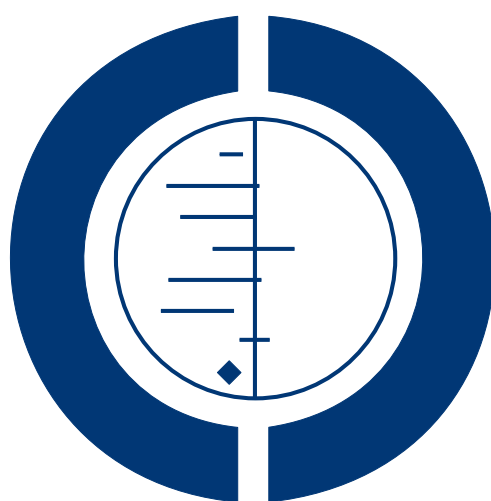


High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma (Review)

Yalçın B, Kremer LCM, Caron HN, van Dalen EC



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[Intervention Review]

High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma

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ABSTRACT

Background

Despite the development of new treatment options, the prognosis of high-risk neuroblastoma patients is still poor; more than half of patients experience disease recurrence. High-dose chemotherapy and haematopoietic stem cell rescue (i.e. myeloablative therapy) might improve survival.

Objectives

To compare the effectiveness of myeloablative therapy with conventional therapy in children with high-risk neuroblastoma.

Search strategy

We searched CENTRAL (*The Cochrane Library* 2009, issue 1), MEDLINE/PubMed (1966 to January 2009) and EMBASE/Ovid (1980 to January 2009). In addition, we searched reference lists of relevant articles, conference proceedings and ongoing trial databases.

Selection criteria

Randomised controlled trials (RCTs) comparing the effectiveness of myeloablative therapy with conventional therapy in high-risk neuroblastoma patients.

Data collection and analysis

Two authors independently performed study selection, data extraction and risk of bias assessment. If possible, we pooled results.

Main results

We identified three RCTs including 739 children. The meta-analysis of event-free survival showed a significant difference in favour of the myeloablative therapy group (HR 0.78; 95% CI 0.67 to 0.90), as did the meta-analysis of overall survival (HR 0.74; 95% CI 0.57 to 0.98). The meta-analysis of secondary malignant disease and treatment-related death did not show a significant difference between the treatment groups. In one study a significant difference in favour of the conventional therapy group was identified for renal effects, interstitial pneumonitis and veno-occlusive disease, whereas for serious infections and sepsis no significant difference between the treatment groups was identified. In the individual studies we evaluated different subgroups, but the results were not univocal in all studies. All studies had some methodological limitations.

Authors' conclusions

Based on the currently available evidence, myeloablative therapy seems to be a good treatment option for children with high-risk neuroblastoma. It results in higher survival rates than conventional therapy, although possible higher levels of adverse effects should be kept in mind. A definitive conclusion regarding the effect of myeloablative therapy in different subgroups is not possible. This systematic review only allows a conclusion on the concept of myeloablative therapy; no conclusions can be made regarding the best treatment strategy. Future trials on the use of myeloablative therapy for high-risk neuroblastoma should focus on identifying the most optimal induction and/or myeloablative regimen. The best study design to answer these questions is a RCT. These RCTs should be performed in homogeneous study populations (for example, regarding stage of disease and patient age) and have a long-term follow up. Different risk groups should be taken into account.

PLAIN LANGUAGE SUMMARY

High-dose chemotherapy and stem cell transplant compared to conventional therapy for children with high-risk neuroblastoma

Despite the development of new treatment options, the prognosis of high-risk neuroblastoma patients is still not good; in more than half of patients the disease returns. High-dose chemotherapy and haematopoietic stem cell rescue, also known as myeloablative therapy, might improve the survival of these patients. A well-informed decision on the use of myeloablative therapy in the treatment of children with high-risk neuroblastoma should be based on high quality evidence on both anti-tumour efficacy and adverse effects.

This systematic review focused on randomised studies comparing the effectiveness of myeloablative therapy with conventional therapy in children with high-risk neuroblastoma. The authors found three studies including 739 patients. These studies provide evidence that myeloablative therapy improves survival. However, adverse effects are more common in patients treated with myeloablative therapy. It should be noted that this systematic review only allows a conclusion on the concept of myeloablative therapy; no conclusions regarding the best treatment strategy with regard to, for example, types of chemotherapeutic agents and the use of radiation therapy, could be made. More high quality research is needed.

BACKGROUND

Neuroblastoma is the most common extracranial solid tumour in children comprising 8% to 10% of all childhood cancers. The incidence is nearly 10 per 1,000,000 children under the age of 15 years and 90% of the cases are diagnosed in the first 10 years of life. Children with neuroblastoma mostly present with abdominal disease and more than half of the cases have advanced disease (defined as stage 3 or 4 disease) (Aydin 2009; Brodeur 2006; Goldsby 2004).

Neuroblastoma is one of the most challenging and enigmatic neoplasms of childhood because of its biological heterogeneity and contrasting patterns of clinical behaviour. Some young infants with favourable disease may experience complete spontaneous regression while older children with metastatic disease mostly relapse despite initial response to chemotherapy.

The prognosis and management of children with neuroblastoma is highly dependent on clinical, histopathological and biological characteristics, and they are stratified into risk groups based on prognostic factors (Goldsby 2004; Maris 2005; Weinstein 2003).

The low-risk disease group includes cases younger than one year who have stage I, II or IVS disease with favourable histopathology and no MYCN oncogene amplification (Brodeur 2006; Goldsby 2004; Maris 2005; Weinstein 2003). Substantial improvement has been achieved in the cure of cases with low risk resulting in survival rates up to 90% (Brodeur 2006; Goldsby 2004).

High-risk neuroblastoma cases are characterised by an age older than one year, disseminated disease, MYCN oncogene amplification and unfavourable histopathologic findings (Brodeur 2006; Goldsby 2004; Maris 2005; Weinstein 2003). In these cases, despite intensified combination chemotherapies, surgery, radiotherapy and the use of differentiation agents, prognosis improves only modestly with long-term survival in less than one-third of the patients (Brodeur 2006; De Bernardi 2003; Goldsby 2004; Weinstein 2003). In the last two decades higher remission rates have been achieved with intensive induction chemotherapy regimens combined with surgical resection, external irradiation or both (Brodeur 2006; Castel 1995; Goldsby 2004; Kaneko 2002; Kushner 2004; Laprie 2004; Sawaguchi 1990). The challenge is to

maintain that remission since more than half of patients with high-risk disease develop systemic disease recurrence with or without a relapse at the primary tumour site (Brodeur 2006; Goldsby 2004; Matthay 1993; Weinstein 2003). Therapy failures are mostly attributed to development of resistance to chemotherapy and minimal residual disease is considered an important cause of recurrence (Burchill 2004; Keshelava 1998; Reynolds 2001; Reynolds 2004).

The idea that further increasing dose intensity may overcome the resistance to drugs has provided a rationale for aggressive high-dose chemotherapy consolidation protocols (Cheung 1991; Pritchard 1995). Such myeloablative chemotherapy regimens utilise effective high-dose drug combinations which can be safely escalated to levels above those causing bone marrow ablation. Rapid bone marrow reconstitution can be achieved by autologous stem cell rescue. Autologous peripheral blood stem cells (PBSCs) are the preferred source for rescue as this has several advantages over autologous bone marrow grafts, e.g. the procedure of PBSC collection is easier, the incidence of tumour cell contamination is lower, and the yield of stem cells is higher (Brodeur 2006; Cohn 1997; Ladenstein 1994). A possible limitation of using autologous products is the risk of tumour cell contamination in the graft, which has been shown to contribute to relapse. Considerable efforts have been made to detect and remove tumour (negative purging) or select progenitor cells (positive purging) before reinfusion (Ladenstein 2004). Disease status prior to stem cell rescue has a crucial influence on final outcome. Patients in complete, very good partial or partial remission have a better prognosis, while those with stable disease or no response have a poor outcome (Ladenstein 2004).

Patients undergoing stem cell rescue may experience toxicities related to conditioning regimens like veno-occlusive disease of the liver or haemorrhagic cystitis (Bollard 2006). Growth failure, endocrine disorders such as gonadal or thyroid dysfunction, as well as the occurrence of secondary malignancies are among the late complications following high-dose chemotherapy and stem cell rescue (Bollard 2006).

Many retrospective and prospective non-randomised studies support the use of a myeloablative consolidation in neuroblastoma. Retrospective studies mostly suggest that intensification of consolidation therapy with autologous stem cell rescue following high-dose chemotherapy improves survival (Castel 1995; Di Caro 1994; Matthay 1995; Philip 1997; Stram 1996; Verdeguer 2004). The results of non-randomised pilot studies by the Children's Cancer Group also suggest a modest prolongation of event-free survival for children with high-risk neuroblastoma overall (Matthay 1995).

This systematic review evaluated the current state of evidence on the effectiveness of high-dose chemotherapy and autologous haematopoietic stem cell rescue compared with conventional therapy in patients diagnosed with high-risk neuroblastoma.

OBJECTIVES

Primary objective

To compare the effectiveness of high-dose chemotherapy and autologous bone marrow or stem cell rescue with conventional therapy in children with high-risk neuroblastoma.

Secondary objectives

To determine adverse effects related to the procedure (such as veno-occlusive disease of the liver) and late effects (such as endocrine disorders or secondary malignancies).

To determine possible effects of these procedures on quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that compare the effectiveness of high-dose chemotherapy and autologous bone marrow or stem cell rescue with conventional therapy.

Types of participants

Children (aged < 21 years) with high-risk neuroblastoma. High-risk neuroblastoma is defined as a combination of the following characteristics: age > 1 year, advanced stage disease (as defined by the authors of the included studies), presence of MYCN oncogene amplification, and/or unfavourable histopathologic findings (as defined by the authors of the included studies).

Types of interventions

High-dose chemotherapy with autologous bone marrow or stem cell rescue versus conventional therapy, i.e. either conventional chemotherapy or no further treatment.

High-dose chemotherapy is defined as chemotherapy sufficient to require stem cell rescue. Conventional chemotherapy is defined as chemotherapy at a lower dose than the high-dose chemotherapy without the need for stem cell rescue.

Types of outcome measures

Primary outcomes

- Event-free survival (usually defined as the time to recurrence or progression of disease or death from any cause or varying definitions, as used by the authors).
- Overall survival (defined as the time to death from any cause).

