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PERSPECTIVES IN ONCOLOGY

What is the optimal (neo)adjuvant strategy of extremity high-risk soft tissue sarcomas (ESTS)?

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Abstract

Currently, the standard treatment for extremity high-risk soft tissue sarcomas (ESTS) combines surgery and pre- or post-op radiation therapy (RT). In some selected cases, chemotherapy (CT) is incorporated into the therapeutic algorithm as a neoadjuvant approach to enable conservative management. Given the risk of local or metastatic relapse, this paper discusses the potential benefits of CT and RT in high-grade ESTs. The role of adjuvant chemotherapy in addition to neoadjuvant CT, the prognostic value of the pathological response to neoadjuvant treatment, and the role for an adjuvant "boost" following resection after pre-operative radiotherapy will be discussed.

Keywords Extremity high risk soft tissue sarcomas · Neoadjuvant strategy · Adjuvant therapy · Pathological response · Boost radiotherapy

Introduction

To date, the standard treatment for extremity high-risk soft tissue sarcomas (ESTS) includes surgery and radiation therapy [1]. However, the risk of local and metastatic relapses exceeds 50% in some cases [2]. Data from meta-analyses [3, 4] and randomized studies [5, 6] suggested a potential benefit of adjuvant chemotherapy on relapse-free survival (RFS) in patients with extremity high-risk soft tissue sarcomas (ESTS), however there is no benefit on overall survival (OS), and this strategy is more and more substituted by neoadjuvant chemotherapy (NACT) when feasible and indicated. Indeed, many studies evaluating NACT, radiotherapy (RT), and radio-chemotherapy (RCT), demonstrated that these neoadjuvant regimen are feasible in this setting [1]. The concept of neoadjuvant treatment in ESTS remains controversial, specifically concerning NACT. Level of evidence of different studies are limited, but tumor shrinkage and treatment of micro metastasis represent the rationale supporting NACT [7].

The aggressiveness of local and metastatic relapses of extremity high-risk soft tissue sarcomas (ESTS), in addition to the paucity of active drug and the inaccessibility of some therapeutic options such as isolated perfusion of the limb in the context of developing countries, are important considerations to consider. In this paper perspective, we

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aimed to discuss the clinical relevance and the rationale of neo (adjuvant) treatments for extremity high-risk soft tissue sarcomas (ESTS).

Methodology

To identify relevant articles in English and French, electronic searches were conducted in MEDLINE (pubmed), Scopus, Google Scholar, and the Web of Science database, using the following key words: extremity high-risk soft tissue sarcomas, neoadjuvant chemotherapy, adjuvant chemotherapy, radiotherapy, pathological response, radiotherapy. Research was also conducted using the references from the systematic review articles, meta-analysis, thesis, and books.

Role of adjuvant chemotherapy in addition to neoadjuvant CT?

Several retrospective and phase II studies suggested improved disease control when using a neoadjuvant treatment followed by adjuvant chemotherapy. In a phase II trial, Delaney et al. evaluated the efficacy of NACT in combination with radiation therapy in adult patients diagnosed with extremity high-risk soft tissue sarcomas (ESTS) (> 8 cm) [8]. This study enrolled 48 patients to receive three cycles of NACT based on an association of adriamycin, ifosfamide, dacarbazine, and mesna (MAID protocol) and concomitant 44 Gy of radiation followed by surgical resection. Three post-operative cycles of MAID were planned and patients who had positive surgical margins received 16 Gy of boost radiation. The outcomes were compared to a historical control group including patients who had received preoperative radiation alone with or without postoperative boost. 76.6% ($n=36$) had stable disease (SD), 10.6% ($n=5$) had a partial response (PR), and 12.8% ($n=6$) progressed (PD) on this treatment. However; no complete response (CR) was observed among patients. The acute hematologic toxicity profile in the MAID group was mainly febrile neutropenia (25%, $n=12$) and wound healing occurrence (29%, $n=14$). Moreover, a MAID-treated patient developed late fatal myelodysplasia. 5-year local control rate in the MAID group was 92% vs. 86% in the control population ($p=0.1155$). This difference was not significant and it is difficult to draw any conclusion since this study was not randomized and comparisons with historical data are always positive thanks to a better selection of patients and the fact that patients included in trials have better outcomes thanks to their better selection. [9].

