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

Peinemann F, Enk H, Smith LA

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[Intervention Review]

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

Frank Peinemann[1], Heike Enk[2], Lesley A Smith[3]

[1]Pediatric Oncology and Hematology, Children's Hospital, University of Cologne, Cologne, Germany. [2]c/o Cochrane Childhood Cancer, Amsterdam, Netherlands. [3]Department of Psychology, Social Work and Public Health, Oxford Brookes University, Oxford, UK

Contact: Frank Peinemann, Pediatric Oncology and Hematology, Children's Hospital, University of Cologne, Kerpener Str. 62, Cologne, 50937, Germany. pubmedprjournal@gmail.com.

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ABSTRACT

Background

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors. Nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise all STS except rhabdomyosarcoma. In people 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. The rationale for this update is to determine whether any randomized controlled trials (RCTs) have been conducted and to clarify whether HDCT followed by autologous HSCT has a survival advantage.

Objectives

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

Search methods

For this update, we revised the search strategy to improve the precision and reduce the number of irrelevant hits. We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8), PubMed from 2012 to 6 September 2016, and Embase from 2012 to 26 September 2016. We searched online trial registries and congress proceedings from 2012 to 26 September 2016.

Selection criteria

Terms representing STS and autologous HSCT were required in the title or abstract. We restricted the study design to RCTs. We included studies if at least 80% of participants had a diagnosis listed in any version of the World Health Organization (WHO) classification and classified as malignant. The search included children and adults with no age limits.

Data collection and analysis

We used standard methodologic procedures expected by Cochrane. The primary outcomes were overall survival and treatment-related mortality.

Main results

We identified 1549 records; 85 items from electronic databases, 45 from study registries, and 1419 from congress proceedings. The revised search strategy did not identify any additional RCTs. In the previous version of the review, we identified one RCT comparing HDCT

followed by autologous HSCT versus standard-dose chemotherapy (SDCT). The trial randomized 87 participants who were considerably heterogeneous with respect to 19 different tumor entities. The data from 83 participants were available for analysis.

In the single included trial, overall survival at three years was 32.7% in the HDCT arm versus 49.4% in the SDCT arm and there was no difference between the treatment groups (hazard ratio (HR) 1.26, 95% confidence interval (CI) 0.70 to 2.29, P = 0.44; 1 study, 83 participants; high quality evidence). In a subgroup of participants who had a complete response before HDCT, overall survival was higher in both treatment groups and overall survival at three years was 42.8% in the HDCT arm versus 83.9% in the SDCT arm and favored the SDCT group (HR 2.92, 95% CI 1.1 to 7.6, P = 0.028; 1 study, 39 participants).

In the single included trial, the authors reported one treatment-related leukemia death two years after HDCT. They also evaluated severe adverse events WHO grade 3 to 4 in 22 participants in the HDCT arm and in 51 participants in the SDCT arm. The authors reported 11 events concerning digestive-, infection-, pain-, or asthenia-related toxicity in the HDCT arm and one event in the SDCT arm (moderate quality evidence). The development of secondary neoplasia was not addressed. We judged the study to have an overall unclear risk of bias as three of seven items had unclear and four items had low risk of bias. For GRADE, we judged three items as high quality and three items were not reported.

Authors' conclusions

The limited data of a single RCT with an unclear risk of bias and moderate to high quality evidence showed no survival advantage for HDCT. If this treatment is offered it should only be given after careful consideration on an individual person basis and possibly only as part of a well-designed RCT.

PLAIN LANGUAGE SUMMARY

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for nonrhabdomyosarcoma soft tissue sarcomas

Review question

We reviewed the evidence about the effect of high-dose chemotherapy (medicines to kill the cancer) followed by autologous hematopoietic stem cell transplantation compared to standard-dose chemotherapy on overall survival (time from cancer diagnosis, or treatment, to death from any cause) in people with nonrhabdomyosarcoma soft tissue sarcomas. We found one randomized controlled trial (RCT; a clinical study where people are randomly put into one of two or more treatment groups) comparing both treatments.

Background

Nonrhabdomyosarcoma soft tissue sarcomas are a group of rare cancers. People with inoperable (cannot be removed during an operation) or metastatic (where the cancer has spread to other parts of the body) disease have a poor prognosis (outcome). It was believed that higher doses of chemotherapy might improve people's survival. However, high doses of chemotherapy stop the production of blood cells in the bone marrow and can be harmful. Stem cells (cells that can form into many cell types) collected from people before high-dose chemotherapy can be transplanted back to the person if the blood cell count gets too low; this is called autologous hematopoietic stem cell transplantation. Due to a lack of research studies, it has not been proven that people treated like this live any longer than people treated with standard chemotherapy. We wanted to determine whether using high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation was better or worse than standard-dose chemotherapy.

Study characteristics

The evidence is current to 6 September 2016. We found one RCT that compared 38 people in the high-dose chemotherapy and transplantation group versus 45 people in the chemotherapy-only group and was judged to have mainly a low risk of bias (as it was well designed). The participants were 18 to 65 years old, had various types of nonrhabdomyosarcoma soft tissue sarcomas and were monitored for about 55 months. The treatment period ranged from 2000 to 2008. The single RCT was funded by a nonprofit organization (the funder did not benefit if the trial found good results).

Key results

The results of the RCT did not favor either of the two treatment arms with respect to overall survival. There was one death related to treatment in the transplantation group and none in the chemotherapy-only group. There were eight cases of severe nonhematologic (not related to the blood) side effects in the transplantation group and one in the chemotherapy-only group.

Quality of evidence

The overall quality of the data was unclear and based on only one RCT. Currently, research evidence is limited for the use of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for people with non-rhabdomyosarcoma soft tissue sarcomas. Further evidence is needed through well-designed clinical trials.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for nonrhabdomyosarcoma soft tissue sarcoma

Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for nonrhabdomyosarcoma soft tissue sarcoma

Patient or population: people with non-rhabdomyosarcoma soft tissue sarcoma

Settings: specialized hospital

Intervention: autologous hematopoietic stem cell transplantation following HDCT

Comparison: SDCT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SDCT	Autologous HSCT following HDCT				
Overall survival Follow-up: median 55 months	**489 per 1000**	**571 per 1000** (375 to 785)	**HR 1.26** (0.7 to 2.29)	83 (1 study)	⊕⊕⊕⊕ **High**	-
Treatment-related mortality Follow-up: 24 months	See comment	See comment	Not estimable	83 (1 study)	⊕⊕⊕⊕ **High**	1 event 2 years after HDCT and 0 events after SDCT
Disease-free survival Follow-up: 3 years	See comment	See comment	Not estimable	-	See comment	Not reported
Progression-free survival Follow-up: median 55 months	**756 per 1000**	**849 per 1000** (681 to 955)	**HR 1.34** (0.81 to 2.2)	83 (1 study)	⊕⊕⊕⊕ **High**	-
Non-hematologic toxicity grade 3 to 4	See comment	See comment	Not estimable	-	See comment	Not adequately reported, people from within and without the randomization were mixed in the control arm.
Health-related quality of life	See comment	See comment	Not estimable	-	See comment	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HDCT:** high-dose chemotherapy; **HR:** hazard ratio; **HSCT:** hematopoietic stem cell transplantation; **SDCT:** standard-dose chemotherapy.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors of nonepithelial extraskeletal body tissue and are classified on a histogenetic basis (Weiss 2001). STS have a significant risk of distant metastasis in addition to the potential for locally destructive growth and recurrence. Nonrhabdomyosarcoma 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) classification and included in any of the 2002 first (Fletcher 2002) or the 2013 updated second version (Fletcher 2013). Rhabdomyosarcoma was addressed in the Cochrane Review by Admiraal 2010.