Secondary outcomes

- Adverse events (such as stomatitis, diarrhoea, fatigue, anaemia, leukopenia, thrombocytopenia or veno-occlusive disease of the liver) and late effects (such as endocrine disorders or secondary malignancies).
- Quality of life.

Search methods for identification of studies

We searched the following electronic databases: the Cochrane Central Register of Controlled trials (CENTRAL) (*The Cochrane Library* 2009, issue 1), MEDLINE/PubMed (from 1966 to January 2009) and EMBASE/Ovid (from 1980 to January 2009).

The search strategies for the different electronic databases are shown in [Appendix 1](#), [Appendix 2](#) and [Appendix 3](#).

We located information about trials not registered in MEDLINE, EMBASE or CENTRAL, either published or unpublished, by searching the reference lists of relevant articles and review articles. We also scanned the conference proceedings of the International Society for Paediatric Oncology (SIOP), American Society for Pediatric Hematology and Oncology (ASPHO) and *Advances*

in Neuroblastoma Research (ANR) from 2002 to 2008, if available electronically and otherwise by handsearching. We searched for ongoing trials by scanning the ISRCTN register and the National Institute of Health Register (both screened January 2009). We imposed no language restriction.

Data collection and analysis

Study identification

After employing the search strategy described previously, two authors independently undertook identification of studies meeting the inclusion criteria. We obtained any study seemingly meeting the inclusion criteria on grounds of the title, or abstract or both in full for closer inspection. We clearly stated details of reasons for exclusion of any study considered for the review. Discrepancies between authors were resolved by consensus. No third party arbitration was needed.

Assessment of risk of bias in included studies

Two authors independently performed assessment of risk of bias in the included studies, according to the following criteria: concealment of treatment allocation, blinding of the care provider, blinding of the patients, blinding of the outcome assessor (for each outcome separately), intention-to-treat analyses (for each outcome separately) and completeness of follow up (for each outcome separately). We have used the definitions as described in the module of the Cochrane Childhood Cancer Group (see [Table 1](#)). Discrepancies between authors were resolved by consensus. No third party arbitration was needed.

Table 1. Criteria for the assessment of risk of bias in included studies

Risk of bias item	Type of bias	Implementation
Allocation concealment	Selection bias	<i>Adequate:</i> use of randomisation method that did not allow investigator and participant to know or influence the allocation of treatment before eligible participants entered the study. <i>Inadequate:</i> use of alternate medical record numbers or unsealed envelopes as randomisation method, and/or there is information in the study indicating that investigators or participants could have influenced the allocation of treatment. <i>Unclear:</i> randomisation stated but no information on method used is available.
Blinding of care providers	Performance bias	Adequate information about blinding must have been provided.
Blinding of patients	Performance bias	Adequate information about blinding must have been provided.
Blinding of outcome assessors	Detection bias	Adequate information about blinding must have been provided.

Table 1. Criteria for the assessment of risk of bias in included studies (Continued)

Intention-to-treat analysis	Attrition bias	<p><i>Yes:</i> all participants are analysed in the treatment group to which they were randomised, regardless of whether or not they received the allocated intervention.</p> <p><i>No:</i> some participants (< 5%, 5% to 10%, 11% to 20%, > 20%) are not analysed in the treatment group to which they were randomised because they did not receive the study intervention, they withdrew from the study, or because of protocol violation.</p> <p><i>Unclear:</i> inability to determine if patients were analysed according to the intention-to-treat principle.</p>
Completeness of follow up	Attrition bias	Percentage of participants excluded or lost to follow up (< 5%, 5% to 10%, 11% to 20%, > 20%) should be stated.

Data extraction

Two authors performed data extraction independently by using standardised forms. We extracted the following data:

- the characteristics of the participants at the time of randomisation (such as age, sex, stage of disease, histology, MYCN oncogene amplification, received induction treatment, received external irradiation, remission status at myeloablative treatment and stem cell rescue);
- the characteristics of interventions (details of myeloablative therapy: drugs used, routes of delivery, dose, timing, use of total body irradiation; details of the stem cell rescue: timing and methods of cell harvest, timing of stem cell rescue, number of cells infused, contamination with tumour cells);
 - details of supportive care (such as the use of prophylactic antibiotics, growth factors, granulocyte infusions);
 - details of outcome measures as described above; and
 - length of follow up.

In case of disagreement between authors, we re-examined the abstracts and articles and discussed these until consensus was achieved. No third party arbitration was needed.

Data analysis

We entered data into RevMan (RevMan 2008) and analysed data according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Dichotomous variables were related to risk using the relative risk or risk ratio (RR). For the assessment of survival, we used the generic inverse variance function of RevMan to combine logs of the hazard ratios (HRs). We used Parmar's method if hazard ratios had not been explicitly presented in the study (Parmar 1998). We extracted data by allocation intervention, irrespective of compliance with the allocated intervention, in order to allow an 'intention-to-treat' anal-

ysis. We assessed heterogeneity both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, i.e. the I^2 statistic. If there was evidence of substantial heterogeneity ($I^2 > 50\%$) (Higgins 2005), this was reported. We used a random-effects model for the estimation of treatment effects throughout the review. All results are presented with the corresponding 95% confidence interval (CI). Where possible, we presented data separately for different prognostic factors such as disease status at the time of stem cell rescue, MYCN amplification status and serum lactate dehydrogenase levels. For all outcomes for which pooling was possible we performed sensitivity analyses for all quality criteria separately. We excluded the low quality studies and the studies for which the quality was unclear and compared the results of the good quality studies with the results of all available studies. The quality of studies included in the analyses was taken into account in the interpretation of the results of the review. We planned to construct a funnel plot to graphically ascertain the existence of publication bias. However, as a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (Higgins 2008). Since only three trials could be included in the review, we did not construct funnel plots.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Running the searches in the electronic databases of CENTRAL, MEDLINE/PubMed and EMBASE/Ovid yielded a total of 1463 references. Initial screening excluded 1427 references which clearly

did not meet all the criteria for considering studies for this review. We obtained 36 references in full for closer inspection. We included three articles which fulfilled all the criteria for considering studies for this review. We excluded the remaining 33 articles for reasons described in the [Characteristics of excluded studies](#) table. Scanning the reference lists of relevant articles and reviews and the conference proceedings of SIOF, ASPHO and ANR did not identify any additional eligible studies. One trial was added to the [Characteristics of excluded studies](#) table. No eligible ongoing trials were identified.

In summary, the total number of included RCTs was three. Characteristics of included studies are summarised below (for further details see the [Characteristics of included studies](#) table).

All three eligible RCTs were multi-centre studies, two of which were based in Europe ([Berthold 2005](#); [Pritchard 2005](#)) and one in North America ([Matthay 1999](#)). Patients were recruited between January 1982 ([Pritchard 2005](#)) and November 2002 ([Berthold 2005](#)). The total number of patients included in the three studies was 739; 370 children received high-dose chemotherapy and stem cell rescue, whereas 369 children received either conventional che-

motherapy ([Berthold 2005](#); [Matthay 1999](#)) or no further treatment ([Pritchard 2005](#)). All trials used different induction regimens (i.e. different chemotherapeutic agents and different (cumulative) dosages) and different myeloablative treatments. In [Berthold 2005](#) and [Matthay 1999](#) there were also differences in treatment patients received in the study itself (for example, in external radiotherapy, therapeutic MIBG-I¹³¹, immunotherapy and retinoic acid treatment). See the [Characteristics of included studies](#) table for further details. All patients were diagnosed with high-risk neuroblastoma; the exact definitions used in each study are stated in the [Characteristics of included studies](#) table. Only one study mentioned that patients were newly diagnosed ([Matthay 1999](#)); in the other studies this is unclear. None of the studies mentioned the exact age of the participants; only the number of cases above and below one year of age was stated.

Risk of bias in included studies

See [Table 2](#) for the exact scores per included study.

Table 2. Risk of bias in included studies

Study	Allocation concealment	Blinding of care providers	Blinding of patients	Blinding of outcome assessors	Intention-to-treat analysis	Completeness of follow up
Berthold 2005	Yes	No	No	Event-free survival, adverse effects (i.e. treatment-related death/secondary malignant disease): unclear	Event-free survival, overall survival, adverse effects (i.e. treatment-related death/secondary malignant disease): yes	Event-free survival, overall survival, adverse effects (i.e. secondary malignant disease): unclear; adverse effects (i.e. treatment-related death): yes
Matthay 1999	Unclear	No	No	Event-free survival, adverse effects (i.e. treatment-related death/secondary malignant disease/veno-occlusive disease/interstitial pneumonitis/renal effects/sepsis/serious infections): yes	Event-free survival, overall survival, adverse effects (i.e. treatment-related death/secondary malignant disease/veno-occlusive disease/interstitial pneumonitis/renal effects/sepsis/serious infections):	Event-free survival, overall survival, adverse effects (i.e. secondary malignant disease/veno-occlusive disease/interstitial pneumonitis/renal effects/sepsis/serious infections): unclear; adverse effects (

Table 2. Risk of bias in included studies (Continued)

					yes	i.e. treatment-related deaths): no (> 20% lost to follow up)
Pritchard 2005	Yes	Unclear	Unclear	Event-free survival: unclear	Event-free survival and overall survival: yes	Event-free survival and overall survival: unclear

Two studies applied a concealed treatment allocation, whereas in one study this was unclear.

Care providers and patients were not blinded to treatment in two studies, whereas in one study this was unclear. However, it should be noted that due to the nature of the interventions blinding of care providers and patients was virtually impossible.

For blinding of the outcome assessor we scored each outcome separately, with the exception of overall survival, since for that outcome blinding was not relevant. Three studies evaluated event-free survival: in one study the outcome assessor was blinded to treatment, whereas in two studies this was unclear. Two studies evaluated adverse effects: in one study the outcome assessor was blinded to treatment, whereas in the other study this was unclear. The presence of an intention-to-treat (ITT) analysis was also scored for each outcome separately. For both overall survival and event-free survival all three studies evaluating these outcomes used an ITT analysis. For adverse effects both studies evaluating this outcome used an ITT analysis.

Completeness of follow up was also scored for each outcome separately. For both overall survival and event-free survival the completeness of follow up was unclear in all three studies evaluating these outcomes. The same was true for adverse effects (evaluated in two studies), with the exception of treatment-related death. In one study no patients were lost to follow up, whereas in the other study more than 20% of patients were lost to follow up.

