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ORIGINAL ARTICLE

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Current trials and new aspects in soft tissue sarcoma of adults

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Abstract *Purpose*: For high-risk soft tissue sarcoma (HR-STS) of adults new treatment strategies are needed to improve outcome with regard to local control and overall survival. Therefore, systemic chemotherapy has been integrated either after (adjuvant) or before (neoadjuvant) optimal local treatment by surgery and radiotherapy in HR-STS. *Methods and results*: The Soft Tissue and Bone Sarcoma Group (STBSG) of the European Organization for Research and Treatment of Cancer (EORTC) is conducting an open randomized trial of adjuvant chemotherapy in high-grade primary or recurrent STS at any site (EORTC 62931). In all cases primary surgery should be curative in intent. All eligible patients are randomized after completion of definitive surgery to receive either radiotherapy alone with no further treatment (observation arm) or five cycles of doxorubicin (70 mg/m^2) plus ifosfamide (5 g/m^2) using G-CSF to support dose intensity followed by radiotherapy (chemotherapy arm). This more aggressive chemotherapy regimen within an adjuvant setting might retain sufficient antitumor activity to convert response rates into survival benefit. At present more than 220 patients have been recruited for this trial. To explain the rationale for the EORTC 62931 protocol, reported results of other clinical adjuvant protocols including a meta-analysis are given. In close collaboration with the European Society of Hyperthermic Oncology (ESHO) the STBSG has also initiated a randomized trial of neoadjuvant chemotherapy in primary or recurrent HR-STS as an EORTC Intergroup study. According to the inclusion criteria as defined (tumor size ≥5 cm + grade II or III + deep location + extracompartmental extension) for the EORTC 62961/ESHO RHT-95 Intergroup study, the majority of patients with HR-STS recruited for this pre- and postoperative multimodality treatment protocol cannot be cured by standard procedures. All eligible patients are randomized to receive either four cycles of EIA (etoposide 250 mg/m^2 + ifosfamide 6 g/m^2 + doxorubicin 50 mg/m^2) within 12 weeks (chemotherapy arm) or the same EIA regimen combined with regional hyperthermia (RHT + chemotherapy arm). The patients then receive optimal local treatment using adequate surgery immediately followed by radiotherapy. Thereafter an additional four cycles of EIA chemotherapy are given with or without RHT according to the initial randomization. At present more than 150 patients have been recruited for this trial. The integration of RHT as a new potent treatment modality if combined with EIA chemotherapy as first-line treatment for well-defined risk groups is based upon encouraging long-term results of phase II studies both in pretreated patients with HR-STS and in those with locally advanced disease. *Conclusions*: In summary, significant prognostic variables recognized for patients with STS have been addressed in the design of two open phase III clinical trials on adjuvant and neoadjuvant chemotherapy. The best chance for offering such treatment strategies following evidence-based medicine criteria to eligible patients with HR-STS depends upon early contact with the coordinator of the individual protocol prior to any treatment.

Keywords Sarcoma · Adjuvant therapy · Neoadjuvant therapy · Hyperthermia · Ifosfamide

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Introduction

The optimal treatment for high-risk soft tissue sarcoma (HR-STS) in adults remains a challenge for the multidisciplinary approach in modern oncology. Patients with large primary or recurrent HR-STS (size >5 cm, grade II/III) remain at increased risk for distant metastases and tumor-related mortality. Despite surgical resection followed by postoperative irradiation as standard practice to achieve optimal local control, median overall survival of only 33 months [5] or 20 months [11, 21] has been reported for patients with extremity or retroperitoneal HR-STS, respectively. Nearly all deaths are due to metastatic disease (e.g. lung, liver). The tendency for early hematogenous spread as a characteristic feature, especially of HR-STS, may explain why distant metastases still occur in these patients despite optimal local treatment. Also the invasiveness or the anatomic location (e.g. retroperitoneal) of locally advanced tumors often prevent resection with adequate margins, and the toxicity of radiotherapy limits the use of potentially therapeutic doses with a negative impact on local control.