A German non-randomized phase II study investigated the efficacy of neoadjuvant and adjuvant CT and RT for sarcomas with high risk of relapse. Fifty patients were enrolled to receive 4 cycles of neoadjuvant intravenous etoposide (125 mg/m^2, days 1 and 4), ifosfamide (1500 mg/m^2, days 1–4), and doxorubicin (50 mg/m^2, day 1) [10]. This was followed by surgery, intraoperative radiotherapy, and adjuvant radiotherapy and chemotherapy with 4 cycles of chemotherapy based on the previous protocol. According to RECIST, 6% of patients had a CR, 24% had a PR, 62% had SD, and 8% progressed after NACT. R0, R1, and R2 resections were achieved in 80% 13%, and 4% of patients, respectively. After 2 years of follow-up, OS and DFS rates were 83% and 63%. In this study, the multivariable proportional Cox regression model did not show any impact of histology, resection status, and tumor necrosis rates on OS or DFS. Serious toxicities included febrile neutropenia (4/50), cardiac toxicity (2/50), and central nervous system toxicity (4/50) which resulted in dose reduction in chemotherapy regimens for 4 patients. No case of secondary leukemia was observed.

Italian and Spanish sarcoma working groups conducted a multicentric, multinational phase III trial to compare three and five CT cycles Patients were randomly assigned to either three cycles of preoperative CT with epirubicin 120 mg/m^2, ifosfamide 9 g/m^2, and granulocyte colony-stimulating factor (arm A) or three cycles of preoperative CT followed by two cycles of postoperative CT (arm B). Survival did not differ between the two arms (HR 1.00; 90% CI 0.72–1.39). The histological type (HR 3.00; 95% CI 1.71–5.28) and tumor size (HR 1.05; 95% CI 1.02–1.08) were found to be significantly associated with survival outcomes in both univariable and multivariable analyses.

Reported toxicities were as usually observed with doxorubicin and ifosfamide including febrile neutropenia (11.4%) in patients who received NACT and in 7% of those who received two additional courses of chemotherapy in the adjuvant setting. Of note, no toxic death due to toxicity was reported and the dose intensity of chemotherapy was maintained. In this population of patients with extremity high-risk soft tissue sarcomas (ESTS), three cycles of full-dose preoperative CT were not inferior to five cycles [11]. This non-inferiority of three cycles of NACT compared with three cycles of NACT with two cycles of adjuvant CT was maintained after a 10-year follow-up [12] (Table 1).

Choice and role of neoadjuvant CT

The only randomized trial comparing neoadjuvant chemotherapy versus surgery alone in adult patients with extremity high-risk soft tissue sarcomas (ESTS), randomized between surgery alone or three cycles of 3-weekly intravenous (i.v.) doxorubicin 50 mg/m^2 bolus and ifosfamide 5 g/m^2 (24 h infusion) before surgery. At a median follow-up of 7.3 years, the 5 year disease-free survival for the no chemotherapy arm was estimated to be 52% and 56% for the chemotherapy arm,

Table 1 Multimodal approach of localized large high-grade extremity soft tissue sarcoma

