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Systematic or Meta-analysis Studies

Multi-agent chemotherapy in advanced soft tissue sarcoma (STS) – A systematic review and meta-analysis

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ABSTRACT

Background: Despite a lack of improvement in overall survival (OS) with doxorubicin-based combinations over doxorubicin alone in advanced STS, the role of multi-agent chemotherapy remains poorly defined.

Methods: We conducted a systematic review and meta-analysis to evaluate benefits and harms of multi-agent chemotherapy in advanced STS. Eligible studies were randomized trials of chemotherapy in advanced STS comparing single agent to multi-agent therapy. Data from studies reporting a hazard ratio (HR) and 95% confidence intervals (CI) for OS and progression-free survival (PFS) were pooled in a meta-analysis. Meta-regression was utilized to explore the association between efficacy (OS and PFS) and both toxicity and dose intensity.

Results: We identified 22 trials published between 1974 and April 2016 and comprising 5044 patients. Overall, multi-agent chemotherapy was associated with improved OS (HR:0.79, p = 0.02), and borderline improvement in PFS (HR:0.86, p = 0.05). While the effect on OS was similar in trials with non-anthracycline controls compared to those with anthracycline controls (HR for OS 0.73 vs. 0.82, p for dif ference = 0.63) there was a non-significantly greater effect for multi-agent chemotherapy on PFS in non-anthracycline RCT (HR for PFS 0.73 vs. 0.91, p for difference = 0.13). Compared to studies with cytotoxic therapy-based multi-agent therapy, a non-significantly greater magnitude of effect among studies with biological/cytostatic experimental groups was seen (HR for OS 0.64 vs. 0.86, p for difference = 0.37). There was a borderline significant association between dose reductions (which were more common in combination arms) and worse PFS (beta = 0.70, p = 0.053).

Conclusion: Multi-agent chemotherapy is associated with a modest, but statistically significant improvement in outcomes in STS. Combining chemotherapy with non-cytotoxic agents might represent a promising strategy.

Introduction

Since the first report of doxorubicin activity in soft tissue sarcomas (STS), several agents have been introduced and evaluated either as single agents or in combinations. A meta-analysis published in 2003 found that compared to single agent chemotherapy, doxorubicin-based combination chemotherapy resulted in marginally superior overall response rate (ORR) without overall survival benefit and at the cost of increased toxicity [1]. Nevertheless, advocates of multi-agent chemotherapy suggested the analysis included trials that used sub-therapeutic doses of anthracyclines and alkylating agents [2]. Five studies investigating doxorubicin intensification among other studies of single versus combination therapy in advanced STS have been published since the above review [3–7], with only one demonstrating a survival benefit for the combination arm. Of particular interest, in the EORTC 62012 study [4] in which patients with advanced, high-grade STS were randomly assigned to receive doxorubicin (75 mg/m^2) or doxorubicin (75 mg/m^2) and ifosfamide (10 g/m^2), at doses considered adequate in STS, there was no significant difference in the primary outcome, overall survival (OS), however, median progression-free survival (PFS) and ORR were significantly higher for combination

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chemotherapy. Despite these negative results, controversy remains. Those in favor of single agent treatment point to the lack of survival benefit and increased toxicity with multi-agent chemotherapy while supporters of combination therapy focus on the increased ORR and improved PFS.

Here we report an updated meta-analysis of all randomized trials in advanced STS comparing single agent versus multi-agent therapy in order to further explore the role of multi-agent chemotherapy. We aimed to better understand the impact of the treatment backbone and the intensification strategy (addition of chemotherapy or biologic/cytostatic agent) on outcomes. We hypothesized that multi-agent chemotherapy would not be associated with improved OS compared to single agent chemotherapy.

Methods

Identification of eligible studies

A systematic search of MEDLINE and EMBASE was conducted by 2 independent reviewers (AZ, RP) to identify reports of randomized controlled trials (RCTs) of systemic therapy in advanced STS, comparing single agent to multi-agent therapy published between 1974 and April 2016.

