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Current Medicinal Chemistry, **2013**, *20,* ????-???? 1

Adjuvant and Neoadjuvant Chemotherapy for Soft Tissue Sarcomas

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Abstract: Sarcomas of the soft tissue are a heterogeneous, rare and complex group of mesenchymal malignant tumors, accounting for less than 1% of all adult malignancies and about 10-15% of childhood cancer. Despite local disease control obtained with surgery and pre- or postoperative radiotherapy, roughly one half of patients with high-grade tumors experience metastatic disease. The adjunction of chemotherapy, either before or after resection, is not currently viewed as standard practice due to the lack of reproducible impact on survival. The 1997 SMAC meta-analysis based on individual data from randomized studies confirmed a significant impact of adjuvant chemotherapy on both local and metastatic relapse, without any significant benefit on survival. Further meta-analyses demonstrated a significant benefit also in overall survival. Yet, the latest adjuvant EORTC trial was disappointedly negative. To date, adjuvant chemotherapy may be recommended as a reasonable option for the high-risk individual patient who should be well informed on the possible risks and benefits of treatment. Also the indications for neoadjuvant chemotherapy remain controversial. A local benefit may be gained, facilitating surgery, but data on survival are limited and affected by a strong patient selection bias. In order to improve our knowledge on sarcomas and to offer patients the best of current standards, we strongly recommend that all patients be referred to a sarcoma multidisciplinary group, under whose supervision they could receive the correct combined-modality management as well as have access to new clinical trials appropriately stratified for risk and histological and/or molecular subtypes.

Keywords: Adjuvant chemotherapy, neoadjuvant chemotherapy, soft tissue sarcomas.

INTRODUCTION

Sarcomas of the soft tissue are a heterogeneous, rare and complex group of mesenchymal malignant tumors, accounting for less than 1% of all adult malignancies and about 10-15% of childhood cancer [1]. The histological classification has been revised by several experienced pathologists and issued by the WHO. Some of the known subtypes have been redistributed into different categories, according to newly discovered data on molecular biology and immunohistochemistry of sarcomas [2, 3]. An attempt has been made to correlate each subtype with the mesenchymal cell of origin: angiosarcoma from endothelial cells, liposarcoma from adipocytes, leiomyosarcoma from smooth muscle cells, etc. Yet, several subtypes still escape this histogenetic classification such as synovial sarcoma, alveolar sarcoma, and some others.

As a general rule, histological grading is the main predictor of prognosis. Sarcomas are usually graded according to three parameters: the mitotic index, the presence of necrosis and cell differentiation, although some sarcomas are intrinsically high-grade such as angiosarcoma and synovial sarcoma. The so-called French classification demonstrated strong prognostic value for the risk of local diffusion, metastatic dissemination or death, with 5-years overall survival (OS) rates of 95%, 75% and 45% in grade 1, 2 or 3 tumors, respectively [4].

Soft tissue sarcomas can occur at any age and in any part of the body. The most common involved sites are lower and upper extremities (50%), the retroperitoneum and the abdominal viscera (30%), the thorax (10%) and head and neck (10%). Exposure to ionizing radiation, chronic inflammation and inherited genetic alterations (such as neurofibromatosis) represents the known etiological factors, but most cases do not show predisposing factors or specific etiology. Sarcomas are frequently larger than 5 cm at first presentation, but malignant behavior is defined better by local aggressiveness, with different degrees of involvement of neighboring structures, and metastatization, occurring mainly through the bloodstream to the lungs, less frequently to the liver, bone, lymph nodes or soft tissues.

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Due to the rarity and heterogeneity of soft tissue sarcomas, a multidisciplinary clinical management is recommended, even before diagnostic procedures are undertaken.

To date, surgical resection with wide margins plus radiotherapy is the cornerstone for patients with localized high-risk sarcomas. An optimal initial R0 resection is one of the best prognostic factors for survival, although microscopically complete resection can be difficult to achieve in cases located near vital structures. Yet, the persistence of disease correlates with an increased risk for both local and distant relapse. With the exception of patients candidate to radical metastasectomy, metastatic disease is usually incurable because chemotherapy with anthracyclines, ifosfamide and other drugs obtains a response rates of around 10-35%, with a median progression free survival (PFS) of 4-6 months and OS of 12 months in old [5] or up to 18 in modern series [6].

The rationale for adjuvant or neoadjuvant chemotherapy stems from about 90% of malignant sarcomas being diagnosed while still in a localized stage, but, despite local disease control, over one half of the patients with high-risk disease will develop unresectable, locally advanced or metastatic disease and will eventually die of sarcoma. Therefore we may hypothesize that early administration of cytotoxic drugs able to kill disseminated tumor cells might improve the relapse free survival and, possibly, also overall survival of patients.

