



Comparison between trabectedin and doxorubicin in soft-tissue sarcomas: a systematic review and meta-analysis

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Background: This study sought to evaluate the differences between trabectedin and doxorubicin in the treatment of soft-tissue sarcoma (STS).

Methods: Multiple databases, including PubMed, Web of Science, Cochrane Library, and China National Knowledge Infrastructure, were searched to retrieve relevant articles. Ultimately, the full text of 10 studies involving the use of trabectedin and doxorubicin in STS were reviewed. Review Manager 5.2 was used to evaluate the heterogeneity of the results of the selected articles. Forest plot, bias, and sensitivity analyses were carried out on the included articles.

Results: Ten papers that met the criteria were included in this analysis. STS patients receiving trabectedin had longer progression-free survival than those receiving doxorubicin [overall mean difference (MD) =1.36, 95% confidence interval (CI): 1.04, 1.68, $I^2=6%$, fixed-effects model]. The experimental group also had a longer overall survival period than the control group (MD =3.92, 95% CI: 0.23, 7.60, $P=0.04$ and $I^2=83%$, random-effects model), and the experimental group had a better disease control rate than the control group (relative risk =1.2, $P=0.03$ and $I^2=45%$, fixed-effects model). From the publication bias analysis and sensitivity analysis, we can guarantee the results are robust and unbiased.

Discussion: Our research showed that STS patients who received trabectedin had better clinical effects and a longer survival time than those who received doxorubicin.

Keywords: Trabectedin; doxorubicin; soft tissue sarcoma (STS); meta-analysis

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Introduction

Soft tissue sarcoma (STS) consists of rare malignancies, and accounts for about 1% of all adult cancers (1). There are more than 70 different histological STS subtypes; however, the most common high-grade STS subtypes include undifferentiated STS, liposarcoma, and smooth

muscle sarcoma (1,2). 60% of patients have local diseases at the time of diagnosis, and about 40% of patients develop metastasis within 5 years, which is associated with inferior survival outcomes (3). According to the medical history, clinical manifestation and laboratory examination, soft tissue sarcoma is not difficult to diagnose. The possibility

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of this disease should be highly suspected in the following cases: the patient found painless progressive mass, fever and weight loss in a few weeks or months. Treatment options for STS include surgical resection, radiotherapy and drug therapy (2,3).

For patients with localized STS, surgery is the main treatment option and has a potential curative effect (3). Other STS treatments include radiotherapy and chemotherapy (4). Anthracyclines (such as doxorubicin) are the common first-line drugs used in unresectable or metastatic STS. The median progression-free survival (PFS) time after doxorubicin treatment is 4 months (5). The median overall survival (OS) time is 12–18 months after doxorubicin monotherapy (5-7).

Forty years after its emergence as a sarcoma treatment drug, Adriamycin remains the standard first-line treatment for STS. Randomized studies comparing doxorubicin to trabectedin did not find that the combined treatment group had a survival advantage, but a slight improvement in response rate was observed (8-10). Thus, the efficacy expectation of STS as a first-line system treatment is low.

In September 2007, trabectedin, the first anti-cancer derivative drug, was approved by the European Drug Administration to treat patients with advanced sarcoma after treatment with Doxorubicin has failed (11,12). At present, trabectedin is used in nearly 80 countries worldwide to treat adult advanced STS after the failure of anthracycline and ifosfamide treatments, or to treat those who cannot be treated with anthracycline and ifosfamide (13,14). In 2015, trabectedin was approved by the United States Food and Drug Administration after a critical randomized phase III trial with patients with advanced liposarcoma or leiomyosarcoma who did not respond to anthracycline-containing chemotherapy (14). trabectedin has a pleiotropic mechanism (15). In addition to its ability to induce the direct growth inhibition and death of malignant cells, trabectedin also has selective anti-inflammatory, immune regulating, and anti-angiogenetic characteristics. The safety of trabectedin is acceptable and manageable, and there is no evidence of cumulative toxicity or end-organ dysfunction even among patients who undergo long-term treatments with trabectedin (16-18). It was reported that the most common adverse reactions were nausea, fatigue, vomiting, constipation in drug treatment of STS (17).