As a reflection of these obstacles, the strategy of systemic chemotherapy has been integrated into the multidisciplinary approach either after (adjuvant) or before (neoadjuvant) locally curative treatment, mainly in order to eradicate distant micrometastases thought to be present at the time of diagnosis. Once inoperative metastatic disease with progression becomes measurable, the intention of systemic chemotherapy remains only palliative. The modest response rates in metastatic disease achieved so far with single-agent or combination chemotherapy in randomized trials have been disappointing. At the present time curative treatment is not an option in this final stage of the disease. Within the last 10 years regional hyperthermia (RHT) as a new treatment modality has entered clinical trials [3]. The results of phase II studies in pretreated and locally advanced patients with STS are encouraging and justify further testing in randomized studies as first-line treatment for well-defined risk groups [13].

Significant prognostic variables recognized for patients with STS [2, 19] have been addressed in the design of recently activated study protocols for adjuvant and neoadjuvant chemotherapy. The best chance for offering such new treatment strategies following good clinical practice (GCP) guidelines to eligible patients with STS depends upon early contact with the coordinator of the individual protocol prior to any treatment. In the following short review, major aspects and guidelines for two ongoing trials which are being conducted in close collaboration with the Soft Tissue and Bone Sarcoma Group (STBSG) of the European Organization for Research and Treatment of Cancer (EORTC) are given in order to provide some information to clinical colleagues involved in the management of patients with HR-STS.

Randomized trial of adjuvant chemotherapy in HR-STS (EORTC 62931 protocol)

In the early 1960s, adjuvant chemotherapy trials were introduced with the aim of increasing disease-free (DFS) and possibly overall (OS) survival. The first generation of randomized adjuvant trials have been reviewed and a quantitative meta-analysis carried out on the basis of updated data from individual patients ($n=1568$) from 14 trials [16]. The main findings are of statistical evidence (hazard ratios) in favor of adjuvant doxorubicin-based chemotherapy for local ($P=0.016$), distant ($P=0.0003$) and overall recurrence-free ($P=0.0001$) survival, corresponding to absolute benefits of 6%, 10% and 10%, respectively, at 10 years.

For overall survival, the hazard ratio was not significant ($P=0.12$), but represents an absolute benefit of 4% at 10 years. Also included in this meta-analysis were the results of the large randomized, prospective EORTC trial of adjuvant CYVADIC chemotherapy for adult STS of the trunk, head and neck and extremities ($n=468$ patients) showing reduced local recurrence but no improvement in survival [1].

A generation of randomized, control-based, adjuvant trials were started in the early 1990s. Their main differences, compared with the previous studies, were the introduction of ifosfamide and the intensification of doses in combination with hematopoietic growth factors (e.g. G-CSF), and more restricted selection criteria.

The STBSG of the EORTC is conducting an open randomized trial of adjuvant chemotherapy in high-grade primary or recurrent STS (EORTC 62931). At present more than 220 patients have been recruited. Patients with histologically proven primary or recurrent STS at any site, with high-grade tumors (grade II or III) only, are eligible. Grading is based upon differentiation, mitosis count and necrosis [18] and all tumors will be reviewed by the EORTC Reference Pathology Panel. In all cases surgery should be radical in intent, removing all macroscopic disease by wide or compartmental excision. In case of prior marginal resection (histopathological clearance margins less than 1 cm) the patient remains eligible for the study if postoperative radiotherapy (60–66 Gy) has been considered to be applicable. However, if the tumor at the time of first presentation is less likely to be removed completely with adequate surgical margins, or only with a loss of function due to mutilative surgery, the patient should be considered for preoperative treatment strategies.

