Year: 2021

High-dose chemotherapy followed by autologous haematopoietic cell transplantation for children, adolescents, and young adults with first recurrence of Ewing sarcoma

Haveman, Lianne M ; van Ewijk, Roelof ; van Dalen, Elvira C ; Breunis, Willemijn B ; Kremer, Leontien C M ; van den Berg, Henk ; Dirksen, Uta ; Merks, Johannes H M

Abstract: BACKGROUND Ewing sarcoma is a solid tumour, which is the second most common primary bone malignancy in children, often occurring in the long bones and pelvis. An incidence rate of 4.5 per million a year is reported, with a peak incidence of 11 per million at the age of 12 years. Despite more intensive chemotherapy, 30% to 40% of young people with Ewing sarcoma will have recurrence of the disease. Less than 30% of young people with a recurrence of Ewing sarcoma are alive at 24 months, and less than 10% are alive at 48 months. High-dose chemotherapy (HDC), followed by autologous haematopoietic cell transplantation (AHCT), is used in a variety of paediatric groups with diverse solid tumours. The hypothesis is that HDC regimens may overcome resistance to standard polychemotherapy, and this way may eradicate minimal residual disease, leading to improved survival after a first recurrence of disease. OBJECTIVES To assess the efficacy of HDC with AHCT versus conventional chemotherapy in improving event-free survival, overall survival, quality-adjusted survival, and progression-free survival in children, adolescents, and young adults with first recurrence of Ewing sarcoma, and to determine the toxicity of the treatment. SEARCH METHODS We searched CENTRAL, MEDLINE, Embase, conference proceedings from the SIOP, ASPHO, CTOS, ASBMT, EBMT, and EMSOS, and two trial registries in January 2020. We also searched reference lists of relevant articles and review articles. SELECTION CRITERIA We planned to include randomised controlled trials (RCTs) or (historical) controlled clinical trials (CCTs) comparing the effectiveness of HDC plus AHCT with conventional chemotherapy for children, adolescents, and young adults (up to 30 years old at the date of diagnostic biopsy) with a first recurrence of Ewing sarcoma. DATA COLLECTION AND ANALYSIS We used standard methodological procedures expected by Cochrane. MAIN RESULTS We did not identify any eligible studies. AUTHORS' CONCLUSIONS Since we did not identify any eligible studies, we are unable to draw any conclusions about the efficacy and toxicity of HDC with AHCT versus conventional chemotherapy in children, adolescents, and young adults with a first recurrence of Ewing sarcoma. Further high-quality research is urgently needed.

DOI: <https://doi.org/10.1002/14651858.CD011406.pub2>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-212918>

Journal Article

Published Version

Originally published at:

Haveman, Lianne M; van Ewijk, Roelof; van Dalen, Elvira C; Breunis, Willemijn B; Kremer, Leontien C M; van den Berg, Henk; Dirksen, Uta; Merks, Johannes H M (2021). High-dose chemotherapy followed

by autologous haematopoietic cell transplantation for children, adolescents, and young adults with first recurrence of Ewing sarcoma. Cochrane Database of Systematic Reviews, 9:CD011406.
DOI: <https://doi.org/10.1002/14651858.CD011406.pub2>

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Haveman LM, van Ewijk R, van Dalen EC, Breunis WB, Kremer LCM, van den Berg H, Dirksen U, Merks JHM.
High-dose chemotherapy followed by autologous haematopoietic cell transplantation for children, adolescents, and young adults with first recurrence of Ewing sarcoma.
Cochrane Database of Systematic Reviews 2021, Issue 9. Art. No.: CD011406.
DOI: [10.1002/14651858.CD011406.pub2](https://doi.org/10.1002/14651858.CD011406.pub2).

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[Intervention Review]

High-dose chemotherapy followed by autologous haematopoietic cell transplantation for children, adolescents, and young adults with first recurrence of Ewing sarcoma

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Editorial group: Cochrane Childhood Cancer Group.

Publication status and date: New, published in Issue 9, 2021.

Citation: Haveman LM, van Ewijk R, van Dalen EC, Breunis WB, Kremer LCM, van den Berg H, Dirksen U, Merks JHM. High-dose chemotherapy followed by autologous haematopoietic cell transplantation for children, adolescents, and young adults with first recurrence of Ewing sarcoma. *Cochrane Database of Systematic Reviews* 2021, Issue 9. Art. No.: CD011406. DOI: [10.1002/14651858.CD011406.pub2](https://doi.org/10.1002/14651858.CD011406.pub2).

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ABSTRACT

Background

Ewing sarcoma is a solid tumour, which is the second most common primary bone malignancy in children, often occurring in the long bones and pelvis. An incidence rate of 4.5 per million a year is reported, with a peak incidence of 11 per million at the age of 12 years. Despite more intensive chemotherapy, 30% to 40% of young people with Ewing sarcoma will have recurrence of the disease. Less than 30% of young people with a recurrence of Ewing sarcoma are alive at 24 months, and less than 10% are alive at 48 months. High-dose chemotherapy (HDC), followed by autologous haematopoietic cell transplantation (AHCT), is used in a variety of paediatric groups with diverse solid tumours. The hypothesis is that HDC regimens may overcome resistance to standard polychemotherapy, and this way may eradicate minimal residual disease, leading to improved survival after a first recurrence of disease.