Rarity of disease, heterogeneity of site, grade and histology have been major determinants for the controversial results obtained in clinical studies conducted so far.

ADJUVANT CHEMOTHERAPY

The first cytotoxic agent active in soft tissue sarcomas was doxorubicin, identified in the early 1970s. Most interestingly, the high rate of relapse and mortality from mesenchymal malignancies prompted trials on adjuvant chemotherapy dating not many years after the pioneering studies on breast cancer. In fact, the National Cancer Institute performed the first randomized trail of adjuvant doxorubicin, cyclophosphamide and methotrexate in high-grade sarcomas between 1977 and 1981 [7]. Investigators reported a significantly lower rate of sarcoma relapse and death in the group of patients who received chemotherapy. Other trials were conducted in the subsequent years, but due to the rarity of the disease, the accrual

0929-8673/13 $58.00+.00

was always lagging behind and final data were not always clinically significant (Table **1**). Moreover, differences in surgery and technical aspects of radiotherapy were substantial. Three meta-analyses of published reports have been conducted in the early 1990s [8-10] and all of them have shown that adjuvant therapy may prolong the disease free survival (DFS) and the OS. Anyway, all adjuvant studies were small and lacked statistical power to reveal benefit in commonly used end-points. In 1997 the Sarcoma Meta-Analysis Collaboration (SMAC) published the most rigorous and careful analysis of data on adjuvant chemotherapy in an attempt to overcome the inadequate power of small trials and to minimize any potential bias [11]. This work is the only meta-analysis of adjuvant chemotherapy for sarcomas conducted so far on individual patient data rather than on published data (Table **2**). The Authors pooled data of 1,568 patients from 14 clinical trials (including one unpublished) comparing adjuvant chemotherapy using doxorubicin alone or with other drugs versus observation, following resection of localized soft tissue sarcomas. After a median follow-up time of 9.4 years, the Authors concluded that adjuvant chemotherapy resulted in a significant risk reduction of both local (HR 0.75, [95% CI 0.56-0.94]) and distant relapse free interval (HR 0.70, [95% CI 0.57-0.85]).

A non significant trend towards increased OS was found in the whole population (HR 0.90, [95% CI 0.77-1.04]), but when only patients with extremity-located disease were considered, a statistically-significant impact was evident (HR 0.80, p = 0.029). The benefit on OS could be quantified in an absolute gain of 7% at ten years. There was no evidence of particular effects according to age, stage, site, grade, histological subtypes, tumor size or extension of resection [12].

The findings have been criticized because of the heterogeneity of the analyzed trials which included also low-grade or small sarcomas and malignancies of variable anatomic sites; there was also a lack of information about size, grade and histology in some enrolled patients. Furthermore, the dose of doxorubicin was non-standar dized in the different trials (range 200-550 mg/m^2 of cumulative dose), ifosfamide was not included in the treatment plan and there was inconsistency in the use of radiation therapy.

After the publication of the SMAC meta-analysis, four further randomized trials of adjuvant chemotherapy have been published (Table **1**). All these controlled trials used a modern regimen of anthracycline plus ifosfamide as experimental arm.

The Austrian Cooperative Soft Tissue Study Group published the results of a small randomized trial of adjuvant doxorubicin, ifosfamide, and dacarbazine versus no chemotherapy in 59 patients with grade 2 or 3 sarcomas [13]. After a mean follow-up period of 41 months, the relapse free survival rate appeared better among the patients with grade 3 sarcomas treated with chemotherapy compared to observation, while no difference in OS was observed. After a follow-up period of 97 months, differences in terms of relapse-free survival between the two arms of the trial were no more detectable [14].

A second randomized trial assessed the efficacy of adjuvant epirubicine with or without ifosfamide versus no chemotherapy in 88 patients with high risk sarcomas [15]. Complete resection was required to be enrolled into the study. After a median follow-up of eight years, the DFS and OS rates for patients receiving chemotherapy were significantly better (69% and 72% versus 44% and 47%, respectively). Unfortunately, the study closed prematurely due to slow rate of accrual (88 patients in over 10 years) and thus remained statistically underpowered.