In conclusion, selection bias (based on concealment of allocation) could not be ruled out in 33.3% of included studies. Performance bias (based on blinding of the care provider and patient) could not

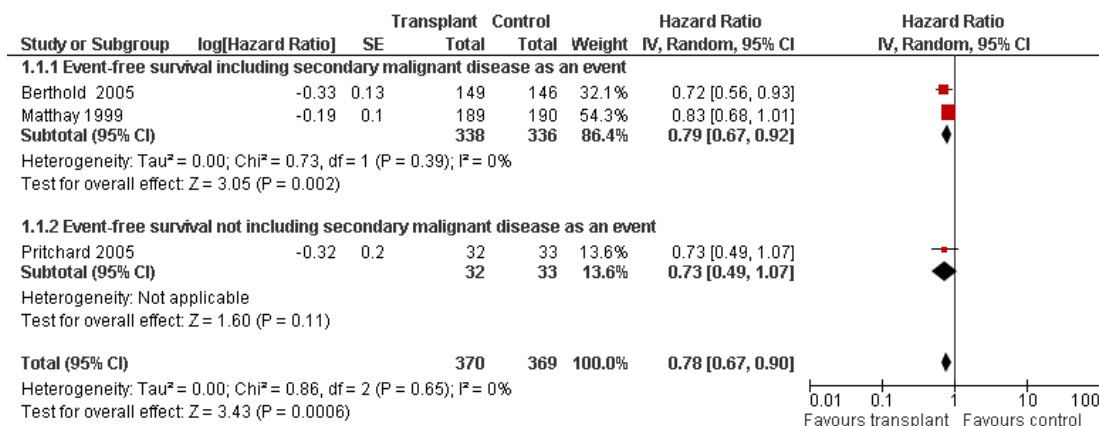
be ruled out in any of the included studies. Detection bias (based on blinding of the outcome assessor) could not be ruled out in 66.7% of included studies evaluating event-free survival and in 50% of included studies evaluating adverse effects. The assessment of the risk of attrition bias was based on the use of an ITT analysis and completeness of follow up. All included studies used an ITT analysis for all evaluated outcomes. For overall survival, event-free survival and adverse effects (with the exception of treatment-related death) completeness of follow up was unclear in 100% of included studies. For treatment-related death loss to follow up was more than 20% in 50% of the included studies.

Effects of interventions

Event-free survival

Data on event-free survival could be extracted from three trials (Berthold 2005; Matthay 1999; Pritchard 2005) with a total of 739 patients (see Figure 1). Two of these trials included secondary malignant disease as an event (Berthold 2005; Matthay 1999), whereas the other did not (Pritchard 2005; see the Characteristics of included studies table for the exact definitions). However, since only a very small percentage of patients developed secondary malignant disease (see the description of adverse effects later on), we were able to pool the results of these three trials. Parmar's method was used to obtain the necessary data for the meta-analysis. It showed a significant difference in event-free survival in favour of the transplant group (hazard ratio (HR) 0.78; 95% CI 0.67 to 0.90, P = 0.0006). No heterogeneity was detected ($I^2 = 0\%$).

Figure 1. Forest plot of comparison: I Transplant versus control, outcome: I.1 Event-free survival.



The meta-analysis of the two trials including secondary malignant disease as an event also showed a significant difference in event-free survival in favour of the transplant group (HR 0.79; 95% CI 0.67 to 0.92, $P = 0.002$, $n = 674$ patients). Again, no heterogeneity was detected ($I^2 = 0\%$). The study not including secondary malignant disease as an event showed no significant difference between the treatment groups (HR 0.73; 95% CI 0.49 to 1.07, $P = 0.11$, $n = 65$ patients).

The above mentioned HRs are calculated using the complete follow-up period of the trials. The individual studies also presented the three or five-year event-free survival: in the studies of [Berthold 2005](#) and [Matthay 1999](#) the three-year event-free survival was significantly better in the transplant group ($P = 0.0221$ and $P = 0.034$ respectively). In the study of [Pritchard 2005](#) no significant difference in five-year event-free survival between the treatment groups was identified ($P = 0.08$).

It should be noted that the individual studies all used different starting points for event-free survival, i.e. either years since randomisation (in [Matthay 1999](#) randomisation was performed a median of 60 days after diagnosis; in [Pritchard 2005](#) the time of randomisation was not mentioned, but the decision to randomise was made five to nine months after diagnosis) or years from diagnosis (in [Berthold 2005](#) randomisation was performed a median of 39 days after diagnosis).

Subgroups

The results in subgroups are summarised descriptively (i.e. as presented in the individual articles).

In the study of [Berthold 2005](#) different subgroups (defined according to commonly accepted risk factors) were evaluated. In some subgroups three-year event-free survival was significantly better in the transplant group: (1) in patients who had a complete remission or very good partial remission to induction chemotherapy/before randomisation ($P = 0.0083$), (2) in patients with raised serum

concentration of lactate dehydrogenase ($P = 0.0357$; cut-off value not mentioned), and (3) in patients receiving antibody treatment ($P = 0.0061$). By contrast, in the following subgroups no significant difference in three-year event-free survival was identified between the treatment groups: (1) in patients who had partial remission, mixed remission or stable disease before randomisation ($P = 0.1809$), (2) in patients treated with retinoic acid ($P = 0.9732$), (3) in patients with MYCN amplification with stage 1, 2, 3 or 4S disease or with stage 4 disease aged younger than one year ($P = 0.2183$), (4) in patients with MYCN amplification ($P = 0.0669$), (5) in patients without MYCN amplification ($P = 0.0643$), (6) in patients with normal concentrations of serum lactate dehydrogenase ($P = 0.3132$; cut-off value not mentioned), and (7) in patients with stage 4 and age more than one year ($P = 0.0549$).

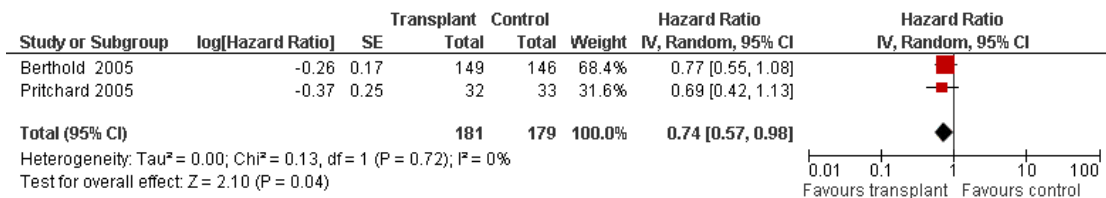
In the study of [Matthay 1999](#) the following subgroups were evaluated: stage IV disease, MYCN amplification, unfavourable histopathological findings, a serum ferritin level of at least 143 ng per millilitre, a partial response to initial chemotherapy (as compared to complete response or nearly complete response), age at diagnosis more than two years and, among stage IV patients, bone metastases at diagnosis, and the presence at diagnosis of more than 100 tumour cells per 10^5 normal nucleated bone marrow cells. They stated that the event-free survival among patients assigned to transplantation was greater in every (univariate) subanalysis than that among patients assigned to chemotherapy (no P values presented), but that it was most pronounced among the subgroup of patients who were older than two years at diagnosis ($P = 0.01$) and among the subgroup of patients with MYCN amplification ($P = 0.03$).

In the study of [Pritchard 2005](#) in patients aged more than one year with stage 4 disease five-year event-free survival was significantly better in the transplant group ($P = 0.01$).

Overall survival

Data on overall survival were reported in three trials (Berthold 2005; Matthay 1999; Pritchard 2005). The results from two of these trials could be pooled (Berthold 2005; Pritchard 2005). Parmar's method was used to obtain the necessary data for the meta-analysis. It showed a significant difference in overall survival in favour of the transplant group (HR 0.74; 95% CI 0.57 to 0.98, $P = 0.04$, $n = 360$ patients). No heterogeneity was detected ($I^2 = 0\%$). See Figure 2. The other study (Matthay 1999) only provided descriptive results: overall survival was similar for both regimens ($n = 379$ patients).

Figure 2. Forest plot of comparison: I Transplant versus control, outcome: I.2 Overall survival.



The above mentioned HR is calculated using the complete follow-up period of the trials. The individual studies also presented the three or five-year overall survival rates: in the studies of Berthold 2005 and Matthay 1999 no significant difference in the three-year overall survival between the treatment groups was identified ($P = 0.0875$ and $P = 0.87$ respectively). In the study of Pritchard 2005 no significant difference in the five-year overall survival between treatment groups was identified ($P = 0.1$).

It should be noted that the individual studies all used different starting points for overall survival, i.e. either years since randomisation (in Matthay 1999 randomisation was performed a median of 60 days after diagnosis; in Pritchard 2005 the time of randomisation was not mentioned, but the decision to randomise was made five to nine months after diagnosis) or years from diagnosis (in Berthold 2005 randomisation was performed a median of 39 days after diagnosis).

Subgroups

The results in subgroups are summarised descriptively (i.e. as presented in the individual articles).

In the study of Berthold 2005 different subgroups (defined according to commonly accepted risk factors) were evaluated. In some subgroups three-year overall survival was significantly better in the transplant group: (1) in patients who had a complete remission or very good partial remission before randomisation ($P = 0.0436$), and (2) in patients receiving antibody treatment ($P = 0.0221$). By

contrast, in the following subgroups no significant difference in three-year event-free survival was identified between the treatment groups: (1) in patients who had partial remission, mixed remission or stable disease before randomisation ($P = 0.1311$), (2) in patients treated with retinoic acid ($P = 0.8918$), (3) in patients with MYCN amplification with stage 1, 2, 3 or 4S disease or with stage 4 disease aged younger than one year ($P = 0.2287$), (4) in patients with MYCN amplification ($P = 0.1658$), (5) in patients without MYCN amplification ($P = 0.1921$), (6) in patients with normal concentrations of serum lactate dehydrogenase ($P = 0.1985$; cut-off value not mentioned), (7) in patients with raised serum concentration of lactate dehydrogenase ($P = 0.1247$; cut-off value not mentioned) and (8) in patients with stage 4 and age more than one year ($P = 0.1820$).

In the study of Matthay 1999 no subgroup analyses regarding overall survival have been presented.

In the study of Pritchard 2005 in patients aged more than one year with stage 4 disease five-year overall survival was significantly better in the transplant group ($P = 0.03$).