NRSTS usually originate de novo and rarely from benign tumors. In most cases, the pathogenesis is unknown; however, some factors are associated with the development of NRSTS (Weiss 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). NRSTS are rare in both children and adults and the distribution of NRSTS differs significantly between children and adults according to Spunt 2006. In the USA, the yearly incidence of STS is 1 per 100,000 population for people 20 years of age or younger and about 7 per 100,000 population for people 20 years of age or older (NCI snapshot 2014). Between 2009 and 2013, the median age at diagnosis of STS, including tumors of the heart, was 59 years (Howlader 2016). Rhabdomyosarcoma represents about 50% of STS in children (Gurney 1997; Miller 1995).

Disease progression may be dichotomized into the two categories of limited and extensive disease. Limited disease is typically localized, small-sized, low-grade, and operable and is an accessible tumor that has no regional lymph node involvement and no distant metastases. Extensive disease can also be denoted as advanced disease, defined as a 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. Many people with limited disease may be cured by surgery whereas extensive disease is associated with a poor outcome and many people may receive chemotherapy as palliative therapy.

The Tumor, Node, Metastasis (TNM) staging system is developed and maintained by the Union for International Cancer Control (UICC 2009). It 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. It is used by other organizations (AJCC 2016; NCI staging 2015) and 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. According to statistics from the National Cancer Institute, the overall five-year survival is around 50% (ACS 2016). The overall survival (OS) varies by stage and was estimated at 16% for sarcomas with distant spread and 83% for localized sarcomas (ACS 2016).

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, and 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). People who relapse or experience progressive disease after therapy or metastasis are commonly called high-risk people because these signs are associated with shorter survival time. Spontaneous recovery from NRSTS is unknown.

Description of the intervention

Surgery is the standard treatment for localized NRSTS (ESMO 2014), and can be curative if distant dissemination is not present (Kotilingam 2006). Chemotherapy is a standard treatment for people with distant metastasis (ESMO 2014), and is regarded mainly as a palliative treatment for high-risk people who are characterized by inoperable, locally advanced and metastatic disease. Doxorubicin, ifosfamide, gemcitabine, dacarbazine, docetaxel, and trabectedin are used in monotherapy or in combinations (ESMO 2014). Riedel 2012 provides an overview of current systemic therapies and discusses possible novel therapeutic agents and treatment strategies.

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 are usually applied in standard-dose chemotherapy (SDCT). HDCT may ablate the person's bone marrow reserves and create an absolute requirement for stem cell rescue. Autologous HSCT applied after HDCT or high-dose radiation is a planned rescue therapy for HDCT-related severe hematologic toxicity (Banna 2007).

HDCT and autologous HSCT are not standard treatment options; they are an experimental approach mainly used to treat high-risk people with an unfavorable prognosis (stage IV with distant metastases). HDCT and autologous HSCT may be used in special cases after careful consideration, usually for people who respond well to standard chemotherapy according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Therasse 2000). Independent of the disease status, HDCT and autologous HSCT are hazardous interventions that carry the risk of life-threatening organ failure. Hematologic 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. Of 23,883 autologous HSCTs that were registered in Europe in 2014 by the European Group for Blood and Marrow Transplantation (EBMT), 19 were undertaken for STS (Passweg 2016).

How the intervention might work

HDCT followed by autologous HSCT was adopted to treat high-risk people because it was believed that escalating doses in chemotherapy might increase survival by capturing putatively

remnant malignant cells and might overcome resistance to SDCT (Banna 2007). HDCT may cause severe hematologic and nonhematologic toxicity and autologous HSCT is a planned rescue therapy for the HDCT-related demise of hematopoietic stem cells.

Why it is important to do this review

Several authors stated a lack of evidence and the need to conduct RCTs to clarify the relevance of HDCT followed by autologous HSCT in high-risk people with STS (Blay 2000; Carvajal 2005; Dumontet 1992; Ek 2006; Elias 1998; Kasper 2007; Ladenstein 1997; Pinkerton 1986; Reichardt 2002; Rosti 2002; Schlemmer 2006; Seeger 1991; Woods 1999). Some authors have warned against the use of HDCT followed by autologous HSCT, indicating the possibility of repositioning of malignant cells (Woods 1999). Others have questioned the use of HDCT with reference to the potential existence of refractory cancer stem cells (Banna 2007; Bonnet 1997; Sanchez-Garcia 2007). In the previous version of this review, we identified and included one RCT (Peinemann 2013). The rationale for this update is to clarify whether additional RCTs have been published or are ongoing.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Inclusion criteria

We adopted WHO classification of soft tissue tumors to define the population of people with malignant soft tissue tumors. This classifies soft tissue tumors as benign, intermediate (locally aggressive), intermediate (rarely metastasizing), and malignant. We included all tumor entities classified as malignant in any of the two published versions (Fletcher 2002; Fletcher 2013). This means that an entity is included in the present review, although it was listed in the 2002 version (Fletcher 2002) but not any longer listed in the 2013 (Fletcher 2013) version. This means also that an entity is included in the present review if it was not listed in the 2002 version but was introduced in the 2013 version. Studies were included if least 80% of participants had a diagnosis listed in any version of the WHO classification and classified as malignant, though we did not apply this limitation to rhabdomyosarcoma. We included children and adults with no age limits. Participants were included regardless of the severity of the disease and the clinical staging information, if they received autologous (from either a peripheral or bone marrow source, or both) HSCT.

Exclusion criteria

While the WHO classification of NRSTS includes the Ewing family of tumors, that is extraosseous tumor types, we excluded these as they are primarily bone sarcomas. Because extraosseous types are rarely diagnosed and share common features, they were regarded as one entity with osseous types and were excluded.

Types of interventions

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

Types of outcome measures

Primary outcomes

- Overall survival (OS): the event was death by any cause, from diagnosis or start of HDCT and autologous HSCT.
- Treatment-related mortality (TRM): incidence of deaths that were classified as treatment related or the participants died of treatment complications.

Secondary outcomes

- Disease-free survival (DFS): time free of disease after diagnosis or start of HDCT and autologous HSCT.
- Progression-free survival (PFS): time staying free of disease progression after diagnosis or start of HDCT and autologous HSCT. We provided the definitions if reported in the studies.
- Event-free survival (EFS): time staying free of any of a particular group of defined events after diagnosis or start of HDCT and autologous HSCT.
- Nonhematologic toxicity grade 3 to 4 affecting organs such as gastrointestinal tract, kidney, liver, nervous system, and heart according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 2016).
- Secondary neoplasia: as classified by the study authors.
- Health-related quality of life measured by validated questionnaires.

Search methods for identification of studies

Electronic searches

We conducted an electronic search in the following medical literature databases. We carefully revised the search strategies to improve precision.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8). The search strategy is shown in Appendix 1. The search dates were limited from 1 January 2012 to 6 September 2016. The search dates of the previous version included references from inception to 5 December 2012.
- PubMed. The search strategy is shown in Appendix 2. The search dates were limited from 1 January 2012 to 6 September 2016. The search dates of the previous version in MEDLINE included references from inception to 5 December 2012.
- Embase. We used the search term "soft tissue sarcoma". The search dates were limited from 01 January 2012 to 29 September 2016. The search dates of the previous version in Embase included references from inception to 05 December 2012.

We searched for ongoing trials by scanning the following online registries on 26 September 2016.

- ClinicalTrials.gov (ClinicalTrials.gov). Search: diagnosis 'soft tissue sarcoma'; intervention 'stem cell transplantation'. Limits: year '2012 to 2016'; study type 'interventional studies'; phase '2' or '3'.
- WHO International Clinical Trials Registry Platform (ICTRP). Search: diagnosis 'sarcoma'; intervention 'transplantation'. Limits: date of registration '1 January 2012 to 26 September 2016'.

