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Anti-GD2 antibody-containing immunotherapy postconsolidation therapy for people with high-risk neuroblastoma treated with autologous haematopoietic stem cell transplantation (Review)

Peinemann F, van Dalen EC, Enk H, Tytgat GAM

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[Intervention Review]

Anti-GD2 antibody-containing immunotherapy postconsolidation therapy for people with high-risk neuroblastoma treated with autologous haematopoietic stem cell transplantation

Frank Peinemann[1], Elvira C van Dalen[2], Heike Enk[3], Godelieve AM Tytgat[2]

[1]Pediatric Oncology and Hematology, Children's Hospital, University of Cologne, Cologne, Germany. [2]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands. [3]c/o Cochrane Childhood Cancer, Amsterdam, Netherlands

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

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ABSTRACT

Background

Neuroblastoma is a rare malignant disease that primarily affects children. The tumours mainly develop in the adrenal medullary tissue, and an abdominal mass is the most common presentation. High-risk disease is characterised by metastasis and other primary tumour characteristics resulting in increased risk for an adverse outcome. The GD2 carbohydrate antigen is expressed on the cell surface of neuroblastoma tumour cells and is thus a promising target for anti-GD2 antibody-containing immunotherapy.

Objectives

To assess the efficacy of anti-GD2 antibody-containing postconsolidation immunotherapy after high-dose chemotherapy (HDCT) and autologous haematopoietic stem cell transplantation (HSCT) compared to standard therapy after HDCT and autologous HSCT in people with high-risk neuroblastoma. Our primary outcomes were overall survival and treatment-related mortality. Our secondary outcomes were progression-free survival, event-free survival, early toxicity, late non-haematological toxicity, and health-related quality of life.

Search methods

We searched the electronic databases CENTRAL (2018, Issue 9), MEDLINE (PubMed), and Embase (Ovid) on 20 September 2018. We searched trial registries and conference proceedings on 28 October 2018. Further searches included reference lists of recent reviews and relevant articles as well as contacting experts in the field. There were no limits on publication year or language.

Selection criteria

Randomised controlled trials evaluating anti-GD2 antibody-containing immunotherapy after HDCT and autologous HSCT in people with high-risk neuroblastoma.

Data collection and analysis

Two review authors independently performed study selection, abstracted data on study and participant characteristics, and assessed risk of bias and GRADE. Any differences were resolved by discussion, with third-party arbitration unnecessary. We performed analyses according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions*. We used the five GRADE considerations, that is study limitations, consistency of effect, imprecision, indirectness, and publication bias, to judge the quality of the evidence.

Main results

We identified one randomised controlled trial that included 226 people with high-risk neuroblastoma who were pre-treated with autologous HSCT. The study randomised 113 participants to receive immunotherapy including isotretinoin, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2, and ch14.18, a type of anti-GD2 antibody also known as dinutuximab. The study randomised another 113 participants to receive standard therapy including isotretinoin.

The results on overall survival favoured the dinutuximab-containing immunotherapy group (hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.31 to 0.80; P = 0.004). The results on event-free survival also favoured the dinutuximab-containing immunotherapy group (HR 0.61, 95% CI 0.41 to 0.92; P = 0.020). Randomised data on adverse events were not reported separately. The study did not report progression-free survival, late non-haematological toxicity, and health-related quality of life as separate endpoints. We graded the quality of the evidence as moderate.

Authors' conclusions

The evidence base favours dinutuximab-containing immunotherapy compared to standard therapy concerning overall survival and event-free survival in people with high-risk neuroblastoma pre-treated with autologous HSCT. Randomised data on adverse events are lacking, therefore more research is needed before definitive conclusions can be made regarding this outcome.

PLAIN LANGUAGE SUMMARY

Anti-GD2 antibody-containing immunotherapy for people with high-risk neuroblastoma treated with autologous haematopoietic stem cell transplantation

Review question

We searched for studies of people with high-risk neuroblastoma who received high-dose chemotherapy (which kills stem cells) followed by autologous (from the same person) haematopoietic stem cell (blood cell precursors) transplantation (to rescue and replace the killed stem cells). We reviewed the evidence concerning the effect of anti-GD2 antibody-containing immunotherapy compared to standard therapy in such people on overall survival, treatment-related death, progression-free survival, event-free survival, early toxicity, late non-haematological toxicity, and health-related quality of life.

