BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005033
Article Type:	Research
Date Submitted by the Author:	10-Feb-2014
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Haematology (incl blood transfusion), Pharmacology and therapeutics
Keywords:	Sarcoma < ONCOLOGY, CHEMOTHERAPY, Bone marrow transplantation < HAEMATOLOGY

Subject: Autologous HSCT following HDCT for NRSTS

Autologous haematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas – a Cochrane Systematic Review*

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*This article is based on a Cochrane Systematic Review published in the Cochrane Database of Systematic Reviews (CDSR) 2013, Issue 8. Art. No.: CD008216. DOI: 10.1002/14651858.CD008216.pub4. (see www.thecochranelibrary.com for information). Cochrane Systematic Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

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Abstract

Background

Non-rhabdomyosarcoma soft tissue sarcomas are a highly heterogeneous group of rare malignant solid tumors. In patients with locally advanced or metastatic disease, autologous haematopoietic stem cell transplantation following high-dose chemotherapy is a planned rescue therapy for its severe haematologic toxicity.

Methods

The aim of this systematic review was to assess the effectiveness and safety of autologous haematopoietic stem cell transplantation following high-dose chemotherapy. We searched the electronic databases CENTRAL (The Cochrane Library 2010, Issue 2), MEDLINE and EMBASE (05 December 2012). We favoured the randomised design but included others. The primary outcomes were overall survival and treatment-related mortality.

Results

We included 57 studies reporting on 175 transplanted patients. We identified one randomised controlled trial with a low risk of bias as the only comparative study. The overall survival at three years was 32.7% versus 49.4% with a hazard ratio of 1.26 (95% confidence interval 0.70 to 2.29, P value 0.44). Data on treatment-related mortality were sparse.

Conclusion

Overall survival in patients with non-rhabdomyosarcoma soft tissue sarcomas was not statistically different after autologous haematopoietic stem cell transplantation following high-dose chemotherapy compared to standard-dose chemotherapy in patients.

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Keywords

Systematic review, soft tissue sarcomas, high-dose chemotherapy, autologous haematopoietic stem cell transplantation

Strengths and limitations of this study

- We conducted a comprehensive literature search and strictly adhered to the projected methodology.
- The WHO classification of soft tissue sarcomas was adopted and modified to define a clear terminology for the study selection process.
- We jugded a low risk of bias for the single identified RCT, which may serve as the major relevant evidence.
- Single-arm studies provided some estimation about serious adverse events with transplantation
- Some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today.
- The included studies report various subtypes of non-rhabdomyosarcoma soft tissue sarcomas and each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately.

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Introduction

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors of non-epithelial extraskeletal body tissue and are classified on a histogenetic basis[1]. The location of the primary tumor can involve any area of the body[2]. STS can involve any type of tissue and typically affect muscles, tendons, adipose tissue, blood vessels and joints and commonly present as a painless mass[3]. In this review we investigated non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) provided that they are categorized as malignant according to the World Health Organization (WHO) 2002 classification[4]. In Western countries about four new cases of NRSTS are estimated per 100,000 population every year, with the Ewing family of tumors excluded from this statistic [5].

Surgery is the standard treatment for localized NRSTS and can be curative if distant dissemination is not present[6 7]. Chemotherapy is regarded mainly as a palliative treatment for high-risk patients who are characterized by inoperable, locally advanced and metastatic disease[6]. Riedel 2012 provides an overview of current systemic therapies and discusses possible novel therapeutic agents and treatment strategies[8]. High-dose chemotherapy (HDCT) has been evaluated as an alternative treatment option for high-risk patients. The rationale for HDCT is that escalating doses of HDCT may increase survival by capturing putatively remnant malignant cells[9]. The rationale for autologous haematopoietic stem cell transplantation (HSCT) following HDCT is a planned rescue for HDCT-related severe haematologic toxicity[9]. The primary objective of the present systematic review is to evaluate effectiveness and adverse events of HDCT followed by autologous HSCT in patients with NRSTS.

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Methods

This article is based on a Cochrane Systematic Review published in The Cochrane Library[10]. Publication of this work is in agreement with the policy of The Cochrane Collaboration[11]. While preparing this systematic review, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist[12].

Study inclusion criteria

We included patients with NRSTS provided that they are categorized as malignant according to the World Health Organization (WHO) 2002 classification[4]. We excluded the Ewing family of tumors (EFT) according to the European Society for Medical Oncology (ESMO) Guidelines Working Group [5]. It is not fully clear whether the so-called 'unclassified' and the 'undifferentiated' tumor types should be regarded as NRSTS. Therefore, we did not consider these tumor types for the present review. Participants were included regardless of age, severity, and clinical stage of disease. Studies were included as long as at least 80% of patients had NRSTS and received the test intervention. The test intervention was HDCT followed by autologous HSCT containing stem cells from peripheral blood or bone marrow. The comparator was standard-dose chemotherapy. The primary outcomes were overall survival and treatment-related mortality. Secondary outcomes were disease-free survival, progression-free survival, event-free survival, non-haematological toxicity grades 3 to 4[13], secondary malignant neoplasia, and health-related quality of life (HRQL).

Search strategy, selection of studies, and data extraction

We conducted an electronic literature database search in MEDLINE (Ovid), EMBASE (Ovid), and Cochrane Library CENTRAL (Wiley) including articles published from inception to 05 December 2012. The corresponding search strategies are depicted in the original Cochrane Review. We retrieved all titles and abstracts by electronic searching and downloaded them to the refer-

ence management database EndNote Version X3[14]. We considered studies written in languages other than English. We searched the online registries[15 16] on 5 December 2012 for additional completed or ongoing studies using the search strategy "sarcoma AND chemotherapy AND transplantation". We searched all retrieved abstracts of annual meetings contained in EMBASE (Ovid). We contacted authors to replenish missing information. All data assessments were performed independently by two independet review authors. We resolved differences by discussion or by appeal to a third review author.

Assessment of risk of bias in included studies

We have used four criteria from The Cochrane Collaboration's tool for assessing risk of bias in RCTs[17]: random sequence generation, allocation concealment, blinding of outcome assessment, and selective reporting such as not reporting pre-specified outcomes. We extended the Cochrane tool for assessing risk of bias by five criteria that consider nonrandomised studies: prospective design, comparable baseline characteristics, assignment of patients to treatment groups, concurrent control, and loss to follow up. We applied The Cochrane Collaboration's criteria for judging risk of bias[18].

Data synthesis

We synthesized aggregate data as narrative because data were too scarce to be pooled. In a sensitivity analysis, individual data from additional studies were pooled and available time-to-event data were analyzed in a Kaplan-Meier survival analysis by using the procedure *Lifetest* of the SAS computer program version 9.2[19]. We accepted time of diagnosis and beginning of treatment as starting points.

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Results

Search results

Figure 1 shows the literature search and study flow. We retrieved 1035 records and evaluated 260 fulltext papers in detail. We included 57 studies with 275 transplanted patients, one randomised controlled trial (RCT)[20], six single-arm studies with aggregate cases data[21-26], and 50 single-arm studies with individual data (references listed in the original Cochrane Review). We retrieved six ongoing but none of them had a comparative design.

Baseline data

Table 1 gives an overview of the main characteristics of studies and patients. The one RCT was an open, multicenter, randomised phase III study with two parallel treatment groups[20]. Patients were eligible for randomisation if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. The intention-to-treat principle was modified to exclude patients found to be ineligible at a histological review after randomisation. Three of the six single-arm studies with aggregate data collected the data prospectively[21-23] and three retrospectively[24-26]. Participants of the remaining 50 single-arm studies with available status on overall survival and length of follow up were considered in a survival analysis of pooled individual data.

The 57 studies were set in 12 different countries in three different continents. Most of the transplanted patients were studied in the United States and France. Patients had 15 different relevant histological diagnoses, most patients had desmoplastic small round-cell tumor. Median age varied roughly between 25 and 45 years and there was a substantial male preponderance.

Primary outcome

Overall survival was not statistically significantly different between HDCT followed by autologous HSCT versus SDCT at three years reported in the RCT by Bui-Nguyen 2012[20] (**Table 2**).

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With respect to the single-arm studies, overall survival for transplanted patients ranged roughly from 20% to 51% and from 32% to 40% at three years (**Table 2**). The graphical presentation of the Kaplan-Meier graph of individual survival data of 80 patients is shown in **Figure 2**. Treatment-related mortality (TRM) was addressed in 12. A conservative estimate would be 5.5% considering a fraction of 15 procedure-related deaths of a total of 275 transplanted patients (**Table 3**).

Secondary outcomes

Progression-free survival was also not statistically significantly different between HDCT followed by autologous HSCT versus SDCT at three years reported in the RCT by Bui-Nguyen 2012[20]. The only comparative study did not report results on disease-free survival and event-free survival. With respect to transplanted patients, a conservative estimate would be 13.8% (38 events of non-haematological toxicity grade 3 to 4 in a total of 275 transplanted patients) (**Table 3**). We identified one secondary neoplasia in one case report. Health-related quality of life scales were not addressed in the included studies.

Data quality

Clinical heterogeneity was substantial because tumor subdiagnosis varied considerable between patients. Furthermore, tumor stage and metastasis was not reported for all participants. The RCT by Bui-Nguyen 2012[20] stands out as it is the only study reporting comparative data. We judged a low risk of bias for this trial for random sequence generation and selective reporting. However, the trial does have some drawbacks. We judged an unclear risk for allocation concealment because masking of allocation was not described in full detail. We judged a high risk of bias for blinding of outcome assessment because it was not reported for any outcome. The other 56 of 57 studies are single-arm studies and therefore not qualified for assessing a treatment effect.

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Discussion

Outcomes

We identified one randomised controlled trial comparing HDCT followed by autologous HSCT to standard chemotherapy (SDCT)[20]. The authors reported a difference in overall survival and progression-free survival after the treatment in favour of SDCT but the difference was not statistically significant, respectively. Therefore, there is evidence that patients may not have a better survival after HDCT followed by autologous HSCT. If at all, this intervention should only be offered after careful consideration and preferably only within a randomised controlled clinical trial. We estimated a treatment-related mortality of 5.5%, which was somewhat higher than 2.0% reported by others[27]. Severe toxicity grade 3 to 4 was sparsely reported in 9 studies. Studies on health-related quality of life were not identified. The frequency of secondary neoplasia in 1 of 275 participants is probably an extreme underestimation of the true frequency due to a relatively short follow up. The detection of secondary neoplasia depends on a long follow up and was estimated from 4.0% to 6.9% by others [28 29].

Strengths and limitations

The search strategy was broad and it is very likely that all relevant studies were identified. The WHO classification of NRSTS was adopted and modified to define a clear terminology for the study selection process. Studies were excluded if the proportion of non-eligible participants were greater or equal to 20% of the total population. Authors were contacted to ask for additional data. We jugded a low risk of bias for the one identified RCT, which may serve as the major relevant evidence. All other identified studies were single-arm studies that are not helpful to decide whether autologous HSCT following HDCT for NRSTS is a meaningful treatment option. Nevertheless, they provide some estimation about the serious adverse events with transplantation. Some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today. Furthermore, the studies report various subtypes of NRSTS and

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each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately. With respect to the individual survival data, follow-up started at different time points, that is, at diagnosis or at start of treatment. The delay between diagnosis and starting high-dose chemotherapy can be considerable.

Other findings and opinions

We want to point out that some authors have warned against the use of HDCT followed by autologous HSCT, indicating the possibility of repositioning of malignant cells[30]. Others have questioned the use of HDCT with reference to the potential existence of refractory cancer stem cells[9]. Pedrazzoli 2006 stated that the potential benefit of this treatment option has not been investigated sufficiently in comparative studies [31]. Kasper 2005 concluded that the use of HDCT for locally advanced or metastatic adult (soft tissue and bone) sarcomas still remains highly investigational and should not be performed outside clinical trials[32]. The identified RCT by Bui-Nguyen 2012 provides meaningful comparative data for the first time and its results questions any benefit of the intervention. Finally, we cannot close the chapter as it can be unsecure to rely on a single trial.