We searched abstracts of annual meeting proceedings issued by the following societies on 26 September 2016:

- American Society of Clinical Oncology (ASCO): ASCO meetings in 2012 to 2016.
- American Society of Hematology (ASH): ASH meetings in 2013 to 2015. Search: 'autologous'.
- Bone Marrow Transplantation (BMT) Tandem Meetings of the American Society for Blood and Marrow Transplantation (ASBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) (BMT Tandem Meeting 2012; BMT Tandem Meeting 2013; BMT Tandem Meeting 2014; BMT Tandem Meeting 2015).
- European Society for Blood and Marrow Transplantation (EBMT) (EBMT Meeting 2014; EBMT Meeting 2015; EBMT Meeting 2016). Search: 'sarcoma'.
- EBMT current study list (EBMT Studies 2016).
- International Society of Paediatric Oncology (SIOP) (SIOP Meeting 2012; SIOP Meeting 2013). Search: 'sarcoma'.

The search strategies used have been developed and executed by the author team.

Searching other resources

We planned to locate information about trials not registered in electronic databases by searching the reference lists of recently published relevant articles and review articles.

Data collection and analysis

Selection of studies

We endorsed the PRISMA statement, adhered to its principles, and conformed to its checklist (Moher 2009). We retrieved all titles and abstracts by electronic searching, downloaded them, and transferred the bibliographical data into an Excel spreadsheet. We removed duplicates and two review authors (FP, HE) examined the remaining references independently. We excluded those studies that clearly did not meet the inclusion criteria and we documented the reasons for the exclusion of studies. We resolved disagreement by discussion and it was not necessary to consult a third review author (LAS). We considered studies written in languages other than English and asked peers familiar with the particular language and with the principles of study evaluation to translate major methodologic issues. We planned to use the Google Translate 2016 program if required, but this was not necessary.

Data extraction and management

We extracted the following data as in the previous version.

- General information on author, title, source, publication date.
- Study characteristics: trial design, setting, inclusion and exclusion criteria, comparability of participants' characteristics between groups, treatment allocation, blinding, subgroup analysis, length of follow-up.
- Participant characteristics: age; gender; number of participants recruited, allocated, affected, analyzed; additional diagnoses; participants lost to follow-up.
- Interventions: type of HDCT, source of stem cells, and type of SDCT.
- Outcomes: OS, TRM, DFS, PFS, EFS including type of event, toxicity, secondary neoplasia, health-related quality of life.

Assessment of risk of bias in included studies

Two review authors (FP, LAS) independently checked the risk of bias in the included studies using the standard criteria to assess RCTs according to the Cochrane 'Risk of bias' tool (Higgins 2011a). With respect to the previous version, we removed the risk of bias items specifically aimed at checking the risk of bias in nonrandomized studies.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting such as not reporting prespecified outcomes (reporting bias).
- Other bias.

We applied Cochrane criteria for judging risk of bias (Higgins 2011a). In general, there was a 'low risk' of bias if the bias was unlikely to seriously alter the results, for example, participants and investigators enrolling participants could not have foreseen assignment. There was a 'high risk' of bias if the bias seriously weakened confidence in the results, for example, participants or investigators enrolling participants could possibly have foreseen assignments. There was 'unclear' risk of bias if the bias raised some doubt about the results, for example, the method of concealment was not described or not described in sufficient detail to allow a definite judgment.

Measures of treatment effect

The primary effect measure was the hazard ratio (HR) for time-to-event data. If the HR was not directly given in the publication, we planned to estimate HRs according to methods proposed by Tierney 2007, but this was not necessary. We planned to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes, but this was not applicable. In the case of rare events, we planned to use Peto OR instead, but this was not applicable. We planned to analyze continuous data and to present them as mean differences, if all results were measured on the same scale (e.g. length of hospital stay), but this was not applicable. If this was not the case (e.g. pain or quality of life), we planned to use standardized mean differences, but this was not applicable.

Dealing with missing data

We conformed to Cochrane's principal options for dealing with missing data and analyzed only the available data (Higgins 2011b). If data were missing or only imputed data were reported, we planned to contact trial authors to request data on the outcomes among participants who were assessed.

In the previous version of the review, we contacted the authors of the study by Bui-Nguyen 2012 by e-mail (1 December 2012) to ask for missing data about the histologic types that were combined as 'others'. The authors responded and as a consequence we could base the inclusion or exclusion of participant data on the additional data (Table 1). In the current version of the review (September 2016), we sent e-mail inquiries as shown in Appendix 3 to two authors (Binh Bui-Nguyen, 3 October 2016; Jean-Yves Blay, 5 October 2016) of the included study (Bui-Nguyen 2012) regarding clarification of survival data and Food and Drug Administration (FDA) warning letter on objectionable conditions and inadequate responses (FDA 2015). We did not receive any reply by 7 March 2017.

Assessment of heterogeneity

We had planned to assess heterogeneity between studies by visual inspection of forest plots; by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (I^2 statistic) (Higgins 2003); by a formal statistical test of the significance of the heterogeneity (Cochran's Q) (Deeks 2011); and, if possible, by subgroup analyses (see Subgroup analysis and investigation of heterogeneity). We had planned to investigate and report possible reasons if there was evidence of substantial heterogeneity. We had planned to use the random-effects model with inverse variance weighting for statistical pooling (DerSimonian 1986). We did not pool estimates.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the Assessment of risk of bias in included studies section, we had planned to assess reporting bias (such as publication bias, time lag bias, multiple (duplicate) publication bias, location bias, citation bias, language bias) by constructing a funnel plot if there were a sufficient number of included studies (i.e. at least 10 studies included in a meta-analysis otherwise the power of the tests would be too low to distinguish chance from real asymmetry (Sterne 2011)). We did not assess reporting bias because of the low number of identified studies.

Data synthesis

We analyzed data using Review Manager 5 (RevMan 2014). This was done by one review author (FP) and checked by another review author (LAS). If sufficient, clinically similar studies were available, we had planned to pool their results in meta-analyses if they used comparable outcome definitions. As we included one RCT, we presented the results descriptively. We had planned to use random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986), but this was not applicable.

For each comparison, we prepared a 'Summary of findings' table using the GRADE profiler software (GRADEpro 2014), in which we presented the following primary outcomes: OS, TRM, DFS, PFS, non-hematologic toxicity grade 3 to 4 and health-related quality of life . For each outcome, two review authors (FP, LAS) independently assessed the quality of the evidence by using the five GRADE considerations, that is, study limitations, inconsistency, indirectness, imprecision, and publication bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

We had planned subgroup analyses based on age, stage, and time period of treatment. However, we found no appropriate data to conduct these analyses.

Sensitivity analysis

We had planned sensitivity analyses to compare the results of studies with low versus high risk of bias. As we included only one study, a sensitivity analysis was not applicable.