Adverse effects

Since all patients receiving antineoplastic treatment will suffer from side effects, we decided to analyse only severe and life-threatening effects. We defined this as toxicity grade 3 or higher. Only adverse effects occurring from the start of the randomised treat-

ment (i.e. transplant or control) were eligible for inclusion in this review.

Treatment-related death

Data on treatment-related death could be extracted from two trials with a total of 574 patients (Berthold 2005; Matthay 1999). There were 12 cases among 278 patients randomised to the transplant group and five among 296 patients randomised to the control group. The meta-analysis showed no significant difference between the treatment groups (RR 2.53; 95% CI 0.17 to 37.12, $P = 0.50$). However, unexplained heterogeneity was detected ($I^2 = 78\%$). It should be noted that it was not possible to perform an intention-to-treat analysis for the study of Matthay 1999, therefore we performed an as-treated analysis.

Secondary malignant disease

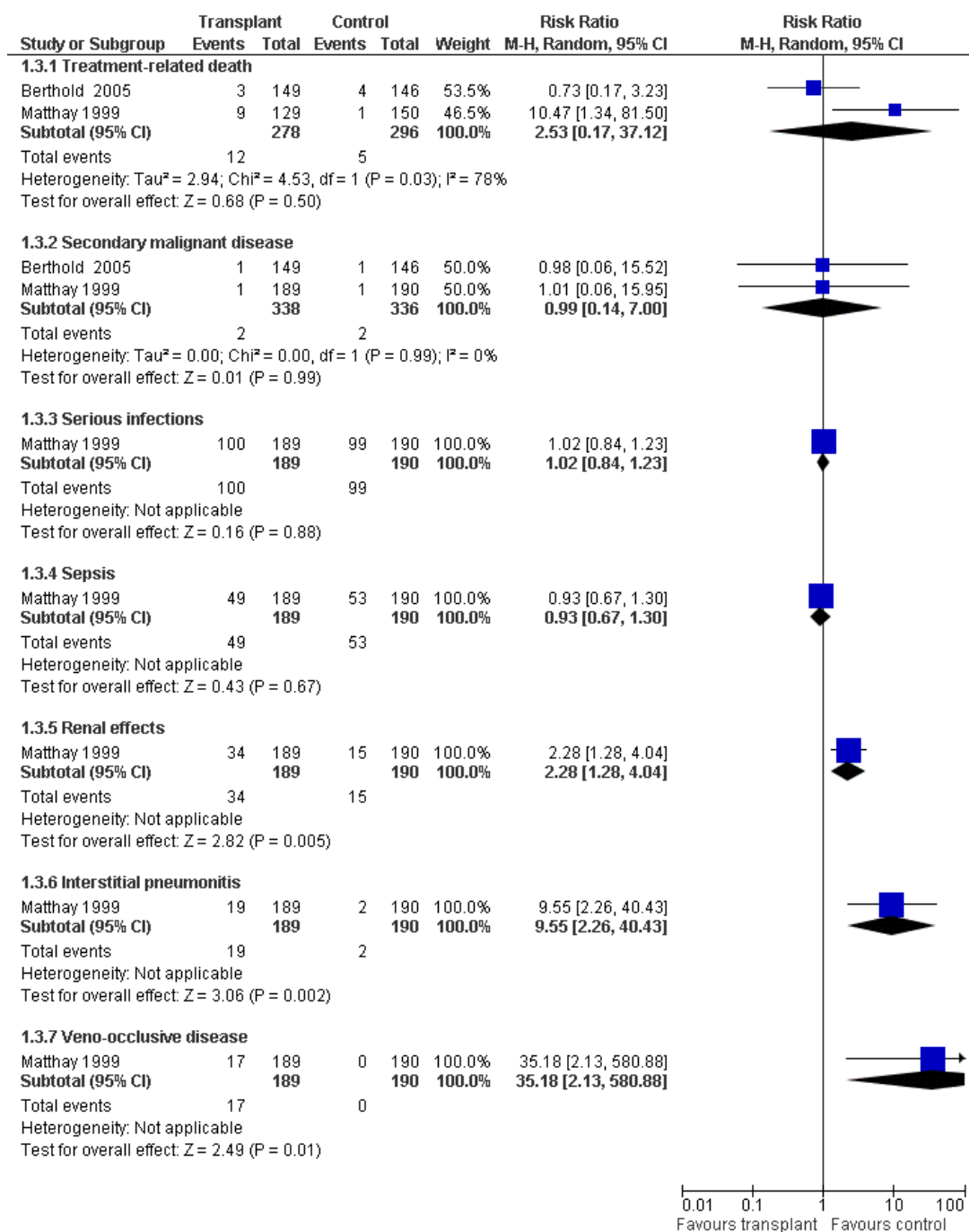
Data on secondary malignant disease could be extracted from two trials with a total of 674 patients (Berthold 2005; Matthay 1999).

There were two cases among 338 patients randomised to the transplant group (one acute myeloid leukaemia and one unknown malignancy) and also two cases among 336 patients randomised to the control group (one acute lymphoblastic leukaemia and one unknown malignancy). The meta-analysis showed no significant difference between the treatment groups (RR 0.99; 95% CI 0.14 to 7.00, $P = 0.99$). No heterogeneity was detected ($I^2 = 0\%$).

Other adverse effects

Data on serious infections, sepsis, renal effects, interstitial pneumonitis and veno-occlusive disease could be extracted from one trial with a total of 379 patients (Matthay 1999). For renal effects, interstitial pneumonitis and veno-occlusive disease a significant difference in favour of the control group was identified, whereas for serious infections and sepsis no significant difference between the treatment groups was identified (see Figure 3 for more information).

Figure 3. Forest plot of comparison: I Transplant versus control, outcome: 1.3 Adverse effects grade 3 or higher.



Quality of life

None of the studies evaluated quality of life.

Sensitivity analyses

The results of the sensitivity analyses for the risk of bias criteria were consistent among the trials and did not differ from the overall analyses.

DISCUSSION

Neuroblastoma is the most common extracranial solid tumour in children. Unfortunately, despite the development of new treatment options, the prognosis of high-risk patients is still not good; in more than half of patients there is recurrence of the disease (Brodeur 2006; Goldsby 2004; Matthay 1993; Weinstein 2003). High-dose chemotherapy and stem cell transplantation might increase survival in these patients. This systematic review evaluated the current state of evidence on the effectiveness of high-dose chemotherapy and autologous haematopoietic stem cell rescue compared with conventional therapy in patients diagnosed with high-risk neuroblastoma. Only randomised controlled trials (RCTs) were included since it is widely recognised that a RCT is the only study design which can be used to obtain unbiased evidence on the use of different treatment options, provided that the design and execution are adequate.

We identified three RCTs comparing high-dose chemotherapy and autologous haematopoietic stem cell rescue (i.e. myeloablative therapy) and conventional therapy. Even though all patients were diagnosed with high-risk neuroblastoma, definitions of high-risk patients differed between the studies, as did the required response to induction therapy to be eligible for randomisation. Randomisation was performed at different time intervals since diagnosis. All trials used different induction treatments, myeloablative treatments and control treatments. Also, in two trials the received treatment slightly differed between patients, but we assumed that as a result of randomisation these differences in treatment were evenly distributed in both treatment groups. Two studies used bone marrow cells and one study used peripheral blood cells. See the [Characteristics of included studies](#) table for more exact information.

The individual studies did present the three or five-year event-free survival; in two out of three studies a significant difference in favour of the transplant group was identified. In the other study this difference was not confirmed. Our meta-analysis using their

complete follow-up period also showed a significant difference in event-free survival in favour of the transplant group (HR 0.78; 95% CI 0.67 to 0.90, $P = 0.0006$). When the two studies in which secondary malignant disease was included as an event were analysed separately, this finding was confirmed. In the study which did not include secondary malignant disease as an event, no significant difference in event-free survival between the treatment groups was identified. However, the direction of the result of this study was the same as the overall result of all trials.

The individual studies also presented the three or five-year overall survival; in all three studies no significant difference between the treatment groups was identified. However, our meta-analysis using their complete follow-up period showed a significant difference in overall survival in favour of the transplant group (HR 0.74; 95% CI 0.57 to 0.98, $P = 0.04$).

For two evaluated adverse effects (grade 3 or higher) it was possible to perform a meta-analysis. No significant difference in secondary malignant disease and treatment-related death between the treatment groups was identified. However, it should be noted that unexplained heterogeneity was detected in the latter analysis. Serious infections, sepsis, renal effects, interstitial pneumonitis and veno-occlusive disease were only evaluated in one study, in which for renal effects, interstitial pneumonitis and veno-occlusive disease a significant difference in favour of the control group was identified, whereas for serious infections and sepsis no significant difference between the treatment groups was identified. No information on quality of life was provided.

In the individual studies different subgroups have been evaluated, but the results were not univocal in all studies. As a result, no definitive conclusions can be made regarding the effect of myeloablative therapy or conventional treatment in the different subgroups.

In this review we only performed intention-to-treat analyses, since they provide the most realistic and unbiased answer to the question of clinical effectiveness (Lachin 2000; Lee 1991). However, for treatment-related death from the Matthay 1999 trial this was not possible and we therefore performed an as-treated analysis.

'No evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. The reason that some studies did not identify a significant difference between study groups could be the fact that the number of patients included in these studies was too small to detect a difference between the treatment groups (i.e. low power). Furthermore, the length of follow up could have been too short to detect a significant difference between the treatment groups.

The risk of bias in the included studies was difficult to assess due to a lack of reporting. As a result, the presence of selection bias,

performance bias, detection bias and attrition bias could not be ruled out. However, at the moment this is the best available evidence from RCTs comparing the effectiveness of high-dose chemotherapy and autologous haematopoietic stem cell rescue with conventional therapy in patients diagnosed with high-risk neuroblastoma. With regard to performance bias, it should be noted that due to the nature of the interventions blinding of care providers and patients was virtually impossible.

The improved outcome with myeloablative therapy must be viewed in the context of the complete therapy, e.g. the effect of the preceding therapy (such as induction chemotherapy, surgery and/or radiotherapy), the myeloablative regimen with or without total body irradiation, the stem cells (such as purging yes or no, origin of stem cells, i.e. bone marrow or peripheral blood) and presence and type of consolidation chemotherapy. We have pooled the results of all eligible studies, but, as stated before, the above mentioned items differed between the studies. As a result, in this systematic review we can only provide conclusions on the concept of myeloablative treatment versus control treatment. We cannot make conclusions with regard to specific versions of these treatments. However, the concept seems to work in terms of survival, both for all randomised patients treated with myeloablative therapy and for specific subgroups. No definitive conclusions can be made regarding adverse effects and quality of life.