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Conclusion

The evidence base does not support the use of HDCT followed by autologous HSCT in high-risk patients with NRSTS. It is doubtful whether further studies are necessary to clarify the relevance of HDCT followed by autologous HSCT in patients with NRSTS. If this treatment is offered it should only be after careful consideration and integrated within randomised, controlled trial. Single-arm studies were helpful to increase the identification of reported adverse events. Criteria for the included tumor types should adhere to the WHO classification.

Acknowledgments

We thank the Cochrane Gynaecological Cancer Review Group for their assistance during the preparation of the Cochrane Review. The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

Ethics statement

An ethics statement was not required for this work.

Financial Disclosure

Provision of fulltexts by the University of Cologne, Germany. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests

No authors have any competing interests.

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Figure legends

Figure 1. Literature search and study flow.

Figure 2. Overall survival of individual cases with various NRSTS.

X-axis: below line: life years; above line: number of patients at risk;Y-axis: probability of overall survival; +: censored. The Kaplan-Meyer analysis of overall survival was conducted using individual data of patients with NRSTS with available follow-up information (total 80, failed 46, censored 34) from 41 case series and case reports. Information about outcome (dead or alive) and follow-up (time of survival after diagnosis or begin of treatment) was required for each individual. Number of subjects at risk after each additional year of follow up.

Abbreviations: NRSTS: non-rhabdomyosarcoma soft tissue sarcoma

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Tables

Table 1. Characteristics of studies and patients

Study	N. centers (country)	Enrollment; years	Pros-pective	N. analyzed patients	Subtype	HDCT	Age; median years (range)	Gender; % males
Aggregate comparative data								
Bui-Nguyen 2012 [20]	16 (France)	2000 to 2008	Yes	38 vs. 45	Various	Ca-Et-If	46 (19 to 65) vs. 43 (18 to 65)	58 vs. 50
Aggregate case series data								
Bertuzzi 2003 [21]	1 (Italy)	1997 to 2002	Yes	10	DSRCT	Me-Mi-Th	29 (NR)	100
Bisogno 2010 [22]	>1 (Italy)	1999 to 2008	Yes	14	DSRCT	Cy-Me-Th	10 (2 to 17)	93
Blay 2000 [23]	1 (France)	1988 to 1994	Yes	24	Various	Ci-Et-If	34 (17 to 57)	57
Bokemeyer 1997 [24]	3 (Germany)	NR	No	16	Various	Do-If	45 (25 to 57	NR
Cook 2012 [25]	29 (USA)	1999 to 2007	No	36	DSRCT	Ca-Cy-Et-Me-Th	19 (8 to 46)	80
Philippe-Chomette 2012 [26]	>1 (France)	1995 to 2006	No	14	DSRCT	Various	NR (4 to 29)	86
Individual cases data								
50 studies	NA	NR	No	123	Various	NR	23 (0 to 65)	NR

Abbreviations: Ca: carboplatin; Ci: cisplatin; Cy: cyclophosphamide; Do: Doxorubicin; DSRCT: desmoplastic small-round cell tumor; Et: etoposide = Vepesid = VP 16; HDCT: high-dose chemotherapy; If: ifosfamide; Me: melphalan; Mi: mitoxantrone; NA: not appropriate; NR: information not reported in the article; Th: thiotepa

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Table 2. Overall survival

Study	All patients assessed (95% CI)
Aggregate comparative data	
Bui-Nguyen 2012 [20]	3 years: 32.7% vs. 49.4%; Hazard ratio 1.26 (0.70 to 2.29), P = 0.44
Aggregate case series data	
Bertuzzi 2003 [21]	2 years: 20%
Bisogno 2010 [22]	2 years: 48%; 3 years: 38.9%
Blay 2000 [23]	NR
Bokemeyer 1997 [24]	Median 13 months, range 3 to 19
Cook 2012 [25]	3 years: 40% (24 to 58)
Philippe-Chomette 2012 [26]	2 years: 51.4% (23.2 to 79.6)
Individual cases data	
80 patients with follow-up data	2 years: 50.6% (38.7 to 62.5); 3 years: 36.7 (24.4 to 49.0)

Some estimates were deduced from Kaplan-Meier plot.
Abbreviation. CI: confidence interval; HSCT: haematopoietic stem cell transplantation; NR: not reported; P: p-value

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Table 3. Adverse events in HSCT arm of all included studies

Study	N. affected / N. evaluated patients	Specification
Treatment-related mortality		
Bertuzzi 2003 [21]	0 / 10	NA
Bisogno 2010 [22]	0 / 14	NA
Blay 2000 [23]	1 / 24	Sudden toxic death of unknown cause at day 29
Bui-Nguyen 2012 [20]	1 / 38	Treatment-related leukemia death 2 years after HDCT
Cook 2012 [25]	2 / 36	Not specified
Doros 2008 [33]	1 / 1	NR
Engelhardt 2007 [34]	3 / 26	Sepsis (2x); pneumonia related to lung metastases (1x)
Kasper 2007 [35]	1 / 16	Cardiac arrest of unknown cause
Navid 2006 [36]	1 / 5	Liver as well as kidney failure
Philippe-Chomette 2012 [26]	1 / 14	Died of treatment toxicity 12 months after HDCT
Saab 2007 [37]	2 / 4	Acute myocardial infarction (1x); veno-occlusive disease (1x)
Slease 1988 [38]	2 / 3	Progressive encephalopathy (1x); sepsis (1x)
Secondary neoplasia		
Yamamura 2003 [39]	1 / 1	Chronic myelogenous leukemia
Non-haematological toxicity*	**N. observed events / N. evaluated patients**	
Bisogno 2010 [22]	1 / 14	Mucositis
Blay 2000 [23]	14 / 24	Nausea, kidney, nervous system
Bokemeyer 1997 [24]	6 / 16	Septic episode, central nervous system
Bui-Nguyen 2012 [20]	10 / 38	Nausea, mucositis, infection, pain
Garrido 1998 [40]	1 / 1	Neuroleptic malignant syndrome
Kozuka 2002 [41]	1 / 1	Nausea
Kushner 2001 [42]	1 / 1	Nervous system
Patel 2004 [43]	3 / 1	Liver, kidney, respiratory distress
Yonemoto 1999 [44]	1 / 4	Liver

*National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade III to IV[13]

Abbreviation. 1x: one item; 2x: two items; HDCT: high-dose chemotherapy; N.: number; NA: not applicable; NR: not reported

Subject: Autologous HSCT following HDCT for NRSTS

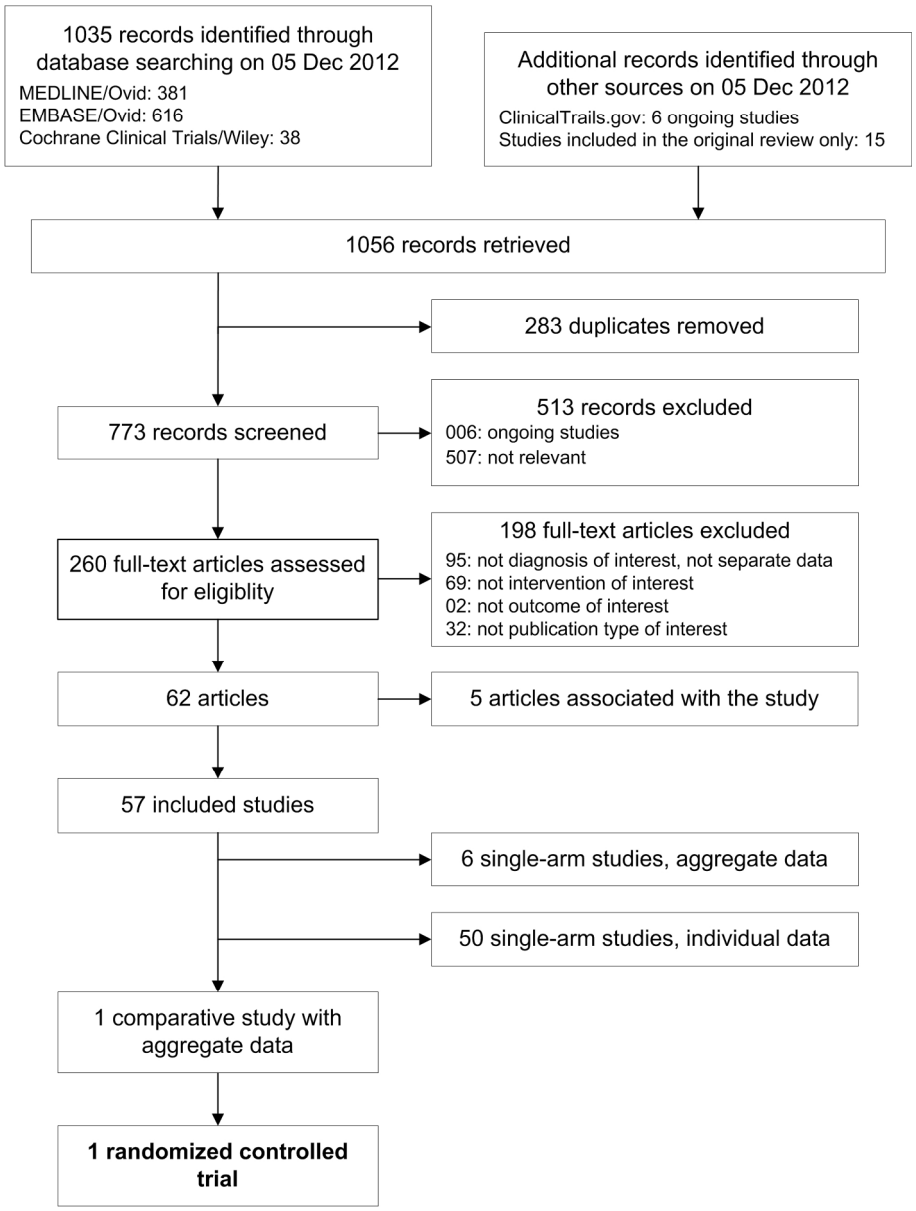
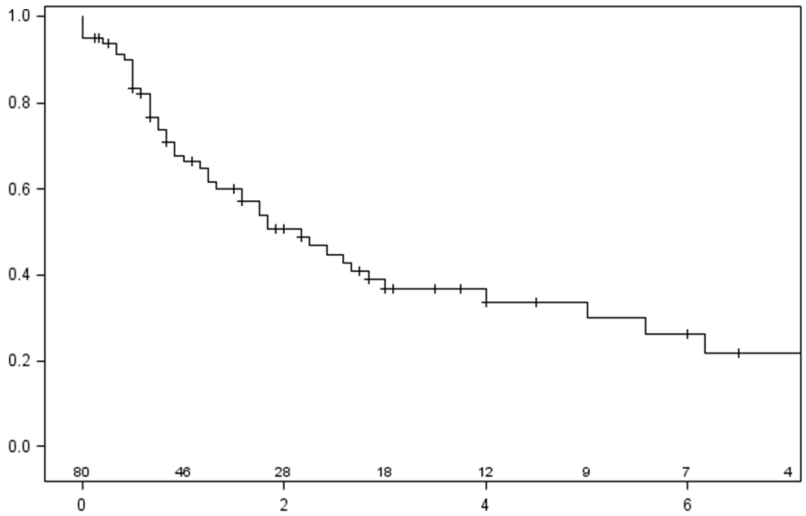


Figure 1. Literature search and study flow.
170x225mm (300 x 300 DPI)



Figue 2. Overall survival of individual cases with various NRSTS.

