PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Autologous haematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas – a Cochrane Systematic Review
AUTHORS	Peinemann, Frank; Labeit, Alexande

VERSION 1 - REVIEW

REVIEWER	Binh BUI Institut Bergonié France
REVIEW RETURNED	08-Apr-2014

GENERAL COMMENTS	this article is based on a Cokhrane sysyematic review. despite its limitations as discussed by the authors (rarity and heterrogneity of the tumors) leading to only one radomiezd study retieved, this meta-analysis is the most informative piece at this time concerning the high dose chemotherapy with hematological stem cell transpantation rescue the methodology reported is very good

REVIEWER	Bilgehan Yalcin Professor of Pediatrics and Pediatric Oncologist, Hacettepe University Faculty of Medicine, Department of Pediatric Oncology Ankara TURKEY
REVIEW RETURNED	14-Apr-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	BLAY, JEAN-YVES Centre Leon Berard, Lyon, France
REVIEW RETURNED	23-Apr-2014

GENERAL COMMENTS	Interesting analysis on a dataset which is unfortunately limited in the literature. Because there is only one randomized clinical trial, most patients were not included with a randomized comparison. Many were included in aretrospective review. Several points also need to be taken into consideration: 1) undifferentiated /non classified NRST represent 15-18% of all adult STS. To which extent has therir exclusion been a bias 2) is there enough data to distinguish between HDCT as consolidation, and HDCT as rescue treatment per se?

	3) to which extent does the retrospective nature of many of the studies included affect the conclusion.

REVIEWER	Julie Stoner University of Oklahoma Health Sciences Center United States of America
REVIEW RETURNED	15-May-2014

GENERAL COMMENTS	The authors present an interesting summary of the available safety and efficacy data related to the use of autologous haematopoietic stem cell transplantation following high-dose chemotherapy among patients with non-rhabdomyosarcoma soft tissue sarcoma. The paper is a brief summary of the published Cochrane Systematic Review that was written by the same authors (Cochrane Database Systematic Reviews 2013; 8: CD008216). In general, the methodology is sound; however, there are several key pieces of data that are missing from the summary and several methodological concerns related to the data presentations that are included in the paper. • Abstract: The results indicate a total sample size of 175 patients while the text indicates a size of 275 – please correct this error. The overall survival data are presented from the randomized trial; however, the 3-year overall survival estimates are not clearly labeled according to group. The authors should indicate which estimate (32.7% or 49.4%) corresponds to the HSCT group and which corresponds to the control group. Also, clearly indicate that the overall survival data are based on the single randomized comparative study and do not reflect pooled estimates from 275 patients. The conclusion should reflect the scarcity of available data; the concluding statement reflects the results from a single, randomized comparative trial with a total of 83 patients. • Results, page 8, first paragraph: The graphical presentation of survival data from 80 individually reported cases is not appropriate. As mentioned by the authors, the reported patients reflect a variety of non-rhabdomyosarcoma soft tissue sarcomas with a range of risk profiles and therefore, pooling data across patients is not appropriate. Furthermore, given the case sampling approach used in case series, where unusual cases are typically reported in case reports, resulting estimates may not be reflective of the target population of patients with non-rhabdomyosarcoma soft tissue sarcoma. • Results, page 8, Secondary Outcomes paragraph: Provide the hazard ratio and confidence interval, as well as the 3-year estimates, of progression-free survival from the Bui-Nguyen 2012 paper. • Results, page 8, Secondary Outcomes paragraph: The statement “a conservative estimate would be 13.8%” is unclear. The endpoint (Grade III/IV non-hematologic toxicity) needs to be specified. Also, Table 3 reflects a total of 100 patients who were evaluated for toxicities, not a total of 275. • Figure 1: Clarify what is meant by “original review” in the top right hand box.

	• Figure 2: This figure should be deleted due to concerns regarding pooling data from small case series of variable subtypes of non-rhabdomyosarcomas, and specifically, the potential for selection bias and lack of representative data relative to the target population. • Table 1: Include a summary of the follow-up duration for each study. For the Bui-Nguyen study, indicate which arm is HDCT and which arm is HSCT+HDCT when presenting the sample sizes. • Table 2: Include the sample size for each study. For the Bui-Nguyen study, indicate which arm is HDCT and which arm is HSCT+HDCT when presenting the 3-year survival estimates. Pooling data from the case series reports (estimates from n=80 patients) is not appropriate given the high potential for selection bias. • Table 3: Is there a difference between “NR” and “Not specified” in the Specification column?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: comment to Author **Binh BUI, Institut Bergonié, France**	**Response by author**
this article is based on a Cochrane systematic review. despite its limitations as discussed by the authors (rarity and heterrogneity of the tumors) leading to only one radomiezd study retieved, this meta-analysis is the most informative piece at this time concerning the high dose chemotherapy with hematological stem cell transpantation rescue	Thank you for acknowledging the review.
the methodology reported is very good	Thank you for your comment.