Eligible patients will be randomized after completion of definitive surgery and radiotherapy assessment to receive either no further treatment (observation arm) or five cycles of doxorubicin (75 mg/m^2) plus ifosfamide (5 g/m^2) using G-CSF to increase dose intensity (chemotherapy arm). The maximum interval between definitive surgery to remove all macroscopic disease and starting chemotherapy should be 4 weeks. Patients on the chemotherapy arm will have radiotherapy deferred

until chemotherapy has been completed but radiotherapy must start within 6 weeks of the last chemotherapy. The rationale for using high-dose doxorubicin and ifosfamide is based upon the encouraging objective response rate of 45% obtained in a previous phase II EORTC study in patients with advanced disease [17], although this schedule when randomly compared in a EORTC phase III study with conventional dosage of both cytotoxic agents for metastatic disease did not show superiority to the high dose arm [12]. This more aggressive chemotherapy regimen might retain sufficient antitumor activity within an adjuvant setting to convert enhanced response rates into survival benefits. Only by sufficient recruitment into the EORTC 62931 protocol can a definitive role of adjuvant chemotherapy in high-grade STS be further evaluated.

For the second generation of adjuvant trials, the results of the Italian cooperative study to which 104 patients were recruited have recently been reported [4]. Intensified adjuvant chemotherapy (4′-epidoxorubicin 120 mg/m^2 + ifosfamide 9 g/m^2 total doses per cycle; five cycles repeated every 3 weeks) had a positive impact on DFS and OS of patients with HR-STS at a median follow-up of 59 months. However, to date 60% of the patients had relapsed and continued to die in both arms almost exclusively from uncontrolled metastatic disease. Therefore, the beneficial impact of adjuvant chemotherapy on DFS and OS has to be further demonstrated by definitive results at a 10-year follow-up and to be confirmed by the results of the ongoing EORTC protocol with a larger sample size.

Randomized trial of neoadjuvant chemotherapy in HR-STS (EORTC 62961/ESHO RHT-95 protocol)

Neoadjuvant chemotherapy (chemotherapy delivered before local therapy) has some advantages over postoperative treatment, because the presence of evaluable tumor allows the determination of chemotherapy sensitivity clinically as well as pathologically, and valuable prognostic information may be obtained. The primary tumor may also be downstaged, and some lesions that were technically unresectable may become more amenable to surgical intervention. In addition, drug delivery to the primary tumor may be improved because surgery and radiation therapy have not yet been delivered and the tumor's vascular supply remains undisturbed.

The EORTC has completed the first randomized trial on neoadjuvant chemotherapy in patients with resectable STS of the extremities, head, neck, and trunk. Only high-risk patients were eligible, based on tumor size (>8 cm) or intermediate/high histological grade (mitotic count ≥3 of 10 high-power fields). Three courses of chemotherapy (doxorubicin 50 mg/m^2 + ifosfamide5 g/m^2) were administered before definitive surgery and radiotherapy. Chemotherapy had to start within 6 weeks of biopsy or at an attempt at definitive surgery. Patients in the control arm proceeded to immediate surgery and postoperative radiotherapy. Of 150 patients entered into the study, 134 were eligible, 67 in each arm [6].

This trial was closed after completion of phase II since accrual was insufficient to justify expanding the study into the scheduled phase III study. Objective response rate to preoperative chemotherapy in 49 patients assessable for response was 29%. At a median follow-up of 7.3 years, the 5-year DFS was 52% (control arm) and 56% (chemotherapy arm), respectively ($P=0.35$).

Several phase II studies of neoadjuvant chemotherapy have been carried out in patients with bulky STS according to risk factors (tumor size, grade, inadequate surgery, local recurrence). It appears that some patients benefit from chemotherapy because formerly inoperable cases were rendered operable [14, 15].

The sarcoma group in Munich has focused their interest in RHT as a new treatment modality for locally advanced sarcomas as a clinical model to evaluate the efficacy of combined systemic chemotherapy with RHT in such tumors [7]. The first results have been obtained from a phase II study in 38 adult patients mainly with STS [8]. These patients had relapsed after prior surgery and radiation and had not responded to previous chemotherapy alone. The local response rate was 37%. A drug combination of ifosfamide + etoposide (VP16) was used, combined with RHT as a second-line treatment. Besides long-term tumor control in a subgroup of patients, the analysis of tumor temperatures (e.g. T_{20}, T_{50}, T_{90}) achieved with the BSD system showed significantly higher temperature parameters in responders than in non-responders. The results have been confirmed in an extended trial to which 65 patients with chemopretreated sarcomas were recruited [9].