X-axis: below line: life years; above line: number of patients at risk;Y-axis: probability of overall survival; +: censored. The Kaplan-Meyer analysis of overall survival was conducted using individual data of patients with NRSTS with available follow-up information (total 80, failed 46, censored 34) from 41 case series and case reports. Information about outcome (dead or alive) and follow-up (time of survival after diagnosis or begin of treatment) was required for each indi-vidual. Number of subjects at risk after each additional year of follow up.
Abbreviations: NRSTS: non-rhabdomyosarcoma soft tissue sarcoma

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 to 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 to 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	in the Cochrane review
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 to 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 to 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 to 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	in the Cochrane review
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8, table 2 to 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	table 2, figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	in the Cochrane review
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10 to 11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Autologous haematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas – a Cochrane Systematic Review

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005033.R1
Article Type:	Research
Date Submitted by the Author:	26-Jun-2014
Complete List of Authors:	Peinemann, Frank; University of Cologne, Children's Hospital Labeit, Alexander; University of Illinois College of Medicine at Peoria, Center for Outcomes Research
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Haematology (incl blood transfusion), Pharmacology and therapeutics
Keywords:	Sarcoma < ONCOLOGY, CHEMOTHERAPY, Bone marrow transplantation < HAEMATOLOGY

Subject: bmjopen-2014-005033.R1: Autologous HSCT following HDCT for NRSTS

Autologous haematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas – a Cochrane Systematic Review*

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*This article is based on a Cochrane Systematic Review published in the Cochrane Database of Systematic Reviews (CDSR) 2013, Issue 8. Art. No.: CD008216. DOI: 10.1002/14651858.CD008216.pub4. (see www.thecochranelibrary.com for information). Cochrane Systematic Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

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Abstract

Objectives: We conducted a systematic review to compare the efficacy and adverse events of autologous haematopoietic stem cell transplantation (HSCT) following high-dose chemotherapy (HDCT) versus standard-dose chemotherapy (SDCT) in patients with locally advanced or metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS).

Setting: Patients were observed in hospital units specialised for cancer therapy.

Participants: The review evaluated 294 patients with 19 different subtypes of malignant NRSTS. The patients had a median age between 10 and 46 yerars of age (range 2 to 65) and were mostly males.

Primary and secondary outcome measure: The planned and measured primary outcomes were overall survival and treatment-related mortality. The planned and measured secondary outcomes were progression-free survival, grade 3 to 4 non-haematological toxicity, and secondary neoplasia. Other secondary outcomes including disease-free survival, event-free survival, and health-related quality of life were not reported.

Results: We included 62 studies reporting on 294 transplanted patients. We identified one randomised controlled trial (RCT) with 38 transplanted and 45 non-transplated patients and judged a low riks of bias. We further identified 61 single-arm studies with 256 transplanted patients. Overall survival in the RCT was reported not statistically significantly different between autologous HSCT following HDCT versus SDCT. The hazard ratio was 1.26 (95% confidence interval 0.70 to 2.29; P = 0.44) and the point estimates at three years were 32.7% versus 49.4%. Data from single-arm studies were used to extract data on adverse events. Treatment-related mortality was reported in 5.1% (15 of 294) transplanted patients.

Subject: bmjopen-2014-005033.R1: Autologous HSCT following HDCT for NRSTS

Conclusion: Overall survival in patients with locally advanced or metastatic NRSTS was not statistically different after autologous HSCT following HDCT compared to SDCT in a single RCT with a total of 83 patients. No other comparative study was available. The proportion of adverse events among the transplanted patients is not clear.

Subject: bmjopen-2014-005033.R1: Autologous HSCT following HDCT for NRSTS

Keywords

Systematic review, soft tissue sarcomas, high-dose chemotherapy, autologous haematopoietic stem cell transplantation

Strengths and limitations of this study

- We conducted a comprehensive literature search and strictly adhered to the projected methodology.
- The WHO classification of soft tissue sarcomas was adopted and modified to define a clear terminology for the study selection process.
- We jugded a low risk of bias for the single identified RCT, which may serve as the major relevant evidence.
- Single-arm studies provided some estimation about serious adverse events with transplantation
- Some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today.
- The included studies report various subtypes of non-rhabdomyosarcoma soft tissue sarcomas and each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately.

Subject: bmjopen-2014-005033.R1: Autologous HSCT following HDCT for NRSTS

Abbreviation	Term
HDCT	High-dose chemotherapy
HSCT	Haematopoietic stem cell transplantation
MFH	Malignant Fibrous Histiocytoma
NRSTS	Non-rhabdomyosarcoma soft tissue sarcomas
RCT	Randomised controlled trial
SDCT	Standard-dose chemotherapy

Introduction

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors of non-epithelial extraskeletal body tissue and are classified on a histogenetic basis[1]. The location of the primary tumor can involve any area of the body[2]. STS can involve any type of tissue and typically affect muscles, tendons, adipose tissue, blood vessels and joints and commonly present as a painless mass[3]. In this review we investigated non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) provided that they are categorized as malignant according to the World Health Organization (WHO) 2002 classification[4]. In Western countries about four new cases of NRSTS are estimated per 100,000 population every year, with the Ewing family of tumors excluded from this statistic [5].

Surgery is the standard treatment for localized NRSTS and can be curative if distant dissemination is not present[6 7]. Chemotherapy is regarded mainly as a palliative treatment for high-risk patients who are characterized by inoperable, locally advanced and metastatic disease[6]. Riedel 2012 provides an overview of current systemic therapies and discusses possible novel therapeutic agents and treatment strategies[8]. High-dose chemotherapy (HDCT) has been evaluated as an alternative treatment option for high-risk patients. The rationale for HDCT is that escalating doses of HDCT may increase survival by capturing putatively remnant malignant cells[9]. The rationale for autologous haematopoietic stem cell transplantation (HSCT) following HDCT is a planned rescue for HDCT-related severe haematologic toxicity[9]. The primary objective of the present systematic review is to evaluate effectiveness and adverse events of autologous HSCT following HDCT in patients with advanced or metastatic NRSTS.

Methods

This article is based on a Cochrane Systematic Review published in The Cochrane Library[10]. Publication of this work is in agreement with the policy of The Cochrane Collaboration[11]. While preparing this systematic review, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist[12].

Study inclusion criteria

We included patients with NRSTS provided that they are categorized as malignant according to the World Health Organization (WHO) 2013 classification on soft tissue sarcomas[4] as well as malignant haemangiopericytoma and anaplastic sarcoma. We excluded the Ewing family of tumors according to the European Society for Medical Oncology (ESMO) Guidelines Working Group[5], chondrosarcomas, osteosarcomas, and rhabdomyosarcomas. While writing the Cochrane Review, we refered to the WHO 2002 classification [13]. For the purpose of the present systematic review, we updated the inclusion criteria and re-evaluated the potentially relevant studies and included the following entities: 'Gastrointestinal Stromal Tumours', 'Malignant peripheral nerve sheath tumor', 'Undifferentiated pleomorphic sarcoma not otherwise specified'. Almost all published studies refer to the 2002 classification. Thus, we continued to include the following entities, though, they were removed and relocated within the 2013 classification: 'malignant fibrous histiocytoma' (MFH), 'undifferentiated sarcoma', 'unclassified sarcoma', and 'haemangiopericytoma'. **Table 1** compares the categories and malignant subtypes of the 2013 versus the 2002 edition of the WHO classification of tumours of soft tissue and indicates which of those are included in the present systematic review. Participants were included regardless of age, severity, and clinical stage of disease. Studies were included as long as at least 80% of patients had NRSTS and received the test intervention. The test intervention was autologous HSCT following HDCT containing stem cells from peripheral blood or bone marrow. The comparator was standard-dose chemotherapy. The primary outcomes were overall survival and treatment-

related mortality. Secondary outcomes were disease-free survival, progression-free survival, event-free survival, non-haematological toxicity grades 3 to 4[14], secondary malignant neoplasia, and health-related quality of life.

Search strategy, selection of studies, and data extraction

We conducted an electronic literature database search in MEDLINE (Ovid), EMBASE (Ovid), and Cochrane Library CENTRAL (Wiley) including articles published from inception to an update search on 12 June 2014. The corresponding search strategies have been published in the corresponding Cochrane Review [10]. We retrieved all titles and abstracts by electronic searching and downloaded them to the reference management database EndNote Version X3[15]. We considered studies written in languages other than English. We searched the online registries[16 17] on 12 June 2014 for additional completed or ongoing studies using the search strategy "sarcoma AND chemotherapy AND transplantation". We searched all retrieved abstracts of annual meetings contained in EMBASE (Ovid). We contacted authors to replenish missing information. All data assessments were performed independently by two independet review authors. We resolved differences by discussion or by appeal to a third review author. We judged whether the autologous HSCT following HDCT could be regarded as a consolidation or a salvage therapy. A consolidation therapy is a treatment that is given after cancer has disappeared following the initial therapy and a salvage therapy is a treatment that is given after the cancer has not responded to other treatments[18]. We considered a consolidation therapy if the status at transplantation was either a complete or a partial response to the preceding therapy and we considered a salvage therapy if the status was less favourable and in case a relapse was described.

Assessment of risk of bias in included studies

We have used four criteria from The Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials (RCTs)[19]: random sequence generation, allocation concealment,

blinding of outcome assessment, and selective reporting such as not reporting pre-specified outcomes. We extended the Cochrane tool for assessing risk of bias by five criteria that consider nonrandomised studies: prospective design, comparable baseline characteristics, assignment of patients to treatment groups, concurrent control, and loss to follow-up. We applied The Cochrane Collaboration's criteria for judging risk of bias[20].

Data synthesis

We synthesized aggregate data as narrative because data were too scarce to be pooled. In difference to the Cochrane Review, we did not pool time-to-event data on overall survival from studies with individual data. With respect to survival data, we accepted time of diagnosis and beginning of treatment as starting points. We evaluated all 62 studies to search for reports on treatment-related mortality and tabulated the identified patient data. We evaluated the 7 studies reporting aggregate data to search for reports on grade 3 to 4 non-haematological toxicity in the autologous HSCT following HDCT arm and tabulated the identified event data.

Results

Search results

Figure 1 shows the literature search and study flow. We retrieved 1035 records and evaluated 260 fulltext papers in detail. We included 62 studies with 294 transplanted patients, one RCT with 38 transplanted and 45 non-transplanted patients[21], six single-arm studies reporting aggregate case series data[22-27], and 55 single-arm studies with individual data. In online registries, we identifiedsix studies with a still pending completion and we did not find additional studies in the update search.

Baseline data

We provide an overview of the main characteristics of studies and treatment (**Table 2**), of the patients (**Table 3**), and of the frequency of the identified subtypes (**Table 4**). The one RCT was an open, multicenter, randomised phase III study with two parallel treatment groups[21]. Patients were eligible for randomisation if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. The intention-to-treat principle was modified to exclude patients found to be ineligible at a histological review after randomisation. Three of the six single-arm studies reporting aggregate case series data collected the data prospectively[22-24] and three retrospectively[25-27]. Data from the remaining 55 single-arm studies were considered for the description of treatment-related mortality only.

The 62 studies were set in 13 different countries in four different continents. Most of the transplanted patients were studied in France, the United States, and Germany. We assume that most patients in the studies reporting aggregate case series data received autologous HSCT following HDCT as a consolidation therapy, whereas a considerable number of the individual case data were associated with autologous HSCT following HDCT as a rescue therapy. The majority of all studies used peripheral blood stem cell transplants. Median age varied roughly between 19 and

46 years and there was a male preponderance. Patients had 19 different relevant histological diagnoses. Most patients had desmoplastic small round-cell tumor (N = 109 of 294) followed by the new category of undifferentiated pleomorphic sarcomas (N = 61), which is composed of MFH (N = 31), unclassified sarcoma (N = 17), and undetermined sarcoma (N = 13).

