Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas (Review)

Peinemann F, Smith LA, Kromp M, Bartel C, Kröger N, Kulig M

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[Intervention Review]

Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas

Frank Peinemann[1], Lesley A Smith[2], Mandy Kromp[3], Carmen Bartel[4], Nicolaus Kröger[5], Michael Kulig[6]

[1]Department of Non-Drug Interventions, Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany. [2]School of Health and Social Care, Oxford Brookes University, Oxford, UK. [3]Medical Biometry, Institute for Quality and Efficiency in Health Care, Cologne, Germany. [4]Quality of Health Care, Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany. [5]Interdisciplinary Clinic for Stem Cell Transplantation, University Hospital Hamburg-Eppendorf, Hamburg, Germany. [6]Non-drug Interventions, Institute for Quality and Efficiency in Health Care, Cologne, Germany

Contact address: Frank Peinemann, Department of Non-Drug Interventions, Institute for Quality and Efficiency in Health Care (IQWiG), Dillenburger Str. 27, Cologne, 51105, Germany. frank.peinemann@iqwig.de.

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ABSTRACT

Background

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise all STS except rhabdomyosarcoma. In patients with advanced local or metastatic disease, autologous hematopoietic stem cell transplantation (HSCT) applied after high-dose chemotherapy (HDCT) is a planned rescue therapy for HDCT-related severe hematologic toxicity.

Objectives

To assess the effectiveness and safety of HDCT followed by autologous HSCT for all stages of soft tissue sarcomas in children and adults.

Search methods

We searched the electronic databases CENTRAL (*The Cochrane Library* 2010, Issue 2), MEDLINE and EMBASE (February 2010). Online trial registers, congress abstracts and reference lists of reviews were searched and expert panels and authors were contacted.

Selection criteria

Terms representing STS and autologous HSCT were required in the title, abstract or keywords. In studies with aggregated data, participants with NRSTS and autologous HSCT had to constitute at least 80% of the data. Comparative non-randomized studies were included because randomized controlled trials (RCTs) were not expected. Case series and case reports were considered for an additional descriptive analysis.

Data collection and analysis

Study data were recorded by two review authors independently. For studies with no comparator group, we synthesised results for studies reporting aggregate data and conducted a pooled analysis of individual participant data using the Kaplan-Meyer method. The primary outcomes were overall survival (OS) and treatment-related mortality (TRM).

Main results

We included 54 studies, from 467 full texts articles screened (11.5%), reporting on 177 participants that received HSCT and 69 participants that received standard care. Only one study reported comparative data. In the one comparative study, OS at two years after HSCT was estimated as statistically significantly higher (62.3%) compared with participants that received standard care (23.2%). In a single-arm study, the OS two years after HSCT was reported as 20%. In a pooled analysis of the individual data of 54 participants, OS at two years was estimated as 49% (95% CI 34% to 64%). Data on TRM, secondary neoplasia and severe toxicity grade 3 to 4 after transplantation were sparse. All 54 studies had a high risk of bias.

Authors' conclusions

Due to a lack of comparative studies, it is unclear whether participants with NRSTS have improved survival from autologous HSCT following HDCT. Owing to this current gap in knowledge, at present HDCT and autologous HSCT for NRSTS should only be used within controlled trials.

PLAIN LANGUAGE SUMMARY

Hematopoietic stem cell transplantation following chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas

Non-rhabdomyosarcoma soft tissue sarcomas are a group of rare cancers. Patients with inoperable or metastatic disease have a poor prognosis. It was believed higher doses of chemotherapy might improve patients' survival. However, high doses of chemotherapy stop the production of blood cells in the bone marrow and are not compatible with life. Stem cells collected from patients before high-dose chemotherapy can be transplanted back to the patient if the blood cell count gets too low. Due to a lack of research studies, it has not been proven that patients treated with this procedure lived longer than patients treated with standard chemotherapy.

We reviewed the published research on this treatment to investigate how effective and safe it is. Unfortunately we identified only one comparative study and the results of this study were not credible. Studies with aggregated data showed that two years after treatment between 20% to 60% of patients were still alive but the treatment had a high level of toxic side effects.

While the results of this systematic review may not be conclusive, they provide a summary of the current knowledge and highlight that more research is needed. Currently the research evidence says that patients with non-rhabdomyosarcoma soft tissue sarcomas should only be treated with high-dose chemotherapy and then autologous hematopoietic stem cell transplantation except within clinical trials.

BACKGROUND

Description of the condition

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 (Enzinger 2001). STS have a significant risk of distant metastasis in addition to the potential for locally destructive growth and recurrence. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise all STS except rhabdomyosarcoma, which primarily affects children and young adults. In this review we investigated NRSTS which are categorized as malignant according to the World Health Organization (WHO) 2002 classification (Fletcher 2002) as adopted by the European Society for Medical Oncology (ESMO) Guidelines Working Group (Casali 2009). This classification excludes the Ewing family of tumors (EFT).

NRSTS usually originate de novo and rarely from benign tumors. In most cases the pathogenesis is unknown; however, some factors

have been found to be associated with the development of NRSTS (Enzinger 2001). These include exposure to ionizing radiation, environmental carcinogenic substances, oncogenic viruses and immunologic factors. Genetic factors can also play a role since some inherited diseases such as neurofibromatosis type 1 are associated with a higher risk of NRSTS (Tsao 2000).

In Western countries about four new cases of NRSTS are estimated per 100,000 population every year (Casali 2009), with rhabdomyosarcoma and the Ewing family of tumors excluded from this statistic. STS constitute about 1% of malignancies in adults and 7% in children (NCI 2009a). Rhabdomyosarcoma represents about 50% of STS in children (Gurney 1997; Miller 1995). NRSTS are rare in both children and adults and the distribution of NRSTS differs significantly between children and adults (Table 1) according to (Spunt 2006).

Based on the Surveillance, Epidemiology and End Results (SEER) cancer statistics review (1975 to 2005) of the National Cancer Institute (NCI), in the US 10,390 new cases and 3680 deaths from STS were estimated for the year 2008 (NCI 2008a). Separate data were not available for rhabdomyosarcoma and NRSTS. The distribution of STS increased with age from 2001 to 2005, according to SEER data. Of all STS cases, 10.3% were in children and young adults less than 20 years of age (NCI 2008b). The median age at diagnosis of STS, including tumors of the heart, was 57 years (NCI 2008c).

Staging

Disease progression may be dichotomized into the two categories of limited and extensive disease. Limited disease is typically a localized, small-sized, low-grade and operable accessible tumor that has no regional lymph node involvement and no distant metastases. Extensive disease can also be denoted as advanced disease defined as localized, large-sized and high-grade tumor that may not be completely removed by surgery, may be invasive and may have regional lymph node involvement or distant metastases. Both categories differ significantly in terms of prognosis and treatment. Where many patients with limited disease may be cured by surgery, extensive disease is associated with a poor outcome and many patients receive chemotherapy as palliative therapy.

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system combines grade, depth and size of the tumor as well as regional lymph node involvement and distant metastases and describes the extent of a cancer's spread from Stage 0 to IV (AJCC 2002). A review reported the 5-year overall survival (OS) estimates for stage I (low-grade, superficial and deep), II (high-grade, superficial and deep), III (high-grade, large and deep) and IV (any metastasis to lymph nodes or distant sites) as approximately 90%, 70%, 50% and 10% to 20%, respectively; information on treatment was not given (Clark 2005). In a multicentre study a total of 2185 participants with advanced STS revealed a median survival of 12 months (Van Glabbeke 1999). In the same study, of the 1922 (26%) eligible participants who responded to chemotherapy, the 5-year OS was 10%; in univariate analyses response to chemotherapy was not predicted by the same factors as was OS.

Symptoms

The location of the primary tumor can involve any area of the body. The distribution is 40% lower limb and girdle, 20% upper limb and girdle, 20% abdominal sites, 10% trunk and 10% head and neck (Clark 2005). NRSTS can involve any type of tissue and typically affect muscles, tendons, adipose tissue, blood vessels, joints (Sondak 2001) and commonly present as a painless mass. The symptoms depend on the anatomical site of origin, the size of the mass and other aspects. Retroperitoneal sarcomas are most often asymptomatic, until the mass grows large enough to be clinically obvious or presses on vital organs and causes pain (Dileo 2005).

Patients who relapse or suffer progressive disease after therapy, or metastasis, are commonly called high-risk patients because these signs are associated with shorter survival time. Spontaneous recovery of NRSTS is unknown.

Description of the intervention

Standard therapy

Surgery is the standard treatment for localized NRSTS (Casali 2009) and can be curative if distant dissemination is not present (Kotilingam 2006). Chemotherapy is a standard treatment for patients with distant metastasis (Casali 2009) and is regarded mainly as a palliative treatment for high-risk patients who are characterized by inoperable, locally advanced and metastatic disease. Doxorubicin, ifosfamide, gemcitabine, dacarbacine, docetaxel and trabectedin are used in monotherapy or in combinations (Casali 2009).

High-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (HSCT)

Autologous hematopoietic stem cell transplantation (HSCT) is defined as the transplantation of stem cells that have been collected previously from bone marrow or peripheral blood of the same person. High-dose chemotherapy (HDCT) uses higher doses of chemotherapeutic agents than is usually applied in standard-dose chemotherapy. HDCT may be tolerated by the patient or it may ablate the patient's bone marrow reserves and create an absolute requirement for stem cell rescue. Instead of HDCT, high-dose radiation therapy may be used to treat NRSTS patients. Autologous HSCT applied after HDCT or high-dose radiation is a

planned rescue therapy for HDCT-related severe hematologic toxicity (Banna 2007). Ideally, a mega-therapy regimen should be used consisting of several non-crossresistant agents that have a steep dose-response curve and little extramedullary toxicity (Ladenstein 1997).

HDCT and autologous HSCT are not a standard treatment option; they are an experimental approach. HDCT and autologous HSCT may be used in special cases after careful consideration, usually for patients who respond well to standard chemotherapy according to RECIST (Therasse 2000) criteria (Kasper 2005; Kasper 2007). Carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, melphalan, mitoxantrone and thiotepa, for example, have been used in HDCT regimens. HDCT and autologous HSCT are an experimental approach mainly used to treat high-risk patients with an unfavourable prognosis (stage IV with distant metastases). Independent of the disease status, HDCT and autologous HSCT are hazardous interventions that carry the risk of life-threatening organ failure.

Autologous HSCT and preceding HDCT were adopted to treat high-risk patients because it was believed that escalating doses in chemotherapy might increase survival by capturing putatively remnant malignant cells and might overcome resistance to standard-dose chemotherapy (Banna 2007).

Adverse events

Non-hematological adverse events, such as short-term and long-term organ toxicities, must be considered when using HDCT (Ladenstein 1997). Hematological adverse events as a result of autologous HSCT are usually manageable but life-threatening consequences of pancytopenia. They generally affect all patients and include, for example, graft failure, severe infections and bleeding.

Frequency

Of a total of 15,278 autologous HSCTs that were registered in 2005 by the European Group for Blood and Marrow Transplantation (EBMT), 69 were indicated for STS (Gratwohl 2007).

How the intervention might work

Escalating doses of chemotherapy may increase survival by capturing putatively remnant malignant cells and thus overcome cell resistance to standard chemotherapy (Banna 2007). High-dose chemotherapy may also cause severe hematologic and non-hematologic toxicity. Autologous HSCT is a planned rescue therapy for the HDCT-related demise of hematopoietic stem cells.

Why it is important to do this review

The potential benefit of this treatment option has not been investigated sufficiently in comparative studies (Pedrazzoli 2006). Some authors have warned against the use of HDCT with autologous HSCT, indicating the possibility of repositioning of malignant cells (Woods 1999). Others have questioned the rationale of HDCT with reference to the potential existence of refractory cancer stem cells (Banna 2007; Bonnet 1997; Sanchez-Garcia 2007). The question has not been answered whether autologous HSCT preceded by HDCT is able to increase OS in patients with NRSTS when compared to standard-dose chemotherapy. Randomized controlled trials (RCTs) have not been published. The rationale for this intervention, as described above, was based on non-comparative studies. We summarized and described the present available evidence to provide an evidence base to inform the design of future comparative studies.

OBJECTIVES

To assess the effectiveness and safety of autologous high-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (HDCT) for all stages of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

- Randomized controlled trials (RCTs).

Since we expected to find few, if any, RCTs non-RCTs were also included as follows.

- Quasi-RCTs, non-RCTs, phase I and II prospective studies, prospective and retrospective cohort studies, case-control studies, case series and case reports.

Results from RCTs and controlled clinical trials may provide data for estimation of effects on overall survival (OS) and answer the question: "Has the intervention a significantly better survival than the control and does the quality of the studies fit with the assumption that the intervention is better than the control?"

Data from non-comparative studies (phase I and II prospective studies, case series and case reports) were collected to estimate treatment-related mortality (TRM) within a cohort of participants, as

a descriptive analysis. Due to the lack of a control group the studies do not provide data for estimation of treatment effect.

Exclusion criteria

None

Rationale for including non-RCTs

Authors of studies on HDCT with autologous HSCT have stated that RCTs are both necessary and feasible. However, NRSTS is a rare disease and, according to the results of a preview literature search, currently there are no published RCTs available. In addition, controlled clinical trials or studies with any comparative data may be unlikely or rare. If they do exist they may be of low methodological quality. Based on the assumption that it is unlikely that the intervention has been or will be studied in RCTs in the near future, this systematic report of the findings and limitations of all available published studies will be useful, for example, for informing the design of appropriate RCTs and providing a summary of all of the evidence on the topic to date.