After finalising the searches for this systematic review, an update of the study of [Matthay 1999](#) was published ([Matthay 2009](#)). The authors stated that this long-term analysis with more than eight years follow up after the completion of patient accrual validated their previously reported results. We will incorporate their results when updating this systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

Our meta-analyses of both event-free and overall survival showed a statistically significant difference in favour of the transplant group. Data on adverse effects are very limited, but significantly more events in the transplant group were identified for renal effects, interstitial pneumonitis and veno-occlusive disease. The fact that no significant differences in the occurrence of other adverse effects between treatment groups were identified could be the result of low power or too short a follow-up period. No information on quality of life was provided. No definitive conclusions regarding the effect of myeloablative therapy or conventional treatment in different subgroups can be made.

Based on the currently available evidence, high-dose chemotherapy and autologous haematopoietic stem cell rescue seems to be a good treatment option for children with high-risk neuroblastoma, although possible higher levels of adverse effects should be kept in mind. This systematic review only allows a conclusion on the concept of myeloablative treatment; no conclusions regarding the best treatment strategy can be made.

Implications for research

Future trials on the use of high-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma should focus on identifying the most optimal induction and/or myeloablative regimen, with regard to survival, adverse effects and quality of life. The best study design to answer these questions is a randomised controlled trial (RCT). RCTs should be performed in homogeneous study populations (with regard, for example, to stage of disease) and have a long-term follow up. Different risk groups should be taken into account. The number of included patients should be sufficient to obtain the power needed for the results to be reliable.

Also, it will be very interesting to examine long-term data from the RCTs already performed. In the upcoming update of this review the long-term data from one of the included trials will be incorporated.

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Reynolds CP. Detection and treatment of minimal residual disease in high-risk neuroblastoma. *Pediatric Transplantation* 2004;**8**(Suppl 5):56–66.

Sawaguchi 1990

Sawaguchi S, Kaneko M, Uchino J, Takeda T, Iwafuchi M, Matsuyama S, et al. Treatment of advanced neuroblastoma with emphasis on intensive induction chemotherapy. A report from the Study Group of Japan. *Cancer* 1990;**66**:1879–87.

Shimada 1984

Shimada H, Chatten J, Newton WA Jr, Sachs N, Hamoudi AB, Chiba T, et al. Histopathologic prognostic factors in neuroblastic tumors: definition of subtypes of ganglioneuroblastoma and an age-linked classification of neuroblastomas. *Journal of the National Cancer Institute* 1984;**73**:405–16.

Stram 1996

Stram DO, Matthay KK, O'Leary M, Reynolds CP, Haase GM, Atkinson JB, et al. Consolidation chemoradiotherapy and autologous bone marrow transplantation vs continued chemotherapy for metastatic neuroblastoma: a report of two concurrent Children's Cancer Group Studies. *Journal of Clinical Oncology* 1996;**14**:2417–26.

Verdeguer 2004

Verdeguer A, Munoz A, Canete A, Pardo N, Martinez A, Donat J, et al. Long-term results of high-dose chemotherapy and autologous stem cell rescue for high-risk neuroblastoma patients: a report of the Spanish working party for BMT in children (Getmon). *Pediatric Hematology and Oncology* 2004;**21**:495–504.

Weinstein 2003

Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. *The Oncologist* 2003;**8**:278–92.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Berthold 2005

Methods	<p>Randomisation was performed centrally by computer-generated sequence with a block size of 8. The stratification criteria were MYCN alone (amplified vs not amplified vs unknown), concentration of serum LDH at diagnosis (raised vs not raised vs unknown), and age (1 to < 2 years vs ≥ 2 years at diagnosis). Randomisation was performed at a median of 39 days (range 7 to 224) after diagnosis. Patients were randomised between myeloablative therapy and conventional chemotherapy.</p>
Participants	<p>295 children with high-risk neuroblastoma.</p> <p><i>High-risk neuroblastoma was defined as:</i> stage 4 disease in patients older than 1 year or as MYCN-amplified tumours in patients with stage 1, 2, 3 or 4S disease or with stage 4 disease and aged younger than 1 year. Staging was done in accordance with the International Neuroblastoma Staging System criteria (Brodeur 1993).</p> <p><i>Age:</i> 22 patients < 1 year and 273 patients > 1 year</p> <p><i>Sex:</i> not mentioned</p> <p><i>Stage of disease:</i> I (n = 2), II (n = 6), III (n = 19), IVS (n = 5) and IV (n = 263)</p> <p><i>Primary disease or recurrence:</i> not mentioned</p> <p><i>Histology:</i> not mentioned</p> <p><i>Bone metastases:</i> yes n = 179, no n = 116 (including 84 stage IV patients)</p> <p><i>Immunocytologic analysis of bone marrow at diagnosis:</i> not mentioned</p> <p><i>MYCN amplification:</i> yes n = 114, no n = 176, unclear n = 5</p> <p><i>Serum LDH level (cut-off values not mentioned):</i> raised n = 262, not raised n = 29, not mentioned n = 4</p> <p><i>Induction regimen:</i></p> <p>Data for all randomised patients were not available; these are data for 212 of the 295 patients. According to protocol, they received 3 N5 cycles with 40 mg/m² cisplatin a day and 100 mg/m² etoposide a day, both given as continuous infusion over 96 hours on days 1 to 4, and 3 mg/m² vindesine given intravenously over 1 hour on day 1; and 3 N6 cycles with 1.5 mg/m² vincristine a day given intravenously over 1 hour on days 1 and 8, 200 mg/m² dacarbazine a day given intravenously over 1 hour on days 1 to 5, 1.5 g/m² ifosfamide a day given as continuous infusion over 120 hours on days 1 to 5, and 30 mg/m² doxorubicin a day given intravenously over 4 hours on days 6 and 7. In a pilot setting, 3 patients received cycles with slightly higher doses of etoposide (125 mg/m² a day given as continuous infusion over 96 hours on days 1 to 4) and a different infusion time for doxorubicin (48 hours continuous infusion instead of 2 infusions of 4 hours each). Actually received cumulative doses not mentioned. The N5 and N6 cycles were alternated; the total duration of the induction regimen was 5 to 7 months.</p> <p><i>External radiotherapy:</i></p> <p>Patients with contrast medium or MIBG uptake in the primary tumour at the end of induction chemotherapy had local radiotherapy to the primary residual tumour. Data for all randomised patients were not available; these are data for 212 of the 295 patients. Yes (36-40 Gy to residual tumour) n = 24, no n = 188.</p> <p><i>Surgery:</i></p> <p>Timing of surgery varied during induction chemotherapy regimen: at diagnosis or after 2nd, 4th or 6th cycles of chemotherapy.</p> <p><i>Therapeutic MIBG-¹³¹I:</i></p> <p>Patients with clear uptake of 123-iodine MIBG in metastatic lesions at the end of induction chemotherapy received MIBG therapy. Data for all randomised patients were not available; these are data for 212 of the</p>

Berthold 2005 (Continued)

	<p>295 patients. Yes n = 28.</p> <p><i>Immunotherapy:</i> For 1 year was started 4 to 6 weeks after the end of the conventional chemotherapy or after recovery of the haemopoiesis after megatherapy. Six infusion cycles (one cycle every 2 months) of 20 mg/m² ch14.18 (chimeric monoclonal antibody against GD2) a day given intravenously over 8 to 12 hours on days 1 to 5 of every cycle. Yes n = 146.</p> <p><i>Retinoic acid:</i> After November 2002, instead of immunotherapy: 160 mg/m²/day, oral on days 1 to 14, followed by a break for 14 days, for 6 months. After 3 months' break, retinoic acid was resumed for another 3 months. Yes n = 35.</p> <p><i>Supportive care:</i> Prophylactic antibiotics not mentioned, growth factors not mentioned, granulocyte infusions not mentioned, other: drugs were given to control pain and allergic reactions during immunotherapy (n = not mentioned).</p> <p><i>Response before randomisation:</i> Complete remission/very good partial remission n = 163, partial remission n = 87, stable disease (or mixed remission) n = 13, progressive disease (or death) n = 25, not mentioned n = 1, not applicable n = 6. Response was assessed by use of the International Neuroblastoma Remission Criteria (Brodeur 1993).</p>
Interventions	<p>Data for all randomised patients were not available; these are data for 212 of the 295 patients.</p> <p><i>Myeloablative therapy (n = 149):</i> According to protocol: melphalan 45 mg/m² a day given intravenously over 30 minutes on days 8 to 5 before transplantation, etoposide 40 mg/kg a day given intravenously over 4 hours on day 4 before transplantation, carboplatin 500 mg/m² a day given intravenously over 1 hour on days 4 to 2 before transplantation. Actually received cumulative doses not mentioned. Note: some dose and drug adjustments were made in 6 patients because of hearing loss: 3 received cyclophosphamide instead of carboplatin and 3 received no carboplatin. In 9 children, melphalan was combined with busulfan. Use of total body irradiation not mentioned.</p> <p>Source of stem cells: autologous peripheral blood Timing of cell harvest: between 2nd and 5th induction regimen Timing of stem cell rescue: after 6th induction chemotherapy cycle Number of cells infused: 1-2 X 10⁶/kg CD 34(+) cells was recommended Contamination with tumour cells: not mentioned Purging: yes n = 96, no n = 1, not mentioned n = 13</p> <p><i>Conventional therapy (n = 146):</i> According to protocol: 4 N7 cycles: cyclophosphamide, 150 mg/m² a day, orally, with mesna 50 mg/m² 3 times a day on days 1 to 8. Actually received cumulative doses not mentioned.</p>
Outcomes	<p><i>Event-free survival</i> (defined as time until disease progression or relapse, a second neoplastic disease, or death from any cause, whichever occurred first, or until the last examination).</p> <p><i>Overall survival</i> (defined as death from any cause or until the last examination if the patient survived).</p> <p><i>Adverse effects</i>, i.e. second malignancies and treatment-related deaths (according to World Health Organization criteria).</p>
Notes	<p>Length of follow up not mentioned (median follow up for all cases alive at the censoring date was 3.57 years (range 1.01 to 7.02)).</p>
Risk of bias	

Berthold 2005 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Yes	Randomisation was performed centrally by computer-generated sequence.