Primary outcome

Overall survival was not statistically significantly different in the RCT by Bui-Nguyen 2012 between autologous HSCT following HDCT versus SDCT regarding the hazard ratio of 1.26 (95% CI 0.70 to 2.29; P = 0.44)[21] (**Table 5**). In this RCT, the point estimates at three years were 32.7% versus 49.4% based on 8 versus 17 remaining patients at risk. The patients at risk at baseline were 38 versus 45 patients. With respect to the studies reporting aggregate case series data, overall survival for transplanted patients ranged roughly from 20% to 51% at 2 years and from 32% to 40% at three years (**Table 5**). In 10 studies, treatment-related mortality (TRM) was associated with 15 of 137 evaluated patients (**Table 6**). Assuming no other TRM in the rest of 157 patients, a risk for procedure-related death might be estimated as 5.1% (15 of 294).

Secondary outcomes

Progression-free survival was also not statistically significantly different in the RCT by Bui-Nguyen 2012 between autologous HSCT following HDCT versus SDCT regarding the hazard ratio of 1.34(95% CI 0.81 to 2.20; P = 0.25)[21]. In this RCT, the point estimates at three years were 9.3% versus 21.6% based on 3 versus 12 remaining patients at risk. The RCT did not report results on disease-free survival and event-free survival. An overview of the number of events of non-haematological toxicity grade 3 to 4 is provided in **Table 7**. In the RCT, 11 events were observed in 38 transplanted patients and 1 event (asthenia) was reported regarding the standard-dose chemotherapy arm. In 3 of the studies reporting aggregate case series data, 25 events were observed in 54 transplanted patients in the HSCT arm. The other 3 studies did not report toxicity

data. We identified one secondary neoplasia in a single case report. Health-related quality of life scales were not addressed in the included studies.

Data quality

Clinical heterogeneity was substantial because tumor subdiagnosis varied considerable between patients. Furthermore, tumor stage and metastasis was not reported for all participants. The RCT by Bui-Nguyen 2012[21] stands out as it is the only study reporting comparative data. We judged a low risk of bias for this trial for random sequence generation and selective reporting. However, the trial does have some drawbacks. We judged an unclear risk for allocation concealment because masking of allocation was not described in full detail. We judged a high risk of bias for blinding of outcome assessment because it was not reported for any outcome. The other 61 of 62 studies are single-arm studies and are therefore not qualified for assessing a treatment effect.

Discussion

Outcomes

We identified one randomised controlled trial comparing autologous HSCT following HDCT versus SDCT[21]. The authors reported a difference in overall survival and progression-free survival after the treatment in favour of SDCT but the difference was not statistically significant, respectively. Therefore, there is evidence that patients may not have a better survival after autologous HSCT following HDCT versus SDCT. If at all, this intervention should only be offered after careful consideration and preferably only within a randomised controlled clinical trial. We estimated a treatment-related mortality of 5.1%, which was somewhat higher than 2.0% reported by others[28]. Severe toxicity grade 3 to 4 was sparsely reported. Studies on health-related quality of life were not identified. The frequency of secondary neoplasia in 1 of 294 participants is probably an extreme underestimation of the true frequency due to a relatively short follow-up. The detection of secondary neoplasia depends on a long follow-up and was estimated from 4.0% to 6.9% by others[29 30].

The WHO 2013 classification

The WHO recently published the 2013 classification on soft tissue sarcomas[4]. The authors inserted the category 'Undifferentiated Pleomorphic Sarcoma Not Otherwise Specified' to lodge those types of soft tissue sarcomas that are difficult to classify using the current available techniques[31 32]. The authors integrated the terms 'MFH', 'Undifferentiated Sarcoma', and 'Unclassified Sarcoma' into this newly created category. MFH was characterized by a apparent lack of specific differentiation[33] and it was considered a diagnosis of exclusion[34]. MFH was regarded as the most common soft tissue sarcoma of adulthood[33] and accounted for up to 25% of patients in clinical trials on soft tissue sarcoma[34]. In 1992, Fletcher et al. reassessed 159 cases with MFH and found 63% (97 of 159) tumors to be specific sarcomas other than MFH[33]. In 2001, Fletcher et al. confirmed that 84% (84 of 100) tumors of patients with MFH showed suffi-

cient differentiation to assign them to specific subtypes of soft tissue sarcomas[35]. The techniques to assess cell differentiation have been substantially improved with the effect that the frequency of the tumor within this category has decreased[36]. It was supposed that the category of 'Undifferentiated Sarcoma – Otherwise Not Specified' may contain liposarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, other sarcomas, and even carcinomas or lymphomas[36 37]. It was estimated that pathologist might have difficulties to identify a specific differentiation in 10% to15% of tumors previously called MFH[37]. The new edition also removed the term 'Haemangiopericytoma'[31 32]. 'Gastrointestinal Stromal tumours' and 'Nerve Sheath tumours' were relocated from other classifications and appear for the first time in the soft tissue classifications[31 32]. Consequently, the term 'Malignant Peripheral Nerve Sheath Tumor' is newly integrated.

Strengths and limitations

The search strategy was broad to aim for the retrieval of all relevant studies. With respect to historical versions of the Cochrane Review[10], we applied two different search strategies and retrieved the same studies with aggregate data but different studies with individual cases data. This results show the substantial difficulty associated with the aim of searching for all published case. This enterprise appears almost impossible. We adopted the new WHO 2013 classification of soft tissue sarcomasand exerted minor modifications to define a clear terminology for the study selection process. The group of NRSTS consists of many subtypes that are difficult to diagnose and separate even today. A considerable number of tumors cannot clearly assigned to a specific histologic category. Thus, we may have tumors with a specific label that might not be true. Otherwise, we may have tumors without a specific label that might belong to a specific category. We excluded studies if the proportion of non-eligible participants were greater or equal to 20% of the total population to prevent considerable mixture with disease or interventions that are not included in the present review. Authors were contacted to ask for additional data. We jugded a low risk

of bias for the one identified RCT, which may serve as the major relevant evidence. All other identified studies were single-arm studies that are not helpful to decide whether autologous HSCT following HDCT for NRSTS is a meaningful treatment option. Therefore, we removed survival data of studies reporting individual data. Nevertheless, they provided data for estimation about treatment-related mortalitywithin all included transplantated patients. We also removed data on non-haematological toxicity of studies reporting individual data because the sparse reporting might have caused a display of not representative information. The description of consolidation and salvage therapy is based on our judgement and might be jugded different by others. These types of therapy were not precisely reported in most studies. Some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today. All studies report various subtypes of NRSTS and each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately. With respect to the individual survival data, follow-up started at different time points, that is, at diagnosis or at start of treatment. The delay between diagnosis and starting high-dose chemotherapy can be considerable.

Other findings and opinions

We want to point out that some authors have warned against the use of autologous HSCT following HDCT, indicating the possibility of repositioning of malignant cells[38]. Others have questioned the use of HDCT with reference to the potential existence of refractory cancer stem cells[9]. Pedrazzoli 2006 stated that the potential benefit of this treatment option has not been investigated sufficiently in comparative studies[39]. Kasper 2005 concluded that the use of HDCT for locally advanced or metastatic adult (soft tissue and bone) sarcomas still remains highly investigational and should not be performed outside clinical trials[40]. The identified RCT by Bui-Nguyen 2012 provides meaningful comparative data for the first time and its results

questions any benefit of the intervention. Finally, we cannot close the chapter as it can be unsecure to rely on a single trial.

Conclusion

Overall survival in patients with locally advanced or metastatic NRSTS was not statistically different after autologous HSCT following HDCT compared to SDCT in a single RCT with a total of 83 patients. No other comparative study was available. A considerable number of patients were not evaluated concerning adverse events and its proportion among the transplanted patients remains unclear. If this treatment is offered it should only be after careful consideration and only within a randomised controlled trial.

Subject: bmjopen-2014-005033.R1: Autologous HSCT following HDCT for NRSTS

FOOTNOTES

Acknowledgments: We thank the Cochrane Gynaecological Cancer Review Group for their assistance during the preparation of the Cochrane Review. The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

Ethics statement: An ethics statement was not required for this work.

Contributorship statement: FP created the search strategy, analysed the data and wrote the manuscript. AML wrote the manuscript.

Competing Interests: No authors have any competing interests.

Funding: Provision of fulltexts by the University of Cologne, Germany. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data sharing statement: No additional data available.

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Tables

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Table 1. Inclusion of malignant soft tissue tumours of the WHO classification 2013 versus 2012

Category	Malignant subtypes	2013	2002	Inclusion
Adipocytic tumours		2013	2002	Included
	Dedifferentiated liposarcoma	2013	2002	Included
	Myxoid liposarcoma	2013	2002	Included
	Pleomorphic liposarcoma	2013	2002	Included
	Liposarcoma, not otherwise specified	2013	2002	Included
	Round cell liposarcoma	No	2002	Included
	Mixed-type liposarcoma	No	2002	Included
Fibrobastic/Myofibroblastic tumours		2013	2002	Included
	Adult fibrosarcoma	2013	2002	Included
	Myxofibrosarcoma	2013	2002	Included
	Low-grade fibromyxoid sarcoma	2013	2002	Included
	Sclerosing epitheloid fibrosarcoma	2013	2002	Included
	Malignangt haemangiopericytoma	No	No	Included
So-called fibrohistiocytic tumours		2013	2002	Included
	Pleomorphic 'MFH'/ Undifferentiated pleomorphic sarcoma (UPS)	No	2002	Included
	Giant cell 'MFH'/ UPS with giant cells	No	2002	Included
	Inflammatory 'MFH'/ UPS with prominent inflammation	No	2002	Included
Smooth muscle tumours		2013	2002	Included
	Leiomyosarcoma (excluding skin)	2013	2002	Included
Pericytic (perivascular) tumours		2013	2002	No
Skeletal muscle tumours		2013	2002	No
	Embryonal rhabdomyosarcoma	2013	2002	No
	Alveolar rhabdomyosarcoma	2013	2002	No
	Pleomorhic rhabdomyosarcoma	2013	2002	No
	Spindle cell/sclerosing rhabdomyosarcoma	2013	No	No
Vascular tumours of soft tissue		2013	2002	Included
	Epithelioid haemangioendothelioma	2013	2002	Included
	Angiosarcoma of soft tissue	2013	2002	Included
Chondro-osseous tumours		2013	2002	No
	Mesenchymal chondrosarcoma	2013	2002	No
	Extraskeletal osteosarcoma	2013	2002	No

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Category	Malignant subtypes	2013	2002	Inclusion
Gastrointestinal stromal tumours		2013	No	Included
	Gastrointestinal stromal tumour, malignant	2013	No	Included
Nerve sheath tumors		2013	No	Included
	Malignant peripheral nerve sheath tumour	2013	No	Included
	Epithelioid malignangt peripheral nerve sheath tumour	2013	No	Included
	Malignant Triton tumour	2013	No	Included
	Malignant granular cell tumour	2013	No	Included
	Ectomesenchymoma	2013	No	Included
Tumours of uncertain differentiation		2013	2002	Included
	Synovial sarcoma NOS	2013	2002	Included
	Epithelioid sarcoma	2013	2002	Included
	Alveolar soft-part sarcoma	2013	2002	Included
	Clear cell sarcoma of soft tissue	2013	2002	Included
	Extraskeletal myxoid chondrosarcoma	2013	2002	No
	Extraskeletal Ewing sarcoma	2013	2002	No
	Desmoplastic small round cell tumour	2013	2002	Included
	Extra-renal rhabdoid tumour	2013	2002	Included
	Neoplasms with perivascular epithelioid cell differentiation	2013	2002	Included
	Intimal sarcoma	2013	2002	Included
	Malignant Mesenchymoma	No	2002	Included
Undifferentiated/ Unclassified sarcomas		2013	No	Included
	Undifferentiated spindle cell sarcoma	2013	No	Included
	Undifferentiated pleomorphic sarcoma	2013	No	Included
	Undifferentiated round cell sarcoma	2013	No	Included
	Undifferentiated epithelioid sarcoma	2013	No	Included
	Undifferentiated sarcoma NOS	2013	No	Included