Types of participants

Inclusion criteria

We have adopted the WHO classification of soft tissue tumors to define the population of patients with NRSTS (Fletcher 2002) with the exception of the Ewing family of tumors (see 'Exclusion criteria'). Studies were included as long as at least 80% of patients had NRSTS. Children as well as adults were investigated and age limits did not apply. Participants were included regardless of the severity of the disease and of clinical staging information, as long as they received autologous (from either a peripheral or bone marrow source, or both) HSCT.

Exclusion criteria

Whilst the WHO classification of NRSTS includes the Ewing family of tumors, that is extraosseous tumor types, we excluded these because they are primarily bone sarcomas. Because extraosseous types are rarely diagnosed and share common features, they were regarded with osseous types as one entity and were excluded.
The clear delineation of soft tissue sarcomas to be included in the present report and the grounds for exclusion of some tumor types was hindered by the presence of more than 30 heterogenous tumor entities, the distinction between malignant tumors and two categories of intermediate malignancies as described in the WHO classification (Fletcher 2002), and a complicated histology and terminology. Therefore, we present the designation of tumors that were regarded as (malignant) soft tissue sarcomas in the present review (Table 2) and we present the terms for tumors that were not considered (Table 3).

Types of interventions

Intervention: autologous hematopoietic stem cell transplantation (HSCT), stem cells from peripheral source or the bone marrow, serving as a rescue therapy usually applied after high-dose chemotherapy (HDCT).
Comparison: standard-dose chemotherapy, which is defined as chemotherapy at a lower dose than HDCT without the need for stem cell rescue.
Allogenic HSCT was excluded.

Types of outcome measures

Primary outcomes

- Overall survival (OS): survival until death, from all causes. Survival was assessed starting from the time when participants received autologous HSCT.
- Treatment-related mortality (TRM): deaths that were classified as treatment related or the participants died of complications after autologous HSCT.

Secondary outcomes

- Disease-free survival (DFS): time free of disease after receiving autologous HSCT; the events were death due to all causes or any sign of the disease. The extent of disease was evaluated by clinical, histologic and imaging studies.
- Progression-free survival (PFS): time staying free of disease progression after receiving autologous HSCT. Participants may still have the disease but their disease is stable or showed a partial response to treatment; the events are death from all causes or any progression of the disease.
- Event-free survival (EFS): time staying free of any of a particular group of defined events after receiving autologous HSCT. Participants may still have the disease; the events are death from all causes, any sign of the disease in participants who had a complete response to treatment, any relapse or progression of the disease, or events that were defined by the individual study protocol.
- Failure-free survival (FFS): time staying free of treatment failure after receiving autologous HSCT; the events are disease- or treatment-related death, any sign of the disease in participants who had a complete response to treatment, refractory disease with no response to treatment, stable disease, or progression of the disease after treatment.
- Toxicity: adverse events classified according to the common toxicity criteria (NCI 2009b) within 90 days of autologous HSCT; grades 3 and 4 of toxicity were extracted and grouped as

hematological (leukopenia, neutropenia, thrombocytopenia) and non-hematological (nausea, kidney, liver, nervous system, heart) toxicities.

- Secondary neoplasia: as classified by the study authors.
- Health-related quality of life (HRQoL): measured using a questionnaire that has been validated through reporting of norms in a peer-reviewed publication.

Search methods for identification of studies

The search methods suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009) and by the Cochrane Gynaecological Cancer Review Group were used. Articles in any language were included. Translations were carried out as necessary.

The literature sources and search steps are shown in Table 4. In the first step, three different bibliographic databases were searched electronically to find topic-related articles. In the second step, online registers were searched to find additional information on completed or ongoing comparative studies that have not been published. References cited in 98 identified reviews (Appendix 4), including three systematic reviews, were evaluated.

Electronic searches

The following electronic databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2), Ovid MEDLINE (from 1950 to February 2010), Ovid EMBASE (from 1980 to February 2010). See Appendix 1, Appendix 2, and Appendix 3 for the appropriate medical subject headings (MeSH) and text words for the search strategies. An updated search was run in PubMed (6 June 2010) using the following terms: ("Transplantation, Autologous"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh]) AND "Sarcoma"[Mesh].

Searching other resources

Information about trials not listed in CENTRAL, MEDLINE or EMBASE, either published or unpublished, were located by searching the reference lists of relevant articles and review articles. We also electronically searched the abstracts of the conference proceedings of the American Society of Clinical Oncology (ASCO) annual meetings (from 2004 to 2009). We searched for ongoing trials by scanning online registers listed in Table 4. We also searched for ongoing trials by contacting researchers involved in the area.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference management database (Reference Manager Version 11) (Thomson Reuters Corp 2009); duplicates were removed and the remaining references were examined by two review authors (FP and TBH) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by two review authors (FP and TBH). Disagreements were resolved by discussion between the two review authors and consultation with a third review author (MK), if necessary. Reasons for exclusion were documented.

Data extraction and management

For included studies, data on characteristics of studies, participants and interventions; risk of bias; duration of follow up; outcomes and deviations from protocol were abstracted independently by two review authors (FP and MaKr). Differences between review authors were resolved by discussion or by appeal to a third review author (CB).

Characteristics of studies

- Study type (RCTs, non-RCTs, non-randomised trials with no control group (phase I or II study), cohort studies, case-control studies, case series, case reports)
- Design (randomization, sequence generation and concealment of allocation, blinding, prospective, retrospective, consecutive enrolment - sample selection)
- Observation period (calendar years)
- Inclusion and exclusion criteria (Ewing family of tumors, other excluded sarcomas, other solid tumors)
- Number and location of participating centres

Characteristics of participants

- Age
- Gender
- Type of histological category
- Status of metastasis
- Number of recruited and analyzed participants

Characteristics of interventions

- High-dose chemotherapy
- Autologous peripheral blood stem cells
- Autologous bone marrow stem cells

Survival measures

- Time to event from treatment with HSCT
- Number of events and participants at risk
- Kaplan-Meier survival estimate
- Hazard ratio (HR)
- 95% confidence interval (CI)
- Log rank P value
- Duration of follow up (median; range)

Treatment-related mortality

- Number of events and participants at risk
- Number of recruited and analyzed participants
- Cause of death

Secondary neoplasia

- Number of events and participants at risk
- Number of recruited and analyzed participants
- Type of secondary neoplasia

Toxicity

- Number of WHO grade 3 or 4 adverse events and participants at risk
- Number of recruited and analyzed participants
- Organ system affected

Quality of life

- Scale
- Number analysed
- Mean or median
- Standard deviation or range

Where relevant and if reported, both unadjusted and adjusted summary statistics were extracted. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis in which participants were analyzed in the groups to which they were assigned. The time points at which outcomes were collected and reported were noted.

Assessment of risk of bias in included studies

The assessment of risks of bias in included controlled studies was independently applied at the study level by two review authors (FP and MaKr) according to Table 5 and to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). Differences were resolved by discussion or by appeal to a third review author (CB). Results of data syntheses were interpreted in light of the findings with respect to risk of bias. Assessment of blinding of the care provider and blinding of the participants was not applicable as blinding is not ethically accepted for studies on stem cell transplantation.

Measures of treatment effect

We used the following measures of the effect of treatment.

- For time to event data we used the HR, if possible.
- For dichotomous outcomes we used the risk ratio (RR) or odds ratio (OR).
- For continuous outcomes we used the mean difference between treatment arms on the condition that the distribution characteristics had been evaluated.

Studies reporting aggregate data that combined the results of several participants (including results from separately reported subpopulations that fulfilled the inclusion criteria) were distinguished from studies with individual data of single participants. Data from these studies were described as narrative summaries.

In some studies diagnoses of NRSTS were mixed with non-NRSTS solid tumors and rhabdomyosarcomas to such an extent that the proportion of NRSTS participants was less than 80% of the study population. In this case, if data on single participants were identified that fulfilled the inclusion criteria of the present review we included the study and data for the individual participant in data analysis.

Estimates of OS were considered for the evaluation if the use of the Kaplan-Meier method was reported in the study. A survival analysis was conducted of individual participant level data based on the Kaplan-Meier method. Data were not used for survival analysis if the follow-up data were only available for selected participants and if the beginning of the follow-up period was not reported clearly, or reported as starting from the time of diagnosis. Statistical analyses of time to event data were performed using SAS Version 9.2 (SAS Institute Corp 2009).

Unit of analysis issues

None

Dealing with missing data

Information on the outcome status and on the follow-up period had to be complete for all participants in each study. We did not impute missing outcome data for the primary outcome. If data were missing or only imputed data were reported we contacted trial authors to request data on the outcomes among participants who were assessed.

Assessment of heterogeneity

The data were entered in Review Manager Version 5 (Review Manager 2008) and analyzed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (

Higgins 2009). We looked for sources of clinical heterogeneity due to differences in:

- risk factors of participants studied, i.e. tumor subdiagnosis or histology, presence or absence of metastasis;
- study design; and
- likelihood of bias.

Heterogeneity between studies was assessed by inspection of the study methods and participants' characteristics. Forest plots and formal statistical tests could not be conducted because the body of studies did not contain sufficient numbers of comparative studies.

Data synthesis

Aggregate data reported in controlled studies or case series were synthesized narratively. In contrast, individual data were pooled and available time-to-event data were analyzed in a Kaplan Meier survival analysis.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were carried out.

Sensitivity analysis

No sensitivity analyses were carried out.

RESULTS

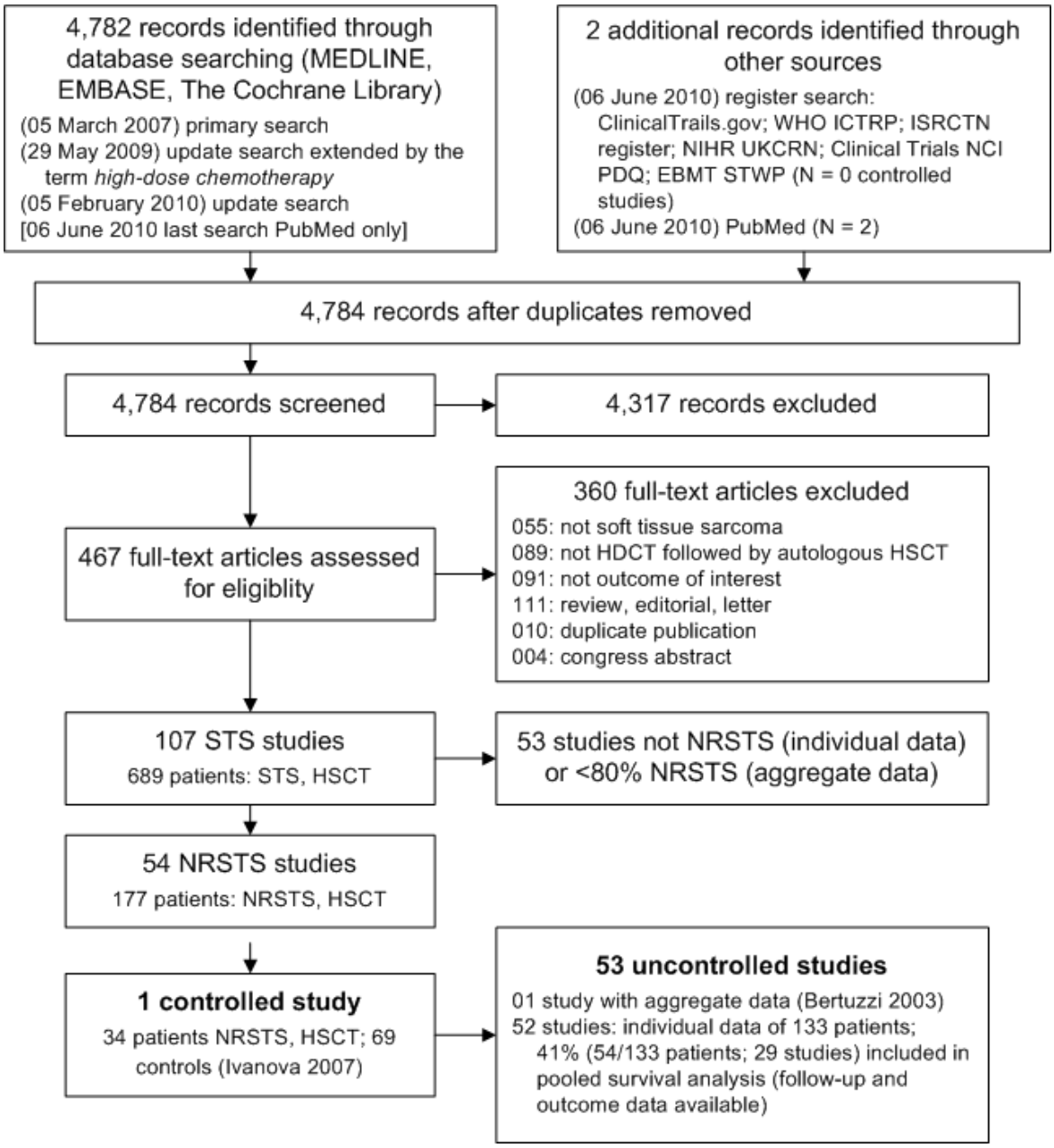
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Considering all sources as shown in Table 4, 4784 different articles (duplicates removed) were identified (Figure 1). The titles and abstracts of 4317 articles did not fulfil the inclusion criteria and 10% (467 of 4784) of the retrieved articles were evaluated in detail using the full text. Of these a total of 11% (54 of 467 references) of the full text articles were included in the present review and the other 413 studies were excluded.