Background

Neuroblastoma is a rare form of cancer that primarily affects children. High-risk disease is characterised by metastasis at diagnosis and other primary tumour characteristics resulting in increased risk for an poor outcome. The GD2 carbohydrate antigen is expressed on the cell surface of neuroblastoma tumour cells and is thus a promising target for anti-GD2 antibody-containing immunotherapy.

Study characteristics

The evidence is current to 20 September 2018. We included a single randomised trial (a type of study in which participants are assigned to one of two or more treatment groups using a random method) with 113 people allocated to immunotherapy including isotretinoin, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2, and ch14.18, a distinct type of anti-GD2 antibody also known as dinutuximab. Another 113 people were allocated to receive standard therapy including isotretinoin.

Key results

The results on overall survival and event-free survival favoured the dinutuximab-containing immunotherapy group. Other outcomes including those on adverse events were not adequately reported; more research is needed before definitive conclusions can be made regarding these outcomes.

Quality of the evidence

We assessed the quality of the evidence as moderate.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Dinutuximab-containing immunotherapy compared to standard therapy for people with high-risk neuroblastoma pre-treated with autologous hematopoietic stem cell transplantation

Dinutuximab-containing immunotherapy compared to standard therapy for people with high-risk neuroblastoma pre-treated with autologous haematopoietic stem cell transplantation

Patient or population: People with high-risk neuroblastoma pre-treated with autologous haematopoietic stem cell transplantation
Setting: Paediatric oncology and haematology, specialised centres
Intervention: Dinutuximab-containing immunotherapy
Comparison: Standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with dinutuximab-containing immunotherapy				
Overall survival (reported as mortality)	549 per 1000[1]	328 per 1000 (219 to 471)	HR 0.50 (0.31 to 0.80)	226 (1 RCT)	⊕⊕⊕⊖ MODERATE[2,3]	The follow-up time regarding all randomised participants is unclear. Median follow-up after randomisation in participants alive without an event was 2.0 years (5 days to 6.5 years) and 2.1 years (4 days to 6.9 years) for the dinutuximab-containing immunotherapy arm and the standard therapy arm, respectively.
Treatment-related mortality - not reported	See comment	See comment	Not estimable	-	See comment	No adequate information on this outcome was provided. Randomised data were mixed with non-randomised data, and the randomised data were not analysed separately, so this outcome could not be assessed.
Progression-free survival - not reported	See comment	See comment	Not estimable	-	See comment	No information on this outcome was provided.
Event-free survival (reported as relapse, progressive disease, secondary cancer, and mortality)	717 per 1000[1]	537 per 1000 (404 to 687)	HR 0.61 (0.41 to 0.92)	226 (1 RCT)	⊕⊕⊕⊖ MODERATE[3,4]	The follow-up time regarding all randomised participants is unclear. Median follow-up after randomisation in participants alive without an event was 2.0 years (5 days to 6.5 years) and 2.1 years (4 days to 6.9 years) for the dinutuximab-containing immunotherapy arm and the standard therapy arm, respectively.

Early toxicity - not reported	See comment	See comment	Not estimable	-	See comment	No adequate information on this outcome was provided. Randomised data were mixed with non-randomised data, and the randomised data were not analysed separately, so this outcome could not be assessed.
Late non-haematological toxicity - not reported	See comment	See comment	Not estimable	-	See comment	No information on this outcome was provided.
Health-related quality of life - not reported	See comment	See comment	Not estimable	-	See comment	No information on this outcome was provided.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR**: hazard ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]The assumed risk is based on the number of events in the control group at the final time point of the survival curve presented in the included study.
[2]The presence of selection bias, performance bias, attrition bias, and other bias is unclear; there is a low risk of detection bias and reporting bias; we downgraded one level for study limitations.
[3]We did not downgrade for imprecision. The study is small but the effect is large and the confidence interval is below no effect.
[4]The presence of selection bias, performance bias, detection bias, attrition bias, and other bias is unclear; there is a low risk of reporting bias; we downgraded one level for study limitations.