To date, very few comprehensive analyses have been conducted comparing the effects of trabectedin and doxorubicin in the treatment of STS. Thus, we conducted a meta-analysis based on relevant randomized control trials

(RCTs) to explore this issue.

We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-6033>).

Methods

Literature search strategy

The PubMed, Excerpta Medica dataBASE, Cochrane library, and China National Knowledge Infrastructure databases were systematically searched from their inception to September 2021, with the keywords: (I) soft-tissue sarcoma OR metastatic soft-tissue sarcomas; (II) chemotherapy OR doxorubicin; (III) trabectedin. The search strategy involved medical subject headings and text words combined with the Boolean operator, “AND”. The literature search was comprehensive, and had no language restrictions or publication status limitations. To maximize the specificity and sensitivity of the retrieval, the authors also checked the reference list of the retrieved studies to identify other relevant studies that have not been identified by the retrieval strategy.

Study selection

Both RCTs and retrospective trials were included in the analysis. To be eligible for inclusion in the meta-analysis, articles had to meet the following inclusion criteria: (I) have full-text availability; (II) comprise a population of patients with mean ages ranging from 10 to 100 years; (III) compare interventions of trabectedin and doxorubicin; (IV) include the comparators; and (V) have a RCT or retrospective trial design. Studies were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) examined other topics; (II) compared other interventions; (III) had unavailable data; and/or (IV) were duplicate publications.

Data extraction and quality assessment

Two of the authors independently screened the papers included in the final analysis and extracted the relevant data directly from the documents. The following data were extracted: the name of the primary author, the country of the study, the number of patients in the study, the number of participants in each condition, and the age of the patients. If the standard deviation (SD) was missing, but the baseline SD was reported, the missing SD was replaced with

baseline SD. If the average value could not be obtained but the median was reported, the median was used.

The risk of bias of the included studies was assessed using Cochrane's risk of bias tool. Two authors conducted risk of bias assessments for all the included RCTs. If there was a disagreement, a 3rd author reviewed the assessments, and the authors engaged in discussion until a consensus was reached.

Statistical analysis

Review manager (version 5.2, Cochrane Collaboration, 2011) was used to evaluate the results of the selected studies. To measure the consistency of the effect size [mean difference (MD) or odds ratio (OR)], a fixed- or random-effects model was chosen for the meta-analysis based on the I^2 value to calculate the combined estimated value between the 2 interventions. Chi-square and I^2 statistical tests were used to test heterogeneity of included comparators. If $I^2 \leq 50\%$, there was no or little heterogeneity between the studies, and the fixed-effects model was used for the analysis. If $I^2 > 50\%$, there was a certain degree of heterogeneity between the studies, and the random-effects model was used for the analysis. A funnel chart was used to assess the publication bias. For the analysis of the included studies, the Begg and Egg tests were used to check for funnel chart symmetry and publication bias. In addition, sensitivity analyses were carried out.

Results

Search process

A total of 952 titles and abstracts were identified using the electronic screening search strategy. Of these, 725 full-text articles met the primary eligibility criteria for assessment. After careful reading, 82 studies were found to meet the preliminary criteria. These 82 articles were also reviewed by a second author, and the agreement between the authors was excellent. Ultimately, 10 articles met the final inclusion criteria and were included in this present meta-analysis. Further information on the search process and inclusion and exclusion criteria are presented in *Figure 1*.

Characteristics of the included studies

Table 1 provides a comprehensive description of each trial included in the meta-analysis. All the 10 articles were RCTs

(19-28). The 10 articles were published between 2015 and 2021. These 10 articles comprised a total of 1,800 patients (999 in the experimental group and 801 in the control group).

Quality assessment results

The studies were assessed using the Cochrane risk of bias tool. Only 1 study had a selection bias problem, and only 1 study had a reporting bias problem. In view of the bias summary, there were limited problems in attrition bias, reporting bias, and other biases (*Figures 2,3*). The funnel plots of the effect size versus the standard error for the studies were quite symmetrical, suggesting an absence of publication bias and a small-study effect. Egger's test confirmed the absence of publication bias ($P=0.245$).