Figure 1. Literature search and study flow. Abbreviations: EBMT STWP: European Group for Blood and Marrow Transplantation Soft Tissue Working Party; HDCT: high-dose chemotherapy; HSCT: hematopoietic stem cell transplantation; N: number; NCI PDQ: National Cancer Institute Physician Data Query Clinical Trials; NIHR UKCRN: National Institute for Health Research (NIHR) UK Clinical Research Network's Portfolio Database; NRSTS: non-rhabdomyosarcoma soft tissue sarcoma; RMS: rhabdomyosarcoma; STS: soft tissue sarcoma. WHO ICTRP: World Health Organization International Clinical Trials Registry Platform.



We were unable to identify any additional studies from screening the reference lists of included studies and reviews or from institutions and authors. Relevant studies were not identified from online trial registries or congress proceedings, described in Table 4, either.

Included studies

We identified 54 studies including a total of 246 participants: 177 that received HDCT followed by autologous HSCT transplant and 69 that received standard therapy. The characteristics of all 54 included studies are described in the section Characteristics of included studies.

We included one retrospective study in which 34 participants who received HDCT followed by autologous HSCT were compared with a historical control group consisting of 69 participants with STS matched for age, gender, histological diagnosis and stage of disease and who received standard care (Ivanova 2007). This study did not provide sufficient detailed information about the control group to allow a meaningful evaluation. One study had a prospective design and included 10 participants with NRSTS who received HDCT and peripheral HSCT (Bertuzzi 2003). The remaining 52 studies comprised 16 phase I or II prospective trials with no control groups and 36 retrospective case series or individual case reports. Whilst not all participants had NRSTS in the studies that were phase I or II prospective trials, data were reported for individual participants so that we were able to include these studies. RCTs and clinical controlled studies with a concurrent control group were not identified.

Excluded studies

A total of 88% (413 of 467 references) of the potentially relevant articles were excluded (Figure 1) based on:

- diagnosis not STS according to Table 2 (n = 55);
- not NRSTS (individual data) or less than 80% NRSTS (aggregate data) (n = 53);
- intervention not autologous HSCT (n = 89);
- primary outcome survival not reported (n = 91);
- study design was a review, editorial, abstract (n = 111);
- duplicate publication (n = 10);
- congress abstract (n = 4).

Excluded studies are described in the Characteristics of excluded studies table.

Risk of bias in included studies

Comparative studies

The design of the study by Ivanova 2007 was not clearly reported; we categorised it as a retrospective comparative study that used historical data to create a control group. Results of 34 participants that received HSCT were compared to 69 participants that did not receive HSCT. The author reported that the groups were matched for age, gender, histology and stage, though we were unable to verify this as insufficient data were reported in the article. Assignment to treatment groups was not described, the participant flow was unclear and loss to follow up was not addressed. Selective outcome reporting was unclear in this retrospective study, study results were reported amidst reports of results from other studies and information about statistical methods was sparse. Therefore, the risk of bias was very large. Data for individual participants were not reported.

Non-comparative studies

The risk of bias was high in all 53 studies due to the study design being either phase I and II non-comparative trials, case reports or case series.

Aggregate data

In one study (Bertuzzi 2003) the characteristics of the participants and the intervention were described in detail and the participants were described as a consecutive sample. The primary outcome, OS, was clearly reported in the text and shown in an appropriate graph; the Kaplan-Meier method was used to conduct a survival analysis. All 10 included participants had the histologic subtype of desmoplastic small round-cell tumor. The prognosis of this subtype may be regarded as specific and not comparable to other subtypes. Data for individual participants were not reported.

Individual participant data

In 52 studies, the characteristics of the participants and the intervention were described in detail. The primary outcome of OS was clearly reported in the text or tables, however the start of the follow-up period varied between the studies and was not reported in every study. We defined the start of the follow up as the time of treatment, either transplantation or high-dose chemotherapy. The start of follow up as the time of diagnosis was not accepted because the time lag between diagnosis and intervention can be considerable, as demonstrated in a study on 22 participants with STS including 11 NRSTS and 11 RMS: "Median delay between diagnosis and intensification was between 4 to 39 months" (Dumontet 1992). Therefore, OS with treatment was estimated using only data with complete outcome and follow-up information for the pooled analysis. Considerable data were incomplete or inappropriate, resulting in 59% (79 of 133 participants) of the pooled

individual data being excluded from the analysis, therefore only 41% (54 of 133 participants in 29 studies) of the data were used in the pooled survival analysis.

Allocation

The allocation of participants to the two alternative treatment groups was not described in the one comparative study.

Blinding

Blinding was not assessed as it is unlikely that blinding of participants or investigators would be adopted in studies evaluating HSCT.

Incomplete outcome data

There was insufficient reporting of attrition and exclusions to permit judgement whether incomplete outcome data were adequately addressed. Participant flow, prospective comparative study design, characteristics of both treatment groups and outcomes were not described in detail. Consecutive recruitment of participants was described in the one case series with aggregate data (Bertuzzi 2003).

Selective reporting

There was insufficient information to permit judgement of whether the reports were free of selective outcome reporting. It is likely that all studies fall into this category. The start of follow up was not stated in one (Ivanova 2007) of two studies that presented aggregate outcome data. Follow-up data were not reported adequately for 59% (79 of 133) of participants of studies that presented individual data, therefore we could not use the data. TRM was not addressed in every study. Secondary neoplasia is a long-term outcome that was not addressed in every study. Data on toxicity outcomes could not be extracted from most studies because they were not reported individually for the population of interest.

Other potential sources of bias

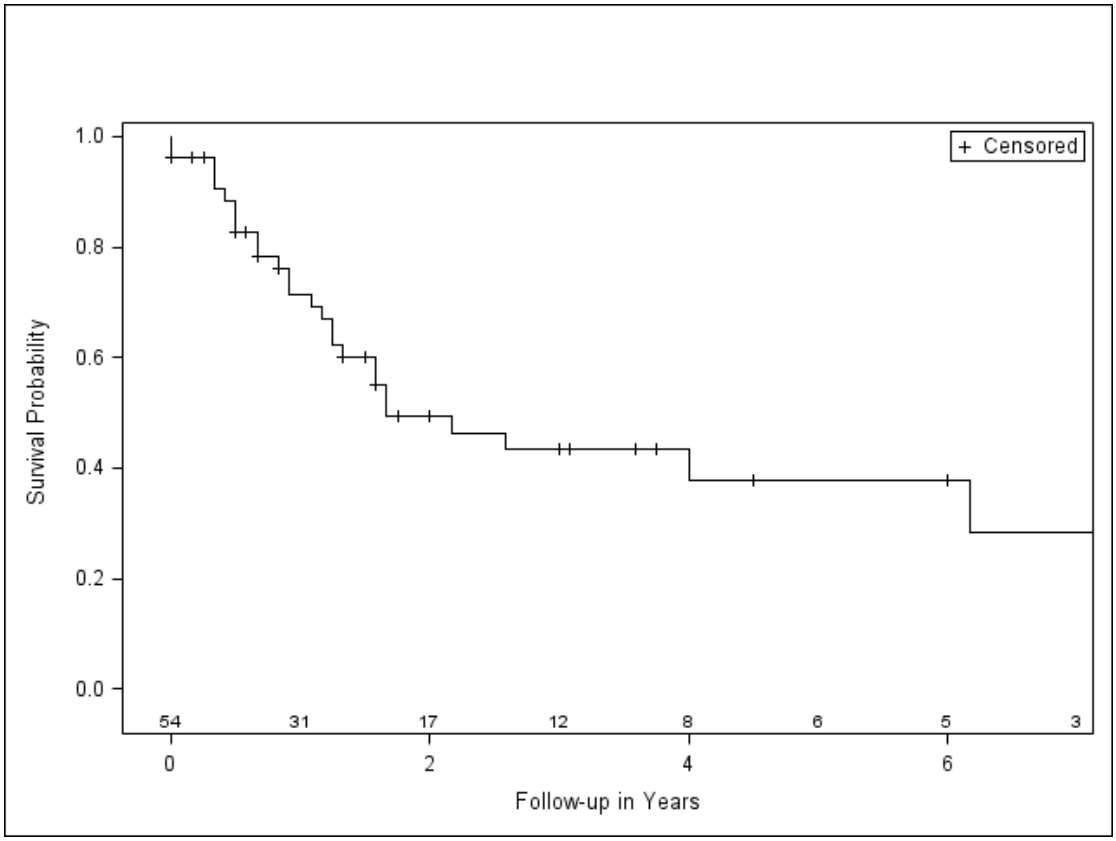
All 54 studies had a potential source of bias related to the specific study design used, such as lack of a control group or no description of the characteristics of a control group, no reporting of how the participants were selected and no reporting of reasons for loss to follow up.

Effects of interventions

Overall survival (OS)

In one comparative study (Ivanova 2007), OS at two years after HSCT was estimated as 62.3% when compared with 23.2% for participants that received standard care. The difference was reported to be statistically significant (Table 6) although the statistical test was not described and a P value was not reported. The Kaplan-Meier estimator for OS at two years after transplantation was reported as 20% in another study (Bertuzzi 2003) with aggregate data of 10 participants with desmoplastic small round-cell tumors (Table 6). In the pooled survival analysis of 54 individuals who received HSCT, OS at two years was estimated as 49% (95% CI 34% to 64%) (Table 6; Figure 2).

Figure 2. Meta-analysis of overall survival of 54 individual patients with complete follow-up information pooled from 29 case series and case reports. Number of patients at risk at 1 year intervals. Abbreviations: HDCT: high-dose chemotherapy; HSCT: hematopoietic stem cell transplantation; NRSTS: non-rhabdomyosarcoma soft tissue sarcoma.



Treatment-related mortality (TRM)

TRM was addressed in eight non-comparative studies (67 transplanted participants) and a procedure-related death was described for 11 participants (Table 7). Severe infection was the main cause of death (4 cases). TRM was not addressed in the study by Ivanova 2007.

Disease-free survival

Not reported

Progression-free survival (PFS)

PFS at two years after transplantation was reported as 0% in one study (Bertuzzi 2003) with aggregate data of participants with desmoplastic small round-cell tumors (Table 6).

Event-free survival

Not reported

Failure-free survival

Not reported

Secondary neoplasia

Secondary neoplasia was addressed in one case report (Table 8) and was not addressed in the comparative study (Ivanova 2007).

Toxicity

Data on hematological and non-hematological severe toxicity grade 3 to 4 (NCI CTEP 2006) after transplantation was sparse and extracted from five non-comparative studies only (Table 9).

Subgroup analysis

Subgroup analyses were not conducted.

Health-related quality of life

Studies on health-related quality of life were not identified.

DISCUSSION

Summary of main results

We identified only one comparative study, with a high likelihood of bias. OS at two years for participants in the HSCT group was significantly higher than for participants in the control group. In one case series of 10 participants with desmoplastic small round-cell tumors, OS at two years was low at 20%, which may reflect that participants with this special tumor type have a lower risk of survival than participants with other NRSTS. Our estimated OS of 49% at two years for the remaining studies with participant level data falls within the range reported above for the two studies with aggregate data. For TRM even the more conservative estimate, 6.2%, is considerably higher than the 2.0% TRM within the first days following HSCT reported by the EBMT registry (EBMT 2009) for the year 1998 (Rosti 2002). Secondary neoplasia was reported for 0.6% of participants and was probably an extreme underestimation of the true frequency because of relatively short follow up in the included studies and the fact that the included studies were not designed to specifically detect secondary neoplasia. The detection of secondary neoplasia depends on a long follow up, which might be provided by cancer registers. This reported incidence compares with a frequency of 4.0% for secondary neoplasia based on register data (Neglia 2001) and 6.9% (Baker 2003) after a long observation period of 20 years. Severe toxicity grade 3 to 4 was sparsely reported.

Overall completeness and applicability of evidence

Many of the studies we identified had to be excluded because they included participants with a mixture of heterogenous tumors and the proportion of participants with NRSTS was fewer than 80%. Furthermore, most treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today. It is also a possibility that the results reflect the course of the disease and an effect of the prior therapy rather than the effect of the test intervention.

Quality of the evidence

All 54 studies have a high risk of bias. The one comparative study lacks information on the characteristics of participants, the intervention and applied statistical methods. Thus, these data do not provide any evidence that HDCT followed by autologous HSCT has additional benefit over standard therapy. An additional descriptive analysis of 52 phase I and II studies, case series or case reports showed that there are many different tumor types of NRSTS treated by transplantation, though each individual NRSTS entity was scarce. We found that a pooled survival analysis of individual participant data from phase I and II studies and case reports was considerably hampered. Specifically, the majority of required follow-up information was incomplete or missing and, therefore, could not be included in the survival analysis. One requirement for survival analysis is a unique definition of the start of the follow-up period for all included participants. This was missing from many studies. As suggested by the low OS for desmoplastic small round-cell tumor, each entity may carry an individual risk profile and, therefore, ideally should be evaluated separately. The body of evidence does not allow robust conclusions in relation to the objectives of the review.

Potential biases in the review process

Strengths

The search strategy was broad and it is 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. The follow up of participants with individual data had to begin at the same time point to be considered in the pooled analysis of survival. Authors were contacted to ask for additional data.

Limitations

RCTs and non-controlled trials with low risk of bias were not identified and only one comparative study with high risk of bias was identified. No database is available for a conclusive comparison. Many studies were excluded because participants with NRSTS were included with participants with other malignant diseases. The heterogeneity of NRSTS and the possible different terminology used in publications may have led us to overlook studies with eligible participants. This may be more an issue for case series but it is highly unlikely for controlled trials. The pooled survival analysis of individual data was based on less than half of all the individual data available and the exclusion of these data whilst intending to reduce bias may also have introduced bias.