BACKGROUND

Description of the condition

Neuroblastoma is a rare malignant disease that primarily affects children (GARD 2016; Park 2013; Pinto 2015). Tumours develop in the sympathetic nervous system (e.g. in the adrenal medullary tissue or paraspinal ganglia) and may be localised or metastatic at diagnosis (Bagatell 2016; Cole 2012; Matthay 2016). The median age at diagnosis is 17 months, and the incidence rate of neuroblastoma is age-dependent: 64 per million children in the first year of life, falling to 29 per million children in the second year of life (Goodman 1999). The incidence rate in adults is less than one per million per year, but adults have a considerably worse prognosis (Esiashvili 2007). The International Neuroblastoma Risk Group (INRG) classification system, proposed by Cohn 2009, is shown in Table 1. The authors of Cohn 2009 have estimated the event-free survival for each of the four risk groups and tested the clinical importance of 13 potential prognostic factors. The Children's Oncology Group (COG) assignment to low-, intermediate-, and high-risk groups, published by the National Cancer Institute (NCI) at the National Institutes of Health (NIH) (NCI PDQ 2018), is shown in Table 2.

Neuroblastoma originates mostly in the abdomen, in the adrenal medulla, or along the sympathetic nervous system side chain. As approximately 70% of children with neuroblastoma have metastatic disease at diagnosis, organ-specific symptoms may be caused by the local presence of metastases, such as eye problems associated with retrobulbar tumours, pancytopenia associated with bone marrow infiltration, abdominal distension and respiratory problems associated with liver enlargement, and paralysis and Horner syndrome associated with ganglion involvement (Maris 2010; Matthay 2016; NCI PDQ 2018). Some neuroblastomas regress spontaneously without therapy, whereas others progress and have a fatal outcome despite therapy (NCI PDQ 2018). A tumour mass and the presence of metastases may be confirmed on ultrasound, X-ray, computed tomography, scintigraphy using metaiodobenzylguanidine (MIBG scan), or magnetic resonance imaging. Guidelines for using imaging methods have been developed in response to the increased importance of image-defined factors in staging and risk assessment (Bleeker 2015; Brisse 2011). The International Neuroblastoma Staging System (INSS) for neuroblastoma is shown in Table 3; INSS definitions of treatment response are shown in Table 4 (Brodeur 1993).

The American Cancer Society has reported the five-year survival rates for neuroblastoma based on the COG risk groups: low risk (95%), intermediate risk (90% to 95%), and high risk (40% to 50%) (American Cancer Society 2016; Park 2013). It was stated: "The 5-year survival rate refers to the percentage of children who live at least 5 years after their cancer is diagnosed." It should be noted that historical survival data should be used cautiously, as medical advancement has achieved more favourable outcomes.

Description of the intervention

According to Pinto 2015, the current standard-of-care treatment strategy for high-risk neuroblastoma consists of three treatment blocks: induction (chemotherapy and primary tumour resection), consolidation (high-dose chemotherapy with autologous stem cell rescue and external-beam radiotherapy), and postconsolidation (anti-GD2 immunotherapy with cytokines and cis-retinoic acid). Rapid COJEC (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide) induction chemotherapy was evaluated by Peinemann 2015b; high-dose chemotherapy with autologous stem cell rescue by Yalcin 2015; anti-GD2 antibody ch14.18 combined with cytokines by Yu 2010; and retinoic acid by Peinemann 2015c.

A small number of tumour cells may survive and cause regrowth and new metastasis. This so-called minimal residual disease is associated with relapse and eventual cancer treatment failure (Kushner 2015). Bone marrow minimal residual disease was an early response marker and a consistent independent predictor of survival after anti-GD2 immunotherapy (Cheung 2015; Stutterheim 2011; Viprey 2014). As the majority of patients relapse even after intense therapy, research tries to identify alternative treatment modalities that hopefully can attain an improved outcome (Cheung 2015). Immunotherapy is one of various alternatives, and it has shown promising effects not only with neuroblastoma but also with other diseases such as metastasising renal cell carcinoma (Unverzagt 2017). Ploessl 2016 stated: "For patients achieving clinical remission, limited treatments exist for preventing relapse." The ganglioside GD2 is a T-cell independent carbohydrate antigen that is expressed on the cell surface during foetal development (Perez-Horta 2016). In healthy people, it is restricted mainly to neurons, melanocytes, and pain fibres (Cheung 2013). However, it is highly expressed on neuroectoderm-derived tumours including neuroblastoma (Ahmed 2014). GD2 is thus a promising target for antibody-based immunotherapy (Cheung 2013). It is believed that anti-GD2 antibody therapy can achieve continual remission (Cheung 2013); may improve relapses (Matthay 2012); and enable long-term progression-free survival (Kushner 2015). Anti-GD2 antibodies may be applied either as monotherapy or as part of an immunotherapy that combines anti-GD2 antibodies with interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Kushner 2015).