Two additional consecutive phase II studies have been performed in HR-STS, but these patients had not received prior chemotherapy (chemonaive patients). In the first study (RHT-91 protocol), 59 patients received four cycles of EIA consisting of etoposide, ifosfamide and doxorubicin combined with concurrent hyperthermia. The RHT was applied using an electromagnetic deep regional heating device (BSD system) and the aim was to achieve a maximum tumor temperature of ≥42°C for a period of 60 min. Following this treatment, those patients whose tumor was judged to be resectable underwent surgery. If the tumor showed signs of response, four additional cycles of combined chemotherapy and hyperthermia were given. All patients not preirradiated also received external beam radiotherapy. Treatment-related toxicity was acceptable. Median survival was 52 months and the 5-year survival rate was 49% (95% CI 36–61%) – values quite impressive in this group of patients. The data are in favour of the patients responding to EIA combined with hyperthermia [10].

In the second study (RHT-95 protocol), a similar high-risk patient group (54 patients) received the same treatment as in the RHT-91 protocol with the exception that the patients did not receive hyperthermia after surgery. This study showed an inferior local failure-free survival rate compared with the RHT-91 protocol, but

no difference in overall survival [20]. Thus, postsurgical hyperthermia may be critical for local control.

These results indicate that hyperthermia may have a future in the treatment of patients with HR-STS. Therefore, the EORTC STBSG is further testing this multimodal concept as a first-line treatment of HR-STS in adults in a multicenter prospective phase III trial (EORTC 62961/ESHO RHT-95), as an intergroup study with the ESHO. Patients meeting all of the eligibility criteria at first presentation (tumor size ≥5 cm, grade II or III, extracompartmental) or after inadequate surgery (resections with microscopic/macroscopic residual tumor) are entered into this protocol with the intention of improving local tumor control and early prevention of systemic metastasis.

According to the inclusion criteria defined above, the majority of patients with HR-STS recruited for this multimodality treatment protocol cannot be cured by standard procedures. All eligible patients will be randomized to receive either four cycles of EIA (etoposide 250 mg/m^2 + ifosfamide 6 g/m^2 + doxorubicin 50 mg/m^2) within 12 weeks (chemotherapy arm) or the same EIA regimen combined with RHT (RHT arm). The patients will then receive optimal local treatment using adequate surgery immediately followed by radiotherapy. After the completion of radiotherapy an additional four cycles of EIA chemotherapy alone (arm B) or in combination with RHT (arm A) will be given. The application of RHT with external annular phased array applicators (60–100 MHz) results in a selective temperature elevation (range 40–44°C) within the tumor and the directly adjacent tissue. The EIA regimen of the neoadjuvant protocol combines conventional doses of the most active single agents (doxorubicin + ifosfamide) in STS with etoposide being added prior to RHT on days 1 and 4 of each cycle. This combination of systemic EIA chemotherapy and RHT has been shown to be effective in HR-STS and allows an adequate conservative surgical approach after four EIA/RHT cycles in responding patients for whom radical resection without mutilation (e.g. hemipelvectomy, amputation) was formerly considered impossible [10]. At present more than 150 patients have been recruited for this intergroup study.

Conclusions

A short description of the background, the special design, and the rationale of two ongoing, randomized multicenter protocols for patients with HR-STS is given above. Other important topics (e.g. perfusion study using TNF + melphalan, preoperative chemotherapy) have not been addressed. Clinical advances in the treatment of STS are often hampered by the difficulty in accruing enough patients for prospective clinical trials. The intention of this review is to emphasize that collaboration among European institutions and among the individual oncologists who are going to enter patients in such trials is the only basis that can provide the long-awaited answers to open questions in the treatment of STS.

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