Agreements and disagreements with other studies or reviews

In the last two decades, from 1986 to 2007, the lack of evidence and need to conduct randomized controlled trials was stated in at least 20 publications (Blay 2000; Carvajal 2005; Dumontet 1992; Ek 2006; Elias 1998; Hale 2005; Kasper 2004; Kasper 2007; Kavan 1997; Ladenstein 1997; Mackall 2001; Meyers 2004; Michon 1999; Pinkerton 1986; Reichardt 2002; Rosti 2002; Schlemmer 2006; Seeger 1991; Weigel 2001; Woods 1999) seeking to clarify the relevance of HDCT followed by autologous HSCT in high-risk patients with STS. We identified reviews on OS at five years after chemotherapy without transplantation. The estimates were 6% (Ramanathan 1999), less than 10% (Banna 2007; Van Glabbeke 1999), 14% (Tumorregister München 2007) and 10% to 20% (Clark 2005). In the control group of Ivanova 2007, OS at two years was 23%. A systematic review (Verma 2008) was performed to determine whether first-line dose-intensive chemotherapy supported by growth factor or autologous bone marrow or stem cell transplantation improves outcomes compared with standard-dose chemotherapy in patients with inoperable, locally advanced or metastatic soft tissue sarcoma. In this review, only one case series (Schlemmer 2006) with HDCT followed by autologous HSCT was reported, which was excluded from the present review. In a narrative review (Banna 2007) of HDCT followed by autologous HSCT in patients with solid tumors, outcomes were reported for three sarcomas (rhabdomyosarcoma, Ewing sarcoma and osteosarcoma) not included in the present review. Predictive values were not reported in a review (Clark 2005) on soft tissue sarcomas in adults. 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.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence base does not support the use of HDCT followed by autologous HSCT in high-risk patients with NRSTS except in prospective concurrent, preferably randomized, controlled trials.

Implications for research

Randomized controlled trials are needed to clarify the relevance of HDCT followed by autologous HSCT in patients with NRSTS. If non-randomized controlled studies are conducted, a low risk of bias should be achieved. Case series and case reports are not helpful. Criteria of included tumor types should adhere to the WHO classification.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al Balushi 2009

Methods	Retrospective report of cases without control in a single-centre, observed in Canada from 2000 to 2007
Participants	5 children with desmoplastic small round-cell tumor with metasteses; 4 male, 1 female; mean age 11 years
Interventions	HDCT followed by autologous HSCT in 3 of 5 children
Outcomes	overall survival; toxicity
Notes	individual data for each child presented

Andres 2006

Methods	Retrospective report of a single case without control in a single-centre, observed in Spain; no information on observation period available
Participants	1 female 21 years of age with desmoplastic small round-cell tumor
Interventions	HDCT followed by autologous HSCT
Outcomes	overall survival; toxicity
Notes	

Bernbeck 2007

Methods	Retrospective report of cases without control in a single-centre study, observed in Germany from 2001 to 2005
Participants	9 participants with high-risk soft tissue sarcomas, 8 of whom had rhabdomyosarcoma or synovial sarcoma at various clinical stages. Children and young adults (3 male, 5 female) ranging from 1 to 21 years of age
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival; toxicity
Notes	individual data for each participant presented

Bertuzzi 2003

Methods	Prospective study of consecutive cases without control in a single-centre, observed in Italy from 1997 to 2002
Participants	10 adults (10 male) aged 15 to 60 years, median 29 years of age with advanced desmoplastic small round-cell tumor at various clinical stages, n=4 with metastases
Interventions	HDCT (melphalan, mitoxantrone, thiotepa) followed by autologous peripheral HSCT
Outcomes	overall survival; progression-free survival; toxicity (NCI-CTC)
Notes	aggregate data

Bley 2004

Methods	Retrospective report of a single case without control in a single-centre, observed in Germany; no information on observation period available
Participants	1 female 22 years of age with liposarcoma
Interventions	HDCT followed by autologous HSCT
Outcomes	overall survival; toxicity
Notes	

Bölke 2005

Methods	Retrospective report of a single case without control in a single-centre, observed in Germany in 1993
Participants	1 female 33 years of age with recurrent malignant fibrous histiocytoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; adverse events
Notes	

Cole 1999

Methods	Retrospective report of a single case without control in a single-centre, observed in the United States; information on observation period not available
Participants	1 male 26 years of age with synovial sarcoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; adverse events

Cole 1999 (*Continued*)

Notes	

Doros 2008

Methods	Retrospective report of a single case without control in a single-centre, observed in the United States; information on observation period not available
Participants	1 male 14 years of age with desmoplastic small round-cell tumor
Interventions	HDCT followed by autologous HSCT
Outcomes	overall survival; adverse events
Notes	

Endo 1996

Methods	Retrospective report of a case series without controls in a single-centre, observed in Japan from 1987 to 1995
Participants	16 participants with high-risk solid tumors; of which 1 male 19 years of age with undifferentiated sarcoma
Interventions	HDCT followed by autologous peripheral and bone marrow HSCT
Outcomes	overall survival; adverse events
Notes	individual data available for each case

Engelhardt 2007

Methods	Retrospective report of a consecutive series of cases without control, observed from 1992 to 2003; the number of centres and the countries were not specified (probably in Germany and the United States of America)
Participants	35 participants with Ewing sarcoma and soft tissue sarcomas, of which 23 had NRSTS (anaplastic soft tissue sarcoma, angiosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant haemangioperiocytoma, synovial sarcoma); 12 male, 11 female, 21 to 56 years of age
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival; toxicity
Notes	individual data for participants with rhabdomyosarcoma and other soft tissue sarcoma. The reported aggregate data were not considered because the proportion of participants with NRSTS plus 3 rhabdomyosarcomas was less then 80% of all participants therefore did not meet our eligibility criteria

Fang 2008

Methods	Retrospective report of cases without control in a single-centre, observed in the United States in 2006
Participants	2 cases, 1 of whom had a desmoplastic small round-cell tumor; female 23 years of age
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival
Notes	individual data presented for each participant

Farruggia 2008

Methods	Retrospective report of a single case in a single-centre, observed in Italy; information on observation period not available
Participants	1 male 10 years of age with synovial sarcoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; toxicity
Notes	

Fetscher 1997

Methods	Retrospective report of a single case in a single-centre, observed in Germany in 1994
Participants	1 female 23 years of age with metastatic leiomyosarcoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival
Notes	

Frapier 1998

Methods	Retrospective report of a single case in a single-centre, observed in France; information on observation period not available
Participants	1 male 11 years of age with high grade undifferentiated sarcoma
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	survival; adverse events

Frapier 1998 (*Continued*)

Notes	

Fraser 2006

Methods	Report of two prospective phase I/II studies of cases without control in a single-centre, observed in the United States from 1995 to 2004
Participants	36 participants with solid tumors that were metastatic or relapsed following therapy, treated on two consecutive trial protocols n=11 and n=25; 5 had desmoplastic small round-cell tumor and rhabdoid tumor; aged from 2 to 20 years
Interventions	HDCT followed by autologous peripheral or bone marrow HSCT
Outcomes	survival; toxicity
Notes	individual data for each participant reported on

Garrido 1998

Methods	Retrospective report of cases in a single centre; observed in the United States; 1991 to 1995
Participants	2 participants, n=1 45 year old man with metastatic liposarcoma
Interventions	HDCT followed by autologous HSCT
Outcomes	adverse events
Notes	individual data available for each case

Graham 1997

Methods	Prospective phase I/II trial in a single centre, observed in the United States from 1991 to 1995
Participants	49 participants with recurrent and high-risk pediatric brain tumors 1 of whom had fibrosarcoma; aged 1 to 32 years, median 12 years
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	survival; toxicity
Notes	individual data available for participants

Hawkins 2002

Methods	Prospective phase I/II trial without controls in a 3-centre study, observed in United States from 1996 to 1998
Participants	23 children and adolescents with metastatic sarcomas of whom 6 had NRSTS (desmoplastic small round-cell tumor, fibromyxoid sarcoma, leiomyosarcoma, undifferentiated sarcoma) 5 male; 1 female, ranging from 5 to 19 years of age
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival, toxicity
Notes	individual data available for each participant

Hoogerbrugge 1997

Methods	Retrospective report of a single case in a single centre, observed in the Netherlands; information on observation period not available
Participants	1 child 1 year of age with fibrosarcoma; information on gender not available
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	overall survival; toxicity
Notes	

Ivanova 2007

Methods	Retrospective report of cases with results from a control group in a single-centre study, observed in Russia from 1990 to 2006
Participants	103 patients with various soft tissue sarcomas were investigated in two treatment groups; individual information on diagnoses, age and gender not available
Interventions	34 children were treated with HDCT (carboplatin, cyclophosphamide, etoposide) followed by autologous HSCT; 69 children as a control; information on the control therapy not available
Outcomes	overall survival, adverse events
Notes	aggregate data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Assignment of patients to treatment groups	High risk	no information about assignment; study report results about transplanted patients

Ivanova 2007 (*Continued*)

		such as a case series; then adds OS of an unspecified control group; control group was matched to the test group, however, the description of this procedure was not comprehensible
Concurrent control	High risk	control group was probably selected from historical data
Comparable baseline characteristics	Unclear risk	no report about patients' characteristics, except the average tumor volume 180 cm^3 which was comparable in both groups; no other baseline characteristics; information insufficient to assess comparability between groups
Loss to follow-up	Unclear risk	loss to follow up was not addressed; no patient flow described
Selective outcome reporting	Unclear risk	the study has a retrospective design and a study protocol is not available
Other causes for high risk of bias	Unclear risk	study results were reported amidst reports of results from other studies; the article resembles a narrative review; information about statistical methods was sparse

Kaminski 2000

Methods	Retrospective report of a single case in a single centre, observed in the United States in 1993
Participants	1 child (female) 6 years of age with fibrosarcoma
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	overall survival; adverse events
Notes	

Kasper 2007

Methods	Retrospective report of cases without control in a single-centre study, observed in Germany from 1998 to 2007
Participants	38 participants with soft tissue and bone sarcomas, of whom 14 had NRSTS (leiomyosarcoma; liposarcoma; malignant fibrous histiocytoma; not otherwise specified soft tissue sarcomas; synovial sarcoma) aged 23 to 65 years; no individivual information available on gender

Kasper 2007 (*Continued*)

Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	toxicity (WHO)
Notes	mainly aggregate data reported

Kasper 2010

Methods	Prospective controlled clinical trial; single-institutional phase II study, observed in Germany from 2003 to 2008
Participants	34 patients with various solid tumors were investigated in two treatment groups
Interventions	9 participants with solid tumors were treated with HDCT (ifosfamide, carboplatin, etoposide) followed by autologous HSCT (peripheral blood stem cell rescue), of whom 7 had NRSTS (leiomyosarcoma; malignant fibrous histiocytoma; not otherwise specified soft tissue sarcomas; synovial sarcoma); aged 29 to 65 years of age 25 participants with solid tumors were treated in a control group with standard-dose chemotherapy (ifosfamide, doxorubicin), of whom 20 had NRSTS (leiomyosarcoma; liposarcoma; malignant fibrous histiocytoma; not otherwise specified soft tissue sarcomas; synovial sarcoma); age was not reported
Outcomes	overall survival; progression-free survival; adverse events
Notes	aggregate data included less than 80% NRSTS patient data; individual data for transplanted data were available but not included in the meta-analysis because follow up did not start at intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Assignment of patients to treatment groups	High risk	no information about assignment; all participants had metastatic disease; study reports results about transplanted and control patients such as a case series
Concurrent control	Low risk	all participants were treated bewteen 2003 and 2008
Comparable baseline characteristics	Unclear risk	tumor classification and metastatic site reported for all participants; age reported for 9 transplanted participants; no other baseline characteristics; information insufficient to assess comparability between groups

Kasper 2010 (*Continued*)

Loss to follow-up	Unclear risk	loss to follow up was not addressed; no patient flow described
Selective outcome reporting	Unclear risk	overall survival was assessed from time of study inclusion and not from time of transplantation; the gap between study inclusion and transplantation may be up to 4 months; reporting makes comparision to other studies difficult; treatment-related mortality not reported; toxicity reported scarcely
Other causes for high risk of bias	Unclear risk	duplicate data because some patients were reported in Kasper 2007 and Kasper 2010

Kozuka 2002

Methods	Retrospective report of cases without control in a single-centre study, observed in Japan from 1999 to 2000
Participants	2 adults (2 male) 21 and 37 years of age with recurrent NRSTS (malignant fibrous histiocytoma or malignant hemangiopericytoma)
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival; adverse events
Notes	individual data for each participant reported

Kretschmar 1996

Methods	Retrospective report of cases in a single-centre study, observed in the United States; information on observation period not available
Participants	3 adolescent males with desmoplastic small round-cell tumor, 1 of whom received HSCT (13 years of age)
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	survival; toxicity
Notes	

Krskova 2007

Methods	Retrospective report of a single case in a single centre, observed in the Czech Republic in 1998
Participants	1 child (male) 9 years of age with synovial sarcoma
Interventions	HDCT followed by autologous HSCT
Outcomes	overall survival; adverse events
Notes	

Kurre 2000

Methods	Retrospective report of 3 cases in a single-centre study, observed in the United States from 1994 to 1998
Participants	3 cases with desmoplastic small round-cell tumor, 2 of whom received HSCT: 1 male aged 5 years and 1 female aged 2.5 years
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival; adverse events
Notes	individual data reported for each participant