Abbreviation. MFH: malignant fibrous histiocytoma; NOS: not otherwise specified; UPS: undifferentiated pleomorphic sarcoma

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Table 2. Characteristics of studies and therapy

Study	N. centers (country)	Enrollment; years	Prospective design	Autologous HSCT following HDCT		
				Drugs	Consolidation vs. salvage vs. NR; N	PBSCT vs. BMT vs. NR; N
Aggregate comparative data						
Bui-Nguyen 2012 [21]	16 (France)	2000 to 2008	Yes	Ca-Et-If	38 vs. 0 vs. 0	38 vs. 0 vs. 0
Aggregate case series data						
Bertuzzi 2003 [22]	1 (Italy)	1997 to 2002	Yes	Me-Mi-Th	10 vs. 0 vs. 0	10 vs. 0 vs. 0
Bisogno 2010 [23]	>1 (Italy)	1999 to 2008	Yes	Cy-Me-Th	14 vs. 0 vs. 0	14 vs. 0 vs. 0
Blay 2000 [24]	1 (France)	1988 to 1994	Yes	Ci-Et-If	0 vs. 0 vs. 24	0 vs. 0 vs. 24
Bokemeyer 1997 [25]	3 (Germany)	NR	No	Do-If	16 vs. 0 vs. 0	16 vs. 0 vs. 0
Cook 2012 [26]	29 (USA)	1999 to 2007	No	Ca-Cy-Et-Me-Th	0 vs. 0 vs. 36	33 vs. 2 vs. 1
Philippe-Chomette 2012 [27]	>1 (France)	1995 to 2006	No	Various	14 vs. 0 vs. 0	0 vs. 0 vs. 14
Individual cases data						
55 studies (142 patients)	Various	Various	No	Various	69 vs. 61 vs. 12	102 vs. 21 vs. 19

Abbreviations: BMT: bone marrow transplant; Ca: carboplatin; Ci: cisplatin; Cy: cyclophosphamide; Do: Doxorubicin; Et: etoposide = Vepesid = VP 16; HDCT: high-dose chemotherapy; HSCT: autologous haematopoietic stem cell transplantation; If: ifosfamide; Me: melphalan; Mi: mitoxantrone; N: number; NR: information not reported in the article; PBSCT: peripheral blood stem cell transplant; Th: thiotepa; vs.: versus

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Table 3. Characteristics of patients

Study	Patients analyzed; N		FU	Subtypes	Age; median years (range)		Gender; % males	
	HSCT	SDCT			HSCT	SDCT	HSCT	SDCT
Aggregate comparative data								
Bui-Nguyen 2012 [21]	38	45	55 (NR)	Various	46 (19 to 65)	43 (18 to 65)	58	50
Aggregate case series data								
Bertuzzi 2003 [22]	10	NA	35 (14 to 60)	DSRCT	29 (NR)	NA	100	NA
Bisogno 2010 [23]	14	NA	27 (NR)	DSRCT	10 (2 to 17)	NA	93	NA
Blay 2000 [24]	24	NA	NR	Various	NR	NA	NR	NA
Bokemeyer 1997 [25]	16	NA	NR	Various	45 (25 to 57	NA	NR	NA
Cook 2012 [26]	36	NA	44 (4 to 89)	DSRCT	19 (8 to 46)	NA	80	NA
Philippe-Chomette 2012 [27]	14	NA	23 (9 to 51)	DSRCT	NR (4 to 29)	NA	86	NA
Individual cases data								
55 studies	142	NA	Various	Various	25 (1 to 65)	NA	NR	NA

Abbreviations: DSRCT: desmoplastic small-round cell tumor; FU: Follow-up of the analyzed patients in median months (range); HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; N: number; NA: not applicable: NR: information not reported in the article; SDCT: standard-dose chemotherapy

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Table 4. Frequency of subtypes

Subtype	All	Aggregate	Individual
Anaplastic sarcoma	5	0	5
Angiosarcoma	10	4	6
Clear cell sarcoma	2	1	1
Desmoplastic small round cell tumor	109	74	35
Epitheloid sarcoma	2	0	2
Fibrosarcoma	6	1	5
Fibromyosarcoma	1	0	1
Leiomyosarcoma	29	14	15
Liposarcoma	15	8	7
Mesenchymal sarcoma	2	2	0
Malignant fibrous histiocytoma	31	13	18
Malignant haemamgiopericytoma	8	5	3
Malignant peripheral nerve sheath tumor	4	0	4
Rhabdoid tumor, extra-renal, extra cerebral	2	0	2
Spindle cell sarcoma	1	0	1
Synovial sarcoma	32	9	23
Unclassified sarcoma	17	12	5
Undetermined sarcoma	13	4	9
Not NRSTS	5	5	0
Total number	294	152	142

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Table 5. Overall survival in studies reporting aggregate data

Study	Overall survival (95% CI), point estimates			Statistics
	HSCT at 2 years	HSCT at 3 years	SDCT at 3 years	
Aggregate comparative data				
Bui-Nguyen 2012 [21]		32.7%	49.4%	Hazard ratio 1.26 (0.70 to 2.29), P = 0.44
Aggregate case series data				
Bertuzzi 2003 [22]	20%	NR	NA	
Bisogno 2010 [23]	48%	38.9%	NA	
Blay 2000 [24]	NR	NR	NÁ	
Bokemeyer 1997 [25]	Median 13 months, range 3 to 19		NA	
Cook 2012 [26]	NR	40% (24 to 58)	NA	
Philippe-Chomette 2012 [27]	51.4% (23.2 to 79.6)	NR	NA	

Some estimates were deduced from Kaplan-Meier plots.
Abbreviation. CI: confidence interval; HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; NA: not applicable; NR: not reported; P: p-value; SDCT: standard-dose chemotherapy

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Table 6. Treatment-related mortality in the HSCT arm of all included studies

Study	N affected / N evaluated patients	Specification
Treatment-related mortality		
Bui-Nguyen 2012 [21]	1 / 38	Treatment-related leukemia death 2 years after HSCT
Cook 2012 [26]	2 / 36	NR
Doros 2008 [41]	1 / 1	NR
Engelhardt 2007 [42]	3 / 24	Sepsis (N = 2); pneumonia related to lung metastases (N = 1)
Kasper 2007 [43]	1 / 14	Cardiac arrest of unknown cause
Matsuzaki 2002	1 / 1	Multiple organ failure
Navid 2006 [44]	1 / 2	Liver as well as kidney failure
Philippe-Chomette 2012 [27]	1 / 14	Died of treatment toxicity 12 months after HSCT
Saab 2007 [45]	2 / 4	Acute myocardial infarction (N = 1); veno-occlusive disease (N = 1)
Slease 1988 [46]	2 / 3	Progressive encephalopathy (N = 1); sepsis (N = 1)
Total	15 / 137	

Abbreviation. HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; N: number; NR: not reported

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Table 7. Grade 3 to 4 NCI-CTCAE non-haematological toxicity in the HSCT arm of studies reporting aggregate case series data

Study	N events / N evaluated patients	Specification
Aggregate comparative data		
Bui-Nguyen 2012 [21]	11 / 38	Digestive (N = 8); infection (N = 2); pain (N = 1)
Aggregate case series data		
Bertuzzi 2003 [22]	NR	NA
Bisogno 2010 [23]	1 / 14	Mucositis grade 4
Blay 2000 [24]	16 / 24	Neurologic grade 4 (N = 1); lung grade 3/4 (N = 2); renal grade 3/4 (N = 5); nausea/vomiting grade 3/4 (N = 8)
Bokemeyer 1997 [25]	8 / 16	No grade 4; neurologic (N = 1); renal (N = 2); infection (N = 1); mucositis (N = 2); nausea/emesis (N = 2)
Cook 2012 [26]	NR	NA
Philippe-Chomette 2012 [27]	NR	NA

Abbreviation. HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; N: number; NA: not applicable; NR: not reported; NCI-CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade III to IV[14]

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Figure legends

Figure 1. Literature search and study flow.

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Autologous haematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas – a Cochrane Systematic Review*

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*This article is based on a Cochrane Systematic Review published in the Cochrane Database of Systematic Reviews (CDSR) 2013, Issue 8. Art. No.: CD008216. DOI: 10.1002/14651858.CD008216.pub4. (see www.thecochranelibrary.com for information). Cochrane Systematic Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

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Abstract

Objectives: We conducted a systematic review to compare the efficacy and adverse events of autologous haematopoietic stem cell transplantation (HSCT) following high-dose chemotherapy (HDCT) versus standard-dose chemotherapy (SDCT) in patients with locally advanced or metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS).

Setting: Patients were observed in hospital units specialised for cancer therapy. ~~and stem cell transplantation (tertiary level of care). There were no limits on the geographical location.~~

Participants: The review evaluated 294 patients with 19 different subtypes of malignant NRSTS. ~~according to the World Health Organization 2013 classification. We excluded Ewing family of tumours.~~ The patients had a median age between 10 and 46 yerars of age (range 2 to 65) and were mostly males.

Primary and secondary outcome measure: The planned and measured primary outcomes were overall survival and treatment-related mortality. The planned and measured secondary outcomes were progression-free survival, grade 3 to 4 non-haematological toxicity, and secondary neoplasia. Other secondary outcomes including disease-free survival, event-free survival, and health-related quality of life were not reported.

Results: We included 62 studies reporting on 294 transplanted patients. We identified one randomised controlled trial (RCT) with 38 transplanted and 45 non-transplated patients and judged a low riks of bias. We further identified 61 single-arm studies with 256 transplanted patients. Overall survival in the RCT was reported not statistically significantly different between autologous HSCT following HDCT versus SDCT. The hazard ratio was 1.26 (95% confidence interval 0.70 to 2.29; P = 0.44) and the point estimates at three years were 32.7% versus 49.4%. Data

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from single-arm studies were used to extract data on adverse events. Treatment-related mortality was reported in 5.1% (15 of 294) transplanted patients.

Conclusion: Overall survival in patients with locally advanced or metastatic NRSTS was not statistically different after autologous HSCT following HDCT compared to SDCT in a single RCT with a total of 83 patients. No other comparative study was available. ~~A considerable number of patients were not evaluated concerning adverse events and~~ The proportion of adverse events among the transplanted patients ~~remains~~ is not clear~~unclear~~.

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Keywords

Systematic review, soft tissue sarcomas, high-dose chemotherapy, autologous haematopoietic stem cell transplantation

Strengths and limitations of this study

- We conducted a comprehensive literature search and strictly adhered to the projected methodology.
- The WHO classification of soft tissue sarcomas was adopted and modified to define a clear terminology for the study selection process.
- We jugded a low risk of bias for the single identified RCT, which may serve as the major relevant evidence.
- Single-arm studies provided some estimation about serious adverse events with transplantation
- Some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today.
- The included studies report various subtypes of non-rhabdomyosarcoma soft tissue sarcomas and each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately.