Matthay 1999

Methods	<p>Randomisation was performed by permuted-block design using strata with and without metastatic disease. Randomisation was performed at week 8, before the 3rd cycle of chemotherapy for patients without disease progression at a median of 60 days after diagnosis.</p> <p>Patients were randomised between myeloablative therapy and conventional chemotherapy.</p>
Participants	<p>379 children with high-risk neuroblastoma.</p> <p><i>High-risk neuroblastoma was defined as:</i> stage IV neuroblastoma; stage III disease with one or more of the following: amplification of the MYCN oncogene, a serum ferritin level of at least 143 ng per millilitre, and unfavourable histopathological findings; stage II disease with amplification of MYCN (age > 1 year); stage I or II disease with bone metastases before therapy other than surgery; and stage IV disease with MYCN amplification for less than 1 year. Staging was done using the Evans staging criteria (Evans 1971). Unfavourable histopathological findings were based on the Shimada classification (Shimada 1984).</p> <p><i>Age:</i> 9 patients < 1 year and 370 patients > 1 year</p> <p><i>Sex:</i> not mentioned</p> <p><i>Stage of disease:</i> I (n = 0), II with MYCN amplification (n = 1), III (n = 44), IVS (n = 0) and IV (n = 334)</p> <p><i>Primary disease or recurrence:</i> all primary disease</p> <p><i>Histology:</i> favourable n = 15, unfavourable n = 248, unclear n = 116</p> <p><i>Bone metastases:</i> yes n = 230, no n = 149 (including 104 stage IV patients)</p> <p><i>Immunocytologic analysis of bone marrow at diagnosis:</i> negative n = 66, positive n = 184, unclear n = 129</p> <p><i>MYCN amplification:</i> yes n = 104, no n = 179, unclear n = 96</p> <p><i>Serum LDH level:</i> not mentioned</p> <p><i>Induction regimen:</i></p> <p>According to protocol all patients received 5 courses at 28-day intervals of cisplatin 60 mg/m² on day 0; doxorubicin 30 mg/m² on day 2; etoposide 100 mg/m² on days 2 and 5; cyclophosphamide 1 gr/m² on days 3 - 4. Actually received cumulative doses not mentioned.</p> <p><i>External radiotherapy:</i></p> <p>Following induction regimen patients with gross residual disease received surgery and radiotherapy. Number of patients not mentioned.</p> <p><i>Surgery:</i></p> <p>Timing of surgery: after cycle 4 of induction chemotherapy.</p> <p><i>Therapeutic MIBG-I¹³¹:</i></p> <p>No</p> <p><i>Immunotherapy:</i></p> <p>No</p> <p><i>Retinoic acid:</i></p> <p>50 children randomised to myeloablative therapy received 13-cis-retinoic acid (whereas 48 did not) and 52 children randomised to conventional chemotherapy received 13-cis-retinoic acid (whereas 53 did not). Treatment with 13-cis-retinoic acid was part of a second randomisation (see notes); not all patients included in the first randomisation were eligible for inclusion in the second one.</p> <p><i>Supportive care:</i></p>

Matthay 1999 (Continued)

	<p>Prophylactic antibiotics not mentioned, growth factors: 250 mcg/m²/day intravenously in patients undergoing myeloablative therapy and 5 mcg/kg/day s.c. in patients undergoing maintenance therapy, granulocyte infusions not mentioned, other not mentioned.</p> <p><i>Response before randomisation:</i> Complete remission n = 117, (very good) partial remission n = 147, stable disease or mixed response n = 34, progressive disease n = 52, not mentioned n = 29. Response was assessed by use of the International Neuroblastoma Remission Criteria (Brodeur 1988; Brodeur 1993).</p>	
Interventions	<p><i>Myeloablative therapy (n = 189):</i> According to protocol: carboplatin 1000 mg/m², 96-hour continuous infusion, day -8; etoposide 640 mg/m², 96-hour continuous infusion, day -8; melphalan 140 mg/m² and 70 mg/m² bolus infusion, days -7 and -6. Cumulative doses not mentioned. Total body irradiation: 333 cGy/day, days -3, -2, -1. Actually received cumulative doses not mentioned. Source of stem cells: bone marrow Timing of cell harvest: between 3rd and 4th and 4th and 5th cycles of induction regimen Timing of stem cell rescue: after 5th induction chemotherapy cycle Number of cells infused: 2 X 10⁸ mnc/kg, day 0 (median dose) Contamination with tumour cells: no Purging: yes (performed by sedimentation, filtration, immunomagnetic separation)</p> <p><i>Conventional therapy (n = 190):</i> According to protocol: 3 cycles of cisplatin 160 mg/m²; etoposide 500 mg/m²; doxorubicin 40 mg/m² 96 hours continuous infusion; simultaneously with bolus ifosfamide 2500 mg/m² + mesna 1500 mg/m² days 0 to 3. Actually received cumulative doses not mentioned.</p>	
Outcomes	<p><i>Event-free survival</i> (defined as the time from randomisation to disease progression, death from any cause and a second neoplasm, whichever occurred first). <i>Overall survival</i> (definition not mentioned). <i>Adverse effects</i>, i.e. treatment-related death/secondary malignant disease/veno-occlusive disease/interstitial pneumonitis/renal effects/sepsis/serious infections (according to the common toxicity criteria of the National Cancer Institute).</p>	
Notes	<p>Length of follow up not mentioned. In this study a second randomisation was included to answer the question of whether subsequent treatment with 13-cis-retinoic acid (isotretinoin) could further improve event-free survival.</p>	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not mentioned in article.

Pritchard 2005

Methods	<p>Randomisation was performed at the co-ordinating data centre by means of a minimisation technique using stages (III or IV) and individual participating centres as stratification factors.</p> <p>Time of randomisation not mentioned (the decision to randomise was made 5 to 9 months after diagnosis)</p> <p>.</p> <p>Patients were randomised between myeloablative therapy and no further treatment.</p>
Participants	<p>65 children with high-risk neuroblastoma.</p> <p><i>High-risk neuroblastoma was defined as:</i> age > 6 months, stage III or IV. Staging was done using the Evans staging criteria (Evans 1971).</p> <p><i>Age:</i> 5 patients < 1 year and 60 patients > 1 year</p> <p><i>Sex:</i> 34 males and 31 females</p> <p><i>Stage of disease:</i> I (n = 0), II (n = 0), III (n = 13), IVS (n = 0) and IV (n = 52)</p> <p><i>Primary disease or recurrence:</i> not mentioned</p> <p><i>Histology:</i> not mentioned</p> <p><i>Bone metastases:</i> yes n = 40/52 stage IV patients, unclear n = 12/52 stage IV patients</p> <p><i>Immunocytologic analysis of bone marrow at diagnosis:</i> not mentioned</p> <p><i>MYCN amplification:</i> not mentioned</p> <p><i>Serum LDH level:</i> not mentioned</p> <p><i>Induction regimen:</i></p> <p>According to protocol all patients received vincristine 1.5 mg/m² on day 1, cyclophosphamide 600 mg/m² on day 1, cisplatin 60 mg/m² on day 2, and teniposide 150 mg/m² on day 4 repeated every 21 days or as soon as possible afterwards if recovery of neutrophil and platelet counts was slow. Cumulative doses not mentioned.</p> <p><i>External radiotherapy:</i></p> <p>No</p> <p><i>Surgery:</i></p> <p>Surgery was performed before randomisation took place.</p> <p><i>Therapeutic MIBG-I¹³¹:</i></p> <p>No</p> <p><i>Immunotherapy:</i></p> <p>No</p> <p><i>Retinoic acid:</i></p> <p>No</p> <p><i>Supportive care:</i></p> <p>Prophylactic antibiotics not mentioned, growth factors no, granulocyte infusions not mentioned, other: nutritional supplementation (n = not mentioned).</p> <p><i>Response before randomisation:</i></p> <p>Complete remission n = 36, good partial remission n = 29. This study was carried out and completed prior to the publication of the International Neuroblastoma Remission Criteria, but the definitions used in this study were agreed unanimously by the trialists as they were considered to be "standard practice" at the time of the study. Complete remission was defined as disappearance of primary tumour as judged by abdominal imaging and of secondary deposits and normal urine catecholamine metabolite levels. Good partial remission was defined as (a) shrinkage of primary tumour by more than 50% in each of three dimensions, (b) reduction of urine catecholamine metabolite levels by more than 50% of the original values and (c) disappearance of secondary deposits including bone marrow involvement. In both types of response, however, isotope bone scan appearances need not have normalised as long as there was improvement at all sites reported as abnormal on the scan performed at diagnosis, with no new lesions.</p>

Pritchard 2005 (Continued)

Interventions	<p><i>Myeloablative therapy (n = 32):</i> According to protocol: melphalan 180 mg/ m², i.v. bolus, 4 to 8 weeks after surgery or final course of chemotherapy (whichever came first). Cumulative doses not mentioned. Total body irradiation not mentioned. Source of stem cells: bone marrow Timing of cell harvest: the day before melphalan Timing of stem cell rescue: after induction regimens Contamination with tumour cells: not mentioned Number of cells infused: 4.6 X 10⁸ nucleated cells of bone marrow per kg (range, 1.8 to 14.2) Purging: no <i>Conventional therapy (n = 33):</i> No further treatment</p>	
Outcomes	<p><i>Event-free survival</i> (defined as the time to relapse or death prior to relapse from randomisation). <i>Overall survival</i> (defined as the time to death from any cause from randomisation).</p>	
Notes	<p>Length of follow up not mentioned (median follow up for 21 surviving children was 14.3 years from randomisation (range 8.8 to 17.1 years)).</p>	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	Randomisation was performed at the co-ordinating data centre.

i.v.: intravenous; LDH: lactate dehydrogenase; s.c.: subcutaneous; vs: versus

Characteristics of excluded studies [ordered by study ID]

Adkins 2004	Patients also included in Matthay 1999
Berthold 1990	Not a RCT
Castel 2001	Not a RCT
Castel 2002	Not a RCT
Dini 1989	All patients underwent BMT
Dini 1991a	All patients underwent BMT
Dini 1991b	All patients underwent BMT

(Continued)