References	Study	*N*	Neo-adjuvant regimen	Adjuvant regimen	Outcome
Delaney et al. [8, 9]	Phase II	48	3 cycles of MAID + 44GY	3 cycles of MAID + 16 Gy if positifs margins	DFS: 70% vs. 42%, $p = 0.0002$ MFS: 75% vs.47%, $p = 0.0016$ 5-year OS: 87% vs. 58%; $p = 0.0003$ 10-year follow-up MFS: 77% vs 43% DFS: 65% vs 30% OS: 66% vs 38%
Schmitt et al. [10]	Phase II	50	4 cycles of Etoposide,Ifosfamide,Doxorubicin, and intraoperative radiotherapy	Adjuvant radiotherapy with 4 cycles of chemotherapy	Local recurrence:6% Distant metastases:24% 2 years of follow-up: OS: 83% DFS: 63%
Gronchi et al. [11, 12]	Phase III	328	Arm A: three cycles of AI protocol (Doxorubicin,ifosfamide) ± Radiotherapy Arm B: three cycles of AI protocol ± Radiotherapy	Arm A: Adjuvant Radiotherapy if no received in neoadjuvant sitting Arm B: two other courses of adjuvant chemotherapy AI protocol And Radiotherapy if no received in neoadjuvant sitting	Median follow-up of 63 months: the probability of death at 5 years: Arm A: 0.68 Arm B: 0.71 HR 1.00; 90% CI 0.72–1.39 The overall cumulative incidence of local relapse at 5 years: arm A:0.065 arm B: 0.059

respectively ($p = 0.3548$), and the 5 year overall survival for both arms was 64 and 65%, respectively ($p = 0.2204$). This negative trial was hampered by a suboptimal doxorubicin dose [13].

The evaluation of the efficacy of the preoperative chemotherapy adapted to tumor histology was the aim of a randomized phase III trial comparing three cycles of anthracycline or epirubicin type combined with ifosfamide at a dose of 9 mg/m^2 versus a treatment adapted to histological subtypes for localized extremity and trunk wall high-grade sarcomas in adults (NCT01710176) [14]. These regimens include trabectedin (1.3 mg/m^2) for high-grade myxoid liposarcoma, gemcitabine for leiomyosarcoma (1800 mg/m^2 plus dacarbazine 500 mg/m^2), high dose ifosfamide for synovial sarcoma (14 mg/m^2), etoposide (150 mg/m^2) plus ifosfamide (9 mg/m^2) for malignant peripheral nerve sheath tumor, and gemcitabine (900 mg/m^2) in association with docetaxel (75 mg/m^2) for non-differentiated pleomorphic sarcoma. The objective was to reduce the risk of relapse with chemotherapy adapted to histological types by 30%. After a median follow-up (FU) of more than a year, patients who received standard chemotherapy showed better DFS compared to those treated with histologically tailored chemotherapeutic regimens. DFS was significantly higher with the epirubicin-ifosfamide (EI) combination versus the experimental arm (62% vs. 38%; $p = 0.004$). Moreover, at 46 months, the standard chemotherapy arm had an OS of 89% and the histology-adapted chemotherapy group had an OS of 64% ($p = 0.034$).

At 60 months, the projected DFS and OS probabilities in the A + I arm and HT arm were 0.55 and 0.47 (log-rank $p = 0.323$) and 0.76 and 0.66 (log-rank $p = 0.018$), respectively, in the updated study with a median follow-up of 52 months. HT was not associated with a better DFS or OS in this population of patients with localized high-risk STS, implying that A + I should remain the regimen of choice whenever neoadjuvant chemotherapy is used in patients with high-risk STS.

A drawback of such an approach is that 8% of the patients in the AI arm received an amputation which is much more higher than that for the same population in recent studies, which may be related to a 7% RECIST progression on RT. It underlines the necessity for a regular MRI control during CT. However this study was not planned to show any OS benefit compared to surgery alone [15].

To evaluate the potential benefit of neoadjuvant CT versus surgery alone, Gronchi team [16] compared the AI arm of their randomized study (ISG-STS 1001, NCT01710176) to the surgery alone patients exhibiting a high-grade ESTS who were included in the retrospective study which was the basis of SARCULATOR° cellular phones application. For the lower risk patients (predicted OS ≥ 60%), there was no OS benefit of neoadjuvant CT. For the higher risk patients (predicted OS< 60%), the magnitude of the potential 5y-OS gain was 10%. A potential bias is that the selection of the patient of the randomized trial was better and that the period of inclusion of the retrospective study was older (with always a worse outcome for older studies).