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Abbreviation	Term
HDCT	High-dose chemotherapy
HSCT	Haematopoietic stem cell transplantation
MFH	Malignant Fibrous Histiocytoma
NRSTS	Non-rhabdomyosarcoma soft tissue sarcomas
RCT	Randomised controlled trial
SDCT	Standard-dose chemotherapy

Introduction

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors of non-epithelial extraskeletal body tissue and are classified on a histogenetic basis[1]. The location of the primary tumor can involve any area of the body[2]. STS can involve any type of tissue and typically affect muscles, tendons, adipose tissue, blood vessels and joints and commonly present as a painless mass[3]. In this review we investigated non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) provided that they are categorized as malignant according to the World Health Organization (WHO) 2002 classification[4]. In Western countries about four new cases of NRSTS are estimated per 100,000 population every year, with the Ewing family of tumors excluded from this statistic [5].

Surgery is the standard treatment for localized NRSTS and can be curative if distant dissemination is not present[6 7]. Chemotherapy is regarded mainly as a palliative treatment for high-risk patients who are characterized by inoperable, locally advanced and metastatic disease[6]. Riedel 2012 provides an overview of current systemic therapies and discusses possible novel therapeutic agents and treatment strategies[8]. High-dose chemotherapy (HDCT) has been evaluated as an alternative treatment option for high-risk patients. The rationale for HDCT is that escalating doses of HDCT may increase survival by capturing putatively remnant malignant cells[9]. The rationale for autologous haematopoietic stem cell transplantation (HSCT) following HDCT is a planned rescue for HDCT-related severe haematologic toxicity[9]. The primary objective of the present systematic review is to evaluate effectiveness and adverse events of autologous HSCT following HDCT in patients with advanced or metastatic NRSTS.

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Methods

This article is based on a Cochrane Systematic Review published in The Cochrane Library[10]. Publication of this work is in agreement with the policy of The Cochrane Collaboration[11]. While preparing this systematic review, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist[12].

Study inclusion criteria

We included patients with NRSTS provided that they are categorized as malignant according to the World Health Organization (WHO) ~~2002~~ 2013 classification on soft tissue sarcomas[4] as well as malignant haemangiopericytoma and anaplastic sarcoma. We excluded the Ewing family of tumors ~~(EFT)~~ according to the European Society for Medical Oncology (ESMO) Guidelines Working Group[5], chondrosarcomas, osteosarcomas, and rhabdomyosarcomas. While writing the Cochrane Review, we refered to the WHO 2002 classification [13]. For the purpose of the present ~~study~~systematic review, we updated the inclusion criteria and re-evaluated the potentially relevant studies and included the following entities: 'Gastrointestinal Stromal Tumours' ~~(GIST)~~, 'Malignant peripheral nerve sheath tumor' ~~(MPNST)~~, 'Undifferentiated pleomorphic sarcoma not otherwise specified' ~~(UPS-NOS)~~. Almost all published studies refer to the 2002 classification. Thus, we continued to include the following entities, though, they were removed and relocated within the 2013 classification: 'malignant fibrous histiocytoma' (MFH), 'undifferentiated sarcoma' ~~(UDS)~~, 'unclassified sarcoma' ~~(UCS)~~, and 'haemangiopericytoma' ~~(HPC)~~. **Table 1** compares the categories and malignant subtypes of the 2013 versus the 2002 edition of the WHO classification of tumours of soft tissue and indicates which of those are included in the present systematic review. Participants were included regardless of age, severity, and clinical stage of disease. Studies were included as long as at least 80% of patients had NRSTS and received the test intervention. The test intervention was autologous HSCT following HDCT containing stem cells from peripheral blood or bone marrow. The comparator was standard-dose chemotherapy.

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The primary outcomes were overall survival and treatment-related mortality. Secondary outcomes were disease-free survival, progression-free survival, event-free survival, non-haematological toxicity grades 3 to 4[14], secondary malignant neoplasia, and health-related quality of life ~~(HRQL)~~.

Search strategy, selection of studies, and data extraction

We conducted an electronic literature database search in MEDLINE (Ovid), EMBASE (Ovid), and Cochrane Library CENTRAL (Wiley) including articles published from inception to an update search on 12 June 2014. The corresponding search strategies have been published in the corresponding Cochrane Review [10]. We retrieved all titles and abstracts by electronic searching and downloaded them to the reference management database EndNote Version X3[15]. We considered studies written in languages other than English. We searched the online registries[16 17] on 12 June 2014 for additional completed or ongoing studies using the search strategy "sarcoma AND chemotherapy AND transplantation". We searched all retrieved abstracts of annual meetings contained in EMBASE (Ovid). We contacted authors to replenish missing information. All data assessments were performed independently by two independet review authors. We resolved differences by discussion or by appeal to a third review author. We judged whether the autologous HSCT following HDCT could be regarded as a consolidation or a salvage therapy. A consolidation therapy is a treatment that is given after cancer has disappeared following the initial therapy and a salvage therapy is a treatment that is given after the cancer has not responded to other treatments[18]. We considered a consolidation therapy if the status at transplantation was either a complete or a partial response to the preceding therapy and we considered a salvage therapy if the status was less favourable and in case a relapse was described.

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Assessment of risk of bias in included studies

We have used four criteria from The Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials (RCTs)[19]: random sequence generation, allocation concealment, blinding of outcome assessment, and selective reporting such as not reporting pre-specified outcomes. We extended the Cochrane tool for assessing risk of bias by five criteria that consider nonrandomised studies: prospective design, comparable baseline characteristics, assignment of patients to treatment groups, concurrent control, and loss to follow-up. We applied The Cochrane Collaboration's criteria for judging risk of bias[20].

Data synthesis

We synthesized aggregate data as narrative because data were too scarce to be pooled. In difference to the Cochrane Review, we did not pool time-to-event data on overall survival from studies with individual data. With respect to survival data, we accepted time of diagnosis and beginning of treatment as starting points. We evaluated all 62 studies to search for reports on treatment-related mortality and tabulated the identified patient data. We evaluated the 7 studies reporting aggregate data to search for reports on grade 3 to 4 non-haematological toxicity in the autologous HSCT following HDCT arm and tabulated the identified event data.

Results

Search results

Figure 1 shows the literature search and study flow. We retrieved 1035 records and evaluated 260 fulltext papers in detail. We included 62 studies with 294 transplanted patients, one RCT with 38 transplanted and 45 non-transplanted patients[21], six single-arm studies reporting aggregate case series data[22-27], and 55 single-arm studies with individual data. In online registries, we identifiedsix studies with a still pending completion and we did not find additional studies in the update search.

Baseline data

We provide an overview of the main characteristics of studies and treatment (**Table 2**), of the patients (**Table 3**), and of the frequency of the identified subtypes (**Table 4**). The one RCT was an open, multicenter, randomised phase III study with two parallel treatment groups[21]. Patients were eligible for randomisation if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. The intention-to-treat principle was modified to exclude patients found to be ineligible at a histological review after randomisation. Three of the six single-arm studies reporting aggregate case series data collected the data prospectively[22-24] and three retrospectively[25-27]. Data from the remaining 55 single-arm studies were considered for the description of treatment-related mortality only.

The 62 studies were set in 13 different countries in four different continents. Most of the transplanted patients were studied in France, the United States, and Germany. We assume that most patients in the studies reporting aggregate case series data received autologous HSCT following HDCT as a consolidation therapy, whereas a considerable number of the individual case data were associated with autologous HSCT following HDCT as a rescue therapy. The majority of all studies used peripheral blood stem cell transplants. Median age varied roughly between 19 and

46 years and there was a male preponderance. Patients had 19 different relevant histological diagnoses. Most patients had desmoplastic small round-cell tumor (N = 109 of 294) followed by the new category of undifferentiated pleomorphic sarcomas (N = 61), which is composed of ~~malignant fibrous histiocytoma~~MFH (N = 31), unclassified sarcoma (N = 17), and undetermined sarcoma (N = 13).

Primary outcome

Overall survival was not statistically significantly different in the RCT by Bui-Nguyen 2012 between autologous HSCT following HDCT versus SDCT regarding the hazard ratio of 1.26 (95% CI 0.70 to 2.29; P = 0.44)[21] (**Table 5**). In this RCT, the point estimates at three years were 32.7% versus 49.4% based on 8 versus 17 remaining patients at risk. The patients at risk at baseline were 38 versus 45 patients. With respect to the studies reporting aggregate case series data, overall survival for transplanted patients ranged roughly from 20% to 51% at 2 years and from 32% to 40% at three years (**Table 5**). In 10 studies, treatment-related mortality (TRM) was associated with 15 of 137 evaluated patients (**Table 6**). Assuming no other TRM in the rest of 157 patients, a risk for procedure-related death might be estimated as 5.1% (15 of 294).

Secondary outcomes

Progression-free survival was also not statistically significantly different in the RCT by Bui-Nguyen 2012 between autologous HSCT following HDCT versus SDCT regarding the hazard ratio of 1.34(95% CI 0.81 to 2.20; P = 0.25)[21]. In this RCT, the point estimates at three years were 9.3% versus 21.6% based on 3 versus 12 remaining patients at risk. The RCT did not report results on disease-free survival and event-free survival. An overview of the number of events of non-haematological toxicity grade 3 to 4 is provided in **Table 7**. In the RCT, 11 events were observed in 38 transplanted patients and 1 event (asthenia) was reported regarding the standard-dose chemotherapy arm. In 3 of the studies reporting aggregate case series data, 25 events were

observed in 54 transplanted patients in the HSCT arm. The other 3 studies did not report toxicity data. We identified one secondary neoplasia in a single case report. Health-related quality of life scales were not addressed in the included studies.

Data quality

Clinical heterogeneity was substantial because tumor subdiagnosis varied considerable between patients. Furthermore, tumor stage and metastasis was not reported for all participants. The RCT by Bui-Nguyen 2012[21] stands out as it is the only study reporting comparative data. We judged a low risk of bias for this trial for random sequence generation and selective reporting. However, the trial does have some drawbacks. We judged an unclear risk for allocation concealment because masking of allocation was not described in full detail. We judged a high risk of bias for blinding of outcome assessment because it was not reported for any outcome. The other 61 of 62 studies are single-arm studies and are therefore not qualified for assessing a treatment effect.

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Discussion

Outcomes

We identified one randomised controlled trial comparing autologous HSCT following HDCT versus SDCT[21]. The authors reported a difference in overall survival and progression-free survival after the treatment in favour of SDCT but the difference was not statistically significant, respectively. Therefore, there is evidence that patients may not have a better survival after autologous HSCT following HDCT versus SDCT. If at all, this intervention should only be offered after careful consideration and preferably only within a randomised controlled clinical trial. We estimated a treatment-related mortality of 5.1%, which was somewhat higher than 2.0% reported by others[28]. Severe toxicity grade 3 to 4 was sparsely reported. Studies on health-related quality of life were not identified. The frequency of secondary neoplasia in 1 of 294 participants is probably an extreme underestimation of the true frequency due to a relatively short follow-up. The detection of secondary neoplasia depends on a long follow-up and was estimated from 4.0% to 6.9% by others[29 30].

The WHO 2013 classification

The ~~World Health Organization (~~WHO~~)~~ recently published the 2013 classification on soft tissue sarcomas[4]. The authors inserted the category 'Undifferentiated Pleomorphic Sarcoma Not Otherwise Specified' to lodge those types of soft tissue sarcomas that are difficult to classify using the current available techniques[31 32]. The authors integrated the terms 'MFH~~Malignant Fibrous Histiocytoma~~', 'Undifferentiated Sarcoma', and 'Unclassified Sarcoma' into this newly created category. ~~Malignant fibrous histiocytoma (~~MFH~~)~~ was characterized by a apparent lack of specific differentiation[33] and it was considered a diagnosis of exclusion[34]. MFH was regarded as the most common soft tissue sarcoma of adulthood[33] and accounted for up to 25% of patients in clinical trials on soft tissue sarcoma[34]. In 1992, Fletcher et al. reassessed 159 cases with MFH and found 63% (97 of 159) tumors to be specific sarcomas other than MFH[33]. In

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2001, Fletcher et al. confirmed that 84% (84 of 100) tumors of patients with MFH showed sufficient differentiation to assign them to specific subtypes of soft tissue sarcomas[35]. The techniques to assess cell differentiation have been substantially improved with the effect that the frequency of the tumor within this category has decreased[36]. It was supposed that the category of 'Undifferentiated Sarcoma – Otherwise Not Specified'~~UPS-NOS~~ may contain liposarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, other sarcomas, and even carcinomas or lymphomas[36 37]. It was estimated that pathologist might have difficulties to identify a specific differentiation in 10% to15% of tumors previously called MFH[37]. The new edition also removed the term 'Haemangiopericytoma'[31 32]. 'Gastrointestinal Stromal tumours' and 'Nerve Sheath tumours' were relocated from other classifications and appear for the first time in the soft tissue classifications[31 32]. Consequently, the term 'Malignant Peripheral Nerve Sheath Tumor' is newly integrated.