Reviewer #2: comment to Author **Bilgehan Yalcin, Hacettepe University Faculty of Medicine, Department of Pediatric Oncology Ankara TURKEY**	**Response by author**
No comments returned.	
Publication recommended.	Thank you for your support.

Reviewer #3: comment to Author **J-Y Blay, Centre Leon Berard, Lyon, France**	**Response by author**
Interesting analysis on a dataset which is unfortunately limited in the literature. Because there is only one randomized clinical trial, most patients were not included with a randomized comparison. Many were included in a retrospective review.	Thank you for acknowledging the review.
Several points also need to be taken into consideration: 1) undifferentiated /non classified NRST represent 15-18% of all adult STS. To which extent has therir exclusion been a bias	The inclusion of undifferentiated/non classified NRSTS did not change the included numbers of studies with aggregate data. It resulted in a light increase of the number of case reports without noteworthy affec on the outcomes. We are grateful for your comment to address undifferentiated /non classified NRSTS. We identified the new WHO 2013 classification of soft tissue sarcomas, which was not described in the Cochrane Review. We also searched for more information concerning the difficulties in dealing with undifferentiated/non classified NRSTS. We changed the inclusion criteria to conform with the major changes introduced by the new classification and we added a section in the discussion chapter to address specifically the issue of the new WHO 2013 classification, especially with reference to undifferentiated/non classified NRSTS and Malignant Fibrous Histiocytoma (MFH). Unfortunately, we did not identify a reference to the proportion of 15% to 18% undifferentiated/non classified NRSTS. We found a reference stating that up to 25% of patients in earlier clinical trials had undifferentiated/non classified NRSTS. We also found references that state a continuous reduction of the proportion due to better methods to classify the tumours.
2) is there enough data to distinguish between HDCT as consolidation, and HDCT as rescue treatment per se?	We re-evaluated the included studies whether autologous HSCT following HDCT was given as a consolidation therapy after the induction therapy could achieve a complete or partial response. We re-evaluated also whether autologous HSCT following HDCT was given as a salvage therapy to patients that did not respond or experienced a relapse.
3) to which extent does the retrospective nature of many of the studies included affect the conclusion.	The retrospective nature of 61 of the 62 studies is overrun by the fact that these 56 studies are merely single-arm studies that are incapable of contributing to the major research question of the systematic review. Therefore, we followed the suggestion of reviewer #4 and removed the survival data of the single-arm studies including the figure 2.
Statistical review needed	Thank you for recommending further assistance.

Reviewer #4: comment to Author **Julie Stoner, University of Oklahoma, USA**	**Response by author**
The authors present an interesting summary of the available safety and efficacy data related to the use of autologous haematopoietic stem cell transplantation following high-dose chemotherapy among patients with non-rhabdomyosarcoma soft tissue sarcoma. The paper is a brief summary of the published Cochrane Systematic Review that was written by the same authors (Cochrane Database Systematic Reviews 2013; 8: CD008216).	Thank you for acknowledging the review.
In general, the methodology is sound; however, there are several key pieces of data that are missing from the summary and several methodological concerns related to the data presentations that are included in the paper.	Thank you for your comment.
Abstract: The results indicate a total sample size of 175 patients while the text indicates a size of 275 – please correct this error. The overall survival data are presented from the randomized trial; however, the 3-year overall survival estimates are not clearly labeled according to group. The authors should indicate which estimate (32.7% or 49.4%) corresponds to the HSCT group and which corresponds to the control group. Also, clearly indicate that the overall survival data are based on the single randomized comparative study and do not reflect pooled estimates from 275 patients. The conclusion should reflect the scarcity of available data; the concluding statement reflects the results from a single, randomized comparative trial with a total of 83 patients.	Thank you very much for your extremely helfpul comments. We corrected the sample size and labeled the treatment groups. We extended the results and conclusion section.
Results, page 8, first paragraph: The graphical presentation of survival data from 80 individually reported cases is not appropriate. As mentioned by the authors, the reported patients reflect a variety of non-rhabdomyosarcoma soft tissue sarcomas with a range of risk profiles and therefore, pooling data across patients is not appropriate. Furthermore, given the case sampling approach used in case series, where unusual cases are typically reported in case reports, resulting estimates may not be reflective of the target population of patients with non-rhabdomyosarcoma soft tissue sarcoma.	We based the reporting of survival on the RCT only. We used the single-arm studies for the reporting of treatment-related mortality. Text added: *In difference to the Cochrane Review, we did not pool time-to-event data on overall survival from studies with individual data. With respect to survival data, we accepted time of diagnosis and beginning of treatment as starting points. We evaluated all 62 studies to search for reports on treatment-related mortality and tabulated the identified patient data. We evaluated the 7 studies reporting aggregate data to search for reports on grade 3 to 4 non-haematological toxicity in the autologous HSCT following HDCT arm and tabulated the identified event data.*
Results, page 8, Secondary Outcomes paragraph: Provide the hazard ratio and confidence interval, as well as the 3-year estimates, of progression-free survival from the Bui-Nguyen 2012 paper.	Hazard ratio and CI as well as 3-year estimates provided for PFS.
Results, page 8, Secondary Outcomes paragraph: The statement “a conservative estimate would be	We changed the text with respect to non-haematological toxicity and treatment-related