Is the pathological response to NACT a prognostic factor to be considered as a determinant of adding adjuvant chemotherapy?

It is well-documented that histological response to NACT is predictive of survival in patients with bone sarcoma and it is a notable factor impacting adjuvant management after surgery, particularly for Ewing sarcoma and osteosarcoma. In case of a very good histological response and a score of Rosen and Huvos of III or IV, the same adjuvant treatment is recommended and if a poor response is noted with a score of Rosen and Huvos of II or I, the selected treatment should be modified.

Yet, the correlation between the histological response to NACT and survival outcomes in patients with ESTS is not well established. The main reason is that, conversely to bone sarcoma, there is no more tumor frame after shrinkage. Then, the percentage of viable cells is not compared to the initial tumor volume. Also, the cut off of viable cells to categorize a « good response» is not standardized, and studies are hardly comparable on this point. The number of studies that tried to answer this question is very limited, had small sample sizes, and their results were conflicting. Recently, an effort was made by EORTC to harmonize the methodology of the assessment of response to treatment [17].

The University of Texas M.D Anderson Cancer Center delivered NACT before surgery to investigate the chemosensitivity of the tumor in vivo [18]. Adjuvant chemotherapy was then given mainly for patients with sensitive tumors to NACT. In a retrospective cohort from MDA cancer Center, forty-six patients with high-grade ESTS were treated with a preoperative adriamycin-based combination (mean 4.4 cycles), followed by local surgery and radiotherapy [19]. Forty % of the patients had an objective clinical response while 60% of patients were not responders. Importantly, this study showed a significant better survival in chemo sensitive patients compared to the non-responding patients (median OS 60 months versus 32.7 months; respectively $p=0.02$). The investigators proposed that pathologic response to NACT could be a determinant factor for patients' selection for additional adjuvant strategies.

Lucas et al. reported a real-world series of 31 cases diagnosed with ESTS, staged as T2 and grade 3 [20]. Of note, patients received the same therapeutic regimen, followed up by the same oncologist, and surgically treated by the same orthopedic surgeon. The histological response was not correlated with OS or event-free survival (EFS). Another retrospective study included 207 patients with high-grade ESTS treated with NACT with or without radiotherapy and then surgery. A histological response greater than 90%, was correlated with an improvement of DFS in the univariable analysis [21]. However, this association was not confirmed in the multivariable analysis after adjustment for confounding factors.

An analysis reported in JAMA oncology by Wang et al. included patient data from two phase II trials: RTOG 0630, which assessed preoperative RT alone ($n=79$), and RTOG 9514, which assessed NACT ($n=64$). Five-year OS was 100% for patients with pathological complete response (pCR) vs 76.5% (95% confidence interval [CI] 62.3%–90.8%) and 56.4% (95% CI 43.3%–69.5%) in trials 9514 and 0630, respectively. Five-year DFS for patients with pCR was 88.9% vs 62.7% in trial 9514 and 90.9% vs 40.0% in trial 0630. Local failure rates at 5 years were 0% in patients with pCR vs 11.7% and 9.1% in trials 9514 and 0630, respectively.

In multivariate analysis, pCR from both trials was associated with improved OS ($p=0.01$), improved DFS(HR 4.91, 95% CI 1.51–15.93, $p=0.008$), improved distant DFS(HR 4.33, 95% CI 1.32–14.14, $p=0.02$), and reduced risk of distant metastases (HR 4.09, 95% CI 1.25–13.36, $p=0.02$). The authors suggest that pCR should be considered a surrogate factor for clinical outcomes in future STS clinical trials [22] , (Table 2).

It is important to note that given the controversial findings of these data, predominantly from real-world studies, prospective randomized clinical trials should be the optimal design for practice changing strategies and to better assess the prognostic value of the pathological response to chemotherapy.

Is there a role for an adjuvant "boost" when surgical margins are positive following resection after pre-operative radiotherapy?