Strengths and limitations

The search strategy was broad to aim for the retrieval of all relevant studies. With respect to historical versions of the Cochrane Review[10], we applied two different search strategies and retrieved the same studies with aggregate data but different studies with individual cases data. This results show the substantial difficulty associated with the aim of searching for all published case. This enterprise appears almost impossible. We adopted the new WHO 2013 classification of soft tissue sarcomasand exerted minor modifications to define a clear terminology for the study selection process. The group of NRSTS consists of many subtypes that are difficult to diagnose and separate even today. A considerable number of tumors cannot clearly assigned to a specific histologic category. Thus, we may have tumors with a specific label that might not be true. Otherwise, we may have tumors without a specific label that might belong to a specific category. We excluded studies if the proportion of non-eligible participants were greater or equal to 20% of the total population to prevent considerable mixture with disease or interventions that are not includ-

ed in the present review. Authors were contacted to ask for additional data. We jugded a low risk of bias for the one identified RCT, which may serve as the major relevant evidence. All other identified studies were single-arm studies that are not helpful to decide whether autologous HSCT following HDCT for NRSTS is a meaningful treatment option. Therefore, we removed survival data of studies reporting individual data. Nevertheless, they provided data for estimation about treatment-related mortalitywithin all included transplantated patients. We also removed data on non-haematological toxicity of studies reporting individual data because the sparse reporting might have caused a display of not representative information. The description of consolidation and salvage therapy is based on our judgement and might be jugded different by others. These types of therapy were not precisely reported in most studies. Some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today. All studies report various subtypes of NRSTS and each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately. With respect to the individual survival data, follow-up started at different time points, that is, at diagnosis or at start of treatment. The delay between diagnosis and starting high-dose chemotherapy can be considerable.

Other findings and opinions

We want to point out that some authors have warned against the use of autologous HSCT following HDCT, indicating the possibility of repositioning of malignant cells[38]. Others have questioned the use of HDCT with reference to the potential existence of refractory cancer stem cells[9]. Pedrazzoli 2006 stated that the potential benefit of this treatment option has not been investigated sufficiently in comparative studies[39]. Kasper 2005 concluded that the use of HDCT for locally advanced or metastatic adult (soft tissue and bone) sarcomas still remains highly investigational and should not be performed outside clinical trials[40]. The identified RCT by Bui-Nguyen 2012 provides meaningful comparative data for the first time and its results

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questions any benefit of the intervention. Finally, we cannot close the chapter as it can be unsecure to rely on a single trial.

Conclusion

Overall survival in patients with locally advanced or metastatic NRSTS was not statistically different after autologous HSCT following HDCT compared to SDCT in a single RCT with a total of 83 patients. No other comparative study was available. A considerable number of patients were not evaluated concerning adverse events and its proportion among the transplanted patients remains unclear. If this treatment is offered it should only be after careful consideration and only within a randomised controlled trial.

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Acknowledgments: We thank the Cochrane Gynaecological Cancer Review Group for their assistance during the preparation of the Cochrane Review. The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

Ethics statement: An ethics statement was not required for this work.

Contributorship statement: FP created the search strategy, analysed the data and wrote the manuscript. AML wrote the manuscript.

Competing Interests: No authors have any competing interests.

~~Financial Disclosure~~Funding: Provision of fulltexts by the University of Cologne, Germany. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data sharing statement: No additional data available.

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Figure legends

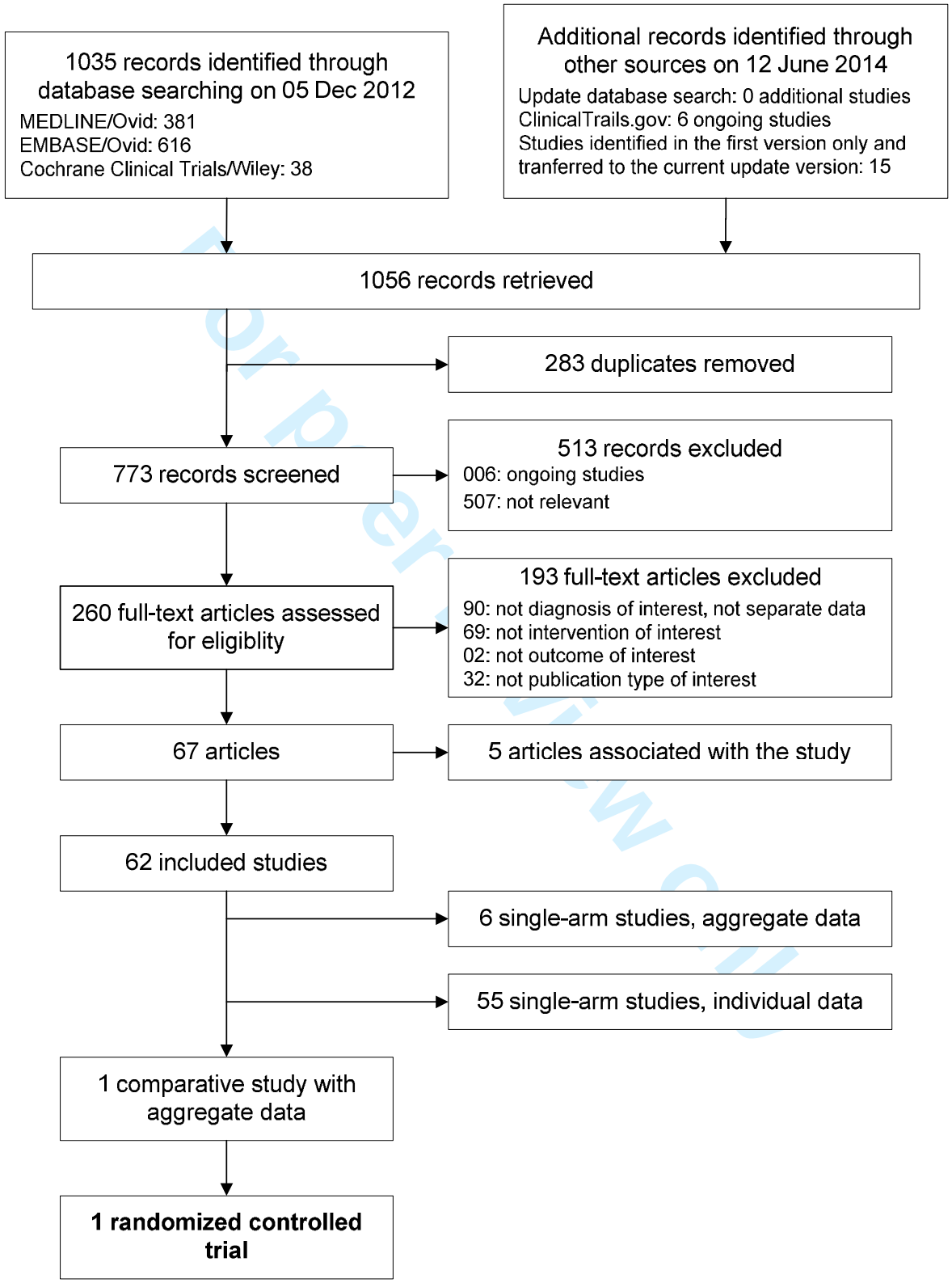

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Figure 1. Literature search and study flow.

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Tables

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Table 1. Inclusion of malignant soft tissue tumours of the WHO classification 2013 versus 2012

Category	Malignant subtypes	2013	2002	Inclusion
Adipocytic tumours		2013	2002	Included
	Dedifferentiated liposarcoma	2013	2002	Included
	Myxoid liposarcoma	2013	2002	Included
	Pleomorphic liposarcoma	2013	2002	Included
	Liposarcoma, not otherwise specified	2013	2002	Included
	Round cell liposarcoma	No	2002	Included
	Mixed-type liposarcoma	No	2002	Included
Fibrobastic/Myofibroblastic tumours		2013	2002	Included
	Adult fibrosarcoma	2013	2002	Included
	Myxofibrosarcoma	2013	2002	Included
	Low-grade fibromyxoid sarcoma	2013	2002	Included
	Sclerosing epitheloid fibrosarcoma	2013	2002	Included
	Malignangt haemangiopericytoma	No	No	Included
So-called fibrohistiocytic tumours		2013	2002	Included
	Pleomorphic 'MFH'/ Undifferentiated pleomorphic sarcoma (UPS)	No	2002	Included
	Giant cell 'MFH'/ UPS with giant cells	No	2002	Included
	Inflammatory 'MFH'/ UPS with prominent inflammation	No	2002	Included
Smooth muscle tumours		2013	2002	Included
	Leiomyosarcoma (excluding skin)	2013	2002	Included
Pericytic (perivascular) tumours		2013	2002	No
Skeletal muscle tumours		2013	2002	No
	Embryonal rhabdomyosarcoma	2013	2002	No
	Alveolar rhabdomyosarcoma	2013	2002	No
	Pleomorhic rhabdomyosarcoma	2013	2002	No
	Spindle cell/sclerosing rhabdomyosarcoma	2013	No	No
Vascular tumours of soft tissue		2013	2002	Included
	Epithelioid haemangioendothelioma	2013	2002	Included
	Angiosarcoma of soft tissue	2013	2002	Included
Chondro-osseous tumours		2013	2002	No
	Mesenchymal chondrosarcoma	2013	2002	No
	Extraskeletal osteosarcoma	2013	2002	No

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Category	Malignant subtypes	2013	2002	Inclusion
Gastrointestinal stromal tumours		2013	No	Included
	Gastrointestinal stromal tumour, malignant	2013	No	Included
Nerve sheath tumors		2013	No	Included
	Malignant peripheral nerve sheath tumour	2013	No	Included
	Epithelioid malignangt peripheral nerve sheath tumour	2013	No	Included
	Malignant Triton tumour	2013	No	Included
	Malignant granular cell tumour	2013	No	Included
	Ectomesenchymoma	2013	No	Included
Tumours of uncertain differentiation		2013	2002	Included
	Synovial sarcoma NOS	2013	2002	Included
	Epithelioid sarcoma	2013	2002	Included
	Alveolar soft-part sarcoma	2013	2002	Included
	Clear cell sarcoma of soft tissue	2013	2002	Included
	Extraskeletal myxoid chondrosarcoma	2013	2002	No
	Extraskeletal Ewing sarcoma	2013	2002	No
	Desmoplastic small round cell tumour	2013	2002	Included
	Extra-renal rhabdoid tumour	2013	2002	Included
	Neoplasms with perivascular epithelioid cell differentiation	2013	2002	Included
	Intimal sarcoma	2013	2002	Included
	Malignant Mesenchymoma	No	2002	Included
Undifferentiated/ Unclassified sarcomas		2013	No	Included
	Undifferentiated spindle cell sarcoma	2013	No	Included
	Undifferentiated pleomorphic sarcoma	2013	No	Included
	Undifferentiated round cell sarcoma	2013	No	Included
	Undifferentiated epithelioid sarcoma	2013	No	Included
	Undifferentiated sarcoma NOS	2013	No	Included