Kushner 1996

Methods	Prospective phase I/II study without controls in a single centre, observed in the United States; information on observation period not available
Participants	12 patients with desmoplastic small round-cell tumor of whom 4 boys from 10 to 14 years of age received HSCT
Interventions	HDCT (P6 protocol) followed by autologous bone marrow HSCT
Outcomes	Survival; toxicity (NCI CTC criteria)
Notes	individual data reported for each participant

Kushner 2001

Methods	Preliminary results from a prospective phase II/III study in a single-centre study, observed in the United States; information on observation period not available
Participants	21 participants with neuroblastoma, brain tumors and other poor-risk solid tumors, of whom 1 male 29 years of age with desmoplastic small round-cell tumor
Interventions	HDCT followed by autologous peripheral HSCT

Kushner 2001 (*Continued*)

Outcomes	overall survival; toxicity according to NCI CTC criteria
Notes	individual data for each participant available

Kushner 2008

Methods	Retrospective report of a case in a single-centre study, observed in the United States; information on observation period not available
Participants	1 adult (male) 18 years of age with desmoplastic small round-cell tumor
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival; adverse events
Notes	individual data

Kühne 2000

Methods	Prospective phase I/II study without control group in a single centre, observed in Switzerland from 1997 to 1999
Participants	11 children with brain tumors, soft tissue sarcomas, germ-cell tumors and neuroblastomas, of whom 1 child (male) 3 years of age with rhabdoid sarcoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; adverse events
Notes	individual data available for each participant

Lafay-Cousin 2000

Methods	Prospective phase II study without controls in a 4-centre study, observed in France from 1986 to 1998
Participants	18 children with recurrent mesenchymal tumors, of whom 4 (2 male; 2 female) from 10 to 16 years of age with NRSTS (desmoplastic small round-cell tumor; undifferentiated sarcoma)
Interventions	HDCT followed by autologous peripheral or bone marrow HSCT
Outcomes	overall survival; adverse events
Notes	individual data reported for each participant

Lashkari 2009

Methods	Prospective phase II study without controls in a single centre, observed in the USA from 1995 to 1999
Participants	13 children with locally advanced or metastatic sarcoma; of whom 2 (1 male; 1 female) 40 and 30 years of age with metastatic NRSTS (malignant fibrous histiocytoma; soft tissue sarcoma without histologic subtype information)
Interventions	HDCT followed by autologous HSCT
Outcomes	survival
Notes	individual data reported for each participant

Lippe 2003

Methods	Retrospective report of 2 cases without controls in a single-centre study; information on observation period not available
Participants	Two participants with desmoplastic small round-cell tumor; of whom 1 adult (male) 27 years of age received HSCT
Interventions	HDCT followed by autologous HSCT
Outcomes	survival; toxicity
Notes	individual data reported for each participant

Livaditi 2006

Methods	Retrospective report of 5 cases without controls in a single centre, observed in Greece; information on observation period not available
Participants	5 children with desmoplastic small round-cell tumor, of whom 2 (1 male aged 7 years and 1 female aged 13 years) received HSCT
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival; adverse events
Notes	individual data reported for each participant

Madigan 2007

Methods	Retrospective report of 14 cases without controls in a single centre, observed in the United States from 1983 to 2003
Participants	14 children with extracranial rhabdoid tumors, of whom 2 (1 male aged 6 months and 1 female aged 30 months) received HSCT for rhabdoid sarcoma
Interventions	HDCT followed by autologous HSCT

Madigan 2007 (*Continued*)

Outcomes	survival; adverse events
Notes	some individual data reported for each participant and aggregate data on survival time in Kaplan-Meier curve

Matsuzaki 2002

Methods	Retrospective report of a single case in a single centre, observed in Japan in 1999
Participants	1 child (female) 11 years of age with synovial sarcoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; adverse events
Notes	individual data

Mazuryk 1998

Methods	Retrospective report of a single case in a single centre, observed in Canada in 1996
Participants	1 female 19 years of age with desmoplastic small round-cell tumor
Interventions	HDCT followed by autologous HSCT
Outcomes	overall survival; adverse events
Notes	

Mesia 1994

Methods	Retrospective report of a series of cases without controls in a single centre, observed in Spain from 1989 to 1992
Participants	9 patients with metastatic sarcomas, of whom 1 male 21 years of age had undifferentiated sarcoma
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	survival; adverse events
Notes	individual data reported for individual patients

Mitchell 1994

Methods	Unclear if retrospective or prospective study without controls in a single centre, observed in the United Kingdom; information on observation period not available
Participants	11 patients with malignant disease, of whom 1 male 16 years of age with angiosarcoma
Interventions	HDCT followed by autologous peripheral and bone marrow HSCT
Outcomes	survival; toxicity
Notes	individual data reported for each participant

Nakamura 2008

Methods	Retrospective report of a case without control in a single-centre study, observed in Japan; information on observation period not available
Participants	1 child (male) 11 years of age with undifferentiated soft tissue sarcoma
Interventions	HDCT followed by autologous HSCT
Outcomes	overall survival; adverse events
Notes	

Navid 2006

Methods	Prospective phase II study without controls in a single centre, observed in the United States from 1996 to 2000
Participants	24 patients with high-risk sarcomas, of whom 4 had desmoplastic small round-cell tumor and 2 received HSCT(2 males aged 14 and 21 years)
Interventions	HDCT followed by autologous peripheral and bone marrow HSCT
Outcomes	survival; adverse events
Notes	individual data reported for each participant

Patel 2004

Methods	Prospective phase II study without controls in a single-centre, observed in the United States from 1994 to 2001
Participants	37 patients with skeletal osteosarcoma and variant bone tumors with poor prognosis, of whom 6 adults had malignant fibrous histiocytoma; individual information on age and gender not available, median age 38 years, range 18-63 years
Interventions	HDCT followed by autologous peripheral HSCT

Patel 2004 (*Continued*)

Outcomes	toxicity according to NCI CTC
Notes	individual data available for toxicity

Peters 1986

Methods	Prospective phase I study without controls in a single centre, observed in the United States; information on observation period not available
Participants	29 patients with metastatic cancer and sarcoma, of whom 2 females aged 24 and 38 years of age with fibrosarcoma and leiomyosarcoma
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	overall survival; toxicity
Notes	individual data reported for each participant

Peters 1989

Methods	Prospective phase I study without controls in a single centre, observed in the United States; information on observation period not available
Participants	23 patients with metastatic cancer and sarcoma, of whom 2 patients aged 15 and 26 years with synovia sarcoma; individual information on gender not available
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	adverse events
Notes	individual data

Recchia 2006

Methods	Retrospective report of a single case in a single centre, observed in Italy; information on observation period not available
Participants	1 adult (male) 40 years of age with malignant fibrous histiocytoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; toxicity
Notes	individual data

Ronghe 2004

Methods	Retrospective report of 2 cases in a single centre, observed in the United Kingdom; information on observation period not available
Participants	2 children with malignant rhabdoid tumors, of whom 1 female 14 months of age received HSCT
Interventions	HDCT followed by autologous bone marrow HSCT
Outcomes	overall survival; adverse events
Notes	individual data reported for each patient

Saab 2007

Methods	Retrospective report of cases in a single centre, observed in the United States; information on observation period not available
Participants	11 participants with desmoplastic small round-cell tumor, of whom 4 males from 5 to 21 years of age received HSCT
Interventions	HDCT followed by autologous HSCT
Outcomes	survival; toxicity
Notes	individual data reported for each participant

Shaw 1996

Methods	Prospective phase I study without controls in Australia, UK and Israel; information on the number of centres not available
Participants	30 patients with malignant solid tumors, of whom 2 children aged 1 and 2 years with NRSTS (rhabdoid sarcoma; not otherwise specified); individual information, gender not available
Interventions	HDCT followed by autologous peripheral or bone marrow HSCT
Outcomes	adverse events
Notes	individual data for each participant reported

Slease 1988

Methods	Phase I trial in a single-centre study, observed in the United States; information on observation period not available
Participants	26 adults with refractory malignant solid tumors, of whom 3 adult males from 41 to 47 years of age with NRSTS (leiomyosarcoma; malignant fibrous histiocytoma)
Interventions	HDCT followed by autologous bone marrow HSCT

Slease 1988 (*Continued*)

Outcomes	survival; adverse events
Notes	individual data for each participant reported

Sung 2003

Methods	Prospective phase I study in a single centre in Korea from 1998 to 2001
Participants	26 participants with high-risk malignant solid tumors, of whom 2 children (1 male aged 20 months and 1 female aged 47 months) with NRSTS (malignant fibrous histiocytoma; rhabdoid sarcoma)
Interventions	successive double HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; adverse events
Notes	individual data

Watanabe 2006

Methods	Retrospective report of a case without control in a single-centre study, observed in Japan; information on observation period not available
Participants	1 child (male) 1 year of age with rhabdoid sarcoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	survival; adverse events
Notes	

Yamamura 2003

Methods	Retrospective report of a single case in a single centre, observed in Japan in 1996
Participants	1 adult (male) 33 years of age with malignant fibrous histiocytoma
Interventions	HDCT followed by autologous peripheral HSCT
Outcomes	overall survival; adverse events
Notes	reports on the development of chronic myelocytic leukemia following chemotherapy

Yonemoto 1999

Methods	Retrospective report of cases without control in a single-centre study, observed in Japan from 1995
Participants	3 young adults (3 male; 0 female) from 17 to 40 years of age with synovial sarcoma, of a total of 10 participants with sarcomas
Interventions	HDCT followed by autologous HSCT
Outcomes	adverse events
Notes	individual data

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdel-Dayem 1999	not intervention of interest
Abidi 2007	not diagnosis of interest
ABMTR 1986	not study design of interest (review)
ABMTR 1989	not diagnosis of interest
Abrahamsen 2000	data of interest not described separately
Admiraal 2007	not diagnosis of interest (rhabdomyosarcoma)
Aleinikova 2002	not diagnosis of interest (rhabdomyosarcoma)
Alpers 1982	not intervention of interest
Anderson 2005	not study design of interest
Antman 1987	not study design of interest (review)
Antman 1990	not intervention of interest
Antman 2001	not study design of interest (review)
Ashihara 2002	not diagnosis of interest (rhabdomyosarcoma)
Atra 1996	not study design of interest (review)
Atra 2002	not study design of interest (review)

(*Continued*)

Avramova 2006	follow-up of study Michalov 2001
Bader 1989	not diagnosis of interest (rhabdomyosarcoma)
Bagnulo 1985	not diagnosis of interest (rhabdomyosarcoma)
Bambakidis 2002	not diagnosis of interest
Banna 2007	not study design of interest (review)
Barfield 2008	not study design of interest (review)
BCBS MAP 1999	not diagnosis of interest
Beaujean 1989	not diagnosis of interest (rhabdomyosarcoma)
Bellmunt 1997	data of interest not described separately
Bertuzzi 2002	data of interest not described separately
Beschorner 2006	not diagnosis of interest
Bezwoda 1994	not diagnosis of interest
Bickert 2002	not study design of interest (review)
Bien 2007	not diagnosis of interest (rhabdomyosarcoma)
Bini-Antunes 2006	not diagnosis of interest
Bisogno 2009	not disease of interest (rhabdomyosarcoma)
Blay 1994	not study design of interest (abstract)
Blay 2000	not disease of interest for 11 of 30 (36%) patients: 5 patients with rhabdomyosarcoma, 3 patients with unclassified sarcoma, 1 paraganglioma, 1 Schwannosarcoma, and 1 peripheral neuroectodarmal tumorwere included in a total of 30 analyzed patients
Bode-Lesniewska 2005	not intervention of interest
Bodey 1981	not diagnosis of interest
Bojko 2002	not diagnosis of interest
Bokemeyer 1997	not diagnosis of interest
Borden 1987	not intervention of interest

(*Continued*)

Boulad 1998	data of interest not described separately
Bramwell 1986	not intervention of interest
Bramwell 1987	not intervention of interest
Bramwell 2001	not intervention of interest
Breitfeld 2001	not intervention of interest
Brugger 1995	not outcome of interest; paper retracted
Brugieres 1988	not diagnosis of interest (rhabdomyosarcoma)
Brun 1984	not intervention of interest
Bylund 2008	not intervention of interest
Cacchione 2008	data of interest not described separately
Caglar 2002	not diagnosis of interest
Carli 1988	not intervention of interest
Carli 1999	not diagnosis of interest (rhabdomyosarcoma)
Casado 2004	not study design of interest (review)
Casanova 2009	not disease of interest
Casper 1991	not intervention of interest
Ceschel 2006	data of interest not described separately
Chan 1991	not diagnosis of interest (rhabdomyosarcoma)
Chan 1999	not intervention of interest
Chang 1979	not intervention of interest
Chang 1979a	not intervention of interest
Chang 1981	not intervention of interest
Chang 1988	not intervention of interest
Chauvin 1991	not study design of interest (abstract)

(*Continued*)

Chen 1999	not study design of interest (review)
Chen 2008	not intervention of interest
Childs 2004	not study design of interest (review)
Cho 2005	data of interest not described separately
Chuman 2000	not study design of interest (review)
Clausen 1993	data of interest not described separately
Corbett 2009	not study design of interest (review)
Coulibalya 2008	not intervention of interest
Couzin 2007	not study design of interest (review)
Czyzewski 1999	data of interest not described separately
Dagher 1997	not intervention of interest
Dallorso 1996	not diagnosis of interest (rhabdomyosarcoma)
Dallorso 2000	not study design of interest (review)
Dantonello 2008	not intervention of interest
De Kraker 1984	not diagnosis of interest
De Pasquale 2003	not outcome of interest
De Sio 2006	not diagnosis of interest (rhabdomyosarcoma)
De Terlizzi 1988	not study design of interest (review)
De Vries 1995	not diagnosis of interest
Demirci 2003	not diagnosis of interest
Demirer 2008	not intervention of interest
Devalck 1992	not study design of interest (review)
Diaz 1999	not diagnosis of interest (rhabdomyosarcoma)
Dicke 1984	not study design of interest (review)