RESULTS

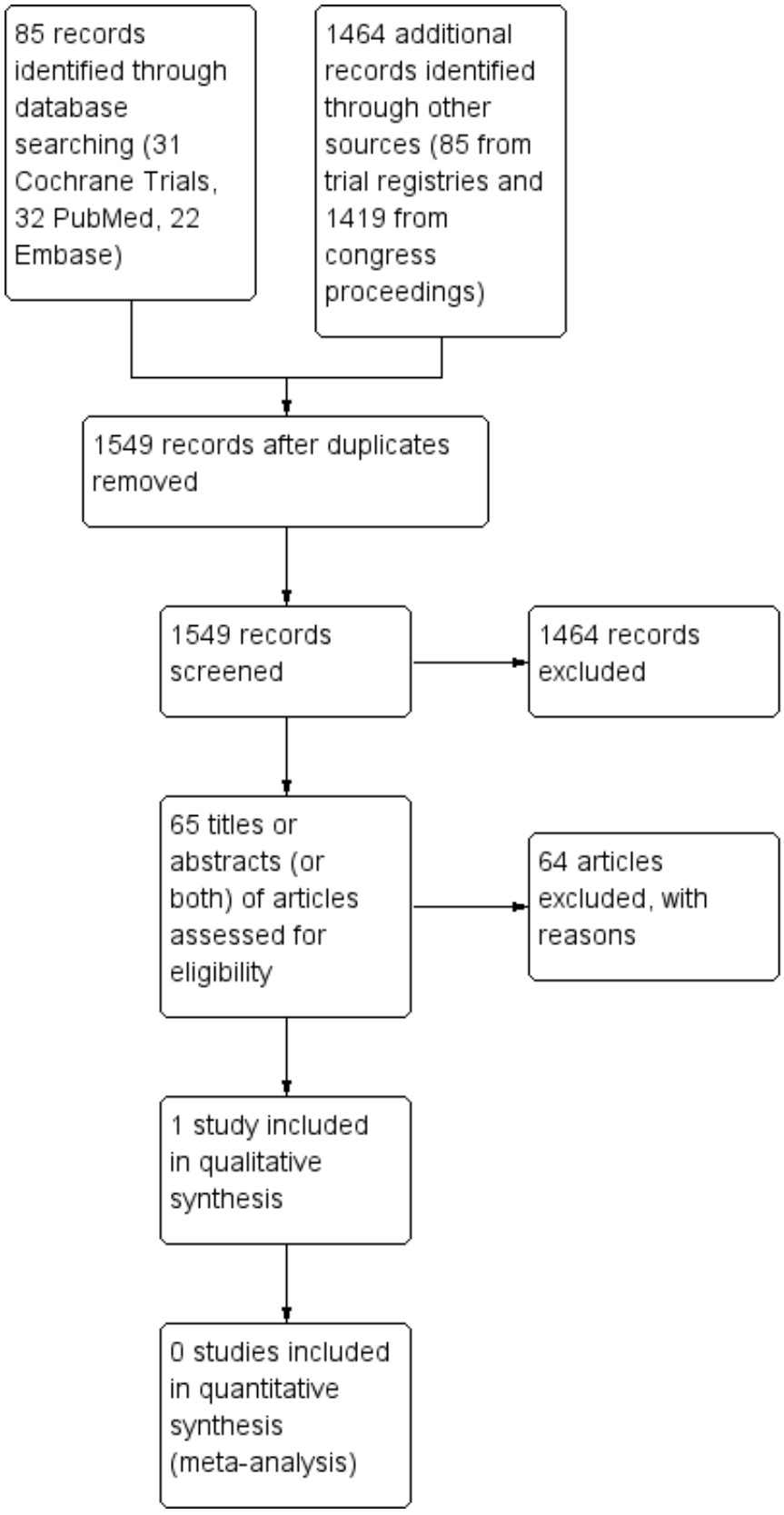
Description of studies

Clinical heterogeneity was substantial because tumor entities varied considerably between participants.

Results of the search

For this update we revised the search strategy to improve the precision and reduce the number of irrelevant hits. We identified a total of 1549 items including 85 items from electronic databases, 45 items from study registries, and 1419 items from congress proceedings (Figure 1).

Figure 1. Study flow diagram.



We retrieved 85 records from the electronic literature databases CENTRAL, PubMed and Embase and screened 65 different articles after removal of duplicates. The titles, abstracts or both of all 65 articles did not fulfil the inclusion criteria and we excluded the articles with reasons (Figure 1).

We identified 45 records from study registries and all 45 items did not fulfill the inclusion criteria. We retrieved 39 studies from ClinicalTrials.gov Studies 2016 and 6 studies from ICTRP Studies 2016. We identified a total of 1419 potentially relevant meeting abstracts and all 1419 items did not fulfil the inclusion criteria. We identified 830 abstracts in ASCO Meetings 2012 to 2016, 128 abstracts in ASH Meetings 2013 to 2015, 21 relevant abstracts in BMT Tandem Meeting 2012, BMT Tandem Meeting 2013, BMT Tandem Meeting 2014, BMT Tandem Meeting 2015, and BMT Tandem Meeting 2016, 149 abstracts in EBMT Meeting 2014, EBMT Meeting 2015, EBMT Meeting 2016, 52 current EBMT Studies 2016, and 239 abstracts from SIOP Meeting 2012, SIOP Meeting 2013, SIOP Meeting 2014, SIOP Meeting 2015, and SIOP Meeting 2016.

For the update, we did not identify any additional studies and it was not necessary to contact authors to for missing information.

Included studies

As the updated classification of STS included some changes, we rechecked the extracted data from the previously included RCT which remains included in the this updated version of the review. Two review authors (FP, LAS) independently checked data for study characteristics, participants and interventions, duration of follow-up, outcomes, and deviations from the protocol. In addition, two review authors (FP, LAS) independently checked the risk of bias. We had planned to resolve differences between review authors by discussion or by appeal to a third review author, but it was not necessary. The update search did not identify any additional RCTs. Therefore, we included one RCT in this update (Bui-Nguyen 2012). Bui-Nguyen 2012 randomized 87 participants and included 83 participants in a modified intention-to-treat analysis. A detailed description of the study is shown in the Characteristics of included studies table.

Design

Bui-Nguyen 2012 reported an RCT with two parallel treatment groups, HDCT followed by autologous HDCT versus SDCT. It was an open, multicenter, randomized phase III study. All participants received the same baseline treatment. Participants were eligible for randomization if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. Randomization was carried out centrally.

Sample sizes

The trial authors modified the intention-to-treat analysis to exclude the data for four participants who were initially randomized but found to be ineligible at central histology review (Bui-Nguyen 2012). Initially, 87 participants were randomized: 41 in the HDCT arm versus 46 in the SDCT arm but only 83 participants were analyzed in a modified intention-to-treat-analysis: 38 in the HDCT arm versus 45 in the SDCT arm.

Setting

The single included RCT was a French multicenter trial set in 16 different centers (Bui-Nguyen 2012).

Participants

Bui-Nguyen 2012 reported a median age of 45.8 years in the HDCT arm and 43.3 years in the SDCT arm. The proportion of males was 58.5% in the HDCT arm and 50% in the SDCT arm. A total of 19 different diagnoses were assigned to the 87 participants. In Table 1, we provide a list of all diagnoses and their incidence among the participants. We clarified the category 'Others' by contacting the trial author.

Interventions

In the study by Bui-Nguyen 2012, 87 participants received courses one to five of SDCT. Forty-one participants were randomized to receive HDCT and transplantation of autologous peripheral stem cells as course six in the HDCT arm. Of these, 38 participants were analyzed in a modified intention-to-treat analysis. Forty-six participants were randomized to again receive SDCT as course six. Of these, 45 participants were analyzed in a modified intention-to-treat analysis.

Primary outcome

OS was the primary outcome of the review and the study (Bui-Nguyen 2012). TRM was the primary outcome of the review but was a secondary outcome among adverse events of the study.

Secondary outcomes

PFS and adverse events were secondary outcomes of the review and the study (Bui-Nguyen 2012). The trial authors evaluated complete remission as a secondary outcome, which was not considered as an outcome in this review.