Heterogeneity test results

Heterogeneity analysis of PFS

To analyze the difference in PFS between the experimental and control groups, a meta-analysis was conducted to calculate the MD using the fixed-effects model based on the heterogeneity analysis. The overall MD was 1.36 [95% confidence interval (CI): 1.04, 1.68]. The P value of the overall effect was <0.0001 , $I^2=6\%$, which demonstrated that the difference of PFS between the experimental and control groups was significant. Patients who received trabectedin had longer PFS than those who received doxorubicin (see *Figure 4*).

Heterogeneity analysis of OS

A meta-analysis of the OS times of the 2 groups was conducted. The results showed that there was significant difference in OS (MD =3.92, 95% CI: 0.23, 7.60, $P=0.04$ and $I^2=83\%$, random-effects model). The experimental (trabectedin) group had a longer OS time than the control (doxorubicin) group (see *Figure 5*).

Heterogeneity analysis of the DCR

A meta-analysis of the disease control rate (DCR) was also conducted. The results showed that there was significant difference in the DCR (RR =1.2, $P=0.03$ and $I^2=45\%$, fixed-effects model), and the experimental group had a better DCR than the control group (see *Figure 6*).

Results of sensitivity analysis and publication bias

In this study, a total of 7 articles reported on PFS. The

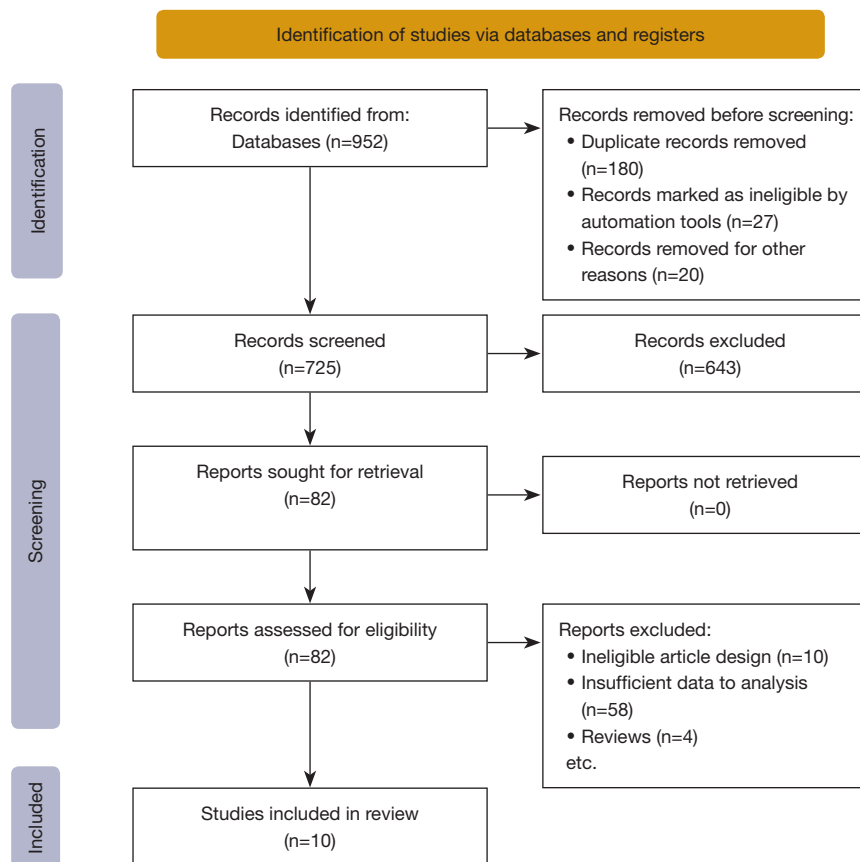


Figure 1 Flow diagram of literature search.

forest plot for PFS showed a significant difference between the 2 groups (MD =1.36, 95% CI: 1.04, 1.68, P value of the overall effect: <0.0001, $I^2=6%$; see *Figure 4*). We performed a sensitivity analysis by deleting the Schöffski (2021) study (26), and the I^2 changed from 6% to 4% (see *Figure 7*), which indicated that the results of the included articles were robust. Finally, we used a funnel chart to evaluate the publication bias of the 2 groups in relation to PFS. As the *Figure 8* shows, the graph is symmetrical. The P value of the Egger test was 0.24, which indicates that there was no significant publication bias in this meta-analysis (see *Figure 8*).