13.8%" is unclear. The endpoint (Grade III/IV non-hematologic toxicity) needs to be specified. Also, Table 3 reflects a total of 100 patients who were evaluated for toxicities, not a total of 275.	mortality. *In 10 studies, treatment-related mortality (TRM) was associated with 15 of 137 evaluated patients (Table 5). Assuming no other TRM in the rest of 157 patients, a risk for procedure-related death might be estimated as 5.1% (15 of 294).* *An overview of the number of events of non-haematological toxicity grade 3 to 4 is provided in Table 6. In the RCT, 11 events were observed in 38 transplanted patients and 1 event (asthenia) was reported regarding the standard-dose chemotherapy arm. In 3 of the studies reporting aggregate case series data, 25 events were observed in 54 transplanted patients in the HSCT arm. The other 3 studies did not report toxicity data.*
Figure 1: Clarify what is meant by "original review" in the top right hand box.	Due to change of the search strategy, 15 studies of the first version were not retrieved by the update search. It was decided to continue including them. We changed the text to: *Studies identified in the first version only and tranferred to the current update version: 15*
Figure 2: This figure should be deleted due to concerns regarding pooling data from small case series of variable subtypes of non-rhabdomyosarcomas, and specifically, the potential for selection bias and lack of representative data relative to the target population.	Figure 2 is removed. Added text: *In difference to the Cochrane Review, we did not pool time-to-event data on overall survival from studies with individual data.*
Table 1: Include a summary of the follow-up duration for each study. For the Bui-Nguyen study, indicate which arm is HDCT and which arm is HSCT+HDCT when presenting the sample sizes.	We added information on follow-up and indicated the treatment arms.
Table 2: Include the sample size for each study. For the Bui-Nguyen study, indicate which arm is HDCT and which arm is HSCT+HDCT when presenting the 3-year survival estimates. Pooling data from the case series reports (estimates from n=80 patients) is not appropriate given the high potential for selection bias.	We rearranged the Tables accordingly. Table 1: Characteristics of studies and therapy: We added information on consolidation vs. salvage therapy and the source of stem cells. Table 2: Characteristics of patients: We added columns and subtitles for each treatment arm. Table 3: Frequency of subtypes: We added this table to show the distribution of the subtypes in all 62 studies. Table 4: Overall survival in studies reporting aggregate data: We confined the reporting of overall survival to the 7 studies with aggregate data. Table 5: Treatment-related mortality in the HSCT arm of all included studies: We listed only studies that reported on treatment-related mortality and included all 62 studies. Table 6: Grade 3 to 4 NCI-CTCAE non-haematological toxicity in the HSCT arm of studies reporting aggregate case series data:

	We confined the the reporting of toxicity to the 7 studies with aggregate data.
Table 3: Is there a difference between “NR” and “Not specified” in the Specification column?	No, there is not a difference. We used 'NR' instead of 'Not specified'.

VERSION 2 – REVIEW

REVIEWER	Julie Stoner, Ph.D. University of Oklahoma Health Sciences Center Oklahoma City, Oklahoma United States of America
REVIEW RETURNED	13-Jul-2014

GENERAL COMMENTS	The authors have sufficiently addressed the previous statistical analysis concerns. There is one remaining concern related to the search strategy. The authors state that the search strategy "sarcoma AND chemotherapy AND transplantation" was used. Please clarify if these were limited to MeSH headings or some other type of search field. Or, state that all fields were searched for these terms.