'Anti-GD2 antibodies' is an umbrella term for various types of anti-GD2 antibodies for GD2-expressing neuroblastoma, for example murine antibodies, chimeric antibody, and humanised antibodies (Cheung 2012; Cheung 2014; Navid 2010). This Cochrane Review includes various possible anti-GD2 monoclonal antibodies. When anti-GD2 antibodies are mentioned, they are identified appropriately, such as 14G2a, ch14.18, ch14.18beta, 3F8, hu3F8, or hu14.18.

Concerning the dose of anti-GD2, Simon 2011a applied 20 mg/m^2/day on five subsequent days, and ANBL0032 applied 25 mg/m^2/day for four subsequent days. According to Navid 2014, "The most common non–dose-limiting grade 3 or 4 toxicities during course one were pain in 68% (26 of 38) patients and fever in 21% (8 of 38) patients." Pain management may include paracetamol (acetaminophen), ibuprofen, morphine, fentanyl, gabapentin, and lidocaine (Ploessl 2016). Other reported toxicities include anaphylactoid reactions, posterior reversible encephalopathy syndrome (Kushner 2016), as well as capillary leak syndrome and hypotension (Ploessl 2016). The application of further toxic drugs is thus required to keep adverse events manageable.

Why it is important to do this review

According to the follow-up analysis of a cohort study, Simon 2011a reported that anti-GD2 antibody ch14.18 provided a better nine-year overall survival compared to no additional therapy.

Simon 2011a also suggested that anti-GD2 antibody ch14.18 may prevent late relapses. This would be a vital improvement because it is known that recurrent disease can occur in any patient including those who have achieved complete remission (Berthold 2018). Based on a randomised study, Yu 2010 concluded that immunotherapy with ch14.18, GM-CSF, and interleukin-2 was associated with a significantly improved outcome as compared with standard therapy in people with high-risk neuroblastoma. It is important to evaluate if such a beneficial outcome can be substantiated with available study data. It is also important to evaluate potential treatment-related complications and to search for ongoing trials that might influence the conclusion in timely updates.

OBJECTIVES

To assess efficacy of anti-GD2 antibody-containing postconsolidation immunotherapy after high-dose chemotherapy (HDCT) and autologous haematopoietic stem cell transplantation (HSCT) compared to standard therapy after HDCT and autologous HSCT in people with high-risk neuroblastoma. Our primary outcomes were overall survival and treatment-related mortality. Our secondary outcomes were progression-free survival, event-free survival, early toxicity, late non-haematological toxicity, and health-related quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials to evaluate efficacy.

Types of participants

People with high-risk neuroblastoma according to the INRG or the COG classification of risk groups shown in Table 1 and Table 2. We planned that if not all participants were eligible for inclusion, we would include such studies when information on eligible participants was presented separately.

Types of interventions

Intervention

Anti-GD2 antibody-containing immunotherapy as part of a postconsolidation therapy after high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation.

Comparator

Standard therapy after high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation.

Types of outcome measures

The outcomes listed here are not used as criteria for including studies, but are the outcomes of interest within studies identified for inclusion.

Primary outcomes

- Overall survival (as defined in the original studies).
- Treatment-related mortality: incidence of deaths that were classified as treatment related or the participants died of treatment complications.

Secondary outcomes

- Progression-free survival (as defined in the original studies).
- Event-free survival (as defined in the original studies).
- Early toxicity: adverse events within 90 days of the therapy; incidence of all reported adverse events and severe (grade 3 and 4) events; and incidence of toxicity-related discontinuations from treatment. Examples of potentially used classification systems: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 2018); World Health Organization (WHO) toxicity grading scale for determining the severity of adverse events (ICSSC 2003).
- Late non-haematological toxicity such as organ toxicity and secondary malignancy.
- Health-related quality of life measured by validated questionnaires.

Search methods for identification of studies

We used search methods as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011) and by Cochrane Childhood Cancer (Kremer 2018). We planned to update the search every two years. We did not apply any publication year or language restrictions. Cochrane Childhood Cancer ran the searches in CENTRAL, MEDLINE, and Embase; the review authors ran all other searches.