In Italy, Frustaci and colleagues of the Italian Sarcoma Group performed one of the largest positive trials, published in 2001 [16]. The study accrued a homogeneous cohort of 104 patients with grade III or IV soft tissue sarcomas located either on the extremities or girdles, at primary diagnosis or local recurrence. All of them had to undergo radical resection and pre- or post-operative radiation therapy. Patients were stratified by tumor size (< 10 cm versus ≥ 10 cm) and type of disease (primary tumor or local recurrence) and were then randomized between chemotherapy, consisting in five cycles of full-dose epirubicine and ifosfamide repeated every three weeks with prophylactic granulocytic growth factors, or observation. After two years, there was a positive trend in distant relapse free survival, and after four years the interim analysis for OS showed superiority of the chemotherapy arm (69% versus 50%), prompting the premature closure of accrual. Updated survival data collected after a median follow-up time of 90 months demonstrated that the trend towards increased survival is still present but the difference is no longer statistically significant [17]. Interestingly, the OS curves of the updated analysis were within the predictive range of the nomogram developed at the Memorial Sloan-Kettering Cancer Center, where adjuvant chemotherapy is not comprised [18]. Had the accrual not been stopped after interim analysis, maybe the statistical power of repeated survival analyses over time might have been increased. The cytotoxic program was aggressive: 35% of the patient experienced grade 4 leucopenia and 4% experienced grade 4 thrombocytopenia; after the third cycle anaemia became the most important side effect, requiring blood transfusion in 24% of the patients. Febrile neutropenia was mostly observed after cycles 1 (9%), 2 (13%), and 3 (11%). Non-hematological toxicities were grade 3 mucositis and nausea/vomiting, toxic deaths were not reported.

More recently, the EORTC 62931 adjuvant chemotherapy trial accrued 351 patients with grade 2 and 3 non-metastatic soft tissue sarcoma, randomized to receive five cycles of doxorubicin and ifosfamide or observation [19]. This is the largest adjuvant doxorubicin and ifosfamide study ever undertaken. It failed to demonstrate any advantage for patients who received adjuvant chemotherapy both in terms of relapses and deaths; most surprisingly, OS in the observation arm trended even better compared to the treated arm (69% versus 64%). According to the Authors, the effect of cytotoxic chemotherapy in this trial was somewhat compensated by the improvement of loco-regional control (better surgery and adequate radiotherapy) and multidisciplinary management of the patients in both trial arms. Final results have not been published so far.

One year later, the same Authors presented at the ASCO meeting a pooled analysis [20] of the two largest EORTC trials exploring adjuvant chemotherapy in soft tissue sarcomas. A total of 819 patients were included, with updated survival data collected at a median follow-up of nearly nine years. Again, adjuvant chemotherapy failed to demonstrate a positive impact in terms of OS. Subgroup analysis showed that males (p=0.035), patients older than 40 years (p=0.041), and patients with marginal resection (p=0.039) had a significantly better PFS and OS in the adjuvant cytotoxic arm compared to observation, while no significant difference was found for the other predictive factors (such as tumor size, histologic subtype and grade).

Two subsequent meta-analyses were conducted, both of them based on published data (Table **2**). Pervaiz and colleagues added four controlled randomized clinical studies of adjuvant chemotherapy to those originally comprised in the database of the SMAC meta-analysis [21]. Over the preceding ten years, the addition of ifosfamide to adjuvant regimens had become frequent in sarcomas and, in fact, all the newly included trials were based on a doxorubicin and ifosfamide regimen [13, 15, 16, 22]. The meta-analysis on pooled data of 1,539 patients demonstrated that adjuvant chemotherapy significantly decreases local recurrence rate (OR 0.73, p=0.02), distant recurrence rate (OR 0.67, p=0.001), and overall recurrence rate (OR 0.67, p=0.0001) in patients receiving chemotherapy with doxorubicin-based regimens or with doxorubicin/ifosfamide combination. Pervaiz also reported on a significantly reduction of the risk of death with a hazard ratio of 0.77 (p=0.01) and an absolute risk reduction of 6%, when only doxorubicin plus

Table 1. Randomized Clinical Trials on Adjuvant Chemotherapy vs.