(*Continued*)

Dicke 1986	not study design of interest (review)
Dileo 2005	not study design of interest (review)
Dillman 1995	data of interest not described separately
Dincol 2000	not intervention of interest
Donaldson 2001	not intervention of interest
Donker 2009	not intervention of interest (allogeneic)
Drabko 2006	not diagnosis of interest (rhabdomyosarcoma)
Dumontet 1992	not diagnosis of interest (rhabdomyosarcoma)
Ederhy 2007	not diagnosis of interest
Eggermont 1997	not intervention of interest
Ek 2006	not study design of interest (review)
Ekert 1982	duplicate publication of study Ekert 1984
Ekert 1984	not diagnosis of interest (rhabdomyosarcoma)
Elias 1998	not study design of interest (review)
Emminger 1991	not diagnosis of interest (rhabdomyosarcoma)
Endo 1995	not study design of interest (review)
Erkisi 1996	not intervention of interest
Espinosa 2001	not diagnosis of interest
Fazekas 2008	not diagnosis of interest
Fekrat 1993	not diagnosis of interest (rhabdomyosarcoma)
Ferrari 2005	not outcome of interest
Fetscher 1996	not study design of interest (abstract)
Figuerres 2000	data of interest not described separately
Fizazi 1994	not intervention of interest

(*Continued*)

Flamant 1998	data of interest not described separately
Foncillas 2004	not diagnosis of interest (rhabdomyosarcoma)
Frustaci 2001	not intervention of interest
Fujita 2005	not diagnosis of interest
Gadner 2002	not study design of interest (review)
Garaventa 1986	not diagnosis of interest (rhabdomyosarcoma)
Garaventa 1987	not diagnosis of interest (rhabdomyosarcoma)
Gardner 2008	not diagnosis of interest
Gebhardt 1999	not intervention of interest
Geisler 2003	not diagnosis of interest
Geissler 1984	not intervention of interest
Gentet 1993	not study design of interest (review)
Ghalie 1994	not diagnosis of interest
Ghavamzadeh 2009	not diagnosis of interest (rhabdomyosarcoma)
Glenn 1985	not intervention of interest
Gonzalez 1989	not diagnosis of interest (rhabdomyosarcoma)
Gortzak 2001	not intervention of interest
Goto 2004	not study design of interest (review)
Graham 1992	not diagnosis of interest (rhabdomyosarcoma)
Graham-Pole 1995	not study design of interest (abstract)
Gratwohl 2002	not outcome of interest
Gratwohl 2004	not study design of interest (review)
Gratwohl 2004a	not study design of interest (review)
Gratwohl 2004b	not outcome of interest

(*Continued*)

Gratwohl 2006	not outcome of interest
Gratwohl 2007	not study design of interest (review)
Gratwohl 2007a	not study design of interest (review)
Grundy 2001	not diagnosis of interest (rhabdomyosarcoma)
Haas 1990	not diagnosis of interest
Hale 2005	not study design of interest (review)
Hara 1998	not diagnosis of interest (rhabdomyosarcoma)
Harmon 2001	not intervention of interest
Hartmann 1986	not diagnosis of interest (rhabdomyosarcoma)
Hartmann 1997	data of interest not described separately
Hartmann 2001	not diagnosis of interest
Hartmann 2005	not diagnosis of interest
He 1999	not intervention of interest
Hensel 2002	not diagnosis of interest
Herzog 2005	not study design of interest (review)
Hilden 1998	not diagnosis of interest
Hilden 2004	not diagnosis of interest
Hiraiwa 1983	not diagnosis of interest
Hoekstra 1994	not study design of interest (review)
Holtta 2005	not diagnosis of interest (rhabdomyosarcoma)
Holtta 2005a	not diagnosis of interest (rhabdomyosarcoma)
Horn 2002	data of interest not described separately
Horowitz 1993	not diagnosis of interest (rhabdomyosarcoma)
Hosoi 2007	not diagnosis of interest (rhabdomyosarcoma)

(*Continued*)

Hotte 2004	data of interest not described separately
Hoy 2007	not diagnosis of interest
Huang 2006	not diagnosis of interest (rhabdomyosarcoma)
Huttmann 2005	not diagnosis of interest
Höffken 1997	not study design of interest (review)
Iankelevich 2000	not outcome of interest
ICR 1994	not diagnosis of interest (rhabdomyosarcoma)
Imbach 1979	not diagnosis of interest
Irle 1989	not study design of interest (review)
Issels 1995	not study design of interest (review)
Issels 2002	not intervention of interest
Issels 2004	not study design of interest (review)
Jamil 2004	data of interest not described separately
Jelic 1994	not intervention of interest
Jelic 1997	not intervention of interest
Kaatsch 2009	not test intervention of interest
Kabickova 2003	data of interest not described separately
Kadan-Lottick 2008	not outcome of interest
Kaizer 1979	not diagnosis of interest (rhabdomyosarcoma)
Kaizer 1980	duplicate paper of Kaizer 1979
Kaizer 1984	not study design of interest (review)
Kalwak 2002	not diagnosis of interest (rhabdomyosarcoma)
Kanabar 1995	not diagnosis of interest (rhabdomyosarcoma)
Kasper 2004	data included in follow-up paper Kasper 2008

(*Continued*)

Kasper 2005	not study design of interest (review)
Kasper 2006	data included in follow-up paper Kasper 2008
Katzenstein 2003	not study design of interest
Kavan 1997	not study design of interest (review)
Kavan 1997a	not diagnosis of interest (rhabdomyosarcoma)
Kinsella 1988	not diagnosis of interest (rhabdomyosarcoma)
Kinsella 1988a	data of interest not described separately
Klaritsch 2006	not diagnosis of interest
Kletzel 1997	not study design of interest (review)
Kletzel 1998	not diagnosis of interest (rhabdomyosarcoma)
Kletzel 2005	not study design of interest (review)
Klingebiel 1989	not study design of interest (review)
Klingebiel 1994	not study design of interest (review)
Klingebiel 2008	not diagnosis of interest (rhabdomyosarcoma)
Kook 1998	not diagnosis of interest
Korfel 2001	not diagnosis of interest (rhabdomyosarcoma)
Koscielniak 1992	data of interest not described separately
Koscielniak 1997	not diagnosis of interest (rhabdomyosarcoma)
Koscielniak 1999	not study design of interest (review)
Koscielniak 2001	not study design of interest (review)
Koscielniak 2002	not study design of interest (review)
Koscielniak 2005	not study design of interest (review)
Kuroiwa 2009	not diagnosis of interest (rhabdomyosarcoma)

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Kushner 2000	not study design of interest (review)
Kwan 1996	not diagnosis of interest (rhabdomyosarcoma)
Kwon 2010	not disease of interest (rhabdomyosarcoma, neuroblastoma)
Ladenstein 1993	not study design of interest (review)
Ladenstein 1997	not study design of interest (review)
Lal 2005	data of interest not described separately
Lang 2006	not diagnosis of interest (rhabdomyosarcoma)
Lange 2004	not intervention of interest (allogeneic HSCT)
Larsen 2000	not diagnosis of interest (rhabdomyosarcoma)
Le Cesne 2000	not intervention of interest
Le Corroller 1997	data of interest not described separately
Lehrnbecher 2006	not diagnosis of interest
Lessnick 2009	not study design of interest (review)
Liseth 2004	data of interest not described separately
Locatelli 2008	not intervention of interest (allogeneic HSCT)
Lorenz 1999	not study design of interest (review)
Lorigan 2007	not intervention of interest
Lucidarme 1998	not diagnosis of interest (rhabdomyosarcoma)
Mace 2003	not intervention of interest
Machado 2007	not diagnosis of interest
Mack 1995	not study design of interest (review)
Mackall 2001	not study design of interest (review)
Madero 1995	not diagnosis of interest (rhabdomyosarcoma)
Maeda 2008	not study design of interest (review)

(*Continued*)

Mankin 2004	not intervention of interest
Marina 1997	not study design of interest (review)
Matsubara 2003	not diagnosis of interest (rhabdomyosarcoma)
Matsuyama 2000	not study design of interest (review)
Matthews 2007	not diagnosis of interest
Medioni 2003	not intervention of interest
Mesia 1995	not diagnosis of interest (rhabdomyosarcoma)
Meyers 2004	not study design of interest (review)
Michailov 2001	not diagnosis of interest (rhabdomyosarcoma)
Michon 1999	not study design of interest (review)
Mikhailova 1998	not outcome of interest
Miliauskas 1993	not intervention of interest
Mimeault 2008	not study design of interest (review)
Minard-Colin 2004	not intervention of interest
Mingo 2005	not intervention of interest
Miyagi 2003	not diagnosis of interest (rhabdomyosarcoma)
Moore 2009	not diagnosis of interest (rhabdomyosarcoma)
Morikawa 2005	not intervention of interest
Munoz 1983	not diagnosis of interest (rhabdomyosarcoma)
Müller 2002	not intervention of interest
Nachbaur 1994	not diagnosis of interest
Nag 1995	not diagnosis of interest (rhabdomyosarcoma)
Nath 2005	not diagnosis of interest (rhabdomyosarcoma)
Nenadov 1995	not diagnosis of interest (rhabdomyosarcoma)

(*Continued*)

Nieboer 2005	not study design of interest (review)
Nieto 1999	not study design of interest (review)
Nieto 2004	not study design of interest (review)
Nieto 2007	data of interest not described separately
Nivison-Smith 2005	not outcome of interest
Nivison-Smith 2007	not outcome of interest
Nobile 1984	not intervention of interest
Notteghem 2003	not diagnosis of interest (rhabdomyosarcoma)
Oeffinger 2008	not study design of interest (review)
Ohira 1983	not diagnosis of interest (rhabdomyosarcoma)
Ohira 1990	not diagnosis of interest (rhabdomyosarcoma)
Ohta 2001	not diagnosis of interest (rhabdomyosarcoma)
Oppenheim 2002	not diagnosis of interest
Ortega 1991	not diagnosis of interest (rhabdomyosarcoma)
Osugi 2000	not diagnosis of interest (rhabdomyosarcoma)
Oue 2003	not diagnosis of interest (rhabdomyosarcoma)
Ozkaynak 1990	not intervention of interest
Ozkaynak 1998	not diagnosis of interest (rhabdomyosarcoma)
Ozkaynak 2008	data of interest not described separately
Pasetto 2003	not study design of interest (review)
Patel 1992	not study design of interest (review)
Patel 1994	not study design of interest (review)
Patzer 1999	not diagnosis of interest (rhabdomyosarcoma)
Paulides 2006	not intervention of interest

(*Continued*)

Pedrazzoli 2006	not study design of interest (review)
Perentesis 1999	not diagnosis of interest (rhabdomyosarcoma)
Pession 1999	not diagnosis of interest (rhabdomyosarcoma)
Philip 1984	not study design of interest (review)
Pick 1988	not study design of interest (review)
Pico 1993	not diagnosis of interest (rhabdomyosarcoma)
Pinedo 1987	not intervention of interest
Pinkerton 1986	not study design of interest (review)
Pinkerton 1987	not study design of interest (review)
Pinkerton 1991	data of interest not described separately
Pinkerton 1991a	not diagnosis of interest (rhabdomyosarcoma)
Pinkerton 1995	not study design of interest (review)
Pohar-Marinsek 2001	not diagnosis of interest (rhabdomyosarcoma)
Pohar-Marinsek 2003	not diagnosis of interest (rhabdomyosarcoma)
Raben 1994	not intervention of interest
Radeva 2005	not study design of interest
Raja 2003	not intervention of interest
Raney 1997	not diagnosis of interest (rhabdomyosarcoma)
Raney 2001	not study design of interest (review)
Rapidis 2008	not diagnosis of interest
Ray-Coquard 2001	not study design of interest (review)
Recchia 1996	not diagnosis of interest
Recchia 2003	not diagnosis of interest
Reich 2001	data of interest not described separately

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Reichardt 1997	not study design of interest (review)
Reichardt 2002	not study design of interest (review)
Rill 1994	not diagnosis of interest
Ritchie 2004	not diagnosis of interest (rhabdomyosarcoma)
Rivera-Luna 2001	not diagnosis of interest
Rodenhuis 1999	not study design of interest (review)
Roh 2001	not diagnosis of interest
Roman-Unfer 1996	not study design of interest (review)
Rosenberg 1981	not intervention of interest
Rosenberg 1982	not intervention of interest
Rosenberg 1983	not intervention of interest
Rosman 2008	data of interest not described separately
Rossbach 1999	not diagnosis of interest (rhabdomyosarcoma)
Rosti 2002	not study design of interest (review)
Rousselet 1994	not diagnosis of interest
Rubie 2003	not diagnosis of interest
Rzepecki 2006	not study design of interest (review)
Rzepecki 2006a	not study design of interest (review)
Saikawa 2006	not diagnosis of interest (rhabdomyosarcoma)
Sajedi 2002	not intervention of interest (allogeneic HSCT)
Sakayama 2008	not diagnosis of interest (rhabdomyosarcoma)
Salutari 1998	not diagnosis of interest (rhabdomyosarcoma)
Sanchez 1986	not study design of interest (review)

