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CLINICAL INVESTIGATION **Sarcoma**

FIVE-YEAR RESULTS FROM A SCANDINAVIAN SARCOMA GROUP STUDY (SSG XIII) OF ADJUVANT CHEMOTHERAPY COMBINED WITH ACCELERATED RADIOTHERAPY IN HIGH-RISK SOFT TISSUE SARCOMA OF EXTREMITIES AND TRUNK WALL

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Purpose: To evaluate adjuvant chemotherapy and interpolated accelerated radiotherapy (RT) for adult patients with high-risk soft tissue sarcoma in the extremities or trunk wall.
Methods and Materials: High-risk soft tissue sarcoma was defined as high-grade malignancy and at least two of the following criteria: size ≥8 cm, vascular invasion, or necrosis. Six cycles of doxorubicin and ifosfamide were prescribed for all patients. RT to a total dose of 36 Gy (1.8 Gy twice daily) was inserted between two chemotherapy cycles after marginal margin resection regardless of tumor depth or after wide-margin resection for deep-seated tumors. RT was boosted to 45 Gy in a split-course design in the case of intralesional margin resection.
Results: A total of 119 patients were eligible, with a median follow-up of 5 years. The 5-year estimate of the local recurrence, metastasis-free survival, and overall survival rate was 12%, 59%, and 68%, respectively. The group receiving RT to 36 Gy had a local recurrence rate of 10%. In contrast, the local recurrence rate was 29% in the group treated with RT to 45 Gy. The presence of vascular invasion and low chemotherapy dose intensity had a negative effect on metastasis-free and overall survival. Toxicity was moderate after both the chemotherapy and the RT.
Conclusions: Accelerated RT interposed between chemotherapy cycles in a selected population of patients with high-risk soft tissue sarcoma resulted in good local and distant disease control, with acceptable treatment-related morbidity. The greater radiation dose administered after intralesional surgery was not sufficient to compensate for the poorer surgical margin. Vascular invasion was the most important prognostic factor for metastasis-free and overall survival. © 2011 Elsevier Inc.

Soft tissue sarcoma, Adjuvant treatment, Accelerated radiotherapy, Chemotherapy, Prognostic factors.

INTRODUCTION

The prognosis of high-grade malignant soft tissue sarcoma (STS) remains poor, with approximately one-half of the patients with initially localized STS dying of their disease (1). It has been well established that adjuvant radiotherapy (RT) for STS improves local control (2–7). The indications for RT depend on the risk factors for local recurrence (LR), of which the quality of surgical margin, malignancy grade, and tumor size are central (4, 8–10). The malignancy grade and tumor size are also important prognostic factors for metastasis-free survival (MFS) and overall survival (OS) (7–11). The results of several attempts to demonstrate a benefit of adjuvant chemotherapy have proved contradictory (12–20). Different drugs have been investigated; however, doxorubicin remains the cornerstone of chemotherapy for STS (1). The effect of ifosfamide is not evident, although the most recently published meta-analysis reported that adding ifosfamide to doxorubicin improved OS (14, 20). Allocating adjuvant treatment to STS patients with poor prognostic factors has not clarified the role of chemotherapy (16, 18, 21–23).

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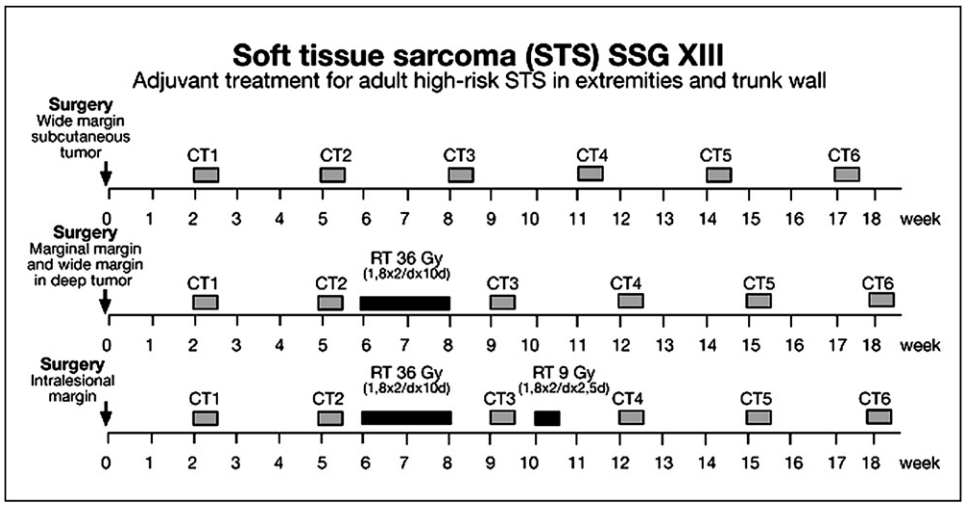

Fig. 1. Treatment schedule of Scandinavian Sarcoma Group (SSG) XIII clinical study. STS = soft tissue sarcoma; CT = chemotherapy (followed by cycle number); RT = radiotherapy (followed by dose).