Author	N	Inclusion Criteria	Regimen	5 Year DFS (Treatment vs. Observation)	5 year OS (Treatment vs Observation)
GOG[26]	156	Stage I or II uterine sarcomas	Doxorubicin	NS, 60% vs. 45%	NS, 60% vs. 47%
DFCI[27]	46	Stages IIB-IVA	Doxorubicin	NS, 67% vs. 59% (p=0.34)	NS, 68% vs. 62% (p=0.89)
ECOG[28]	47	Stages IIB-IVA	Doxorubicin	NS	NS
SSG[29]	181	Grade III-IV	Doxorubicin	NS, 59% vs. 53%	NS, 63% vs. 60%
Rizzoli[30]	77	Stages III-IVA, extremities, 16-70 yrs	Doxorubicin	91% vs. 76% (p=0.05)	56% vs. 32% (p=0.015)
Mayo[31]	76	Grade 2 or 3	Doxorubicin + CTX + VCR + ActD + DTIC	NS, 82% vs. 65% (p=0.15)	NS, 90% vs. 77% (p=0.55)
NCI 4[32]	65	High grade, extremities	Doxorubicin + CTX + MTX	92% vs. 60% (p=0.0008)	95% vs. 74% (p=0.04)
NCI 5[33]	80	High grade, extremities, trunk, breast, H&N	Doxorubicin + CTX + MTX	NS, 77% vs. 49% (p=0.075)	NS, 68% vs. 58% (p=0.38)
NCI 6[32,33]	41	High grade, extremities	Doxorubicin + CTX + MTX	75% vs. 54% (p=0.037)	NS, 83% vs. 60% (p=0.12)
Bergonie[34]	59	High risk according to grade and location	Doxorubicin + CTX + VCR + DTIC	62% vs. 28% (p=0.002)	74% vs. 37% (p=0.002)
MDA[35]	43	High grade, extremities and trunk	Doxorubicin + CTX + VCR + ActD	60% vs. 35% (p=0.05)	75% vs. 61% (p=0.025)
Saak[11]	29	*(Unpublished data)*	Doxorubicin + Ifosfamide	*(Unpublished data)*	*(Unpublished data)*
Brodowicz[13]	59	Grade 2 or 3, size > 5 cm, 18-80 yrs	Ifosfamide + Doxorubicin + DTIC	NS (p=0.1)	NS (p=0.4)
Petrioli[15]	88	Grade 3	Epirubicin ± Ifosfamide	69% vs. 44% (p=0.01)	72% vs. 47% (p=0.06)
Frustaci[16]	104	Grade 3, size > 5 cm, 18-65 yrs	Epirubicin + Ifosfamide	HR 0.59 (95% CI 0.36-0.99)	HR 0.52 (95% CI 0.29-0.93)
EORTC[36]	317	Grade 3	CTX + VCR + DTIC + Doxorubicin	56% vs. 43% (p=0.07)	NS, 63% vs. 56% (p=0.64)
Woll[19]	351	Grade 2 or 3, <70 yrs	Doxorubicin + Ifosfamide	NS, 52% both arms (p=0.49)	NS, 64% vs. 69% (p=0.93)

DFS= diasease free survival; OS= overall survival; NS= not significant; HN= head and neck; CTX= cyclophosphamide; VCR= vincristine; MTX= methotrexate; DTIC= dacarbazine; ActD= actinomycin D, HR= hazard ratio.

Table 2. Adjuvant Chemotherapy Compared to Observation: Meta-Analyses

Author	Number of Trials Analysed	Chemotherapy Regimen	DFS (95% CI)	OS (95% CI)
Tierney[10]	15	DOXO-based, various regimens	NA	OR 0.59 (0.45-0.78)
SMAC[11]	14	DOXO-based, various regimens	HR 0.75 (0.64-0.87)	HR 0.91 (0.78-1.07)
Pervaiz[21]	18	DOXO-based or DOXO+IFO, various regimens	OR 0.67 (0.56-0.82)	HR 0.77 (0.64-0.93)
O'Connor[24]	18	DOXO-based or DOXO+IFO, various regimens	OR 0.71 (0.54-0.85)	OR 0.79 (0.58-0.85)
Afonso[25]	18	DOXO-based or DOXO+IFO, various regimens	Significant difference (p<0.0001)	RR 0.88 (0.80-0.97)

NA: not available; DOXO= doxorubicin; IFO= ifosfamide; DFS= disease free survival; OS= overall survival; HR= hazard ratio; OR= odds ratio.

ifosfamide-based regimens were considered. The results are most appreciable considering that the survival benefit equals that obtained by the addition of taxanes to adjuvant regimens for early breast cancer [23].

Another SMAC update was presented at the 2008 ASCO annual meeting [24]; it included the SMAC 1997 data and four additional randomized, controlled phase III trials [13, 15, 16, 19]. The new meta-analysis collected published data of a total of 2,170 patients, confirmed previous conclusions on beneficial effects of adjuvant chemotherapy in terms of DFS and OS after 5 years (OR 0.71 [95% CI 0.54-0.85] and OR 0.79 [95% CI 0.66-0.94], respectively), but statistical significance for OS was lost after ten years (OR 0.87; p = 0.12).