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Sanchez-Garcia 2007	not diagnosis of interest
Santana 1992	not diagnosis of interest (rhabdomyosarcoma)
Sanz 1997	not diagnosis of interest (rhabdomyosarcoma)
Sato 1998	not diagnosis of interest (rhabdomyosarcoma)
Sauer 1998	not study design of interest (review)
Sauer 1998a	not study design of interest (review)
Savasan 2005	not study design of interest (review)
Savolainen 2005	not diagnosis of interest (rhabdomyosarcoma)
Sawyer 1999	not study design of interest (review)
Schimmer 2002	data of interest not described separately
Schlemmer 2006	not disease of interest for 22 of 55 (40%) patients: 3 patients with rhabdomyosarcoma, 3 patients with peripheral neuroectodarmal tumor, and 16 patients with not identified tumors were included in a total of 55 analyzed patients
Schmidt 1994	not intervention of interest (allogeneic HSCT)
Schulz 1991	data of interest not described separately
Schuster 2008	data of interest not described separately
Schwella 1998	data of interest not described separately
Secondino 2007	not intervention of interest (allogeneic HSCT)
Seeger 1991	not study design of interest (review)
Segura 2001	not diagnosis of interest (rhabdomyosarcoma)
Seregard 2002	not diagnosis of interest (rhabdomyosarcoma)
Seynaeve 1999	not study design of interest
Shea 1995	not diagnosis of interest
Shen 1993	duplicate paper of Shen 1994

(*Continued*)

Shen 1994	not intervention of interest (allogeneic HSCT)
Shimizu 2008	not diagnosis of interest (rhabdomyosarcoma)
Shinkoda 2009	not diagnosis of interest (rhabdomyosarcoma)
Simon 2007	data of interest not described separately
Skinner 1974	not intervention of interest
Sola 1999	not diagnosis of interest
Somlo 1995	not intervention of interest
Spitzer 1980	not diagnosis of interest
Spitzer 1984	not diagnosis of interest
Spitzer 1994	not study design of interest (review)
Spitzer 1995	not diagnosis of interest
Spruce 1983	not study design of interest (review)
Stea 1987	not diagnosis of interest (rhabdomyosarcoma)
Steinbrenner 2005	data of interest not described separately
Stöhr 2006	not intervention of interest
Suita 2005	not diagnosis of interest (rhabdomyosarcoma)
Sussman 2008	not study design of interest (review)
Takata 1997	not intervention of interest
Takaue 2002	not diagnosis of interest (rhabdomyosarcoma)
Takenaka 2007	not intervention of interest
Tang 2009	not disease of interest (rhabdomyosarcoma)
Thomson 1999	not diagnosis of interest (rhabdomyosarcoma)
Toma 1992	not intervention of interest
Trigg 2002	not study design of interest (review)

(*Continued*)

Unal 2006	data of interest not described separately
Urban 1997	not outcome of interest
Urbano-Ispizua 2002	not outcome of interest
Vadhan 1996	not study design of interest (abstract)
Vadhan-Raj	not intervention of interest
Valkova 2003	not intervention of interest
Valteau-Couanet 2007	not study design of interest (review)
Valteau-Couanet 2007a	not diagnosis of interest
Van Dalen 2009	not intervention of interest
Van den Berg 2006	not study design of interest (review)
Van den Berg 2007	not study design of interest (review)
Van den Berg 2008	not intervention of interest
Van Glabbeke 1993	not intervention of interest
Varterasian 1997	not intervention of interest
Vassal 2005	not study design of interest (review)
Vaughan 2001	not study design of interest (review)
Verma 2002	not study design of interest (review)
Verma 2008	not study design of interest (review)
Verma 2008a	not study design of interest (review)
Wachowiak 2008	not outcome of interest
Walterhouse 1999	not diagnosis of interest (rhabdomyosarcoma)
Wasserman 1997	not diagnosis of interest
Watanabe 2006a	not study design of interest
Weaver 1997	data of interest not described separately

(*Continued*)

Weh 1995	not study design of interest (review)
Weh 1996	not intervention of interest
Weigel 2001	not study design of interest (review)
Werchniak 2005	not diagnosis of interest
Wexler 1996	not intervention of interest
Willenbacher 1998	data of interest not described separately
Williams 2004	not diagnosis of interest (rhabdomyosarcoma)
Womer 1996	not study design of interest (review)
Womer 2000	not study design of interest (review)
Woods 1999	not study design of interest (review)
Worden 2005	not intervention of interest
Yamada 2007	not diagnosis of interest (rhabdomyosarcoma)
Yaniv 1990	not study design of interest (review)
Yaniv 2000	not study design of interest (review)
Yaqoob 2006	not study design of interest (review)
Yin 2009	not intervention of interest
Young 1989	data of interest not described separately
Zoubek 1994	not intervention of interest

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Frequency of subtypes of included NRSTS in patients of young versus advanced age

Young age (< 20 years)		**Advanced (≥ 20 years)**	
Subtype	%	Subtype	%
Synovial sarcoma	7.7	Leiomyosarcoma	13.7
Malignant fibrous histiocytoma	4.9	Malignant fibrous histiocytoma	10.1
Fibrosarcoma	4.5	Liposarcoma	8.0
Liposarcoma	2.8	Hemangiosarcoma	2.5
Epitheloid sarcoma	2.0	Spindle cell sarcoma	2.3

*according to Spunt 2006

Table 2. Included non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)

Diagnosis(*)
Alveolar soft part sarcoma
Anaplastic soft tissue sarcoma
Angiosarcoma 1. Angiosarcoma of soft tissue 2. Hemangiosarcoma 3. Hemangiopericytoma 4. Lymphangiosarcoma
Clear cell myomelanocytic tumor
Clear cell sarcoma of soft tissue
Desmoplastic small round cell tumor
Epithelioid sarcoma

Table 2. Included non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) (*Continued*)

Fibrosarcoma 1. Adult fibrosarcoma 2. Myxofibrosarcoma 3. Low grade fibromyxoid sarcoma; hyalinizing spindle cell tumor 4. Sclerosing epithelioid fibrosarcoma
Fibromyxoid sarcoma
Epithelioid hemangioendothelioma
Intimal sarcoma
Leiomyosarcoma 1. Leiomyosarcoma (excluding skin)
Liposarcoma 1. Dedifferentiated liposarcoma 2. Myxoid liposarcoma 3. Round cell liposarcoma 4. Pleomorphic liposarcoma 5. Mixed-type liposarcoma 6. Liposarcoma, not otherwise specified
Mesenchymal sarcoma
Malignant glomus tumor
Malignant fibrous histiocytoma 1. Pleomorphic malignant fibrous histiocytoma; undifferentiated pleomorphic sarcoma 2. Giant cell malignant fibrous histiocytoma; undifferentiated pleomorphic sarcoma with giant cells 3. Inflammatory malignant fibrous histiocytoma; undifferentiated pleomorphic sarcoma with prominent inflammation 4. Undifferentiated pleomorphic sarcoma 5. Spindle cell sarcoma
Malignant haemangiopericytoma
Malignant mesenchymoma
Neoplasms with perivascular epithelioid cell differentiation (PEComa)
Rhabdoid sarcoma 1. Extra-renal rhabdoid tumor
Synovial sarcoma
Unclassified sarcoma
Undifferentiated sarcoma

* category of malignant tumors according to the *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Soft Tissue and Bone* (Fletcher 2002)

Table 3. Excluded tumor types

Diagnosis	Reason for exclusion(*)
Atypical teratoid/rhabdoid tumors	WHO classification of tumors of the central nervous system
Chondrosarcoma 1. Mesenchymal chondrosarcoma 2. Extraskeletal myxoid chondrosarcoma ('chordoid type')	Extraskeletal types are difficult to separate
Dermatofibrosarcoma protuberance	WHO classification of tumors of the skin
Endometrial stroma sarcoma	WHO classification of tumors: pathology and genetics of tumors of the breast and female genital organs
Ewing family of tumors 1. Ewing sarcoma 2. Skeletal Ewing's sarcoma 3. Extraskeletal Ewingsarcoma 4. Peripheral primitive neuroectodermal tumour (pPNET) 5. Extraskeletal peripheral primitive neuroectodermal tumor (pPNET) 6. Askin tumor	Extraskeletal types are difficult to separate; the Ewing family of tumors is one entity
Extragonadal germ cell sarcoma	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs WHO classification of tumors: pathology and genetics of tumors of the breast and female genital organs
Follicular dendritic cell sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Ganglioneuroblastoma	WHO classification of nervous system tumors
Gastrointestinal stromal tumor	WHO classification of tumors: pathology and genetics of tumors of the digestive system
Giant cell fibroblastoma	WHO classification of tumors of the skin
Giant cell tumour of bone	WHO classification for tumors of bone tissue
Histiocytic sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Interdigitating dendritic cell sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues

Table 3. Excluded tumor types (*Continued*)

Interdigitating reticulum cell sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Kaposi sarcoma	Intermediate malignancy (rarely metastasizing)
Lymphoblastic lymphosarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Medulloblastoma	WHO classification of tumors of the central nervous system
Myeloid sarcoma	WHO classification of tumors of hematopoietic and lymphoid tissues
Myxosarcoma (cardiac tumor)	WHO classification of tumors: pathology and genetics of tumors of the lung, pleura, thymus and heart
Nephroblastoma	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs
Neuroblastoma (Wilms tumor)	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs
Osteosarcoma 1. Extraskeletal osteosarcoma	Extraskeletal types are difficult to separate
Peripheral nerve sheath tumor, malignant (neurofibrosarcoma)	WHO classification of nervous system tumors
Rhabdoid tumour, renal	WHO classification of tumors: pathology and genetics of tumors of the urinary system and male genital organs
Rhabdoid tumour, cerebral	WHO classification of tumors of the central nervous system
Rhabdomyosarcoma 1. Embryonal rhabdomyosarcoma (including spindle cell, botryoid, anaplastic) 2. Alveolar rhabdomyosarcoma (including solid, anaplastic) 3. Pleomorphic rhabdomyosarcoma 4. Undifferentiated rhabdomyosarcoma	A soft tissue sarcoma that is excluded to separate rhabdomyosarcomas from non-rhabdomyosarcoma soft tissue sarcomas
Schwannoma, malignant	WHO classification of nervous system tumors
Uterine endometrial stromal sarcoma	WHO classification of tumors: pathology and genetics of tumors of the breast and female genital organs

* WHO: World Health Organization

Table 4. Literature sources and search steps

Category	Sources
Step 1	
Bibliographic databases	1. MEDLINE via Ovid; via PubMed, includes Clinical Queries 2. EMBASE via Ovid 3. The Cochrane Library via Wiley InterScience i) Cochrane central register of controlled trials ii) Cochrane database of systematic reviews (CDSR; Cochrane reviews) iii) database of abstracts of reviews of effects (DARE; other reviews) iv) health technology assessment database (HTA; technology assessments) v) National Health Services economic evaluation database (NHSEED; economic evaluations)
Step 2	
Online trial registers	1. ClinicalTrials.gov (ClinicalTrials.gov 2010) 2. International Standard Randomised Controlled Trial Number (ISRCTN 2010) Register 3. National Institute for Health Research UK Clinical Research Network's (NIHR UKCRN 2010) Portfolio Database 4. National Cancer Institute Physician Data Query (NCI PDQ 2010) Clinical Trials 5. European Group for Blood and Marrow Transplantation Solid Tumor Working Party (EBMT STWP 2010) 6. World Health Organization International Clinical Trials Registry Platform (ICTRP 2010)
Step 3	
Reviews	systematic reviews (rhabdomyosarcoma included): Admiraal 2007 (Cochrane Protocol); Verma 2008; Weigel 2001 narrative reviews (rhabdomyosarcoma included): 95 articles from 1983 to 2008
Step 4	
Congress proceedings	Blood (American Society of Hematology Annual Meeting Abstracts) 2004 to 2007
Step 5	
Institutions(*)	1. Scientific Institute San Raffaele, Milan, Italy 2. Istituto Nazionale dei Tumori, Milan, Italy 3. Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO), Berlin, Germany 4. St. Jude Children's Research Hospital, Memphis, Tennessee, USA 5. Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany 6. National CancerCenter Hospital, Tokyo, Japan 7. Memorial Sloan-Kettering Cancer Center, New York City, New York, USA 8. European Group for Blood and Marrow Transplantation (EBMT), Leipzig, Germany 9. Ospedale Niguarda Ca'Granda, Milano, Italy 10. Universitätsklinikum Charite, Berlin, Germany 11. Medizinische Universitätsklinik, Ulm, Germany 12. Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Table 4. Literature sources and search steps (*Continued*)

	13. Italian sarcoma Group (ISG), Bologna, Italy
Step 6	
Authors(*)	Blay 2000; Ivanova 2007; Kasper 2007; Kasper 2009; Schlemmer 2006; Simon 2007; Suita 2005

* direct enquiries by e-mail and post

Table 5. Assessment of risks of bias

Type of comparative study	**Randomized controlled intervention trial**	**Non-randomized comparative intervention studies** • non-randomized controlled clinical intervention trial • prospective cohort study • retrospective cohort study • case-control study
Assignment of patients to treatment groups	Was the allocation sequence adequately generated? • yes ○ e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers • unclear ○ e.g. not reported, information not available An answer *no* would mark a non-randomized study and, therefore, this option is not provided	Were relevant details of criteria for assignment of patients to treatment groups provided? • yes ○ e.g. participants assigned alternating to treatments on basis of date of birth, clinic id-number or surname, at the discretion of the responsible physician, or no attempt to randomise participants • no • unclear
Concurrent control	not applicable	Were data of the control group collected during the same time period as data of the test group? • yes • no ○ historical control data collected earlier than for the test group • unclear
Concealment of allocation	Was allocation adequately concealed? • yes ○ e.g. where the allocation sequence could not be foretold • no ○ e.g. allocation sequence could be foretold by patients, investigators or	not applicable