Objectives

To assess the efficacy of HDC with AHCT versus conventional chemotherapy in improving event-free survival, overall survival, quality-adjusted survival, and progression-free survival in children, adolescents, and young adults with first recurrence of Ewing sarcoma, and to determine the toxicity of the treatment.

Search methods

We searched CENTRAL, MEDLINE, Embase, conference proceedings from the SIOP, ASPHO, CTOS, ASBMT, EBMT, and EMSOS, and two trial registries in January 2020. We also searched reference lists of relevant articles and review articles.

Selection criteria

We planned to include randomised controlled trials (RCTs) or (historical) controlled clinical trials (CCTs) comparing the effectiveness of HDC plus AHCT with conventional chemotherapy for children, adolescents, and young adults (up to 30 years old at the date of diagnostic biopsy) with a first recurrence of Ewing sarcoma.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We did not identify any eligible studies.

Authors' conclusions

Since we did not identify any eligible studies, we are unable to draw any conclusions about the efficacy and toxicity of HDC with AHCT versus conventional chemotherapy in children, adolescents, and young adults with a first recurrence of Ewing sarcoma. Further high-quality research is urgently needed.

PLAIN LANGUAGE SUMMARY

High-dose chemotherapy (HDC) and autologous haematopoietic cell transplantation (AHCT) for children, adolescents, and young adults with a first recurrence of Ewing sarcoma

Review question

We were looking for evidence on whether HDC plus AHCT improved event-free survival, overall survival, quality-adjusted survival, and progression-free survival better than conventional chemotherapy in children, adolescents, and young adults with their first recurrence of Ewing sarcoma. We were also looking for adverse effects that occurred because of these treatments.

Background

Ewing sarcoma is a tumour that occurs in the bone and soft tissue, especially in the long bones and pelvis, and mainly in children, adolescents and young adults. Since the introduction of chemotherapy following surgery, with or without radiation, the outcome of people with Ewing sarcoma has improved. However, even with improved chemotherapy, there are still too many people who eventually die of the disease, because it has progressed or come back. People with a first recurrence of Ewing sarcoma do not have a great prognosis: fewer than 3 out of 10 young people are still alive at 24 months, and fewer than 1 out of 10 are alive at 48 months. Improved therapy is essential for these people. High-dose chemotherapy (HDC), followed by autologous haematopoietic cell transplantation (AHCT; intravenous infusion of earlier collected stem cells to re-establish bone marrow), is successfully used for young people with a variety of tumours. Theoretically, this seems to be a good option to treat the small number of remaining cancer cells, and to improve the survival rate after the first recurrence of Ewing sarcoma.

Key results

We conducted an extensive search of the medical literature, including related conference proceedings, and registers for ongoing trials, but we did not find any relevant studies. Therefore, we are unable to draw any conclusions as to whether HDC with AHCT improves event-free survival, overall survival, quality-adjusted survival, or progression-free survival better than conventional chemotherapy, or if it causes any side effects, in children, adolescents, and young adults with their first recurrence of Ewing sarcoma. Our results show that further research is needed.

How current is the evidence

The evidence is current to January 2020.

SUMMARY OF FINDINGS

Summary of findings 1. High-dose chemotherapy with autologous haematopoietic cell transplantation versus conventional chemotherapy

High-dose chemotherapy with autologous haematopoietic cell transplantation versus conventional chemotherapy

Patient or population: children, adolescents, and young adults with the first recurrence of Ewing sarcoma

Settings: (paediatric) oncology departments

Intervention: high-dose chemotherapy (HDC) with autologous haematopoietic cell transplantation (AHCT)

Comparison: conventional chemotherapy

Outcomes	Comments
Event-free survival	No studies included
Overall survival	No studies included
Quality-adjusted survival	No studies included
Toxicity	No studies included
Progression-free survival	No studies included

BACKGROUND

Description of the condition

Ewing sarcoma is a group of solid tumours consisting of small, blue, round cell neoplasms of neuroectodermal origin. Ewing sarcoma belongs to the Ewing family of tumours. The other types of tumours in the group are primitive neuroectodermal tumour (PNET), extraosseous Ewing sarcoma (EES), and Askin's tumour (Ewing sarcoma of the chest wall). These tumours are thought to arise from the same primordial stem cell. All of these tumours are defined by the presence of *EWSR1-ETS* gene re-arrangements. In 85% of cases, ETS transcription factor fuses with *FLI1*, resulting in the *EWS-FLI1* fusion protein. This t(11;12)(q24;q12) chromosomal translocation can take place at different intron-exon sites, with more than 18 different translocations described (Delattre 1994; Potratz 2012). Ewing sarcoma is the second most common primary bone malignancy in children, accounting for 10% to 15% of all primary bone tumours, and approximately 3% of all malignancies in children (Cotterill 2000; Potratz 2012). Most often, Ewing sarcoma appears in bones; however, extraosseous manifestations do occur (Gurney 2006). The disease most often occurs in children, adolescents, and young adults, with an incidence rate of 4.5 per million a year, and a peak incidence of 11 per million at the age of 12 years (van den Berg 2008).