Electronic searches

We conducted an electronic literature database search in the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library) on 20 September 2018 in Issue 9 of 2018 (Appendix 1). We searched in MEDLINE (PubMed format) on 20 September 2018 for articles published from 1946 onwards using the search strategy shown in Appendix 2, and we searched in Embase (Ovid format) on 20 September 2018 for articles published from 1980 onwards (Appendix 3). We tailored the terms and syntax used for the search in MEDLINE to the requirements of the other two databases.

We scanned the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) for ongoing trials on 28 October 2018 using the term 'neuroblastoma' in the field condition and 'anti gd2' in the field intervention. We also scanned the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/) for ongoing trials on 28 October 2018 using the term 'neuroblastoma AND anti gd2' in the search field.

Searching other resources

We searched for information about trials not registered in electronic databases, either published or unpublished, in the reference lists of relevant articles and review articles. We asked experts in the field for missing information on potentially eligible studies.

We searched for abstracts presented at the annual meetings of the American Society of Clinical Oncology (ASCO), the American Society of Pediatric Hematology/Oncology (ASPHO), the International Society of Paediatric Oncology (SIOP), and the Advances in Neuroblastoma Research (ANR) Association using the terms 'neuroblastoma' and 'anti-gd2'. We planned to search the abstracts of the last five consecutive annual meetings. We searched the abstracts in the congress proceedings of the following ANR

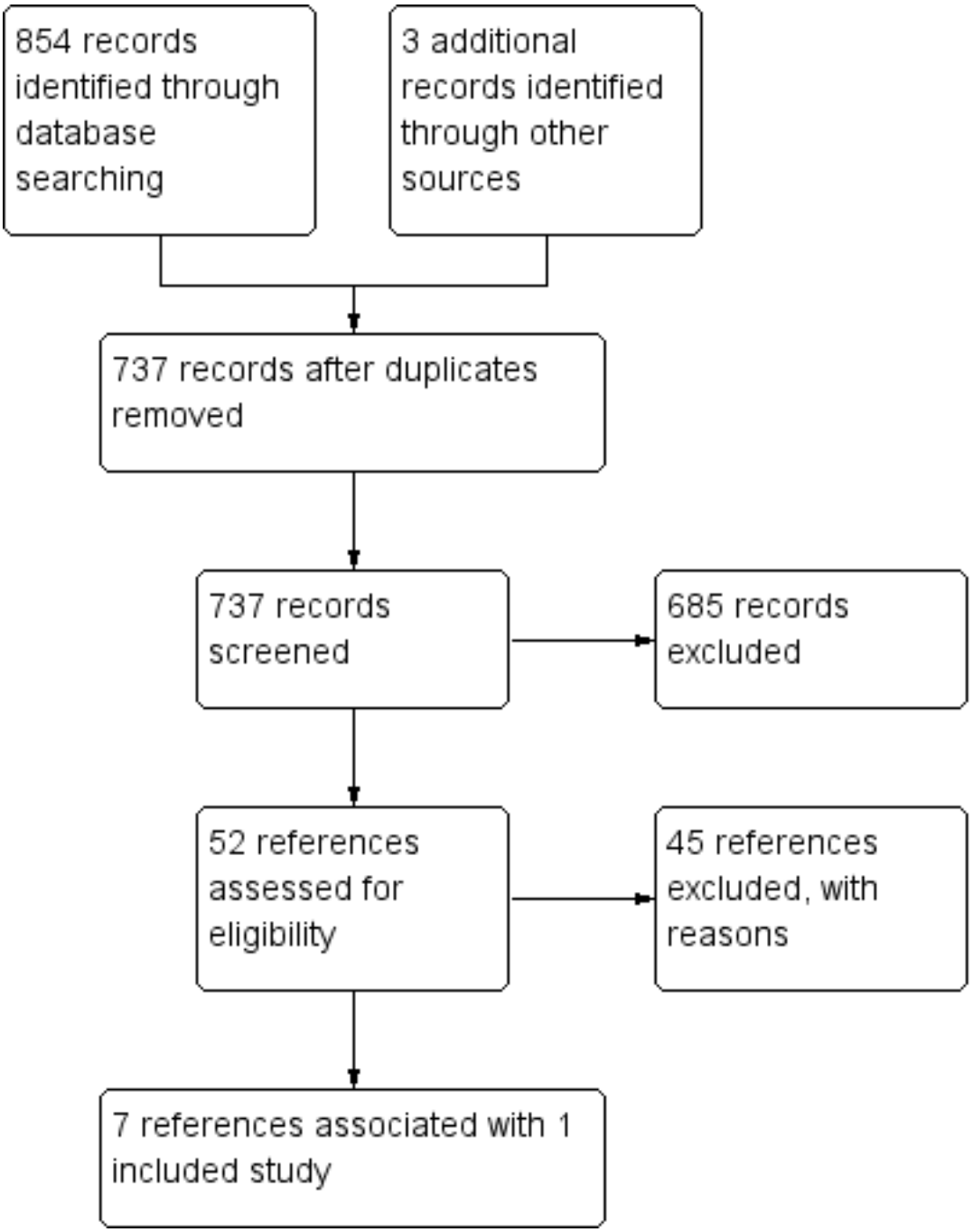
meetings, which took place every other year: ANR Meeting 2012; ANR Meeting 2014; ANR Meeting 2016; ANR Meeting 2018. We searched the abstracts in the congress proceedings of SIOP Meeting 2017 and SIOP Meeting 2018, and we searched the online meeting archive of ASCO Meeting 2018. We did not search abstracts of meetings before 2012. The abstracts of the following meetings were covered by the search results from the Embase database: ASCO meetings from 2012 to 2017, ASPHO meetings from 2012 to 2018, and SIOP meetings from 2012 to 2016; we therefore did not double search the congress proceedings of those.