Excluded studies

We excluded 65 references of the potentially relevant articles with the following reasons (Figure 1):

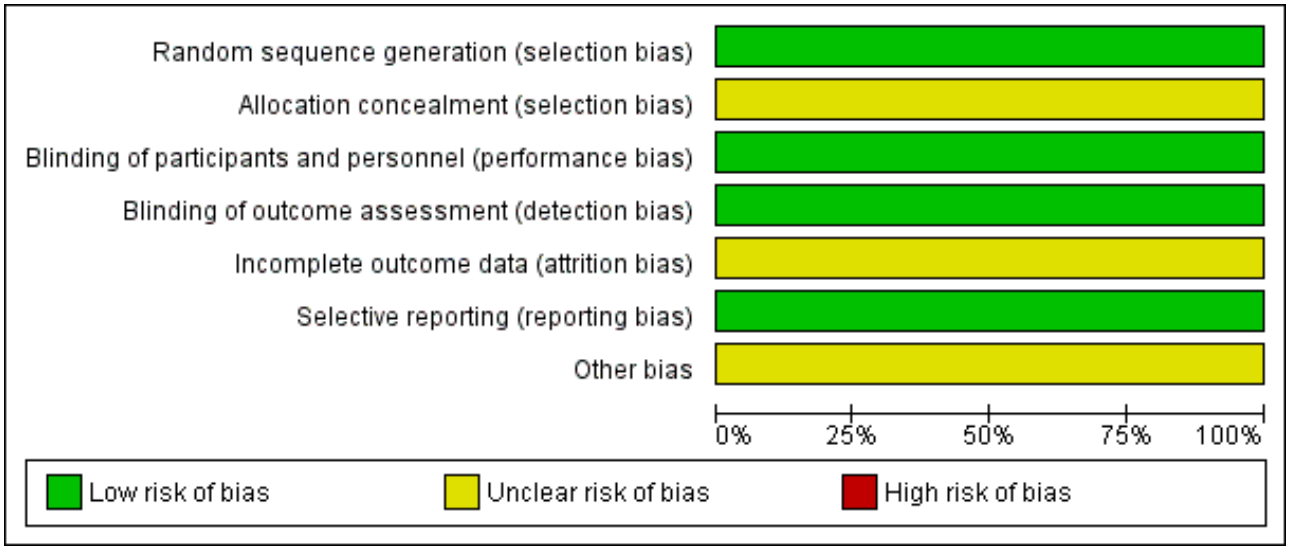
- not study type of interest (14);
- not population of interest (34);
- not intervention of interest (16).

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

Risk of bias in included studies

An overview of the risk of bias of Bui-Nguyen 2012 is shown in Figure 2.

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Allocation

Reporting appeared to be compatible with an adequate random sequence generation and we judged it at low risk of bias. Allocation concealment was not described and it is unclear whether it was carried out adequately, therefore, we judged it at unclear risk of bias.

Blinding

The study did not address blinding of participants and blinding of outcome assessment. Nevertheless, blinding is not relevant for OS and TRM. Therefore, we judged it at low risk of bias. The previous version of this review did not judge blinding of participants and we added it to the present version. The result of the judgment of blinding of outcome assessment was changed from high risk (blinding not reported) to low risk (blinding not relevant for the primary outcomes).

Incomplete outcome data

The previous version of this review did not judge incomplete outcome data and we added it to this update. From the 87 participants, the data of four participants had not been included in the analysis. At 36 months from randomization (HDCT versus SDCT), 51 participants had died (24 in HDCT arm versus 27 in SDCT arm) and 25 were alive (eight in HDCT arm versus 17 in SDCT arm). Of the 83 participants (38 in HDCT arm versus 45 in SDCT arm) included in the modified intention-to-treat survival analysis, 76 participants (32 in HDCT arm versus 44 in SDCT arm) were accounted for but seven participants (six in HDCT arm versus one in SDCT arm) were not adequately explained.

Figure 1 in Bui-Nguyen 2012 showed that 41 participants were randomized to the HDCT arm, but only 22 participants of these received HDCT and were evaluated. Also 46 participants were randomized to the SDCT arm and 40 participants received SDCT and were evaluated.

Table 2 of Bui-Nguyen 2012 showed WHO grades 3/4 toxicity for all randomized participants, 22 in the HDCT arm and 51 in the SDCT arm. There was an inconsistency in the number of randomized and evaluated participants between Figure 1 and Table 2. It appeared conflicting that 51 participants were reported to be randomized to the SDCT arm in Table 2, although, according to Figure 1, only 46 participants were randomized and only 40 participants actually received SDCT treatment. Therefore, it appears that only 40 participants were actually eligible to evaluate adverse events after SDCT. As we were unable to contact the trial authors, we could not clarify this issue.

The potential influence of the reported missing information was unclear, therefore we judged it at unclear risk of bias.

Selective reporting

We did not identify any selective reporting and judged it at low risk of bias.

Other potential sources of bias

The previous version of this review did not judge other potential sources of bias and we added it to this update. The FDA sent a warning letter (Reference 15-HFD-45-05-01) addressed to the first author of the trial on 4 May 2015 to inform of objectionable conditions observed during an inspection at the clinical site between 17 and 19 September 2014 (FDA 2015). The inspection happened after conclusion of the study and may not be related to the risk of bias. The potential influence of this information was unclear, therefore we judged it at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for nonrhabdomyosarcoma soft tissue sarcoma

Primary outcome

Overall survival

The HR between the survival functions of the HDCT and the SDCT arms in Bui-Nguyen 2012 was reported as 1.26 (95% CI 0.70 to

2.29; P = 0.44; 1 study, 83 participants; high quality evidence). Therefore, the data did not favor either treatment arm with respect to OS. The trial authors reported the probability of OS at three years postrandomization as 32.7% in the HDCT arm versus 49.4% in the SDCT arm. The trial authors conducted a subgroup analysis of participants who had achieved a complete response before HDCT. The estimated HR for OS of 2.92 (95% CI 1.1 to 7.6; P = 0.028; 1 study, 39 participants) favored the SDCT arm.

Treatment-related mortality

The trial authors reported a single treatment-related leukemia death two years after HDCT.

Secondary outcomes

Disease-free survival

The study did not address DFS.

Progression-free survival

The HR between the survival functions of the HDCT and the SDCT arms in Bui-Nguyen 2012 was reported as 1.34 (95% CI 0.81 to 2.20; P = 0.25; 1 study, 83 participants). Therefore, the data did not favor either treatment with respect to PFS. The trial authors reported the probability of PFS at the time point of three years postrandomization of 9.3% in the HDCT arm versus 21.6% in the SDCT arm. The trial authors conducted a subgroup analysis of participants who had achieved a complete response before HDCT. The estimated HR for PFS of 2.87 (95% CI 1.3 to 6.3; P = 0.009; 1 study, 39 participants) favored the SDCT arm.

Event-free survival

The study did not address event-free survival.

Nonhematologic toxicity grade 3 to 4

The study evaluated severe adverse events in 22 participants in the HDCT arm and 51 participants in the SDCT arm according to Table 2 in Bui-Nguyen 2012. The trial authors reported 11 events including digestive-, infection-, pain-, or asthenia-related toxicity in 22 participants of the HDCT arm and one event in 51 participants of the SDCT arm. However, the study also stated that 40 participants had been randomized to the SDCT arm. We can only assume that the authors mixed participants who were part of the randomization process and other people who were not. As it was not possible to continue a communication with the authors, we could not clarify this issue.

Secondary neoplasia

The study did not address secondary neoplasia.

Health-related quality of life

The study did not address health-related quality of life.

DISCUSSION

Summary of main results

In this update, we identified no additional RCTs other than the one RCT that was included in the previous version of this review (Bui-Nguyen 2012). The data did not favor the HDCT with respect to OS, PFS, or adverse events. The considerable heterogeneity of the tumor entities included in the study may be an important factor as OS may differ between the entities.

Overall completeness and applicability of evidence

The search was comprehensive and we considered the risk of not detecting an RCT (either published or ongoing) to be very small. The participants included in the trial were recruited from 2000 to 2008 and, considering the advancement in medicine, the results may not be applicable to the current treatment of people with NRSTS.