Much progress has been made in the treatment of Ewing sarcoma. With multi-modal treatment including multi-agent chemotherapy, surgery, and radiotherapy, young people with localised disease have survival rates of approximately 65% to 75%. Several risk factors have been identified in young people with primary Ewing sarcoma: age above 14 years, tumour volume more than 200 mL, more than one bone metastatic site; bone marrow metastases and additional lung metastases are correlated with a worse outcome (Ladenstein 2010). In young people with localised disease, those with tumours that respond poorly to chemotherapy, those with pelvic tumours, and those with high lactate dehydrogenase level at diagnosis have a worse prognosis (Bacci 2003; Cotterill 2000). Despite more intensive chemotherapy, 30% to 40% of young people with Ewing sarcoma will have recurrence of disease. For those with metastatic disease, overall survival is lower than 30% (Cotterill 2000; Ladenstein 2010; Potratz 2012; Rodriguez-Galindo 2008).

Relapse of Ewing sarcoma occurs at an average of 1.6 to 2.3 years after starting initial treatment (Bacci 1989; Rodriguez-Galindo 2007), although very late recurrences, more than 16 years after treatment of a primary tumour, have also been reported (Hanna 2008). In case of recurrence, about 70% of people present with metastatic disease. About 15% of people have a local recurrence and about 15% of people have combined local and metastatic disease (Bacci 1989; Barker 2005; Rodriguez-Galindo 2007; Stahl 2011). Isolated local recurrences occur less frequently, and are associated with a poor chemotherapeutic response (Lin 2007). Less than 30% of young people with recurrent Ewing sarcoma are alive at 24 months, and less than 10% are alive at 48 months (Barker 2005; Cotterill 2000; Shankar 2003; Stahl 2011). Higher survival of young people with recurrences seems to be associated with the type of relapse and site of the metastases, treatment of relapse, response to second-line therapy, relapse more than two years after diagnosis, and no metastases at initial diagnosis (Bacci 2003; Barker 2005; Lin 2007; Shankar 2003).

Description of the intervention

The poor outcome for young people with recurrence of disease has led to the use of high-dose chemotherapy (HDC), followed by autologous haematopoietic cell transplantation (AHCT) in those who achieved a second complete remission after second-line treatment (Bacci 2003; Barker 2005; Burdach 2003; Gardner 2008; McTiernan 2006; Shankar 2003). Theoretically, this seems like a good treatment strategy to treat minimal residual disease, and to improve the survival rate after recurrence of disease.

How the intervention might work

After multi-modal treatment, including re-introduction of chemotherapy, the majority of young people will still harbour micro-metastatic deposits. The hypothesis is that HDC, or myeloablative conditioning regimens may overcome the resistance to standard multi-agent chemotherapy. Besides destroying the Ewing sarcoma cells, HDC also ablates the bone marrow reserve. Therefore, HDC is always followed by autologous haematopoietic cell transplantation.

Why it is important to do this review

The relative benefit of HDC followed by autologous haematopoietic cell rescue in recurrent disease is still controversial. Moreover, this treatment is associated with severe toxicity and adverse effects, including mucositis, metabolic problems, and long-lasting bone marrow aplasia, with the risk of life-threatening bleeding and infection (Burdach 2003; Gardner 2008). Some studies have reported improved disease-free survival (Al-Faris 2007; Barker 2005; McTiernan 2006), while other studies have shown no durable benefit over conventional therapies (Gardner 2008; Shankar 2003). This systematic review will contribute to the knowledge about the efficacy of HDC followed by AHCT in children, adolescents, and young adults with first recurrence of Ewing sarcoma.

OBJECTIVES

To assess the efficacy of high-dose chemotherapy with autologous haematopoietic cell transplantation versus conventional chemotherapy in improving event-free survival, overall survival, quality-adjusted survival, and progression-free survival in children, adolescents, and young adults with the first recurrence of Ewing sarcoma, and to determine the toxicity of the treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or (historical) controlled clinical trials (CCTs) comparing the effectiveness of high-dose chemotherapy (HDC) and autologous haematopoietic cell transplantation (AHCT) with conventional chemotherapy for children, adolescents, and young adults with first recurrence of Ewing sarcoma.

To answer our objectives, the best study design, provided that the design and execution are correct, is an RCT. CCTs can also provide reliable information, keeping in mind their limitations, but other study designs were not eligible for this review due to the high risk of bias associated with other designs.

Types of participants

Children, adolescents, and young adults (younger than 30 years on the date of diagnostic biopsy) with an earlier diagnosis of Ewing sarcoma confirmed by pathology, and with a first relapse of the disease. We excluded young people who received HDC with AHCT as the primary treatment, to make the groups more comparable. Previous HDC with AHCT is also associated with a higher risk of existing and worsening toxicity. We would have included studies that also included people who were not eligible for this review (e.g. people older than 30 years at tumour diagnosis), if separate data were available for the participants eligible for this review.