The most recent meta-analysis on adjuvant chemotherapy in adult soft tissue sarcoma was performed on published trials by Afonso and colleagues [25] and reported at the 2010 ASCO Meeting. Eighteen randomized clinical trials were pooled together and the subgroup of patients treated with anthracycline plus ifosfamide showed an increase of OS (HR 0.88, p=0.015), DFS (p<0.0001), local recurrence (p=0.009) and metastases-free survival (p<0.001). Final publication is still pending at the time of this writing.

Much of the controversy upon the use of adjuvant chemotherapy stems from the paradox that single randomized trials are mostly negative but then, pooling them together, positive results are coherently produced by different Authors. Numerosity of the sample is crucial: it has been estimated that to detect differences of 10% in survival, a study would request at least 900 patients [11], while the largest trial (EORTC 62931) enrolled only 468 patients.

Moreover, an updated meta-analysis based on individual data from all the old and new randomized clinical trials has not been carried out yet.

Due to biological and clinical heterogeneity as well as rarity of the disease which limit the conduction of large phase III studies,

valuable information can also be obtained from retrospective cohort studies. Cormier *et al.* [37] conducted a large retrospective analysis on data from 674 patients with high grade (grade 3) soft tissue sarcomas, 50% of whom had been treated with local therapy plus chemotherapy in neoadjuvant or adjuvant setting. Local relapse-free rate was 83% and 77% at 5 and 10 years, respectively, while distant relapse-free rate was 56% and 49%. The overall DFS rates were 48% and 41%. Tumor size more than 15 cm (HR 1.62, p=0.001) and female sex (HR 0.79, p=0.04) were the only prognostic factors for DFS. Further data suggest that the use of adjuvant chemotherapy may be associated with time-varying effects. In fact, improvement in clinical endpoints is evident in the first year, then progressively decreases. At 5 years, adjuvant chemotherapy is associated with higher rates of disease recurrence and lower DFS: thus it seems that treatment does not achieve long term benefits.

A second cohort study was conducted on the French Sarcoma Group Database, to explore the benefit of adjuvant chemotherapy in a subset of 1,513 adult patients with non-metastatic soft tissue sarcoma, grade 2 and 3 according to FNCLCC staging system [38]. Median follow-up time is nine years. This is the largest cohort study ever conducted, including central histological review of all the selected cases. OS decreases over time throughout the period of follow-up: 1-, 5-, and 10-year OS were 92.8%, 64.9% and 52.4%, respectively. Chemotherapy significantly benefits patients with grade 3 sarcoma with a reduced risk of metastases by 29% (HR 0.71, 95% CI 0.57-0.87) and death by 29% (HR 0.81, 95% CI 0.60-0.86), but this effect was not observed in patients with grade 2 sarcoma. Moreover, the benefit of adjuvant chemotherapy in reducing the development of metastatic disease lost its significance after three years.

Some factor may be identified as potential explanations for the variable effect of adjuvant chemotherapy over different studies.

First, differences in histological subtypes in small cohorts of patients hampers the identification of histological variants that may derive benefit from adjuvant chemotherapy. Data from advanced disease demonstrate there are chemosensitive histotypes such as synovial sarcoma, round cell liposarcoma, and pleomorphic sarcoma, while other sarcomas seem to respond less (leiomyosarcoma). Other sarcomas are even categorized as chemoresistant such as clear cell sarcoma or alveolar soft-part sarcoma: for these sarcomas, no adjuvant chemotherapy is recommended, while the role of innovative anticancer agents is under study [39, 40].

Secondly, patients with extremity sarcomas develop lung metastases more frequently than patients with retro-peritoneal or trunk-wall sarcomas, who experience much more local recurrences. In the former subgroup of patients adjuvant chemotherapy should have a more significant impact on survival, while for the second group local treatments (aggressive surgery, radiotherapy) should be more important. The subgroup analysis of the SMAC meta-analysis demonstrated a survival benefit for extremity sarcomas; moreover, in the Italian experience published by Frustaci *et al.*, as well as in the EORTC 62931 trial, only extremity or girdle sarcomas were enrolled.

Thirdly, the improvement of local therapies over the last years may have somewhat reduced the magnitude of the effect of adjuvant chemotherapy on survival, if we hypothesize that killing of residual loco-regional disease is a relevant component of the activity of chemotherapy. Anyway, we underline that adjuvant chemotherapy should not substitute for inadequate margins of bad surgery.

In addition, some trials accrued also patients with relapsed loco-regional disease, and these patients may be at higher risk of bearing occult metastases compared to newly diagnosed patients, creating some bias when all relapse are eventually pooled together and analyzed.