Quality of the evidence

Using the 'Risk of bias' tool for randomized studies we judged an overall unclear risk of bias. We judged a low risk of bias for four items (selection bias, performance bias, detection bas, and reporting bias) and unclear for the remaining three items. Each tumor entity may carry an individual risk profile and, therefore, ideally should be evaluated separately. However, the frequency of the population and the intervention of interest is tiny. In 2014, only 19 autologous HSCTs indicated for STS were registered by the European Group for Blood and Marrow Transplantation (Passweg 2016). We presented estimates in the Summary of findings for the main comparison for outcomes that mainly constitute death as the endpoint. These outcomes included OS, TRM, and PFS. The lack of blinding did not result in judging a high risk of bias. In Summary of findings for the main comparison, we assigned high quality with respect to those outcomes using GRADE criteria. Other outcomes were not reported or were not adequately reported. The authors reported a secondary analysis carried out to investigate the effects of surgery. According to the authors, "Overall, there were no survival differences observed (HR = 0.63, 95% CI 0.35-1.12), according to the performance of surgery (54.3%) or not (33.2%)." We were unable to determine the number of participants in this subgroup. Therefore, we did not include the information in the 'Results' section.

Potential biases in the review process

Strengths: the search strategy was broad and it is very likely that the search identified all relevant studies. We contacted authors to request additional data.

Limitations: heterogeneity of the tumor entities and the time period of treatment may limit the conclusions that may be drawn from the data.

Agreements and disagreements with other studies or reviews

We agree with Kasper 2005 and would like to extend the views that the use of HDCT followed by autologous HSCT for locally advanced or metastatic adult STS is highly experimental, might be even be less effective than SDCT, and should not be performed outside of RCTs.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence base does not support the use of high-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (HSCT) in high-risk people with non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). If this treatment is offered, it should only be after careful consideration on an

individual person basis and possibly only as part of a well-designed randomized controlled trial (RCT).

Implications for research

It is doubtful whether further studies are necessary to clarify the relevance of HDCT followed by autologous HSCT in people with NRSTS. However, if appropriate, any future studies would need to be methodologically well-designed RCTs with a low risk of bias as nonrandomized studies are not beneficial in addressing this topic. Criteria for the included tumor types in any future trial 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]*

Bui-Nguyen 2012

Methods	Duration: 2000 to 2008 Study design: randomized controlled trial: "This open, multicenter, randomized phase III study [...]". "All patients eligible for preenrollment received the same baseline treatment [...]". "[...] eligible for randomization if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. Patients were ineligible for randomization if they had progressed or had only stable disease with no possibility for complete resection of the primary and/or metastatic tumor". "Randomization was stratified by center using a blocked method with block size of four and was carried out centrally". "The intention to treat (ITT)-modified population included all randomly assigned patients excluding patients found to be ineligible at central histology review." Treatment: number of arms: 2 Follow-up time: time to event analysis at 3 years with a median follow-up of 55 months for survivors

Participants	Setting: multicenter trial in 16 centers in France
	
	Eligibility criteria: people aged 18 to 65 years with histologically confirmed, inoperable locally advanced or metastatic soft tissues sarcomas; Eastern Cooperative Oncology Group performance status of 0 or 1; normal cardiac, hepatic, and renal function; adequate bone marrow reserve; participants had received no prior chemotherapy or concurrent therapy
	
	Exclusions: people for whom it was possible to perform potentially curative locoregional treatments and people with uterine, bone, or digestive tumors
	
	Number of participants: 264 participants pre-enrolled; 207 participants received first 4 of 6 chemotherapy courses:
	
	• 87 participants were randomized: tumor entities listed in Table 1
	  ○ 41 participants were randomized to the HDCT + autologous HSCT arm
	  ○ 46 participants were randomized to the SDCT arm
	• 4 participants were not included in the analysis
	  ○ 3 participants of the HDCT + autologous HSCT arm
	  ○ 1 participant of the SDCT arm
	• 83 participants were included in a modified (removal of 4 ineligible participants) intention-to-treat analysis with respect to overall survival and progression-free survival
	  ○ 38 participants of the HDCT + autologous HSCT arm
	  ○ 45 participants of the SDCT arm
	• 62 participants received the assigned treatment and were included in the toxicity analysis
	  ○ 22 participants of the HDCT + autologous HSCT arm
	  ○ 40 participants of the SDCT arm

Bui-Nguyen 2012 *(Continued)*

	Age • HDCT + autologous HSCT arm: median 45.8 years (range 18.5 to 65.0) • SDCT arm: median 43.3 years (range 18.7 to 65.0) Gender • HDCT + autologous HSCT arm: 58.5% (24/41) males; 41.5% (15/41) females • SDCT arm: 50% (23/46) males; 50% (23/46) females
Interventions	All participants received 5 courses of SDCT: doxorubicin 60 mg/m^2, ifosfamide 7500 mg/m^2, dacarbazine 900 mg/m^2, total doses; the 6th course was different between HDCT + autologous HSCT arm and SDCT arm: HDCT + autologous HSCT arm, 6th course: • HDCT: ifosfamide 10,000 mg/m^2, carboplatin, and etoposide 1200 mg/m^2, total doses • autologous HSCT: stem cell source: peripheral blood • actually 22-41 randomized participants received HDCT followed by HSCT SDCT arm, 6th course: • SDCT: doxorubicin 60 mg/m^2, ifosfamide 7500 mg/m^2, dacarbazine 900 mg/m^2, total doses • actually 40/46 randomized participants received SDCT
Outcomes	Primary outcomes as defined by the study • Overall survival Secondary outcomes as defined by the study • Progression-free survival • Adverse effects • Complete remission
Notes	Financial support: Programme Hospitalier de Recherche Clinique, French Health Ministry (nonprofit organization); French National Federation for Comprehensive Cancer Centers (nonprofit organization). Information about the histologic type of sarcoma designated as "Others" in the article were communicated by personal contact with the first author and listed in Table 1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was stratified by center using a blocked method with block size of four and was carried out centrally". We assumed an adequate random sequence generation and judged at low risk of bias.
Allocation concealment (selection bias)	Unclear risk	Allocation was carried out centrally, though masking of allocation was not described in full detail. We assumed an adequate allocation concealment. However, we missed a clarifying statement. Therefore, we judged at unclear risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not reported; very likely not possible and not relevant for the reported outcomes of overall survival, treatment-related mortality, and progression-free survival. Blinding of participants has no influence on overall survival and treatment-related mortality, which are defined as primary outcomes of the present review. Therefore, we judged at low risk of bias.

Bui-Nguyen 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported; very likely not possible and not relevant for the reported outcomes overall survival, treatment-related mortality, and progression-free survival. The study was denoted as an "open, multicenter, randomized phase III study". Blinding of outcome assessment has no influence on overall survival and treatment-related mortality, which are defined as primary outcomes of the present review. Therefore, we judged at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At 36 months from randomization (HDCT versus SDCT), 51 participants had died (24 versus 27) and 25 were at risk (8 versus 17). Of 83 participants (38 versus 45) included in the modified intention-to-treat survival analysis, 76 participants (32 versus 44) are accounted for but 7 participants (6 versus 1) may not be explained. The number of participants with missing information was small. The potential influence of this missing information was unclear, therefore we judged at unclear risk of bias. Figure 1 of Bui-Nguyen 2012 showed that 41 participants were randomized to the HDCT arm, but 22 participants actually received high dose and were evaluated. Figure 1 also showed that 46 participants were randomized to the SDCT arm, but 40 participants actually received standard dose and were evaluated. The potential influence of this missing information was unclear, therefore we judged atn unclear risk of bias. Table 2 of Bui-Nguyen 2012 showed WHO grades 3/4 toxicity for all randomized participants, 22 in the HDCT arm and 51 in the SDCT arm. There was an inconsistency concerning the number of randomized and evaluated participants between Figure 1 and Table 2. It appeared conflicting that 51 participants were reported to be randomized to the SDCT arm in Table 2, although, according to Figure 1, only 46 participants were randomized and only 40 participants actually received SDCT. Thus, instead of 51 participants, it appeared that only 40 participants were actually eligible to evaluate adverse events after SDCT.
Selective reporting (reporting bias)	Low risk	We did not identify any selective outcome reporting.
Other bias	Unclear risk	The US Food and Drug Administration sent a warning letter (Reference 15-HFD-45-05-01) addressed to the first author on 4 May 2015 to inform of objectionable conditions observed during an inspection at the clinical site between 17 and 19 September 2014 (FDA 2015). The inspection happened after the conclusion of the study included in the present review and may not have been related to the risk of bias. The potential influence of this information was unclear, therefore we judged it at unclear risk of bias.