Types of interventions

HDC with AHCT as part of second-line treatment versus conventional chemotherapy. We defined HDC as chemotherapy that ablated the person's bone marrow reserves and created an absolute requirement for stem cell rescue. We defined conventional chemotherapy as chemotherapy given at a lower dose than HDC, which did not require stem cell rescue. We planned to include studies that added an immunotherapy to HDC with AHCT, however, we did not identify any.

Types of outcome measures

We did not use the outcomes listed here as criteria for including studies; instead, these were the outcomes of interest in studies identified for inclusion.

Primary outcomes

1. Event-free survival (as defined by the authors of the original study)
2. Overall survival (as defined by the authors of the original study)
3. Quality-adjusted survival (as defined by the authors of the original study)
4. Toxicity of the treatment (as defined by the authors of the original study)

Secondary outcomes

1. Progression-free survival (as defined by the authors of the original study)

Search methods for identification of studies

We used Cochrane Childhood Cancer's search strategy ([Module CCG](#)). We did not apply any language restrictions. The review authors ran all searches.

Electronic searches

We searched the following electronic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 12) in the Cochrane Library (searched 1 January 2020);
2. MEDLINE PubMed (1966 to 1 January 2020);
3. Embase Ovid (1980 to 1 January 2020).

The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in [Appendix 1](#); [Appendix 2](#); and [Appendix 3](#).

Searching other resources

We located information about trials not registered in CENTRAL, MEDLINE, and Embase, either published or unpublished, by searching the reference lists of relevant articles and review articles. We also screened the conference proceedings of the International Society for Paediatric Oncology (SIOP; 2009 to 2019), the American Society of Pediatric Hematology/Oncology (ASPHO; 2009 to 2019), the Connective Tissue Oncology Society (CTOS; 2009 to 2019), the American Society for Blood and Marrow Transplantation (ASBMT; 2009 to 2019), the European Society for Blood and Marrow Transplantation (EBMT; 2009 to 2019), and the European Musculo-Skeletal Oncology Society (EMSOS; 2009 to 2019); we performed these searches electronically, if available, or by handsearching. We scanned ClinicalTrials.gov (www.clinicaltrials.gov; searched 1 January 2020), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictip/en/; searched 1 January 2020) for ongoing trials.

The search strategies for the different conference proceedings and trial registries (using a combination of controlled vocabulary and text words) are shown in [Appendix 4](#) and [Appendix 5](#).

Data collection and analysis

Selection of studies

After the search, two review authors independently identified studies that met the inclusion criteria for this review. We resolved discrepancies between review authors by discussion. If we could not reach consensus, we achieved final resolution using a third-party arbitrator. We obtained full reports of any study that seemed to meet the inclusion criteria on the grounds of the title or abstract, or both, for closer inspection. As we did not include any studies, we did not produce a 'Characteristics of included studies' table. We clearly stated detailed reasons for exclusion of any full-text study considered for the review in the 'Characteristics of excluded studies' table. We created a PRISMA flow diagram of the selection of studies in the review ([Figure 1](#)). Had there been multiple reports of the same study, we would have used the most recent report as the primary publication; we would have checked the other available reports for data not reported in the primary publication.

Figure 1. Flowchart for study identification and selection

Data extraction and management

We did not identify any eligible studies. As a result, we did not extract or manage data. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Assessment of risk of bias in included studies

We did not identify any eligible studies, so risk of bias assessment was not applicable. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Measures of treatment effect

Measures of treatment effect were not an issue. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Unit of analysis issues

Unit of analysis issues were not an issue. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Dealing with missing data

Missing data was not an issue in this review, but for future updates we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Assessment of heterogeneity

Heterogeneity was not an issue. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Assessment of reporting biases

We did not identify any eligible studies. Therefore, we did not construct a funnel plot to assess reporting bias. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Data synthesis

As we did not identify any eligible studies, data synthesis was not an issue. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Subgroup analysis and investigation of heterogeneity

We had not planned any subgroup analyses.

Sensitivity analysis

Sensitivity analyses were not an issue. Should we find eligible studies during future updates of this review, we will follow the methods set out in our protocol, which are available in the [Differences between protocol and review](#) section.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table, in which we presented the lack of evidence for event-free survival, overall survival, quality-adjusted survival, toxicity, and progression-free survival.

If we include studies during future updates, two review authors will independently assess the certainty of the evidence using the five GRADE considerations (i.e. study limitations, inconsistency, indirectness, imprecision, and publication bias).

RESULTS

Description of studies

Results of the search

We electronically searched CENTRAL, MEDLINE, and Embase on 1 January 2020, and identified 3524 records; see [Figure 1](#). We identified one ongoing study through the search of ClinicalTrials.gov and WHO ICTRP, on 1 January 2020. Examining conference proceedings of aforementioned organisations did not identify any other studies. After removing duplicates, we screened the titles and abstracts of 3417 records. We excluded 3376 records for the following reasons: studies were duplicates, review articles, editorials or letters, or case reports, studies did not include participants with recurrent Ewing sarcoma. We evaluated the full text of 41 studies, all of which we excluded after full-text assessment because of an ineligible study design.