The search was not limited by language, sample size, phase, type of design, endpoint selection, line of treatment, blinding, geographic origin or sponsorship (full search strategy is available in supplementary data). We additionally searched the American Society of Clinical Oncology and European Society of Medical Oncology/European Cancer Congress meeting abstracts. Abstracts of studies subsequently reported in full were excluded.

Due to their distinct biological characteristics, RCTs involving bone-sarcoma and gastrointestinal stromal tumors (GIST) were excluded. We also excluded review articles, meta-analyses, systematic reviews, non-randomized clinical trials, observational studies and case reports.

Data extraction

A standardized pre-designed data extraction form was used. Data were extracted from each eligible RCT independently by two authors (AZ, RP). The following data were collected: publication date, sample size, sarcoma subtype, phase II vs III RCT, line of treatment, endpoints included, PFS, OS and ORR in each study

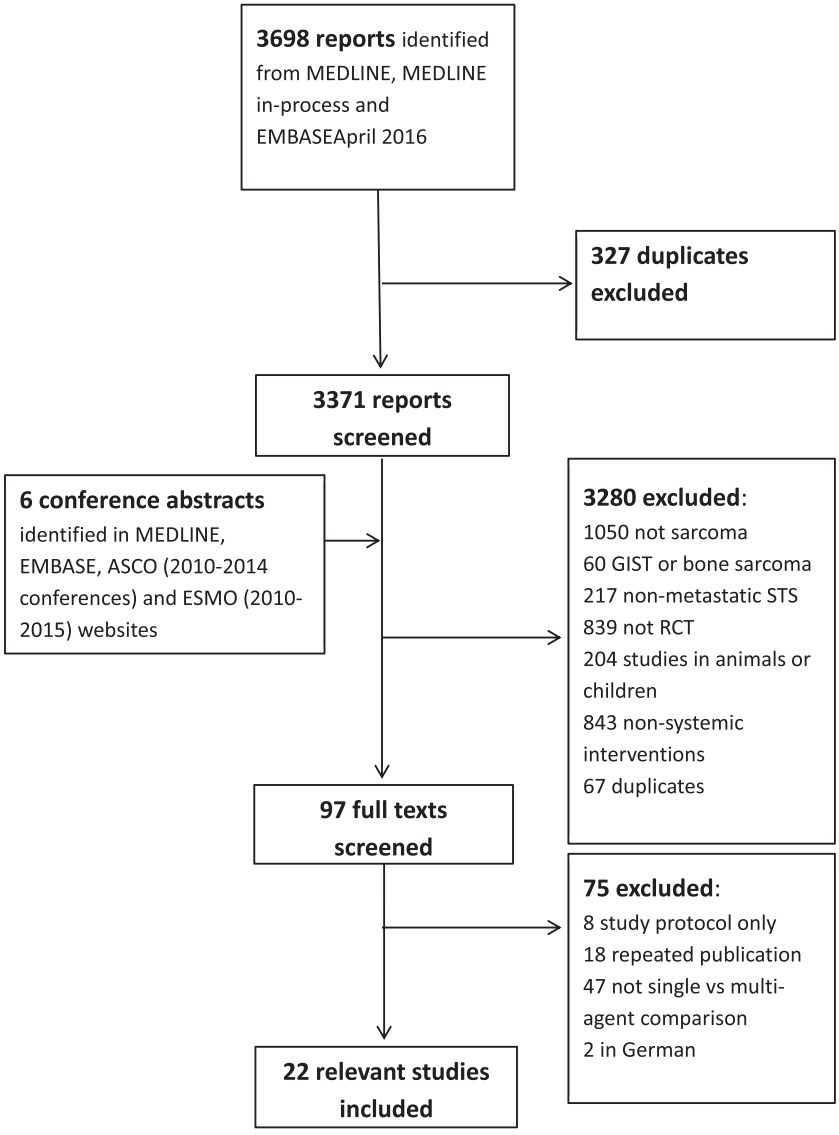

Fig. 1. Study flow diagram.