Discussion

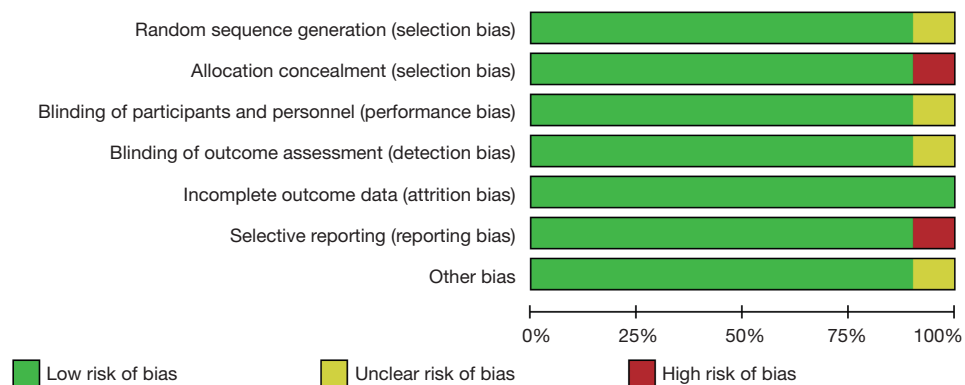
This analysis showed that trabectedin significantly increased the PFS of patients compared to doxorubicin, which is consistent with Chen's results. In this study, the OS time of the trabectedin group was considerably longer than that of the doxorubicin group ($P<0.05$), which indicates that trabectedin increases the OS time of STS patients. In

addition, patients treated with trabectedin also had a better DCR than those treated with doxorubicin; thus, trabectedin had better clinical effects than doxorubicin in STS patients.

Mizuta's trial documented the efficacy of trabectedin in controlling advanced STS after previous cytotoxic chemotherapy failure (29). The patients studied underwent a great deal of pretreatment; however, the last systematic treatment, surgery, and radiotherapy failed, and their condition progressed rapidly. Compared to doxorubicin, the risk of disease progression or death in high-risk groups taking trabectedin was statistically reduced by 45% ($P<0.001$) (30). The benefits of disease control can be observed regardless of a patient's disease histology or whether they had received previous systemic therapy. Notably, the most significant increase in the median PFS occurred in the liposarcoma subgroup. These findings are consistent with early findings on this unique and sensitive STS subtype, and recent reports on trabectedin activity in patients with translocation-related sarcoma (31). These findings provide further evidence that trabectedin plays a

Table 1 Characteristics of included trials

Study	Year	Type of study	Country	Intervention	n	Mean age (years)
Cesne	2021	RCT	France	Trabectedin	52	66.5
				Best supportive care	51	63.7
Chawla	2015	RCT	USA	Trabectedin	83	54
				Doxorubicin	40	54
Demetri	2016	RCT	USA	Trabectedin	345	57
				Dacarbazine	173	56
Hartmann	2020	RCT	Germany	Trofosfamide	80	70
				Doxorubicin	40	70.5
Hensley	2015	RCT	UK	Gemcitabine-docetaxel + trabectedin	53	54.8
				Gemcitabine-docetaxel + placebo	54	56.2
Jones	2019	RCT	UK	Trabectedin + G/D	139	55
				Placebo + G/D	70	54
Martin-Broto	2016	RCT	Spain	Trabectedin + doxorubicin	54	53
				Doxorubicin	59	52
Schöffski	2021	RCT	Belgium	Trabectedin	40	59.5
				Dacarbazine	40	56
Seddon	2017	RCT	UK	Trabectedin	129	56
				Dacarbazine	128	55
Tian	2020	RCT	China	Trabectedin	24	38.58±14.01
				Doxorubicin standard-dose	146	43.30±12.10

