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Original Research

First-line anthracycline-based chemotherapy for angiosarcoma and other soft tissue sarcoma subtypes: Pooled analysis of eleven European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials

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Abstract ***Background:*** Angiosarcoma is a rare subtype of soft tissue sarcoma (STS). Doxorubicin is the standard first-line chemotherapy for advanced STS. It is not known whether angiosarcoma response to anthracycline-based chemotherapy is different to other STS subtypes.
Methods: Pooled data were analysed from 11 prospective randomised and non-randomised European Organisation for Research and Treatment of Cancer (EORTC) clinical trials of first-line anthracycline-based chemotherapy for advanced STS. Baseline patient characteristics, chemotherapy response, progression free survival (PFS) and overall survival (OS) of angiosarcoma patients were compared with other STS patients. Analysis was performed to identify factors prognostic for angiosarcoma response to chemotherapy, PFS and OS.
Results: With a median follow-up of 4.2 years, data from 108 locally advanced and metastatic angiosarcoma patients and 2557 patients with other STS histologies were analysed. 25% of angiosarcoma patients had a complete or partial response to chemotherapy compared to 21% for other STS histotypes. The median PFS was 4.9 months and OS 9.9 months, which were not significantly different from other STS histotypes. In univariate analysis, bone metastases were an adverse prognostic factor for OS (hazard ratio (HR) 1.66, 95% confidence interval

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(CI) 1.03–2.67; $p = 0.036$). Tumour grade was as an adverse prognostic factor for PFS (HR 1.72, 95% CI 1.01–2.92; $p = 0.044$) and OS (HR 2.03; 95% CI 1.16–3.56; $p = 0.011$). Compared to single agent anthracyclines, doxorubicin + ifosfamide was associated with improved PFS (HR 0.53, 95% CI 0.33–0.86; $p = 0.010$) and OS (HR 0.53, 95% CI 0.32–0.90; $p = 0.018$).

Conclusions: Angiosarcoma response and survival following first-line anthracycline-based chemotherapy was similar to other STS histotypes. Our analysis provides a useful measure of angiosarcoma response to chemotherapy for comparison with future clinical trials.

1. Introduction

Angiosarcoma is a rare subtype of soft tissue sarcoma (STS) with endothelial differentiation [1]. It represents 4.1% of all STS with an incidence rate of 2.1 per million as reported by the US Surveillance Epidemiology and End Results (SEER) program [2]. Similarly, the United Kingdom (UK) National Cancer Intelligence Network (NCIN) reported that angiosarcomas represent 3.3% of all STS with an incidence rate of 1.5 per million [3]. Both SEER and NCIN data show that the incidence of angiosarcoma is increasing in women, which has been attributed to the increased use of radiotherapy for the breast-conserving treatment of primary breast cancer.

Angiosarcomas usually present as cutaneous tumours, most frequently developing on the head and neck of elderly white men. However primary tumours can develop at any site, including breast, bone or viscera [1]. Secondary angiosarcoma of the breast or chest wall can be induced by chronic lymphoedema after treatment for primary breast cancer, the so-called Stewart–Treves syndrome, or maybe radiation induced, not necessarily in combination with lymphoedema [4,5]. Hepatic angiosarcomas are associated with exposure to carcinogens such as vinyl chloride, arsenic and thorium dioxide [1]. Localised disease may be successfully treated with radical surgery and post-operative radiotherapy, but angiosarcomas have a high risk of recurrence and the prognosis with advanced disease is poor. A large, single-centre study of 222 angiosarcoma patients reported that 179 patients with localised disease had a median survival of 49 months compared to 10 months for 43 patients with metastatic disease [6].

As angiosarcomas are malignant vascular tumours, there is interest in defining the role of angiogenic growth factors in their pathogenesis, and in using vascular targeted agents as therapy. Single-arm phase II clinical trials of anti-angiogenic therapy for advanced disease have reported response rates of 15% to treatment with the vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI) sorafenib [7,8], and 10% with the anti-VEGF antibody bevacizumab [9]. Case reports suggested an excellent response to taxane chemotherapy which has anti-angiogenic properties in addition to direct anti-tumour effects [10]. However, a prospective phase II study of weekly paclitaxel for unresectable angiosarcoma reported a response rate of only 18% [11].

Whilst interesting, the results from these phase II clinical trials are limited by the absence of any comparator. Anthracycline-based regimens are considered the standard-of-care first-line chemotherapy for advanced STS including angiosarcoma [12]. However, there have been no angiosarcoma-specific clinical trials that define their response to first-line anthracycline-based chemotherapy. The Soft Tissue and Bone Sarcoma Group (STBSG) of the European Organisation for Research and Treatment of Cancer (EORTC) have undertaken a number of prospective clinical trials of different chemotherapy regimens for the first-line treatment of advanced STS, with similar eligibility criteria [13–23]. Data from these studies have been collated into a large central database. We interrogated this database to define the response of advanced angiosarcoma to first-line anthracycline-based chemotherapy for future comparison with response to treatment with other therapeutic agents, to compare angiosarcoma response to first-line anthracycline-based chemotherapy with that of the other STS histological subtypes in the database, and to identify prognostic factors associated with angiosarcoma response to anthracycline-based chemotherapy.

2. Methods

2.1. Patients included in the analysis

The EORTC-STBSG database contains 3151 patients with locally advanced or metastatic STS, prospectively registered and treated in 11 different clinical trials of first-line anthracycline-based chemotherapy between 1977 and 2010 (Table 1). Patients who received prior (adjuvant or palliative) chemotherapy for soft tissue sarcoma, those with missing histology, or those treated with docetaxel or ifosfamide chemotherapy only were excluded from the analysis. The study population therefore consisted of 2665 patients, which included 108 patients with angiosarcoma, with a median follow up of 4.2 years (interquartile range (IQR) 2.7–6.5). The age eligibility criteria varied between the EORTC-STBSG clinical trials, but patients over 75 years were largely excluded; EORTC-62012 had an upper age limit of 60, and EORTC-62971 had an upper age limit of 65.