Garaventa 1993	Not a RCT; all patients underwent BMT
Haas-Kogan 2003	Patients also included in Matthay 1999
Hartmann 1985	All patients underwent BMT
Kaneko 1999	Not a RCT
Klingebliel 1994	All patients underwent transplant
Ladenstein 1991	Not a RCT; all patients underwent BMT
Ladenstein 1996	Not a RCT; all patients with stage IV underwent BMT
Madon 1985	Randomisation between chemotherapy and chemotherapy + immunotherapy
Matthay 1995	Not a RCT
Matthay 1996	Review of different study protocols
Matthay 1998	Not a RCT
Mugishima 1999	Not a RCT; review
Ohnuma 1995	Not a RCT
Olgun 2008	Not a RCT (even though this was stated in the abstract)
Paolucci 1989	Not a RCT
Philip 1991	All patients underwent BMT
Pinkerton 1991	Preliminary results of Pritchard 2005
Saarinen 1996	Not a RCT
Sawaguchi 1989	Not a RCT
Sawaguchi 1990	Not a RCT
Schmidt 2005	Patients also included in Matthay 1999
Seeger 1991	All patients underwent BMT
Seeger 2000	Patients also included in Matthay 1999
Shuster 1991	Not a RCT

(Continued)

Stram 1994	Not a RCT
Stram 1996	Not a RCT
Zucker 1991	All patients underwent BMT

RCT: randomised controlled trial; BMT: bone marrow transplant

DATA AND ANALYSES

Comparison 1. Transplant versus control

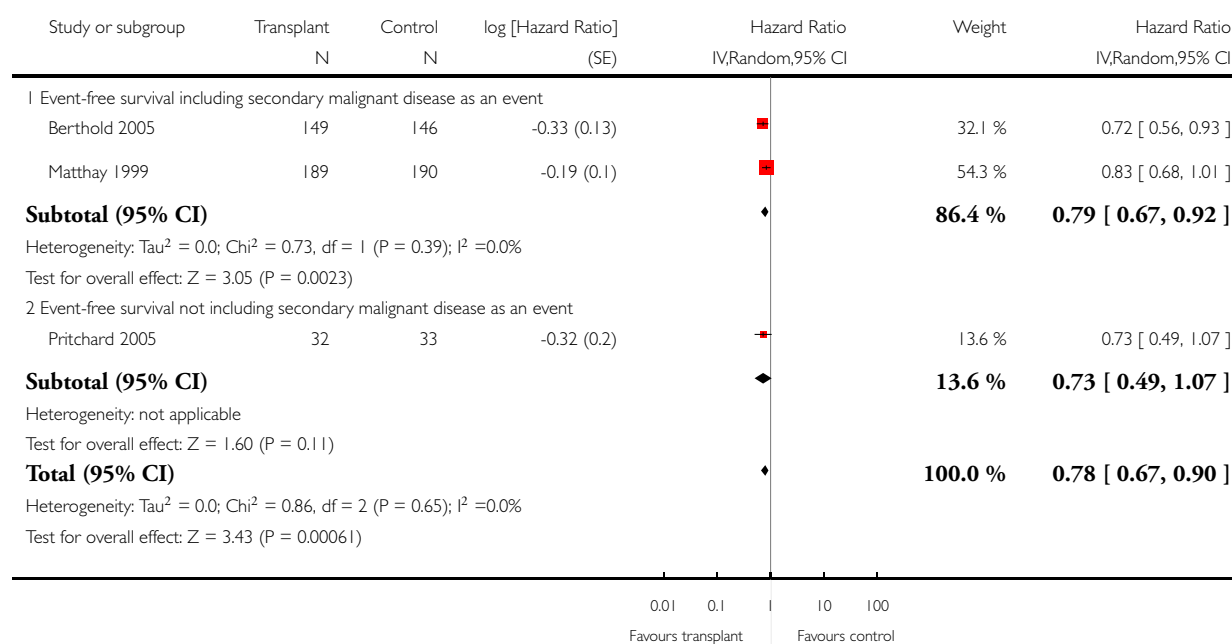
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Event-free survival	3	739	Hazard Ratio (Random, 95% CI)	0.78 [0.67, 0.90]
1.1 Event-free survival including secondary malignant disease as an event	2	674	Hazard Ratio (Random, 95% CI)	0.79 [0.67, 0.92]
1.2 Event-free survival not including secondary malignant disease as an event	1	65	Hazard Ratio (Random, 95% CI)	0.73 [0.49, 1.07]
2 Overall survival	2	360	Hazard Ratio (Random, 95% CI)	0.74 [0.57, 0.98]
3 Adverse effects grade 3 or higher	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Treatment-related death	2	574	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.17, 37.12]
3.2 Secondary malignant disease	2	674	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.14, 7.00]
3.3 Serious infections	1	379	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.84, 1.23]
3.4 Sepsis	1	379	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
3.5 Renal effects	1	379	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.28, 4.04]
3.6 Interstitial pneumonitis	1	379	Risk Ratio (M-H, Random, 95% CI)	9.55 [2.26, 40.43]
3.7 Venous-occlusive disease	1	379	Risk Ratio (M-H, Random, 95% CI)	35.18 [2.13, 580.88]

Analysis 1.1. Comparison 1 Transplant versus control, Outcome 1 Event-free survival.

Review: High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma

Comparison: 1 Transplant versus control

Outcome: 1 Event-free survival

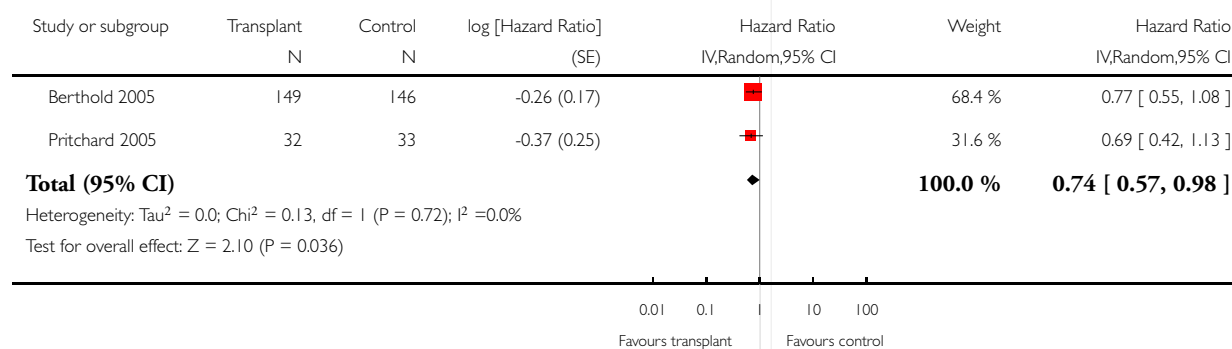


Analysis 1.2. Comparison 1 Transplant versus control, Outcome 2 Overall survival.

Review: High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma

Comparison: 1 Transplant versus control

Outcome: 2 Overall survival

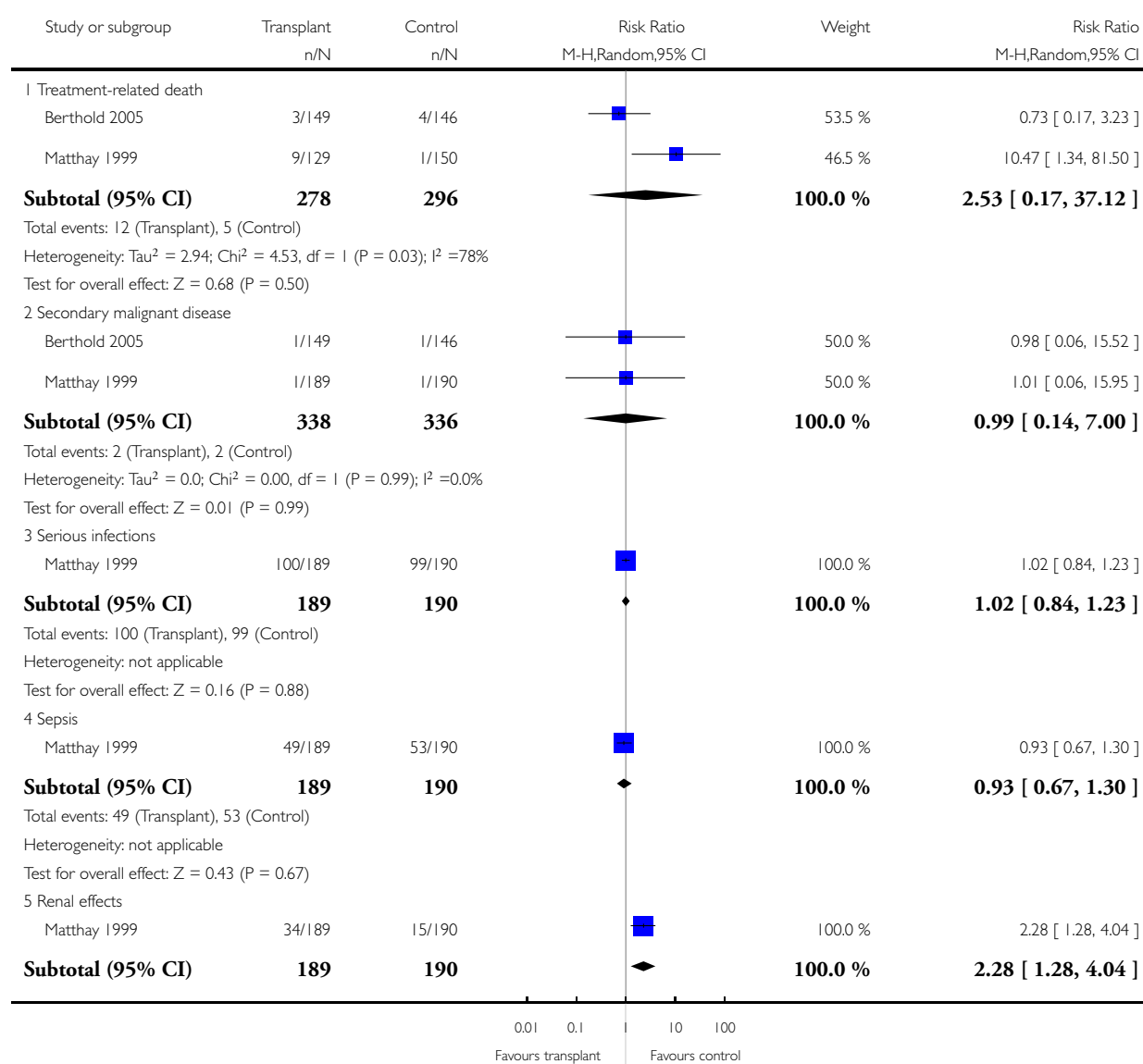


Analysis 1.3. Comparison 1 Transplant versus control, Outcome 3 Adverse effects grade 3 or higher.