Table 5. Assessment of risks of bias (*Continued*)

	treatment providers • unclear ○ e.g. not reported	
Comparable baseline characteristics	Were the two treatment groups comparable? Were the groups balanced in respect to confounders? Were there no differences of baseline characteristics between the two treatment groups or were differences controlled for, in particular with reference to prognostic factors, such as, age, gender, histological diagnosis, year of transplantation? • yes ○ groups were comparable or differences between groups were considered (e.g. adjusted for), or factors were matched and groups were balanced in respect to confounders • no ○ if the two groups differed and differences were not controlled for • unclear	
Loss to follow-up	Was loss to follow-up less than 20% and were the reasons for loss to follow-up similar in both arms? • yes • no • unclear	
Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting? • yes • no ○ e.g if protocol reports all outcomes specified in the protocol • unclear	
Other causes for high risk of bias	Was the study apparently free of other problems that could put it at a high risk of bias? • yes • no • unclear	

Table 6. Overall survival (OS) and progression-free survival (PFS)

Study	Follow up started at	OS	PFS
		2 years	**2 years**
Controlled trials (HSCT after HDCT versus standard-dose chemotherapy)			
Ivanova 2007	unclear	62.3% vs. 23.2%*	-
No control group (only patients with HSCT after HDCT)			
Bertuzzi 2003	"therapy"	20%†	0%†
Pooled meta-analysis of individual data (only patients with HSCT after HDCT)			

Table 6. Overall survival (OS) and progression-free survival (PFS) (*Continued*)

54 patients (29 studies)	HSCT	49% (95% CI: 34% to 64%)	-

* "statistically significant", no detailed description of statistical method
† reading from Kaplan-Meier curve

Table 7. Treatment-related mortality (TRM) in transplanted patients

Study	TRM, n	Cause of death
No control group, individual data (only patients with HSCT)		
Doros 2008	1	not specified
Engelhardt 2007	3	(1) sepsis; (2) sepsis; (3) pulmonary metastases, pneumonia, respiratory failure
Kasper 2007	1	cardiac arrest of unknown origin
Navid 2006	1	hepatic and renal failure
Saab 2007	2	(1) acute myocardial infarction; (2) veno-occlusive disease
Shaw 1996	1	veno-occlusive disease and necrotising interstitial pneumonitis
Slease 1988	2	(1) progressive encephalopathy; (2) sepsis

Table 8. Secondary neoplasia in transplanted patients

Study	Secondary neoplasia, n	Diagnosis
No control group, individual data (only patients with HSCT)		
Yamamura 2003	1	chronic myelogenous leukemia

Table 9. Toxicity, National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) grade 3-4, in transplanted patients

Study	Hematological toxicity (Number of affected / total patients)			Non-hematological toxicity (Number of affected / total patients)				
	Leukopenia	Neutropenia	Thrombopenia	Nausea	Kidney	Liver	Nervous system	Heart
No control group, individual data (only patients with HSCT)								

Table 9. Toxicity, National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) grade 3-4, in transplanted patients (*Continued*)

Kasper 2007	14 / 14	14 / 14	14 / 14	-	-	-	-	-
Kozuka 2002	-	1 / 1	1 / 1	1 / 1	-	-	-	-
Kushner 2001	-	-	-	-	-	-	1 / 1	-
Patel 2004	-	-	-	-	1 / 1	1 / 1	-	-
Yonemoto 1999	-	-	-	-	-	1 / 4	-	-

APPENDICES

Appendix 1. MEDLINE/Ovid search strategy

1. exp SARCOMA/
2. (sarcom$ or sarkom$).mp.
3. exp LIPOSARCOMA/
4. liposar#om$.mp.
5. exp FIBROSARCOMA/
6. fibrosar#om$.mp.
7. exp HISTIOCYTOMA, MALIGNANT FIBROUS/
8. malign$ fibrous histio#ytom$.mp.
9. exp LEIOMYOSARCOMA/
10. leiomyosar#om$.mp.
11. malign$ glom$ tumo$.mp.
12. exp RHABDOMYOSARCOMA/
13. rhabdomyosar#om$.mp.
14. exp HEMANGIOENDOTHELIOMA/
15. (hemangioendotheliom$ or haemangioendotheliom$).mp.
16. exp HEMANGIOSARCOMA/
17. (angiosar#om$ or hemangiosar#om$ or haemangiosar#om$).mp.
18. exp SARCOMA, SYNOVIAL/
19. synovia$ sar#om$.mp.
20. epithelioid sar#om$.mp.
21. exp SARCOMA, ALVEOLAR SOFT PART/
22. (alveolar soft part sar#om$ or alveolar soft tissue sar#om$).mp.
23. exp SARCOMA, CLEAR CELL/
24. clear cell sar#om$.mp.
25. exp SARCOMA, SMALL CELL/
26. (desmoplastic and small round cell tumo$ or small cell tumo$)).mp.
27. exp RHABDOID TUMOR/
28. ((extrarenal or extra-renal) and rhabdoid tumo$).mp.

29. (malignan$ and mesenchymom$).mp.
30. clear cell myomelano#ytic tumo$.mp.
31. intima$ sar#om$.mp.
32. exp STEM CELL TRANSPLANTATION/
33. exp BONE MARROW TRANSPLANTATION/
34. exp TRANSPLANTATION, AUTOLOGOUS/
35. exp TRANSPLANTATION, HOMOLOGOUS/
36. exp TRANSPLANTATION, CONDITIONING/
37. (autolog$ hemato$ or autolog haemato$ or autolog$ stem cell or autolog$ bone marrow or autolog$ periph$ or autolog$ transplant$ or autolog$ graft$ or autotransplant$ or auto-transplant$ or autograft$ or auto-graft$).mp.
38. (homolog$ hemato$ or homolog$ haemato$ or homolog$ stem cell or homolog$ bone marrow or homolog$ cord or homolog$ umbilical or homolog$ peripheral or homolog$ transplant$ or homolog$ graft$ or homolog$ transplant$).mp.
39. (stem cell transplant$ or bone marrow transplant$ or periph$ blood stem cell or periph$ stem cell or cord blood transplant$).mp.
40. (reduced intens$ or myeloablat$ or nonmyeloablat$ or non-myeloablat$).mp.
41. high dose chemotherapy.mp.
42. or/1-31
43. or/32-41
44. and/42-43
45. (ANIMALS not (ANIMALS and HUMANS)).sh.
46. 44 not 45

Appendix 2. EMBASE/Ovid search strategy

1. exp SARCOMA/
2. (sarcom$ or sarkom$).mp.
3. exp LIPOSARCOMA/
4. liposar#om$.mp.
5. exp FIBROSARCOMA/
6. fibrosar#om$.mp.
7. exp MALIGNANT FIBROUS HISTIOCYTOMA/
8. malign$ fibrous histio#ytom$.mp.
9. exp LEIOMYOSARCOMA/
10. leiomyosar#om$.mp.
11. malign$ glom$ tumo$.mp.
12. exp RHABDOMYOSARCOMA/
13. rhabdomyosar#om$.mp.
14. exp HEMANGIOENDOTHELIOMA/
15. (hemangioendotheliom$ or haemangioendotheliom$).mp.
16. exp HEMANGIOENDOTHELIOSARCOMA/
17. (hemangioendotheliosar#om$ or haemangioendotheliosar#om$).mp.
18. exp ANGIOSARCOMA/
19. angiosar#om$.mp.
20. exp SYNOVIAL SARCOMA/
21. synovia$ sar#om$.mp.
22. exp EPITHELIOID SARCOMA/
23. (epithelioid$ sar#om$ or epitheloid$ sar#om$).mp.
24. exp ALVEOLAR SOFT PART SARCOMA/
25. (alveolar soft part sar#om$ or alveolar soft tissue sar#om$).mp.
26. exp CLEAR CELL SARCOMA/
27. clear cell sar#om$.mp.
28. exp DESMOPLASTIC SMALL ROUND CELL TUMOR/
29. exp SMALL CELL SARCOMA/

30. (desmoplastic and (small round cell tumo$ or small cell tumo$)).mp.
31. ((extrarenal$ or extra-renal$) and rhabdoid$ tumo$).mp.
32. (malign$ and mesenchymom$).mp.
33. clear cell myomelano#yt$ tumo$.mp.
34. intima$ sar#om$.mp.
35. exp STEM CELL TRANSPLANTATION/
36. exp BONE MARROW TRANSPLANTATION/
37. exp NONMYELOABLATIVE STEM CELL TRANSPLANTATION/
38. exp NONMYELOBLATIVE CONDITIONING/
39. exp REDUCED INTENSITY CONDITIONING/
40. exp MYELOABLATIVE CONDITIONING/
41. (autolog$ hemato$ or autolog haemato$ or autolog$ stem cell or autolog$ bone marrow or autolog$ periph$ or autolog$ transplant$ or autolog$ graft$ autotransplant$ or auto-transplant$ or autograft$ or auto-graft$).mp.
42. (homolog$ hemato$ or homolog$ haemato$ or homolog$ stem cell or homolog$ bone marrow or homolog$ cord or homolog$ umbilical or homolog$ periph$ or homolog$ transplant$ or homolog$ graft$).mp.
43. (stem cell transplant$ or bone marrow transplant$ or periph$ blood stem cell or periph$ stem cell or cord blood transplant$).mp.
44. (reduced intens$ or myeloablat$ or nonmyeloablat$ or non-myeloablat$).mp.
45. high dose chemotherapy.mp.
46. or/1-34
47. or/35-45
48. and/46-47
49. (ANIMALS not (ANIMALS and HUMANS)).sh.
50. 48 not 49

Appendix 3. Cochrane/Wiley search strategy

1. exp SARCOMA/
2. (sarcom$ or sarkom$).mp.
3. exp LIPOSARCOMA/
4. liposar#om$.mp.
5. exp FIBROSARCOMA/
6. fibrosar#om$.mp.
7. exp HISTIOCYTOMA, MALIGNANT FIBROUS/
8. malign$ fibrous histio#ytom$.mp.
9. exp LEIOMYOSARCOMA/
10. leiomyosar#om$.mp.
11. malign$ glom$ tumo$.mp.
12. exp RHABDOMYOSARCOMA/
13. rhabdomyosar#om$.mp.
14. exp HEMANGIOENDOTHELIOMA/
15. (hemangioendotheliom$ or haemangioendotheliom$).mp.
16. exp HEMANGIOSARCOMA/
17. (angiosar#om$ or hemangiosar#om$ or haemangiosar#om$).mp.
18. exp SARCOMA, SYNOVIAL/
19. synovia$ sar#om$.mp.
20. (epithelioid sar#om$ or epitheloid sar#om$).mp.
21. exp SARCOMA, ALVEOLAR SOFT PART/
22. (alveolar soft part sar#om$ or alveolar soft tissue sar#om$).mp.
23. exp SARCOMA, CLEAR CELL/
24. clear cell sar#om$.mp.
25. exp SARCOMA, SMALL CELL/
26. (desmoplastic and (small round cell tumo$ or small cell tumo$)).mp.

27. exp RHABDOID TUMOR/
28. ((extrarenal or extra-renal) and rhabdoid tumo$).mp.
29. (malignan$ and mesenchymom$).mp.
30. clear cell myomelano#ytic tumo$.mp.
31. intima$ sar#om$.mp.
32. exp STEM CELL TRANSPLANTATION/
33. exp BONE MARROW TRANSPLANTATION/
34. exp TRANSPLANTATION, AUTOLOGOUS/
35. exp TRANSPLANTATION, HOMOLOGOUS/
36. exp TRANSPLANTATION, CONDITIONING/
37. (autolog$ hemato$ or autolog haemato$ or autolog$ stem cell or autolog$ bone marrow or autolog$ periph$ or autolog$ transplant$ or autolog$ graft$ or autotransplant$ or auto-transplant$ or autograft$ or auto-graft$).mp.
38. (homolog$ hemato$ or homolog$ haemato$ or homolog$ stem cell or homolog$ bone marrow or homolog$ cord or homolog$ umbilical or homolog$ periph$ or homolog$ transplant$ or homolog$ graft$).mp.
39. (stem cell transplant$ or bone marrow transplant$ or periph$ blood stem cell or periph$ stem cell or cord blood transplant$).mp.
40. (reduced intens$ or myeloablat$ or nonmyeloablat$ or non-myeloablat$).mp.
41. high dose chemotherapy.mp.
42. or/1-31
43. or/32-41
44. and/42-43
45. (ANIMALS not (ANIMALS and HUMANS)).sh.
46. 44 not 45

Appendix 4. Reviews (n = 98) checked for additional studies

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CONTRIBUTIONS OF AUTHORS

FP: designing and coordinating the review, data collection for the review, designing search strategies, undertaking searches, screening search results, organizing retrieval of papers, screening retrieved papers against eligibility criteria, appraising quality of papers, extracting data from papers, writing to authors of papers for additional information, data management for the review, entering data into RevMan, analysis of data, interpretation of data, writing the review and the protocol.

LAS: providing methodological advice, screening included papers to verify data, interpretation of data, writing the review and the protocol

MaKr: analysis of data, interpretation of data, appraising quality of papers

CB: screening retrieved papers against eligibility criteria, extracting data from papers

NK: providing a clinical perspective

MiKu: appraising quality of papers, interpretation of data, providing a methodological perspective

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The authors declare that they have no competing interests.

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