**Figure 2** Proportion of studies with low (green), high (red), or unclear (yellow) risk of bias.

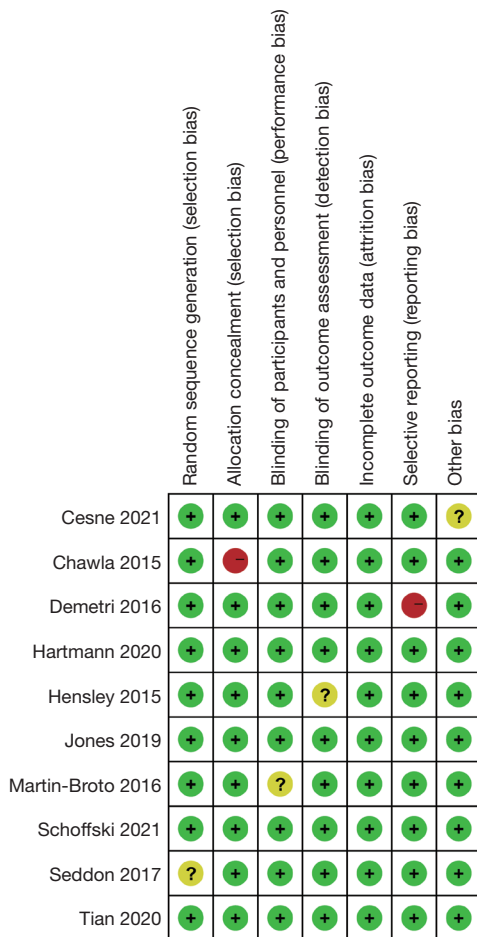


Figure 3 Risk of bias summary for included studies (red shading denotes a high risk of bias, yellow shading denotes an unclear risk of bias, and green shading denotes a low risk of bias).

role as a direct inhibitor. Oncoproteins produced by fusion translocation produce transcriptional regulatory activity in these tumors. Our findings are also consistent with those of Mizut.

STS is a rare and diverse solid tumor that originates from mesenchymal precursors. STSs account for about 1% of all new adult malignancies (32). Doxorubicin, either alone or in combination with other chemotherapy, remains a standard treatment. However, the survival time of patients with metastatic diseases is only 12–16 months, and the 2-year survival rate is only about 30% (32,33).

In preclinical studies, the combination of trabectedin and doxorubicin has been shown to have a synergistic effect in sarcoma cell lines and tumor cells following human sarcoma xenotransplantation in mice (33). In these experiments, the order of first exposure to trabectedin and second exposure to doxorubicin proved to be more cytotoxic (34). Federica’s trial could not exclude the potential advantages of trabectedin combined with doxorubicin in treating STS, such as leiomyosarcoma (35). In addition, there is convincing evidence of trabectedin activity in liposarcoma or leiomyosarcoma. Recent data confirm the effects of trabectedin even in more uncommon sarcomas (36,37).

In conclusion, our research showed that patients who received trabectedin had better clinical effects and a longer survival time than those who received doxorubicin. However, this study had some limitations; for example, the included research areas should be expanded and more indicators for evaluating trabectedin in STS should be examined in the future.

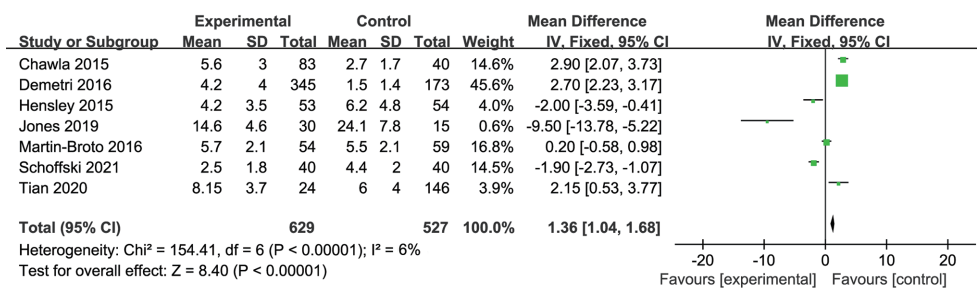


Figure 4 Forest plot of mean difference (MDs) with corresponding 95% confidential intervals (CIs) in progression-free survival (PFS).