Review: High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma

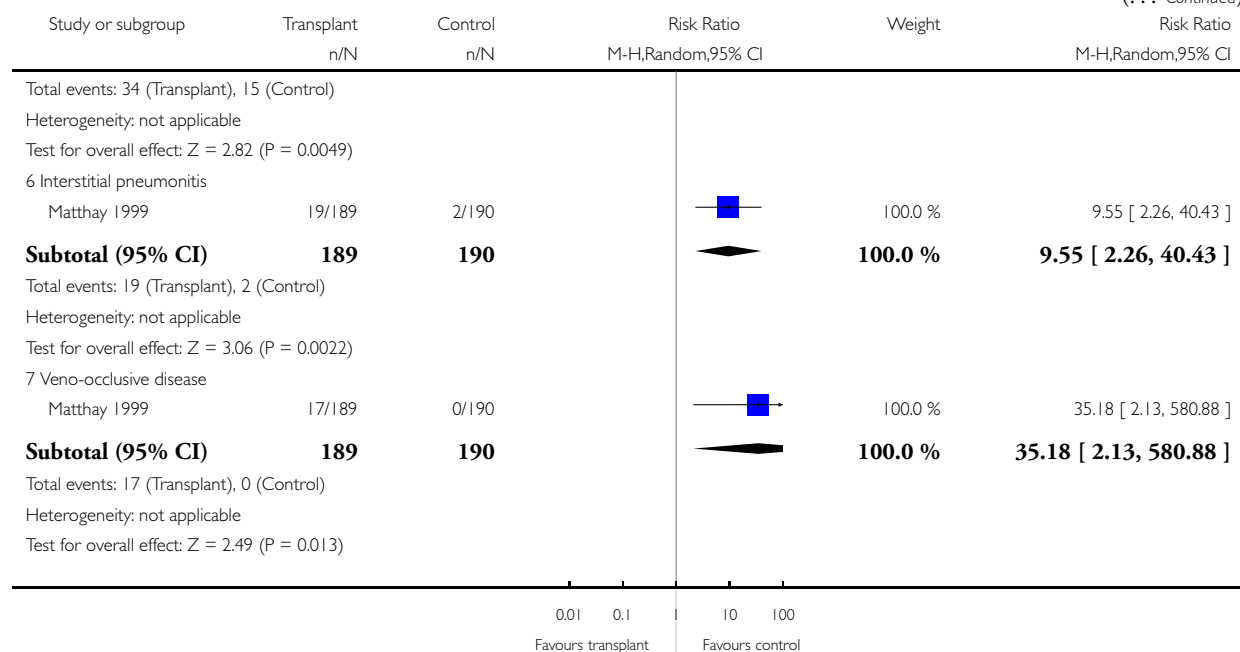
Comparison: 1 Transplant versus control

Outcome: 3 Adverse effects grade 3 or higher



(Continued . . .)

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APPENDICES

Appendix I. MEDLINE/PubMed search strategy

(1) For **neuroblastoma** we have used the following subject headings and text words:

neuroblastoma OR neuroblastomas OR ganglioneuroblastoma OR ganglioneuroblastomas OR neuroepithelioma OR esthesioneuroblastoma, olfactory OR neuroblast*

(2) For **bone marrow and stem cell rescue** the following subject headings and text words were used:

stem cell rescue OR bone marrow rescue OR 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 peripheral blood stem cell transplantation OR peripheral stem cell transplantation OR cord blood stem cell transplantation OR placental blood stem cell transplantation OR umbilical cord stem cell transplantation OR autograft OR autografts OR transplantation, autologous OR autotransplant OR autotransplants OR ABMT OR transplant* OR autolog* OR BMT OR myeloablative therapy OR myeloablative agonist OR myeloablative agonists OR myeloablative* OR mega therapy OR high-dose therapy OR high dose therapy

(3) For **children** the following subject headings and text words were used:

infant OR infan* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peditric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery

(4) For identifying **RCTs and CCTs** we used the highly sensitive search strategy as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005).

Finally, searches were combined as (1) AND (2) AND (3) AND (4).

[RCT: randomised controlled trial; CCT: controlled clinical trial].

Appendix 2. EMBASE/Ovid search strategy

(1) For **neuroblastoma** we have used the following subject headings and text words:

(neuroblastoma or neuroblastomas or ganglioneuroblastoma or ganglioneuroblastomas or neuroepithelioma or olfactory esthesioneuroblastoma or neuroblast\$ or neuroganglioblastoma).mp or neuroblastoma/ or olfactory neuroepithelioma/ or neuroepithelioma/ or esthesioneuroblastoma/ or neuroblastoma cell/

(2) For **bone marrow and stem cell rescue** the following subject headings and text words were used:

(stem cell rescue or bone marrow rescue).mp or (bone marrow transplantation or bone marrow grafting).mp or (bone marrow cell transplantation or stem cell transplantation or stem cell transplantations).mp or (hematopoietic stem cell transplantation or peripheral blood stem cell transplantation).mp or (peripheral stem cell transplantation or cord blood stem cell transplantation).mp or (placental blood stem cell transplantation or umbilical cord stem cell transplantation).mp or (autograft or autografts).mp or (autologous transplantation or autotransplant or autotransplants).mp or (BMT or ABMT or PBSCT).mp or transplant\$.mp or autolog\$.mp or (bone marrow transplant or bone marrow transfusion or bone marrow graft).mp or myeloablative therapy.mp or (myeloablative agonist or myeloablative agonists).mp or myeloablative\$.mp or mega therapy.mp or (high-dose therapy or high dose therapy).mp or autologous bone marrow transplantation/ or allogenic bone marrow transplantation/ or bone marrow transplantation/ or bone marrow rescue/ or myeloablative agent/ or stem cell transplantation/ or allogenic bone marrow transplantation/ or allogenic stem cell transplantation/ or autologous stem cell transplantation/ or peripheral blood stem cell transplantation/ or cord blood stem cell transplantation/ or hematopoietic stem cell transplantation/ or autograft/ or autotransplantation/ or allotransplantation/

(3) For **children** the following subject headings and text words were used:

Infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/ or adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/ or primary school/ or high school/ or kindergarten/ or nursery school/ or school/ or infant\$.mp or newborn\$.mp or new born\$.mp or (baby or baby\$ or babies).mp or neonate\$.mp or child\$.mp or (school child\$ or schoolchild\$).mp or (school age\$ or schoolage\$).mp or (pre school\$ or preschool\$).mp or (kid or kids).mp or toddler\$.mp or adoles\$.mp or teen\$.mp or boy\$.mp or girl\$.mp or minors\$.mp or (under ag\$ or underage\$).mp or juvenil\$.mp or youth\$.mp or puber\$.mp or pubescen\$.mp or prepubescen\$.mp or prepubert\$.mp or (pediatric\$ or paediatric\$ or peadiatric\$).mp or (school or schools).mp or (high school\$ or highschool\$).mp or primary school\$.mp or nursery school\$.mp or elementary school.mp or secondary school\$.mp or kindergar\$.mp

(4) For **RCTs and CCTs** the following subject headings and text words were used:

(a) clinical trial/ or controlled study/ or randomized controlled trial/ or double blind procedure/ or single blind procedure/ or comparative study/ or randomization/ or prospective study/ or placebo/ or phase 2 clinical trial/ or phase 3 clinical study.mp or phase 4 clinical study.mp or phase 3 clinical trial/ or phase 4 clinical trial/ or allocat\$.mp or blind\$.mp or control\$.mp or placebo\$.mp or prospectiv\$.mp or random\$.mp or ((singl\$ or doubl\$ or trebl\$ or tripl\$) and (blind\$ or mask\$)).mp or (versus or vs).mp or (randomized controlled trial\$ or randomised controlled trial\$.mp or controlled clinical trial\$.mp or clinical trial\$.mp

(b) human/ or nonhuman/ or animal/ or animal experiment/

(c) (b) not human/

(d) (a) not (c)

Finally, searches were combined as (1) AND (2) AND (3) AND (4).

[mp: title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name; RCT: randomised controlled trial; CCT: controlled clinical trial].

Appendix 3. CENTRAL search strategy

(1) For **neuroblastoma** we have used the following subject headings and text words:

(neuroblastoma OR neuroblastomas OR ganglioneuroblastoma OR ganglioneuroblastomas OR neuroepithelioma OR olfactory esthesioneuroblastoma OR neuroblast*) in Clinical Trials

(2) For **bone marrow and stem cell rescue** the following subject headings and text words were used:

(stem cell rescue OR bone marrow rescue OR 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 peripheral blood stem cell transplantation OR peripheral stem cell transplantation OR cord blood stem cell transplantation OR placental blood stem cell transplantation OR umbilical cord stem cell transplantation OR autograft OR autografts OR autologous transplantation OR

autotransplant OR autotransplants OR ABMT OR transplant* OR autolog* OR BMT OR myeloablative therapy OR myeloablative agonist OR myeloablative agonists OR myeloablative* OR mega therapy OR high-dose therapy OR high dose therapy) in Clinical Trials (3) For **children** the following subject headings and text words were used:

(infant OR infan* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy) in Clinical Trials

Finally, searches were combined as (1) AND (2) AND (3).

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 5, 2010

CONTRIBUTIONS OF AUTHORS

Bilgehan Yalçın designed the study and wrote the protocol. He identified studies meeting the inclusion criteria. He searched for unpublished and ongoing studies. He contributed to the interpretation of the results. He critically reviewed the review.

Leontien CM Kremer designed the study and critically reviewed the protocol. She contributed to the interpretation of the results. She critically reviewed the review.

Huib N Caron designed the study and critically reviewed the protocol. He contributed to the interpretation of the results. He critically reviewed the review.

Elvira C van Dalen designed the study and wrote the protocol. She developed the search strategy. She identified the studies meeting the inclusion criteria. She searched for unpublished and ongoing studies. She interpreted the results. She wrote and revised the review.

All authors approved the final version.

DECLARATIONS OF INTEREST

None.

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