Included studies

We did not identify any studies that met our inclusion criteria.

Excluded studies

All excluded studies had an ineligible study design, i.e. not randomised controlled trials (RCT) or controlled clinical trials (CCT) comparing the effectiveness of high-dose chemotherapy (HDC) and autologous haematopoietic cell transplantation (AHCT) with conventional chemotherapy for children, adolescents, and young adults with the first recurrence of Ewing sarcoma. See [Characteristics of excluded studies](#) for more information.

Risk of bias in included studies

As we did not include any studies, there were no studies to assess for risk of bias.

Effects of interventions

See: [Summary of findings 1 High-dose chemotherapy with autologous haematopoietic cell transplantation versus conventional chemotherapy](#)

We did not identify any studies, therefore, the effects of HDC with AHCT compared with standard chemotherapy remain unclear for event-free survival, overall survival, quality-adjusted survival, toxicity, and progression-free survival in children, adolescents, and young adults with the first recurrence of Ewing sarcoma. See [Summary of findings 1](#).

DISCUSSION

Summary of main results

We did not identify any studies, therefore, the effects of high-dose chemotherapy (HDC) and autologous haematopoietic cell transplantation (AHCT) compared with standard chemotherapy remain unclear for event-free survival, overall survival, quality-adjusted survival, toxicity, and progression-free survival in children, adolescents, and young adults with the first recurrence of Ewing sarcoma.

In this Cochrane Review we assessed the efficacy of HDC with AHCT versus conventional chemotherapy in improving event-free survival, overall survival, quality adjusted survival and progression-free survival of children, adolescents and young adults with first recurrence of Ewing sarcoma and to determine the toxicity of the treatment. To answer this type of question the best study design, provided that the design and execution are correct, is an RCT. CCTs can also provide reliable information, keeping in mind their limitations, but other study designs were not eligible for inclusion in this review due to the high risk of bias associated with such designs. Unfortunately no eligible studies were identified.

Overall completeness and applicability of evidence

There is currently no evidence from randomised controlled or controlled clinical trials that assess the effects of HDC and AHCT with conventional chemotherapy for children, adolescents, and young adults with the first recurrence of Ewing sarcoma.

Potential biases in the review process

We attempted to ensure that we did not overlook any relevant evidence by performing a very extensive search for randomised controlled trials, and even included non-randomised controlled clinical studies. Therefore, it is very unlikely that we missed any eligible studies.

Agreements and disagreements with other studies or reviews

Our extensive literature search did not find any studies that were eligible for inclusion, which is in line with previously published reviews. One systematic review included all clinical studies with participants with a recurrence of Ewing sarcoma who were treated with HDC followed by AHCT. [Tenetti 2018](#) included 24

studies, with total of 345 participants with a recurrence of Ewing sarcoma. None of the included studies were clinical trials that were either randomised or (historically) controlled. Therefore, a high level of any bias, especially selection of participants who were eligible for HDC with AHCT, might have influenced the observation by most studies that using HDC AHCT improved survival compared to conventional chemotherapy. The main conclusion was that prospective randomised controlled studies were needed to definitively define the role of HDC with AHCT in young people with a recurrence of Ewing sarcoma.

This is in line with the conclusions of this review, and a general Ewing sarcoma management review by international experts ([Gaspar 2015](#)). At the moment, we did not identify any ongoing trials.

AUTHORS' CONCLUSIONS

Implications for practice

Due to the current absence of evidence, we are unable to make any definitive conclusions concerning the role of high-dose chemotherapy (HDC) and autologous haematopoietic cell transplantation (AHCT) in the treatment of a recurrence of Ewing sarcoma.

Implications for research

Randomised clinical trials, or well-executed controlled clinical trials, with sufficient numbers of people with recurrent Ewing sarcoma to obtain the power needed for reliable results, and an adequate duration of follow-up, are necessary to determine the efficacy of HDC with AHCT.

ACKNOWLEDGEMENTS

We would like to thank Dr Allen R Chen, MD, PhD of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, who peer reviewed this manuscript. We would also like to thank Prof. Heribert Juergens for his contribution to the development of the protocol. The Editorial base of Cochrane Childhood Cancer has been funded by KiKa, and is located in the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands. We would like to thank Edith Leclercq, former Information Specialist of Cochrane Childhood Cancer, for designing the search strategies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al-Faris 2007	Ineligible design
Avramova 2006	Ineligible design
Avramova 2011	Ineligible design
Barker 2005	Ineligible design
Burdach 1991	Ineligible design
Burdach 1993	Ineligible design
Clara 2012	Ineligible design