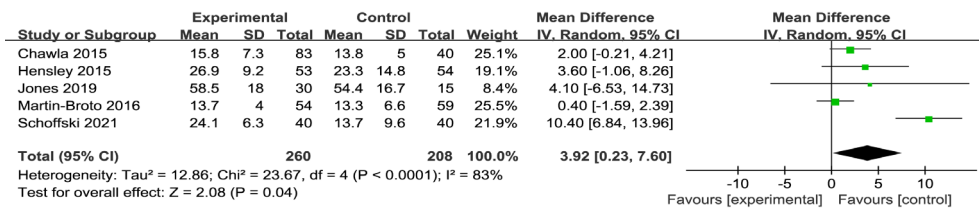


Figure 5 Forest plot of mean difference (MDs) with corresponding 95% confidential intervals (CIs) in overall survival (OS).

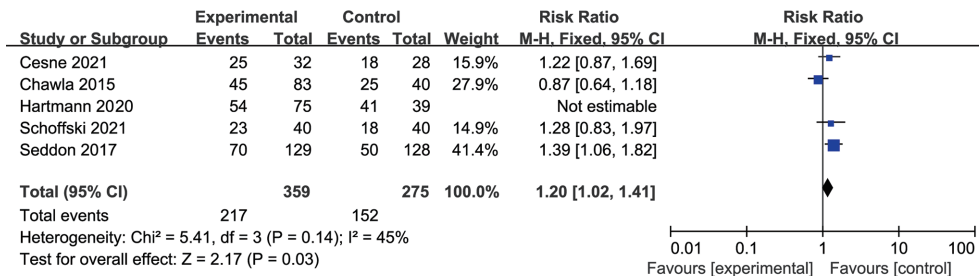


Figure 6 Forest plot of RRs with corresponding 95% CIs in disease control rate (DCR).

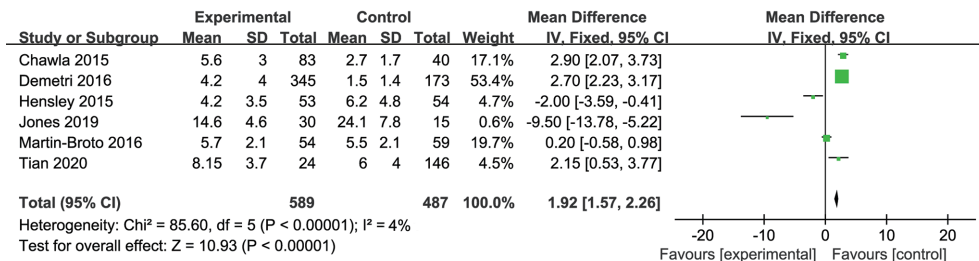


Figure 7 Sensitivity analysis of the forest plot of progression-free survival (PFS).

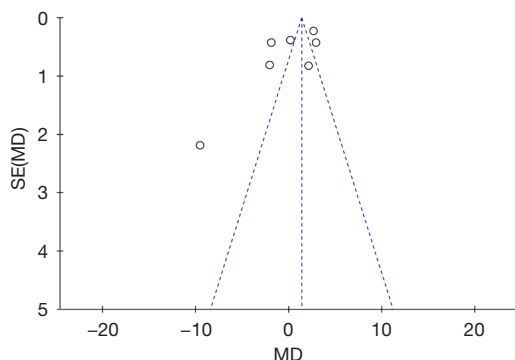


Figure 8 Funnel plot showing publication bias.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://dx.doi.org/10.21037/atm-21-6033>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-6033>)

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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