To date, except for pediatric histologies (rhabdomiosarcoma), bone sarcomas (osteosarcoma and Ewing's sarcoma) and GIST (adjuvant imatinib), adjuvant chemotherapy is not included in international guidelines as a standard of care. Nevertheless, the European Society of Medical Oncology (ESMO) Guidelines Working Group has recently stated that "data have been provided that adjuvant chemotherapy might improve, or at least delay, distant and local recurrence in high-risk patients (…) However, studies are conflicting, and a final demonstration of efficacy is lacking" [41]. Current guidelines of the National Comprehensive Cancer Network (NCCN) report that adjuvant chemotherapy is an option, for high-risk sarcomas, which needs to be discussed in multidisciplinary meetings [42].

It is left at the treating physician's discretion how to weight the different parameters such as risk of relapse, location, chemosensitivity as well as general conditions of the patient in order to decide when to propose adjuvant chemotherapy. Detailed discussion with patients is also of paramount importance in determining willingness to accept the risk of toxicities with uncertain gain of OS. A most reasonable algorithm may be the following [43]: patients with deep-tissue sarcomas larger than 5 cm, with preserved function of organs and optimal functional health, chemosensitive histology, originating in the extremities, girdles or in the thoracic or abdominal wall could be candidates for intensive-dose treatment with anthracycline and ifosfamide. In selected subgroups with rare histologies (clear cell, alveolar, high-grade solitary fibrous tumor) the profile of chemoresistance might leave room for exploring alternative agents such as tyrosine-chinase inhibitors (suntinib or pazopanib) or monoclonal antibodies (bevacizumab). In fact, the era of "on shoe fits all" for soft-tissue sarcomas is going to the conclusion. New drugs, including molecular targeted therapies, have been introduced in the treatment of specific subgroup of mesenchymal malignancies [44]. It is necessary to think to deliver treatments which have the higher chances of response for the specific subtypes, in a sort of histotype-tailored therapy. In this sense, Patrikidou and colleagues [45] suggest four future options to be explored as follow.

Firstly, controlled phase II trials and retrospective studies have demonstrated relevant activity of some drugs on specific histological subtypes (ifosfamide in synovial sarcoma [46], trabectedin in liposarcoma and leiomyosarcoma [47], paclitaxel in angiosarcoma [48] gemcitabine and docetaxel or dacarbazine in leiomyosarcoma [49, 50], temozolomide and bevacizumab in solitary fibrous tumor). According to this preliminary data and taking into account the multiple histologies of sarcoma, several anticancer agents should be incorporated into the future adjuvant chemotherapy trials, in order to optimize the clinical benefits of chemotherapy. An Italian Sarcoma Group trial is now ongoing to evaluate histotypes-tailored chemotherapy in adjuvant or neoadjuvant setting (EUDRA-CT 2010-023484-17).

Secondly, in the next future it will be very important to identify new diagnostic and molecular markers which might enable us to better understand the mechanism of transformation and to predict aggressive behavior and chemosensitivity of sarcomas. Thus, we should be able to identify patients with the higher chances of relapse coupled with sensitivity to either conventional chemotherapy or specific targeted therapies. Recently, a gene expression signature has been identified by the French Sarcoma Group [51]. This signature, called CINSARC has been validated in a second independent cohort of patients, where it was able to predict the metastatic outcome. Although still experimental, CINSARC could be implemented in future adjuvant trials in order to test prospectively its reliability.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy consists in the administration of cytotoxic systemic agents soon after diagnosis, before surgery. Two

main aims are pursued: to reduce the size of the tumor facilitating its removal without local residuals, especially for masses located near vessels of nerves, and to kill microscopic metastatic disease. In several other malignancies neoadjuvant chemotherapy preceding surgery is now preferred, such as rectal and head & neck cancer, as well as locally-advanced breast cancer. In soft tissue sarcomas, the concept of neoadjuvant therapy remains highly controversial. Several single-centre or multicentre phase II trials have been performed in the last years, and they not only assessed the feasibility of this approach but demonstrated that chemotherapy in preoperative setting achieves a higher response rate and increases the chance of conservative surgery [52]. Nevertheless, the benefits in terms of PFS or OS have not been prospectively addressed.

The EORTC Soft Tissue Bone Sarcoma Group performed a randomized phase II clinical trial [22] in which patients with high-risk sarcoma underwent three cycles of preoperative chemotherapy with doxorubicin and ifosfamide before surgery. With a median follow-up time of seven years, the survival analysis does not show a large benefit from preoperative chemotherapy in terms of DFS and OS: the curves for patients receiving chemotherapy were only slightly superior to those who underwent surgery only (5-yr OS 65% *vs*. 64%, p=0.22; 5-yr DFS 56% *vs.* 52%, p=0.35). Unfortunately, the accrual was very slow and it was not possible to extend the trial to the subsequent phase III as it had been originally planned.