Study	Reason for exclusion
Cristofani 2013	Ineligible design
Diaz 2010	Ineligible design
Dirksen 2019	Ineligible design
Drabko 2005	Ineligible design
Drabko 2006	Ineligible design
Drabko 2009	Ineligible design
Elhasid 2012	Ineligible design
Escobar 2010	Ineligible design
Ferrari 2015	Ineligible design
Fraser 2006	Ineligible design
Frohlich 1999	Ineligible design
Gardner 2008	Ineligible design
Hazar 2015	Ineligible design
Jodele 2010	Ineligible design
Kabickova 2003	Ineligible design
Kasper 2004	Ineligible design
Kasper 2007	Ineligible design
Ladenstein 1995	Ineligible design
Ladenstein 2014	Ineligible design
Malis 2000	Ineligible design
MarcusJr 1988	Ineligible design
McTiernan 2006	Ineligible design
Palmerini 2009	Data published in Ferrari 2015 .
Pape 1999	Ineligible design
Pawlowska 2012	Ineligible design
Perentesis 1999	Ineligible design
Petrovitch 2009	Ineligible design
Pimenov 2009	Ineligible design

Study	Reason for exclusion
Pimenov 2013	Ineligible design
Rasper 2013	Ineligible design
Seo 2013	Ineligible design
Stradella 2011	Ineligible design
Suzuki 2015	Ineligible design
Whelan 2018	Ineligible design

APPENDICES

Appendix 1. Search strategy for CENTRAL

1. For **Ewing sarcoma**, we used the following text words:

ewing OR ewings OR ewing* OR ewing sarcoma OR peripheral neuroectodermal tumor OR peripheral neuroectodermal tumour OR peripheral neuroectodermal tumors OR peripheral neuroectodermal tumours OR primitive neuroectodermal tumor OR primitive neuroectodermal tumour OR primitive neuroectodermal tumors OR primitive neuroectodermal tumours OR Primitive Neuroepithelial Tumor OR Primitive Neuroepithelial Tumors OR Primitive Neuroepithelial Tumour OR Primitive Neuroepithelial Tumours OR Primitive Neuroepithelial Neoplasm OR Primitive Neuroepithelial Neoplasms OR PNET OR PNETs OR neuroepithelioma OR neuroepitheliomas OR (askin AND (tumor OR tumors OR tumour OR tumours))

2. For **autologous hematopoietic cell transplantation**, we used the following text words:

bone marrow transplantation or bone marrow grafting or bone marrow cell transplantation or stem cell transplantation or stem cell transplantations or hematopoietic stem cell transplantation or haematopoietic stem cell transplantation or hematopoietic cell transplantation or haematopoietic cell transplantation or HSCT or HCT or peripheral blood stem cell transplantation or peripheral stem cell transplantation or autograft or autografts or transplantation, autologous or autotransplant or autotransplants or ABMT or PBSCT or transplant* or homolog* or autolog* or BMT or myeloablative therapy or myeloablative agonist or myeloablative agonists or myeloablative* or mega therapy or stem cell rescue or bone marrow rescue or high-dose therapy or high dose therapy or homograft or homografts or homologous transplantation or homologous transplantations or transplantations, homologous or transplantation, homologous or transplantations

Final search 1 and 2

The search was performed in title, abstract or keywords

(* = zero or more characters)

Appendix 2. Search strategy for MEDLINE PubMed

1. For **Ewing sarcoma**, we used the following MeSH headings and text words:

ewing OR ewings OR ewing* OR ewing sarcoma OR ewing's sarcoma OR "peripheral neuroectodermal tumor" OR "peripheral neuroectodermal tumour" OR "peripheral neuroectodermal tumors" OR "peripheral neuroectodermal tumours" OR "primitive neuroectodermal tumor" OR "primitive neuroectodermal tumour" OR "primitive neuroectodermal tumors" OR "primitive neuroectodermal tumours" OR "Primitive Neuroepithelial Tumor" OR "Primitive Neuroepithelial Tumors" OR "Primitive Neuroepithelial Tumour" OR "Primitive Neuroepithelial Tumours" OR "Primitive Neuroepithelial Neoplasm" OR "Primitive Neuroepithelial Neoplasms" OR "PNET" OR "PNETs" OR neuroepithelioma[tw] OR neuroepitheliomas[tw] OR neuroectodermal tumors, primitive, peripheral[Mesh:NoExp] OR neuroectodermal tumors, primitive[Mesh:NoExp] OR (askin AND (tumor OR tumors OR tumour OR tumours))

2. For **autologous hematopoietic cell transplantation**, we used the following MeSH headings and text words:

bone marrow transplantation OR bone marrow grafting OR bone marrow cell transplantation OR stem cell transplantation OR stem cell transplantations OR hematopoietic stem cell transplantation OR haematopoietic stem cell transplantation OR hematopoietic cell

transplantation OR haematopoietic cell transplantation OR HSCT OR HCT OR peripheral blood stem cell transplantation OR peripheral stem cell transplantation OR autograft OR autografts OR transplantation, autologous OR autotransplant OR autotransplants OR ABMT OR PBST OR transplant* OR homolog* OR autolog* OR BMT OR "myeloablative therapy" OR myeloablative agonist OR myeloablative agonists OR myeloablative* OR "mega therapy" OR stem cell rescue OR bone marrow rescue OR "high-dose therapy" OR "high dose therapy" OR homograft OR homografts OR homologous transplantation OR homologous transplantations OR transplantations, homologous OR transplantation, homologous OR transplantations