Abbreviation. MFH: malignant fibrous histiocytoma; NOS: not otherwise specified; UPS: undifferentiated pleomorphic sarcoma

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Table 2. Characteristics of studies and therapy

Study	N. centers (country)	Enrollment; years	Prospective design	Autologous HSCT following HDCT		
				Drugs	Consolidation vs. salvage vs. NR; N	PBSCT vs. BMT vs. NR; N
Aggregate comparative data						
Bui-Nguyen 2012 [21]	16 (France)	2000 to 2008	Yes	Ca-Et-If	38 vs. 0 vs. 0	38 vs. 0 vs. 0
Aggregate case series data						
Bertuzzi 2003 [22]	1 (Italy)	1997 to 2002	Yes	Me-Mi-Th	10 vs. 0 vs. 0	10 vs. 0 vs. 0
Bisogno 2010 [23]	>1 (Italy)	1999 to 2008	Yes	Cy-Me-Th	14 vs. 0 vs. 0	14 vs. 0 vs. 0
Blay 2000 [24]	1 (France)	1988 to 1994	Yes	Ci-Et-If	0 vs. 0 vs. 24	0 vs. 0 vs. 24
Bokemeyer 1997 [25]	3 (Germany)	NR	No	Do-If	16 vs. 0 vs. 0	16 vs. 0 vs. 0
Cook 2012 [26]	29 (USA)	1999 to 2007	No	Ca-Cy-Et-Me-Th	0 vs. 0 vs. 36	33 vs. 2 vs. 1
Philippe-Chomette 2012 [27]	>1 (France)	1995 to 2006	No	Various	14 vs. 0 vs. 0	0 vs. 0 vs. 14
Individual cases data						
55 studies (142 patients)	Various	Various	No	Various	69 vs. 61 vs. 12	102 vs. 21 vs. 19

Abbreviations: BMT: bone marrow transplant; Ca: carboplatin; Ci: cisplatin; Cy: cyclophosphamide; Do: Doxorubicin; Et: etoposide = Vepesid = VP 16; HDCT: high-dose chemotherapy; HSCT: autologous haematopoietic stem cell transplantation; If: ifosfamide; Me: melphalan; Mi: mitoxantrone; N: number; NR: information not reported in the article; PBSCT: peripheral blood stem cell transplant; Th: thiotepa; vs.: versus

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Table 3. Characteristics of patients

Study	Patients analyzed; N		FU	Subtypes	Age; median years (range)		Gender; % males	
	HSCT	SDCT			HSCT	SDCT	HSCT	SDCT
Aggregate comparative data								
Bui-Nguyen 2012 [21]	38	45	55 (NR)	Various	46 (19 to 65)	43 (18 to 65)	58	50
Aggregate case series data								
Bertuzzi 2003 [22]	10	NA	35 (14 to 60)	DSRCT	29 (NR)	NA	100	NA
Bisogno 2010 [23]	14	NA	27 (NR)	DSRCT	10 (2 to 17)	NA	93	NA
Blay 2000 [24]	24	NA	NR	Various	NR	NA	NR	NA
Bokemeyer 1997 [25]	16	NA	NR	Various	45 (25 to 57	NA	NR	NA
Cook 2012 [26]	36	NA	44 (4 to 89)	DSRCT	19 (8 to 46)	NA	80	NA
Philippe-Chomette 2012 [27]	14	NA	23 (9 to 51)	DSRCT	NR (4 to 29)	NA	86	NA
Individual cases data								
55 studies	142	NA	Various	Various	25 (1 to 65)	NA	NR	NA

Abbreviations: DSRCT: desmoplastic small-round cell tumor; FU: Follow-up of the analyzed patients in median months (range); HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; N: number; NA: not applicable: NR: information not reported in the article; SDCT: standard-dose chemotherapy

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Table 4. Frequency of subtypes

Subtype	All	Aggregate	Individual
Anaplastic sarcoma	5	0	5
Angiosarcoma	10	4	6
Clear cell sarcoma	2	1	1
Desmoplastic small round cell tumor	109	74	35
Epitheloid sarcoma	2	0	2
Fibrosarcoma	6	1	5
Fibromyosarcoma	1	0	1
Leiomyosarcoma	29	14	15
Liposarcoma	15	8	7
Mesenchymal sarcoma	2	2	0
Malignant fibrous histiocytoma	31	13	18
Malignant haemamgiopericytoma	8	5	3
Malignant peripheral nerve sheath tumor	4	0	4
Rhabdoid tumor, extra-renal, extra cerebral	2	0	2
Spindle cell sarcoma	1	0	1
Synovial sarcoma	32	9	23
Unclassified sarcoma	17	12	5
Undetermined sarcoma	13	4	9
Not NRSTS	5	5	0
Total number	294	152	142

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Table 5. Overall survival in studies reporting aggregate data

Study	Overall survival (95% CI), point estimates			Statistics
	HSCT at 2 years	HSCT at 3 years	SDCT at 3 years	
Aggregate comparative data				
Bui-Nguyen 2012 [21]		32.7%	49.4%	Hazard ratio 1.26 (0.70 to 2.29), P = 0.44
Aggregate case series data				
Bertuzzi 2003 [22]	20%	NR	NA	
Bisogno 2010 [23]	48%	38.9%	NA	
Blay 2000 [24]	NR	NR	NÁ	
Bokemeyer 1997 [25]	Median 13 months, range 3 to 19		NA	
Cook 2012 [26]	NR	40% (24 to 58)	NA	
Philippe-Chomette 2012 [27]	51.4% (23.2 to 79.6)	NR	NA	

Some estimates were deduced from Kaplan-Meier plots.
Abbreviation. CI: confidence interval; HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; NA: not applicable; NR: not reported; P: p-value; SDCT: standard-dose chemotherapy

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Table 6. Treatment-related mortality in the HSCT arm of all included studies

Study	N affected / N evaluated patients	Specification
Treatment-related mortality		
Bui-Nguyen 2012 [21]	1 / 38	Treatment-related leukemia death 2 years after HSCT
Cook 2012 [26]	2 / 36	NR
Doros 2008 [41]	1 / 1	NR
Engelhardt 2007 [42]	3 / 24	Sepsis (N = 2); pneumonia related to lung metastases (N = 1)
Kasper 2007 [43]	1 / 14	Cardiac arrest of unknown cause
Matsuzaki 2002	1 / 1	Multiple organ failure
Navid 2006 [44]	1 / 2	Liver as well as kidney failure
Philippe-Chomette 2012 [27]	1 / 14	Died of treatment toxicity 12 months after HSCT
Saab 2007 [45]	2 / 4	Acute myocardial infarction (N = 1); veno-occlusive disease (N = 1)
Slease 1988 [46]	2 / 3	Progressive encephalopathy (N = 1); sepsis (N = 1)
Total	15 / 137	

Abbreviation. HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; N: number; NR: not reported

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Table 7. Grade 3 to 4 NCI-CTCAE non-haematological toxicity in the HSCT arm of studies reporting aggregate case series data

Study	N events / N evaluated patients	Specification
Aggregate comparative data		
Bui-Nguyen 2012 [21]	11 / 38	Digestive (N = 8); infection (N = 2); pain (N = 1)
Aggregate case series data		
Bertuzzi 2003 [22]	NR	NA
Bisogno 2010 [23]	1 / 14	Mucositis grade 4
Blay 2000 [24]	16 / 24	Neurologic grade 4 (N = 1); lung grade 3/4 (N = 2); renal grade 3/4 (N = 5); nausea/vomiting grade 3/4 (N = 8)
Bokemeyer 1997 [25]	8 / 16	No grade 4; neurologic (N = 1); renal (N = 2); infection (N = 1); mucositis (N = 2); nausea/emesis (N = 2)
Cook 2012 [26]	NR	NA
Philippe-Chomette 2012 [27]	NR	NA

Abbreviation. HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; N: number; NA: not applicable; NR: not reported; NCI-CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade III to IV[14]

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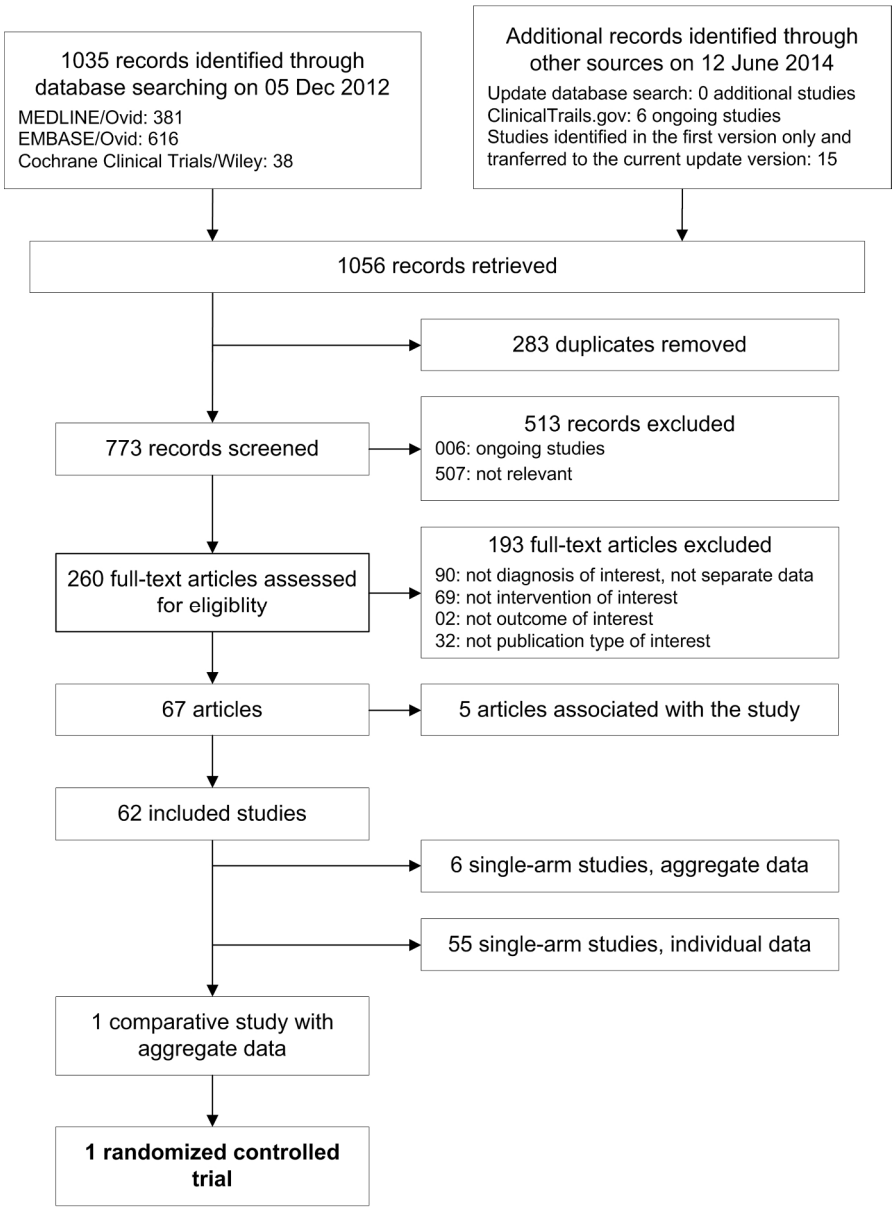

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 to 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 to 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	in the Cochrane review
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 to 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 to 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 to 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	in the Cochrane review
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8, table 2 to 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	table 2, figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	in the Cochrane review
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10 to 11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12

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FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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