HDCT: high-dose chemotherapy; HSCT: hematopoietic stem cell transplantation; SDCT: standard-dose chemotherapy; WHO: World Health Organization.

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

Study	Reason for exclusion
Araki 2016	Not intervention of interest
Benesch 2014	Not study design of interest
Brana 2014	Not population of interest
Calabro 2015	Not population of interest

Study	Reason for exclusion
Cohen 2012	Not intervention of interest
Conter 2013	Not population of interest
Czarnecka 2014	Not population of interest
Davis 2015	Not intervention of interest
Delannes 2013	Not intervention of interest
Demetri 2016	Not intervention of interest
Diez-Tejedor 2014	Not population of interest
Drabko 2012	Not population of interest
Ehlert 2012	Not study design of interest
Engelhard 2013	Not population of interest
Friedman 2014	Not population of interest
Froeb 2012	Not population of interest
Gaspar 2012	Not population of interest
Grignani 2015	Not population of interest
Gronchi 2012	Not intervention of interest
Halland 2012	Not population of interest
Hartmann 2013	Not study design of interest
Hensley 2013	Not population of interest
Infante 2015	Not population of interest
Ishida 2014	Not study design of interest
Ishida 2016	Not study design of interest
Joensuu 2012	Not intervention of interest
Judson 2014	Not intervention of interest
Kawai 2015	Not intervention of interest
Khmelevsky 2015	Not population of interest
Lanza 2015	Not study design of interest
Laws 2014	Not population of interest
Le Deley 2014	Not population of interest

Study	Reason for exclusion
Liu 2012	Not population of interest
Liu 2013a	Not study design of interest
Liu 2013b	Not population of interest
Maher 2014	Not population of interest
Merker 2015	Not intervention of interest
Meyers 2015	Not population of interest
Munir 2016	Not population of interest
Narumi 2012	Not study design of interest
Oberlin 2012	Not population of interest
Palassini 2015	Not intervention of interest
Pavlyk 2013	Not intervention of interest
Peinemann 2013	Not study design of interest
Peinemann 2014	Not study design of interest
Porta 2014	Not population of interest
Rettinger 2012a	Not population of interest
Rettinger 2012b	Not population of interest
Schmidinger 2012	Not population of interest
Schoffski 2016	Not intervention of interest
Shvarova 2012	Not study design of interest
Smolen 2014	Not population of interest
Stahel 2015	Not population of interest
Teichert von Luettichau 2014	Not intervention of interest
Teppo 2016	Not study design of interest
Uehara 2015	Not study design of interest
Vecsei 2014	Not population of interest
Verweij 2013	Not intervention of interest
Woll 2012	Not intervention of interest
Womer 2012	Not population of interest

Study	Reason for exclusion
Yamada 2012	Not study design of interest
Yuan 2015	Not population of interest
Zhang 2013	Not population of interest
Zhou 2013	Not population of interest
Zhu 2014	Not population of interest

ADDITIONAL TABLES

Table 1. Tumor entities reported by Bui-Nguyen 2012

Sarcoma type	Sarcoma type 'Others'	Both arms	HDCT arm	SDCT arm
Leiomyosarcoma	-	16	7	9
Liposarcoma	-	10	6	4
Synovial sarcoma	-	9	2	7
Angiosarcoma	-	6	2	4
Malignant peripheral nerve sheath tumor	-	2	1	1
Clear cell sarcoma	-	1	1	0
Desmoplastic small round cell sarcoma	-	1	0	1
Rhabdomyosarcoma	-	9	4	5
Malignant fibrous histiocytoma	-	16	8	8
Extraskeletal osteosarcoma	-	1	0	1
*Melanoma**	-	*1*	*1*	*0*
'Others'	Leiomyosarcoma	1	1	0
	Fibrosarcoma	1	1	0
	Myofibrosarcoma	1	0	1
	Undifferentiated sarcoma	2	1	1
	Desmoplastic small round cell sarcoma	2	2	0
	Gastrointestinal stromal tumor	1	0	1

Table 1. Tumor entities reported by Bui-Nguyen 2012 *(Continued)*

	Malignant Triton tumor	1	0	1
	Unclassified sarcoma	1	1	0
	*Myoepithelioma**	*2*	*2*	*0*
	*Endometrial stromal sarcoma**	*3*	*1*	*2*
Total		**87**	**41**	**46**
Not listed in the WHO classification		*6*	*4*	*2*

HDCT: high-dose chemotherapy; SDCT: standard-dose chemotherapy; WHO: World Health Organization.
Bui-Nguyen: the table lists the sarcoma types assigned to each individual of all randomized participants of the study by Bui-Nguyen 2012.
*Soft tissue sarcomas: tumor entities not listed in either versions of the WHO classification (Fletcher 2002; Fletcher 2013), or soft tissue tumors not categorized as malignant are italicized. Myoepithelioma is categorized as an intermediate soft tissue tumor. Melanoma and endometrial stromal sarcoma are not listed in the classification.

APPENDICES

Appendix 1. CENTRAL search strategy

ID	Search	Hits
#1	MeSH descriptor: [Sarcoma] explode all trees	704
#2	MeSH descriptor: [Carcinoma, Small Cell] explode all trees	748
#3	MeSH descriptor: [Hemangioendothelioma] explode all trees	2
#4	MeSH descriptor: [Mesenchymoma] explode all trees	2
#5	MeSH descriptor: [Perivascular Epithelioid Cell Neoplasms] explode all trees	13
#6	MeSH descriptor: [Rhabdoid Tumor] explode all trees	1
#7	MeSH descriptor: [Gastrointestinal Stromal Tumors] explode all trees	112
#8	alveolar soft part sarcoma*	8
#9	alveolar soft tissue sarcoma*	12
#10	angiosarcoma*	21
#11	hemangiosarcoma*	9
#12	clear cell sarcoma*	130
#13	clear cell tumor* or clear cell tumour*	1228
#14	desmoplastic small round cell tumor* or desmoplastic small round cell tumor*	6

(Continued)

#15	epithel* sarcoma*	55
#16	fibrosarcoma*	34
#17	myxofibrosarcoma*	3
#18	hemangioendothelioma*	7
#19	hemangioendotheliosarcoma*	1
#20	intimal sarcoma*	1
#21	leiomyosarcoma*	111
#22	liposarcoma*	58
#23	malignant glomus tumor* or malignant glomus tumour*	2
#24	malignant mesenchymoma*	2
#25	perivascular epithelioid cell tumor* or perivascular epithelioid cell tumour*	1
#26	rhabdoid tumor* or rhabdoid tumour*	15
#27	rhabdoid sarcoma*	7
#28	synovial sarcoma*	31
#29	gastrointestinal stromal tumor* or gastrointestinal stromal tumour*	263
#30	malignant peripheral nerve sheath tumour*	8
#31	undifferentiated pleomorphic sarcoma*	10
#32	MeSH descriptor: [Stem Cell Transplantation] explode all trees	1861
#33	MeSH descriptor: [Bone Marrow Transplantation] explode all trees	1421
#34	MeSH descriptor: [Transplantation, Autologous] explode all trees	1528
#35	MeSH descriptor: [Consolidation Chemotherapy] explode all trees	41
#36	autologous transplant*	4038
#37	bone marrow rescue	203
#38	bone marrow support	2824
#39	bone marrow cell	3820
#40	stem cell rescue	211
#41	stem cell support	2117
#42	peripheral blood stem cell	1487

(Continued)

#43	high dose chemotherapy	5860
#44	intensified chemotherapy	373
#45	intensive chemotherapy	2053
#46	myeloablative chemotherapy	234
#47	dose intensive treatment	4499
#48	high dose combination	11065
#49	MeSH descriptor: [Randomized Controlled Trial] explode all trees	157
#50	randomized controlled trial or randomised controlled trial	562380
#51	randomized controlled study or randomised controlled study	495206
#52	randomized trial or randomised trial	564855
#53	randomized study or randomised study	498484
#54	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31	3040
#55	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 #42 or #43 or #44 or #45 or #46 or #47 or #48	25564
#56	#49 or #50 or #51 or #52 or #53	612136
#57	#54 and #55 and #56	928

Limits: publication date from 01 January 2012 to 06 September 2016.

