISG-STS-1001 trial

Histology	Standard regimen	Histology-tailored regimen	Rationale/reference
Myxoid LPS (n=65 (23%))	Epirubicin 120 mg/m^2+IFX 9 g/m^2, Q21d	Trabectedin 1.3 mg/m^2 intravenous infusion, Q21d	n=23, open-label single-arm neoadjuvant setting PR: 24%; SD 76%; pCR 13% (Gronchi *et al*)[14]
LMS (n=28 (10%))		Gem 1800 mg/m^2 on D1 over 180 min+DTIC 500 mg/m^2, Q14d	n=113, open-label, randomised, previously treated advanced/metastatic setting ORR (PR+SD) 49% in advanced patients, median PFS 4.2 months vs 2.0 months in Gem+DTIC vs DTIC alone (Garcia-del-Muro *et al*)[15]
SS (n=97 (34%))		IFX 14 g/m^2 over 14 days via pump, Q28d	Preoperative nomogram supporting patients with SS treated with IFX-containing therapy had better DFS in the first 3 years than those who did not receive IFX (Canter *et al*)[17]
MPNST (n=70 (24%))		Etoposide 150 mg/m^2 D1+2+3 and IFX 3 g/m^2 D1+2+3, Q21d	Two cycles of IFX+ADR followed by two cycles of IFX+etoposide in metastatic/inoperable chemo-naive MPNST appeared to have higher rates of response (SARC006 trial* —Widemann *et al*)[16]
UPS (n=27 (9%))		Gem 900 mg/m^2 over 90 min D1+D8 and docetaxel 75 mg/m^2 on D8, Q21d	n=119, open-label, randomised, P+1 phase II of Gem+docetaxel vs Gem alone in metastatic patients. 2:1 randomisation. Total patients with UPS: 19 (n=8 in Gem arm, n=11 in Gem+docetaxel arm) CBR (CR+PR+SD≥24 weeks) in 64% with Gem+docetaxel vs 33% Gem alone in patients with MFH/UPS (Maki *et al*)[13]

*Trial terminated before completion due to slow accrual. Not published: data are only available in abstract form.
CBR, clinical benefit rate; DFS, disease-free survival; DTIC, dacarbazine; Gem, gemcitabine; IFX, ifosfamide; LMS, leiomyosarcoma; LPS, liposarcoma; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour; ORR, objective response rate; pCR, pathological complete response; PR, partial response; SD, stable disease; SS, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma.

of chemotherapy. On the contrary, (c) in patients whom we feel would benefit from adjuvant chemotherapy but at the same time knowingly will be at a high risk of chemotherapy postoperatively (eg, definitive surgery will entail a nephrectomy), we would also discuss within the multi-disciplinary team and consider its use. Our preference is that for patients whom both neoadjuvant chemotherapy and neoadjuvant RT are planned for; neoadjuvant chemotherapy should precede RT mainly due to the treatment logistics involved. A separate group of patients whom we routinely administer neoadjuvant chemotherapy to are (d) those with small volume distant metastases on presentation or equivocal radiological findings of distant metastases, in whom we would still consider radical definitive localised therapy at a later juncture. Regardless of the indication, a prerequisite for neoadjuvant chemotherapy is that the patient must be of reasonable performance status and possess adequate haematological and biochemical reserves to receive ifosfamide plus an anthracycline. Regular imaging during neoadjuvant treatment must be preplanned and readily available to monitor the treatment progress, as it is imperative that patients who are obviously refractory to systemic treatment should stop chemotherapy and proceed with the next planned treatment modality. For patients with either responding disease or disease stabilisation with improvement of symptoms, our practice is to complete the full course of chemotherapy.

CONCLUSIONS

To rationalise the use of neoadjuvant chemotherapy in STS, there is a need to prospectively identify patients who will likely benefit the most. Tumour factors including tumour histology, which dictates tumour biology as well as sensitivity to chemotherapy, size and location of the tumour, in association with patients' factors including presence or absence of medical co-morbidities that may render the use of chemotherapy hazardous, are all likely to influence any survival advantages or detrimental effects of a neoadjuvant approach. There is an urgent need for the establishment of robust predictive biomarkers towards neoadjuvant chemotherapy. The recent advancement of functional imaging and radiomics may provide us with an early insight into how initial cycles of neoadjuvant chemotherapy are affecting tumour growth and may allow us to select out patients who shall continue with further cycles of neoadjuvant chemotherapy in the face of early response versus abandoning neoadjuvant chemotherapy and proceeding directly to surgery and/or RT when there is evidence of tumour refractoriness. With the increasing use and acceptance of neoadjuvant radiation therapy, the study of neoadjuvant chemotherapy can no longer be done in isolation and should be studied as a package of neoadjuvant treatment in conjunction with RT. In conclusion, a multi-disciplinary approach in the management of

patients with STS is now considered as an inseparable factor towards overall treatment success.

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