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Original Research

Adjuvant chemotherapy and postoperative radiotherapy in high-risk soft tissue sarcoma patients defined by biological risk factors—A Scandinavian Sarcoma Group study (SSG XX)☆

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Survival

Abstract ***Purpose:*** To investigate the outcome following adjuvant doxorubicin and ifosfamide in a prospective non-randomised study based on a soft tissue sarcoma (STS) patient subgroup defined by specific morphological characteristics previously shown to be at a high-risk of metastatic relapse. The expected 5-year cumulative incidence of metastases in patients with this risk profile has previously been reported to be about 50% without adjuvant chemotherapy.

Methods: High-risk STS was defined as high-grade morphology (according to the Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade II–III) and either vascular invasion or at least two of the following criteria: tumour size ≥8.0 cm, infiltrative growth and necrosis. Six cycles of doxorubicin (60 mg/m^2) and ifosfamide (6 g/m^2) were given. Postoperative accelerated radiotherapy was applied and scheduled between cycles 3 and 4.

Results: For the 150 eligible patients, median follow-up time for metastases-free survival was 3.9 years (range 0.2–8.7). Five-year metastases-free survival (MFS) was 70.4% (95% confidence interval [CI]: 63.1–78.4) with a local recurrence rate of 14.0% (95% CI: 7.8–20.2). For overall survival (OS), the median follow-up time was 4.4 years (range: 0.2–8.7). The five-year OS was 76.1% (95% CI: 68.8–84.2). Tumour size, deep location and reduced dose intensity (<80%) had a negative impact on survival. Toxicity was moderate with no treatment-related death.

Conclusions: A benefit of adjuvant chemotherapy, compared to similar historical control groups, was demonstrated in STS patients with defined poor prognostic factors. Vascular invasion, tumour size, growth pattern and necrosis may identify patients in need of adjuvant chemotherapy.

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1. Introduction

Adjuvant chemotherapy is not a standard treatment for soft tissue sarcoma (STS), and clinical practice guidelines are vague in their recommendations in this regard [1,2]. Furthermore, in STS, there is no consensus on which prognostic factors that may identify patients benefiting from adjuvant chemotherapy.

Outcomes of the former adjuvant protocol from the Scandinavian Sarcoma Group (SSG) conducted in high-risk STS, SSG XIII, showed that 5-year metastases-free (MFS) and overall survival (OS) were 59% and 68%, respectively [3]. In that study, classification of a high-risk STS was based on tumour size, vascular invasion and tumour necrosis [4–6]. In the current phase II non-randomised study (SSG XX), peripheral tumour growth was added as a risk factor [7]. The key inclusion criteria were either vascular invasion or presence of at least two of the three risk factors: size ≥8.0 cm, infiltrating peripheral growth pattern and necrosis. High-risk STS, as defined by this system (SING), had a five-year cumulative incidence of metastases of 0.51 (95% confidence interval [CI]: 0.41–0.60) as shown by Engellau *et al.* [7,8]. In SSG XIII, low chemotherapy dose intensity had a negative impact effect on both MFS and OS [3]. In SSG XX, the doses of doxorubicin and ifosfamide were increased by 20%. This publication reports data on MFS and OS with a focus on the impact of chemotherapy.

2. Methods

2.1. Criteria for inclusion

The main eligibility criteria were ages ≥18 to ≤75 years, World Health Organization (WHO) performance status ≤ 1, high-risk primary STS located in the extremities or trunk wall and surgery with an R0 or R1 excision. High-risk tumours were defined as high-grade (grade III or IV on a 4-grade scale) with risk factors as previously described, all defined microscopically by the pathologist on the surgical specimen [9].

The SSG Pathology Reference Group reviewed the morphology in all cases, according to WHO classification and malignancy grade with the FNCLCC system [10–12]. Vascular invasion and infiltrative peripheral tumour growth pattern were also reviewed. The tumour size was measured by the local pathologist. Tumour depth was defined in relation to the deep fascia.

The following histotypes were excluded: extraskeletal osteosarcoma and chondrosarcoma, Ewing's sarcoma, rhabdomyosarcoma, Kaposi sarcoma, clear cell sarcoma, alveolar soft part sarcoma, epithelioid sarcoma and radiation-induced sarcoma.

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