DeLaney and colleagues [53] designed a study of preoperative chemotherapy interdigitated with radiotherapy in patients with high grade sarcomas. The patients received three cycles of mesna, adriamycin, ifosfamide and dacarbazine (MAID) concurrent with 44 Gy of neoadjuvant radiotherapy. No clinically complete responses were observed in the chemotherapy group, while 5 patients had partial responses (10.6%), 36 remained stable (76.6%); 6 patients had disease progression (12.8%). DFS, metastases free survival and OS at 5 years were significantly improved in the MAID group compared to historical control group (who received only preoperative RT with or without postoperative boost): 70% *vs.* 42% (p=0.0002); 75% *vs.* 47% (p=0.0016), 87% *vs.* 58% (p=0.0003), respectively. This aggressive neoadjuvant chemo-radiotherapy provided high rates of disease control in this cohort of high risk sarcoma patients compared with the historical control group.

An update of the MAID trial has been recently published [54]. At ten years, freedom from metastases, DFS and OS still remained appreciably high compared to control arm: 77% *vs.* 43%; 65% *vs.* 30%, 66% *vs.* 38%, respectively. Nevertheless, it is still not possible to infer from this trial that neoadjuvant chemo-radiation should be the preferred multimodality approach: confirmatory multi-institutional, prospective randomized trials are warranted. Indeed, other experiences on neoadjuvant chemotherapy in soft tissue sarcomas have been reported in the last years. A phase III trial has been performed by Italian Sarcoma Group and Spanish Sarcoma Group to evaluate three versus five cycles of chemotherapy in localized high risk sarcomas of the extremities and trunk wall in adults [55]. The study enrolled 328 patients; with a median follow-up of 63 months. Patients were randomized to receive three cycles of full-dose epirubicine and ifosfamide given in the preoperative setting with or without two additional cycles after surgery. Radiotherapy could be delivered in the neoadjuvant or in the adjuvant setting. At 5 years, there were no significant differences in OS probability: 0.68 in arm A (95% CI 0.60-0.75) and 0.71 in arm B (0.63-0.77). Hazard ratio for OS at 5 years was 1.00 (0.72-1.39). Overall 5-year cumulative incidence of local recurrence was 0.065 (SE, 0.020) in arm A, and 0.059 (SE, 0.019) in arm B, while the overall 5-year cumulative incidence of distant metastases was 0.326. Univariable and multivariable analyses showed that histologic subtype (HR 3.00 (95% CI 1.71-5.28)) and tumor size (HR 1.05, (1.02-1.08)) were significantly associated with OS. Hematologic and non-hematologic toxicities reported were consistent with those already known for this therapeutically regimen: febrile neutropenia was reported in 11.4% of the patients who received neoadjuvant treatment, and in about 7% of the patients who received five cycles of chemotherapy (7.4% during preoperative therapy and 6.1% during postoperative therapy). No toxicity-related death was reported. The main conclusion of this trial is that three preoperative cycles of chemotherapy are not inferior to three preoperative plus two adjuvant cycles.

A further analysis has been recently reported by the same authors [56], focusing on the behavior of different histological subtypes of sarcomas. In this series of localized soft tissue sarcomas treated with full dose anthracycline/ifosfamide regimen leiomyosarcoma displayed more events of progressive disease, and fared significantly worse compared to other subtypes. With a median follow-up of 60 months, OS probability for undifferentiated pleomorphic sarcoma, leiomyosarcoma, synovial sarcoma and other histotypes was 76%, 48%, 64% and 73%, respectively. A better outcome for patients who received neoadjuvant chemo- and radiotherapy versus chemotherapy alone was also observed in the same trial [57].

A phase II non-randomized trial has been performed by German investigators [58] to evaluate efficacy of neoadjuvant and adjuvant chemoradiation therapy in high risk soft tissue sarcoma. After four cycles of neoadjuvant chemotherapy (etoposide, ifosfamide and doxorubicin), patients underwent surgery with intraoperative radiotherapy, followed by adjuvant radio- and chemotherapy for further four cycles. At 2 years, OS and DFS rates were 83% and 63%, respectively.

Finally, a retrospective chart review conducted at Mayo Clinic has been recently reported at ASCO Meeting [59]. The Authors analyzed data on neoadjuvant chemoradiotherapy in the treatment of stage II and III extremity sarcomas. They observed a trend towards improved OS versus surgery alone for patients with tumors larger than 5 cm.

In general, localized high risk soft tissue sarcoma with tumor exceeding 5 cm could be considered an indication for neoadjuvant treatment, in particular when immediate surgery is expected to ensue in severe functional limitation or amputation. Patients treated with neoadjuvant chemotherapy are fitter than those with metastases, and this could be one of the reasons why they appear to tolerate chemotherapy better.