Positive surgical margins after surgery for high-grade ESTS are correlated with a high risk of localrecurrence. The addition of boost radiotherapy when surgical margins are positive in patients pretreated with neoadjuvant radiotherapy at a dose of 50 Gy was studied in several studies [23]. One randomized trial compared pre- (50 Gy) and postoperative (66 Gy) radiotherapy in combination with surgery with an update with longer follow-up [24, 25]. Preoperative radiotherapy was associated with a greater risk of wound complications than postoperative radiotherapy, but long-term follow-up showed that patients treated with postoperative radiotherapy have greater fibrosis, joint stiffness and edema, which is related to the higher RT dose and larger irradiation fields. The long-term advantage of pre-op radiotherapy on morbidity gave rise to its more frequent use recently when

Table 2 Pronostic value of the pathological response to NACT

References	Study	*N*	Neoadjuvant regimen	Results
[19]	Retrospective cohort	46	Adriamycin-based combination (mean 4.4 cycles) followed by local surgery and radiotherapy	Patients with sensitive tumors had significantly superior **OS** (> 60 vs. 32.7 months; $p = 0.02$), **DFS** (> 60 vs. 15.1 months; $p = 0.04$), distant **MFS** (> 60 vs. 28.5 months; $p = 0.006$)
[20]	Real-world series	31	Chemotherapy followed by local surgery	The histological response was not correlated with OS or event-free survival (EFS)
[21]	Retrospective study	207	NACT with or without radiotherapy and then surgery	Histological response > 90% -Improvement of DFS in the univariable analysis - Not confirmed in the multivariable analysis
[22]	Phase II	123	RTOG 0630: preoperative radiotherapy alone RTOG 9514: which assessed preoperative chemo-radiotherapy	-5-year OS was 100% for patients with pCR vs 76.5% (95% [CI] = 62.3%–90.8%) and 56.4% (95% CI = 43.3%–69.5%) in trials 9514 and 0630, respectively -5 Five-year DSF for patients with pCR was 88.9% vs 62.7% in trial 9514 and 90.9% vs 40.0% in trial 0630 - Local failure rates at 5 years were 0% in patients with pCR

possible. One study examined whether a postoperative radiation boost reduced the risk of local recurrence in patients with extremity high-risk soft tissue sarcomas (ESTS) treated with preoperative RT and positive margins [26] Six of 52 patients in the preoperative radiation alone group developed an LR, compared to nine of 41 in the boost group. The estimated 5-year LR-free survival rates were 90.4% and 73.8%, respectively ($p = 0.13$). The authors concluded that a postoperative radiation boost following preoperative radiation and a margin-positive excision did not provide a benefit in preventing LR. Consequently, ESMO and NCCN guidelines do not recommend the addition of this boost [1]. Moreover, 31.9% of patients in the preoperative radiotherapy alone group developed metastatic recurrence compared to 30.9% in the boost group. Kaplan–Meier estimation of MFS at 5 years showed no significant difference for preoperative radiotherapy alone versus the boost approach (68.9% and 67.3%, $p = 0.95$).

Conclusion and perspectives

Based on the literature analysis, we conclude that there is no demonstrated benefit of the addition of post-operative chemotherapy. Furthermore, boost after preoperative radiation and a margin-positive excision do not improve LR prevention in high-grade ESTS. Wide excision and RT are the standard treatments for high-grade (G2-3) tumors according to the ESMO guidelines for 2021 [1]. The order of the two treatments varies by institution, but there is a general trend toward using preoperative RT, particularly when preserving a critical structure is one of the goals. Limb-saving surgery options include neoadjuvant CT and/or RT, or ILP or regional hyperthermia combined with CT which are technics not available everywhere. Adjuvant/neoadjuvant AI CT for at least three cycles is an option to patients at high risk of death. In the future, collaboration between countries and institutions could help to achieve randomized trials in specific situations such are recurrences, or some subtypes. Finally, the prognosis of patients with localized ESTS begins with an adapted diagnosis pathway, including percutaneous biopsy, and is strongly corelated with a treatment in a specialized center after a multidisciplinary tumor board [27, 28].

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Declarations

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