Final search 1 AND 2

(* = zero or more characters; tw = text word)

Appendix 3. Search strategy for Embase Ovid

1. For **Ewing sarcoma**, we used the following Emtree terms and text words:

1. (ewing or ewings or ewing\$).ti,ab.
2. exp Ewing sarcoma/
3. (ewing sarcoma or ewing's sarcoma).mp.
4. (PNET or PNETs).mp.
5. (peripheral neuroectodermal tumor or peripheral neuroectodermal tumors or peripheral neuroectodermal tumour or peripheral neuroectodermal tumours).mp.
6. (primitive neuroectodermal tumor or primitive neuroectodermal tumors or primitive neuroectodermal tumour or primitive neuroectodermal tumours).mp.
7. (primitive neuroepithelial tumor or primitive neuroepithelial tumors or primitive neuroepithelial tumour or primitive neuroepithelial tumours).mp.
8. neuroectoderm tumor/ or neuroepithelioma/ or (neuroepithelioma or neuroepitheliomas).mp.
9. (Primitive Neuroepithelial Neoplasm or Primitive Neuroepithelial Neoplasms).mp.
10. (askin and (tumor or tumors or tumour or tumours)).mp.
11. or/1-10

2. For **autologous hematopoietic cell transplantation**, we used the following Emtree terms and text words:

1. (bone marrow transplantation or bone marrow grafting).mp.
2. (bone marrow cell transplantation or stem cell transplantation or stem cell transplantations).mp.
3. (hematopoietic stem cell transplantation or haematopoietic stem cell transplantation or HSCT or HCT or peripheral blood stem cell transplantation).mp.
4. peripheral stem cell transplantation.mp.
5. (autograft or autografts).mp.
6. autograft/
7. (autologous transplantation or autotransplant or autotransplants).mp.
8. (BMT or ABMT or PBST).mp.
9. transplant\$.mp.
10. (autolog\$ or homolog\$).mp.
11. myeloablative therapy.mp.
12. (myeloablative agonist or myeloablative agonists).mp.
13. myeloablative\$.mp.
14. mega therapy.mp.
15. (high-dose therapy or high dose therapy).mp.
16. (stem cell rescue or bone marrow rescue).mp.
17. (homograft or homografts).mp.
18. (homologous transplantation or homologous transplantations).mp.
19. transplantations.mp.
20. or/1-19

Final search 1 and 2

(mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; ti,ab = title, abstract; / = Emtree term; \$ = zero or more characters)

Appendix 4. Search strategy for conference proceedings

We scanned the conference proceedings of the International Society for Paediatric Oncology (SIOP; 2009 to 2019), the American Society of Pediatric Hematology/Oncology (ASPHO; 2009 to 2019), the Connective Tissue Oncology Society (CTOS; 2009 to 2019), the American Society for Blood and Marrow Transplantation (ASBMT; 2009 to 2019), the European Society for Blood and Marrow Transplantation (EBMT;

2009 to 2019) and the European Musculo-Skeletal Oncology Society (EMSOS; 2009 to 2019). Conference proceedings were available in pdf. All pdf files were assessed using the term 'Ewing' and scanned for applicability for this review.

Appendix 5. Search strategy for ongoing trials

For [ClinicalTrials.gov](https://clinicaltrials.gov), we used the following search strategy:

We used the advanced search option for studies first received or first posted to 01 January 2020. The search terms used were: Ewing OR Ewing sarcoma. We applied the following search filters: recruitment [not yet recruiting; recruiting; enrolling by invitation; active, not recruiting; suspended]; Age [child; adult]; study type [interventional (clinical trial)].

For the World Health Organization International Clinical Trials Registry Platform ([WHO ICTRP](https://www.who.int/clinical-trials-registry-platform)), we used the following search strategy:

1. Ewing OR Ewing sarcoma in the title field
2. Ewing OR Ewing sarcoma in the conditions field
3. Busulfan OR Treosulfan OR Melphalan OR High dose OR Autologous OR stem cell

We used the advanced search option with recruitment status 'recruiting' and date of registration to 1 January 2020.

HISTORY

Protocol first published: Issue 12, 2014

CONTRIBUTIONS OF AUTHORS

LH: designed and drafted the protocol, performed the study selection, created tables, drafted the manuscript

RE: performed the study selection, created tables, drafted the manuscript

WB: designed and drafted the protocol, revised the manuscript

ED: designed and drafted the protocol, third party arbitration for study selection, provided methodological support, and drafted the manuscript

LK, UD, HvdB: reviewed the draft protocol, gave general advice on the review, and revised the manuscript

JM: revised the protocol and manuscript, supervised the review process, third party arbitrator for study selection.

All authors approved the final version.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Tom Voûte Fund, Netherlands
- Stichting Kinderen Kankervrij; Children Cancer Free Foundation (KiKa), Netherlands
- SKOCA Foundation (Pediatric Oncology Center Amsterdam), Netherlands

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As we did not include any studies in this review, most of the methodology described in the protocol for this review was not applicable ([Haveman 2014](#)). However, to comply with Cochrane MECIR standards, we are including them below.