The diverging results from the adjuvant chemotherapy trials might have resulted from the case-mix because of the heterogeneous biology of STS; thus, meticulous selection of patients might yield more positive results. Recently studied factors of prognostic importance in STS have included vascular invasion (microscopic foci of tumor cells within small vessels), tumor necrosis, growth pattern (infiltrative growth vs. pushing tumor margins), and the immunohistochemical profile, leading to modified prognostication systems (24–26). In the current Scandinavian Sarcoma Group (SSG) clinical study (SSG XIII), the SIN system was applied: tumor Size and the presence of vascular Invasion or Necrosis in the tumor specimen, factors previously shown strongly correlated to survival (9). In high-grade STS, this system provides two distinct prognostic groups and has been validated with high reproducibility (24).

The prospective, nonrandomized SSG XIII clinical study was designed to investigate the combination of doxorubicin and ifosfamide in a well-defined subgroup of STS patients with a high risk of developing metastases (Fig. 1). The aim was to improve the 5-year MFS from 40% to 70% (24). With increasing evidence of the benefit of adjuvant RT, depending on the surgical margins and tumor location (3), a concept of accelerated RT interspersed between chemotherapy cycles was proposed. A similar approach was featured in a Scandinavian study of Ewing's sarcoma (27). The rationale was to minimize the delay between surgery and adjuvant chemotherapy and RT instead of the sequential delivery of the two treatment modalities.

METHODS AND MATERIALS

Eligibility

The SSG XIII clinical study was conducted from July 1998 to August 2007. Patients 18–70 years old with localized, high-risk STS in the extremities or trunk wall were included. High risk was defined as a high-grade malignant tumor (Grade III or IV in the four-tiered Scandinavian grading system comparable to Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] Grade 3), with at least two of the following: tumor size ≥8 cm and macroscopic or microscopic necrosis or vascular invasion (9, 28). The SSG Pathology Reference Group reviewed the morphology. The following histotypes were excluded: extraskeletal Ewing's sarcoma, osteosarcoma or chondrosarcoma, malignant mesenchymoma, clear cell sarcoma, alveolar soft part sarcoma, epithelioid sarcoma, rhabdomyosarcoma, and Kaposi's sarcoma. The study was conducted in accordance with the Helsinki Declaration of 1975 (revised in 2000).

Surgery

The surgical margin was classified according to the SSG guidelines (SSG VII:4) (29). An intralesional margin was recorded if microscopic or macroscopic tumor tissue was left behind in the tumor bed and re-excision was not feasible. A wide margin was recorded when a cuff of healthy tissue or uninvolved fascia surrounded the whole tumor circumference. If the cuff of healthy tissue was absent, even in only a small area, but without any signs of microscopic margin involvement, a marginal margin was recorded. All patients underwent surgical treatment at a sarcoma center, with the intention of a wide resection when possible.

Radiotherapy

Radiotherapy was administered as an accelerated regimen with 1.8 Gy twice daily (Monday–Friday) with ≥6-h interval between each fraction. A total dose of 36 Gy within 2 weeks was prescribed to patients with deep-seated tumors resected with a wide or marginal margin and to those with subcutaneous tumors resected with a marginal margin. In cases of an intralesional margin, a boost dose of 9 Gy was added (1.8 Gy twice daily within 2.5 days) to a total dose of 45 Gy. RT was not considered indicated after wide margin surgery for subcutaneous tumors. The 36-Gy radiation dose was interposed between the second and third cycle of chemotherapy with a 1-week prolongation of the interval between these cycles (Fig. 1). The greater dose level was administered using a split-course design, with the boost dose delivered between the third and fourth chemotherapy cycles. An option was allowed of giving 45/50 Gy as a continuous preoperative course, in which case no postoperative RT was given.

The biologic effects of the accelerated RT to a total dose of 36 Gy or 45 Gy were calculated to be equivalent to that with conventional fractionation with 2 Gy daily to a total dose of 50 or 60 Gy, respectively. An α/β ratio of 10 (acute effects and tumor) or α/β ratio of 3 (late effects) was assumed using the equation: biologic effective