Appendix 2. PubMed search strategy

ID	Search
#1	"Sarcoma"[Mesh]
#2	"Carcinoma, Small Cell"[Mesh]
#3	"Hemangioendothelioma"[Mesh]
#4	"Mesenchymoma"[Mesh]
#5	"Perivascular Epithelioid Cell Neoplasms"[Mesh]
#6	"Rhabdoid Tumor"[Mesh]
#7	"Gastrointestinal Stromal Tumors"[Mesh]

(Continued)

#8	alveolar soft part sarcoma*
#9	alveolar soft tissue sarcoma*
#10	angiosarcoma*
#11	hemangiosarcoma*
#12	clear cell sarcoma*
#13	clear cell tumor* or clear cell tumour*
#14	desmoplastic small round cell tumor* or desmoplastic small round cell tumor*
#15	epithel* sarcoma*
#16	fibrosarcoma*
#17	myxofibrosarcoma*
#18	hemangioendothelioma*
#19	hemangioendotheliosarcoma*
#20	intimal sarcoma*
#21	leiomyosarcoma*
#22	liposarcoma*
#23	malignant glomus tumor* or malignant glomus tumour*
#24	malignant mesenchymoma*
#25	perivascular epithelioid cell tumor* or perivascular epithelioid cell tumour*
#26	rhabdoid tumor* or rhabdoid tumour*
#27	rhabdoid sarcoma*
#28	synovial sarcoma*
#29	gastrointestinal stromal tumor* or gastrointestinal stromal tumour*
#30	malignant peripheral nerve sheath tumor* or malignant peripheral nerve sheath tumour*
#31	undifferentiated pleomorphic sarcoma*
#32	"Stem Cell Transplantation"[Mesh]
#33	"Bone Marrow Transplantation"[Mesh]
#34	"Transplantation, Autologous"[Mesh]
#35	"Consolidation Chemotherapy"[Mesh]

(Continued)

#36	autologous transplant*
#37	bone marrow rescue
#38	bone marrow support
#39	bone marrow cell
#40	stem cell rescue
#41	stem cell support
#42	peripheral blood stem cell
#43	high dose chemotherapy
#44	intensified chemotherapy
#45	intensive chemotherapy
#46	myeloablative chemotherapy
#47	dose intensive treatment
#48	high dose combination
#49	"Randomized Controlled Trial" [Publication Type]
#50	randomized controlled trial or randomised controlled trial
#51	randomized controlled study or randomised controlled study
#52	randomized trial or randomised trial
#53	randomized study or randomised study
#54	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#55	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 #42 or #43 or #44 or #45 or #46 or #47 or #48
#56	#49 or #50 or #51 or #52 or #53
#57	#54 and #55 and #56

Limits: publication date from 01 January 2012 to 06 September 2016.

Appendix 3. Inquiry to trial authors

For this review update, we sent e-mail inquiries to two authors (Binh Bui-Nguyen, Jean-Yves Blay) of the included study (Bui-Nguyen 2012) regarding clarification of survival data and the US Food and Drug Administration (FDA) warning letter on objectionable conditions and inadequate responses. The warning letter sent by the FDA was addressed to the first author Binh Bui-Nguyen (Reference 15-HFD-45-05-01). It informs of objectionable conditions observed during an inspection at the clinical site between 17 and 19 September 2014 (FDA 2015).

E-mail sent to Binh Bui-Nguyen on 3 October 2016, quote: "I am conducting an update of my Cochrane Review and I would like to add some questions. At the moment, I am working on judging the Incomplete outcome data (attrition bias). On page 781, I extracted the following information from section 'Survival outcomes' and from Figure 2: At 36 months from randomization (HDCT versus SDCT), 51 patients had died (24 versus 27) and 25 are at risk (8 versus 17). Of 83 patients included in the modified ITT survival analysis, 76 are accounted for but 7 patients may not be explained. My question: Did I extract correctly? Does 'at the time of analysis' correspond to 36 months after randomization? Do the figures that I extracted or deduced correspond to 36 months after randomization?"

E-mail sent to Jean-Yves Blay on 5 October 2016, which contains the above quoted text sent to Binh Bui-Nguyen and the following additional text, quote: "I also would like to ask about the importance of the attached FDA warning letter on objectionable conditions and inadequate responses. Is there any connection or conflict with the study of Bui-Nguyen 2012?"

We did not receive any reply by 7 March 2017.

WHAT'S NEW

Date	Event	Description
17 July 2018	Amended	Next expected date amended
28 June 2018	Review declared as stable	Intervention not in general use for solid tumours.

HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 2, 2011

Date	Event	Description
19 April 2017	Amended	Minor corrections for figures.
8 March 2017	New citation required but conclusions have not changed	No additional RCTs identified. One new author added and one removed and acknowledged. WHO classification extended to include recently updated version.
8 March 2017	New search has been performed	Search strategy revised and study design limited to RCTs. Risk of bias assessment revised; overall assessment changed from low to unclear risk of bias.
10 June 2013	New citation required and conclusions have changed	We identified a single randomized controlled trial and judged it to have a low risk of bias. The results did not support high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation compared to standard-dose chemotherapy in patients with non-rhabdomyosarcoma soft tissue sarcoma.
5 December 2012	New search has been performed	Searches re-run and one new study included.

CONTRIBUTIONS OF AUTHORS

FP: designed and co-ordinated the review, collected data, designed search strategies, undertook searches, screened search results, organized retrieval of papers, screened retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, wrote to authors of papers for additional information, managed data, entered data into Review Manager 5, analyzed data, interpreted data, wrote manuscript.

HE: screened retrieved papers against eligibility criteria, reviewed manuscript.

LAS: provided methodologic advice, appraised quality of papers, reviewed manuscript.

DECLARATIONS OF INTEREST

FP: none known.

HE: none known.

LAS: none known.

SOURCES OF SUPPORT

Internal sources

- University of Cologne, Germany.

  Provision of full texts

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the previous version and the current version of the review

We revised the criteria for considering studies for this review. First, we confined the types of studies to RCTs. Therefore, we removed non-randomized studies and associated data from the review. The single RCT included in the previous version was carried over to the current version of the review. Second, we extended the previous WHO classification of soft tissue sarcomas by adding information from the recently updated version of the WHO classification of soft tissue sarcomas. We revised the search strategies to improve precision and reported the results of the update search.

We changed the items of the 'Risk of bias' tool. We removed the items that were designed to judge the risk of bias of non-randomized studies. We extended the rest of the items to complete all items of the risk of bias for RCTs. Thus, we included the judgment of some items of risk of bias that were not part of the previous version. Subsequently, the risk of bias was different between the previous and the current version of the review and the judgment changed from low to unclear risk of bias.

We identified additional inconsistencies in the reporting of the included study and sent inquiries to two authors of that study, but we did not receive a response. We identified a published warning letter sent by the FDA to the first author. We do not know if the cause of this letter was associated with conducting the study.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [*administration & dosage] [adverse effects]; Hematopoietic Stem Cell Transplantation [*methods] [mortality]; Salvage Therapy [*methods] [mortality]; Sarcoma [*drug therapy] [mortality]; Transplantation, Autologous

MeSH check words

Adult; Aged; Humans; Middle Aged