Retroperitoneal sarcomas represent a different clinical scenario due to the high rate of loco-regional relapse and rarity of metastases. Taking into account the potential benefits deriving from neoadjuvant radiotherapy in terms of size reduction, better demarcation of tumor against adjacent structures, early tumor cells inactivation, some centers have adopted neoadjuvant radiotherapy as standard of care notwithstanding the paucity of clinical trials on such approach. In the past, some phase III trials were halted due to poor accrual; the EORTC Soft Tissue And Bone Sarcoma Group has recently started a new phase III study exploring the role or neoadjuvant RT (50.4Gy/28F) plus surgery compared to surgery alone (EORTC trial 62092).

The Italian Sarcoma Group recently presented preliminary data from a phase II study of chemoradiation therapy for retroperitoneal sarcoma [60]. High-dose ifosfamide as single agent (1g/m2 daily for 14 days, continuous infusion, every 28 days for three cycles) was administrated in combination with radiotherapy (50.4 Gy in 28 fractions). A partial response was observed in 7 patients, while stable disease was observed in 62 patients. Only one patient experienced progressive disease. The combination therapy appeared feasible, and preoperative chemo-radiation therapy could be completed in most patients. Yet, response rate was lower than expected and further exploration of this strategy is not foreseen at the moment.

CONCLUSIONS

Soft tissue sarcomas are a heterogeneous group of rare mesenchymal malignancies encompassing over 50 different histological subtypes whit a various natural history. The grade is a good indicator of biology and metastatic potential. Despite local disease control obtained with surgery and pre- and postoperative radiotherapy, one half of patients with high-grade tumors experience metastatic disease. In spite of its strong biological rationale, the adjunction of chemotherapy, either before or after resection, is not currently viewed as standard practice due to the lack of reproducible impact on survival. Because of the complexity of this rare disease, most trials have involved a relatively small number of patients, with heterogeneous histological/molecular subtypes and disease sites, variable patients' characteristics as well as different quality of surgery and radiotherapy.

The 1997 SMAC meta-analysis based on individual data from randomized studies confirmed a significant impact of adjuvant chemotherapy on both local or metastatic relapse, without any significant benefit on survival. Further meta-analyses on published data and clinical trials employing also ifosfamide, demonstrated a significant benefit also in OS. Yet, the latest adjuvant EORTC trial was disappointedly negative. Apart from performing new meta-analyses on updated patient survival data, there is an urgent need to determine which are the categories of soft tissue sarcomas most likely to gain benefit from adjuvant chemotherapy in order to run new and more selective trials. New surrogate endpoints (*i.e.*, metabolic parameters, functional imaging) should be incorporated in such trials in order to correlate tumor response with long-term benefits in terms of reduced relapse rate.

To date, adjuvant chemotherapy may be recommended as a reasonable option for the high-risk individual patient (having a G2–3, deep, >5 cm tumor, chemosensistive histology) who should be well informed on the possible risks and benefits of treatments. Patients with R1 resection could benefit from post-operative chemotherapy, but whenever possible they should be re-operated since chemotherapy should not be viewed as a substitute for inadequate surgery.

Also the indications for neoadjuvant chemotherapy remain controversial. For chemosensitive subtypes, chemotherapy may well be used preoperatively, with close monitoring of patients in order not to miss early progression. A local benefit may be gained, facilitating surgery, but data on survival are limited and affected by a strong patient selection bias. The recent ISG trial showed that postoperative chemotherapy may be omitted after three neoadjuvant cycles.

Under this perspective, the Italian Sarcoma Group and the Spanish Sarcoma Group have launched a new exciting neoadjuvant chemotherapy trial with an innovative proof of concept design. It was decided to compare in terms of disease-free survival three preoperative cycles of standard chemotherapy (the same regimen of the previous Italian adjuvant and neoadjuvant trials) with three preoperative cycles of a different tailored chemotherapy for each selected histotype (leiomyosarcoma, myxoid-round cell liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, undifferentiated pleomorphic sarcoma). Radiological and pathological analysis of responses will be carried out in order to evaluate if response might become an early surrogate for benefit in terms of DFS and, ultimately, OS (EUDRA-CT 2010-023484-17).

In order to improve our knowledge on sarcomas and to offer patients the best of current standards, we strongly recommend that all patients be referred to a sarcoma multidisciplinary group, under whose supervision they could receive the correct combined-modality management as well as have access to new clinical trials appropriately stratified for risk and histological and/or molecular subtypes.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

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