European Journal of Cancer 94 (2018) 187–198

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Prognostic relevance of distant metastases versus locally advanced disease in soft tissue sarcomas: An EORTC-STBSG database study

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Received 5 June 2017; received in revised form 3 February 2018; accepted 8 February 2018

KEYWORDS
Soft tissue sarcoma;
Survival;
Chemotherapy;
Prognostic factors;
Retrospective study

Abstract ***Introduction:*** In patients with advanced soft tissue sarcoma (STS) treated with chemotherapy, WHO performance status, histologic subtype and histologic grade are known prognostic factors. Although the difference between the subgroups: locally advanced disease only, metastatic disease only and both local and metastatic disease is easily made, its prognostic relevance is thus far unknown. The aim of this EORTC database study was to study the difference in prognosis between these subgroups in patients receiving first-line chemotherapy for advanced STS.

Methods: A retrospective database analysis was performed on 2473 patients receiving first-line chemotherapy for advanced STS from 12 EORTC sarcoma trials to establish the difference in prognosis for the three subgroups. End-points were overall survival, progression-free survival and overall response rate. Factors studied were age, sex, histologic subtype, histologic grade, WHO performance status, treatment and time since initial diagnosis.

Results: Overall survival differed significantly between patients with locally advanced disease only, with metastatic disease only and with both locally advanced and metastatic disease with

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https://doi.org/10.1016/j.ejca.2018.02.015

a median overall survival of 15.4, 12.9 and 10.6 months, respectively. Similar differences were seen for progression-free survival (5.8, 4.3 and 3.2 months, respectively).
Conclusion: This large retrospective database study shows that patients with advanced STSs treated with first-line chemotherapy with locally advanced disease, metastatic disease and both local and metastatic disease have different outcomes. This should be accounted for in future study design, interpretation and comparison of study results and daily practice.

1. Introduction

Soft tissue sarcomas (STSs) are a rare group of tumours consisting of more than 70 histological different subtypes [1]. For the treatment of most subtypes, doxorubicin alone or in combination remains first-line treatment with e.g. pazopanib and trabectedin as second-line options [2–5]. For anthracycline and ifosfamide-based treatments, prognostic and predictive factors were established [6–9]. These studies identified response to chemotherapy, WHO performance score, histological subtype and time since initial diagnosis to be prognostic for overall survival (OS) in STS [6–9]. One of these studies also identified a difference in OS between patients with locally advanced disease (LAD) and patients with distant metastases (DM), favouring the first subgroup when treated with first-line ifosfamide therapy [6].

Although the difference between LAD and DM is easily made, no study investigated whether differences in outcome and response exist between these two subgroups, which could make them factors of prognostic relevance. The identification of prognostic factors is necessary for patient care and design of clinical trials. The aim of this study is to investigate whether important differences exist in OS, progression-free survival (PFS) and response rate (ORR) between the different disease subgroups and is an exploratory analysis of the prognostic factors for OS, PFS and ORR in patients with STS and either LAD or DM at the moment of inclusion in a first-line chemotherapy study of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG).

2. Methods

2.1. Patients

The EORTC-STBSG database contains data of 3708 patients from 15 EORTC advanced STS trials considering first-line treatment [4,5,10–22]. Supplementary Tables 1 and 2 describe the different studies and the number of patients included in this study. From this database patients were excluded who had no documentation of lesions at trial entry, who had no survival data available, who were treated with a CYVADIC (cyclophosphamide/vincristine/doxorubicin/dacarbazine) regimen (EORTC-study 62761) [10] or docetaxel (1 arm of 62941) [17], who had prior (adjuvant or palliative) chemotherapy, for whom not enough information was available to distinguish primary from metastatic disease (62883 and 62901; 14, 15), or who were diagnosed with gastrointestinal stromal tumour (GIST) or an ineligible tumour, being not STS.

Patients were grouped in a group with local disease only (LAD), a group with metastatic disease only (DM) and both locally advanced and metastatic disease. LAD was defined either as locally advanced disease not amenable to surgery or locally recurrent disease. DM only was defined as distant metastatic disease without evidence for local disease. Patients in the group with both had local disease and distant metastatic disease at study inclusion.

2.2. End-points

Study end-points were OS, PFS and ORR to therapy. OS was computed from the date of randomisation or the date of prospective registration (nonrandomised trials) to date of death. Patients alive at last follow-up were censored. PFS was defined as time interval between date of randomisation or prospective registration and date of first documented progression or death, whichever comes first. ORR to chemotherapy was evaluated according to WHO or RECIST criteria depending on the study [23–25]. In this study, it was analysed as binary variable, i.e. complete response and partial response are considered response and stable disease, progression or non-evaluable assessment were considered failures.

2.3. Statistical methods

2.3.1. Covariates

Demographic data included were age, sex and performance status before the start of chemotherapy. Performance status was measured on the WHO scale. Variables related to the history of the sarcoma were the site of the primary tumour, the use of prior radiotherapy and/or prior surgery and time since first diagnosis of sarcoma. Because information on prior radiotherapy or prior surgery was not collected in the more recent trials,