Selection of studies

After applying the search strategy, two review authors will independently identify studies meeting the inclusion criteria for this review. We will resolve discrepancies between review authors by discussion. If we cannot reach consensus, we will achieve final resolution using a third-party arbitrator. We will obtain the complete article of any study that seems to meet the inclusion criteria, in accordance with the title

or the abstract, or both. We will produce a Characteristics of included studies table, and include detailed information for each study. We will clearly state details of the reasons for exclusion of any study considered for the review in the [Characteristics of excluded studies](#) table. We will include a PRISMA flow diagram of the selection of studies in the review. If there are multiple reports of the same study, we will use the most recent report as the primary publication; we will check the other available reports for data not reported in the primary publication.

Data extraction and management

Two review authors will independently extract data, using standardised forms. We will resolve discrepancies between review authors by discussion. If we cannot reach consensus, we will achieve final resolution using a third-party arbitrator. We will extract data on the characteristics of participants (e.g. age, gender, and other known risk factors in participants (tumour volume, primary metastatic disease, time of relapse after primary diagnosis, type of relapse and sites of metastases, response to second-line therapy)), interventions, outcome measures, study design, length of follow-up, details of funding sources, and declaration of interests for each included study.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in included studies (i.e. selection bias, performance bias, detection bias (for each outcome separately), attrition bias (for each outcome separately), reporting bias, and other bias). We will use the risk of bias items and definitions of low risk of bias, unclear risk of bias, and high risk of bias as described in the module of the Childhood Cancer Group ([Module CCG](#)), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve discrepancies between review authors by discussion. If we cannot reach consensus, we will achieve final resolution using a third-party arbitrator. We will take into account the risk of bias in included studies in the interpretation of the review's results.

Measures of treatment effect

We will analyse dichotomous variables using risk ratios (RR). We will analyse survival using hazard ratios (HR). We will use Parmar's method if HRs have not been explicitly presented in the study ([Parmar 1998](#)). We will present all results with the corresponding 95% confidence interval (CI).

Dealing with missing data

When relevant data regarding study selection, data extraction, and risk of bias assessment are missing, we will attempt to contact the study authors to retrieve the missing data. We will extract data by the allocated intervention, irrespective of compliance with the allocated intervention, in order to allow an intention-to-treat analysis. If this is not possible, we will state this, and we will perform an as treated analysis.

Assessment of heterogeneity

We will assess heterogeneity both by visual inspection of the forest plots, and by a formal statistical test for heterogeneity (i.e. the I^2 statistic). In the absence of significant heterogeneity (I^2 less than 50%), we will use a fixed-effect model for the estimation of treatment effects ([Higgins 2011](#)). Otherwise, we will explore possible reasons for the occurrence of heterogeneity, and take appropriate measures, such as using a random-effects model.

Assessment of reporting biases

In addition to evaluating reporting bias as described in the [Assessment of risk of bias in included studies](#) section, we will assess reporting bias by constructing a funnel plot, when there are a sufficient number of included studies (i.e. at least 10 studies included in a meta-analysis). When there are fewer studies, the power of the test is too low to distinguish chance from real asymmetry ([Higgins 2011](#)).

Data synthesis

We will enter data into Cochrane's Review Manager 5 software, and undertake analyses according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#); [Review Manager 2020](#)). We will include outcome measures only if it was the intention of the study to perform the necessary assessments in all randomised participants (i.e. not only optional, or only performed in some centres). When the results of a particular outcome measure are available for less than 50% of the participants of a study, due to the associated high risk of attrition bias, we will not report the results of this outcome measure. We will pool results only if both treatment groups are comparable, including the definition of outcomes used. We will provide a descriptive summary for studies for which pooling of results is not possible. We do not expect multi-arm studies (i.e. including more than two treatment groups); however, if we include these studies, we will take appropriate measures as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will analyse historical controlled clinical trials separately. We will analyse studies that compare immunotherapy plus high-dose chemotherapy with autologous haematopoietic cell transplantation.

For each comparison, we will prepare a summary of findings table, using [GRADEpro GDT](#) software to calculate absolute effects, and the certainty of the evidence for each outcome ([GRADEpro GDT](#)). Two review authors will independently assess the certainty of the evidence, which we will rate as very low, low, moderate, or high according to the five GRADE considerations (i.e. study limitations, inconsistency, indirectness, imprecision, and publication bias), described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins](#)

2011). For each comparison, we will include evidence for the following outcomes: event-free survival, overall survival, quality-adjusted survival, toxicity, and progression-free survival.

Subgroup analysis and investigation of heterogeneity

We will not perform subgroup analyses.

Sensitivity analysis

For all outcomes for which pooling is possible, we will perform sensitivity analyses for all risk of bias criteria separately. We will exclude studies with a high risk of bias or unclear risk of bias, and compare the results of studies with a low risk of bias, with the results of all available studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [therapeutic use]; *Bone Neoplasms [drug therapy]; *Hematopoietic Stem Cell Transplantation; *Sarcoma, Ewing [drug therapy]; Transplantation, Autologous

MeSH check words

Adolescent; Child; Humans; Young Adult