Data collection and analysis

Selection of studies

While preparing this systematic review, we endorsed the PRISMA statement, adhered to its principles, and conformed to its checklist (Moher 2009). We downloaded all titles and abstracts retrieved by electronic searching to an Excel spreadsheet and removed any duplicates (Microsoft Corp 2011). Two review authors independently examined any remaining references. We included a study selection flow chart in the review (Figure 1).

Figure 1. Study flow diagram.



We excluded those studies that clearly did not meet our inclusion criteria and obtained full-text copies of potentially relevant references. Two review authors independently assessed the eligibility of retrieved papers. Any disagreements were resolved by discussion between the two review authors, with no third-party arbitration needed. We documented reasons for exclusion. If we identified multiple reports of one study, we used the most-up-to-date full-text results. We checked the multiple reports for possible duplicate data, addressed the issue, and did not include duplicate data in the analysis.

Data extraction and management

Two review authors independently extracted from the included studies data on characteristics of participants (inclusion criteria, age, stage, comorbidity, previous treatment, number enrolled in each arm) and interventions (type of anti-GD2 antibody-containing immunotherapy and standard induction therapy, dose applied, duration of therapy, control treatment), risk of bias, duration of follow-up, outcomes, funding source, conflicts of interest of primary investigators, and deviations from protocol into the review. We noted the time points at which outcomes were collected and reported. Any differences between review authors were resolved by discussion with no third-party arbitration needed.

Assessment of risk of bias in included studies

Two review authors independently appraised the risk of bias in the included studies. Any differences between review authors were resolved by discussion with no third-party arbitration needed. We used the items listed in the module of Cochrane Childhood Cancer (Kremer 2018), which is based on Cochrane's tool for assessing risk of bias (Higgins 2011a):

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants (performance bias);
- blinding of personnel (performance bias);
- blinding of outcome assessment (detection bias) for each outcome separately if appropriate;
- incomplete outcome data such as missing data (attrition bias) for each outcome separately;
- selective reporting, such as not reporting prespecified outcomes (reporting bias); and
- other sources of bias, such as bias related to the specific study design (other bias).

We applied Cochrane's criteria for judging risk of bias (Higgins 2011a). In general, a 'low risk' of bias was attributed if plausible bias was unlikely to have a marked effect on the results; for example, participants and investigators enrolling participants could not have foreseen assignment. A 'high risk' of bias was attributed if plausible bias seriously weakened confidence in the results; for example, participants or investigators enrolling participants could possibly have foreseen assignments. An 'unclear' risk of bias was attributed if plausible bias raised some doubts about the results; for example, the method of concealment was not described or not described in sufficient detail to permit a definitive judgement. In addition to a 'Risk of bias' table, we included a methodological quality summary figure. We took into account the results of the 'Risk of bias' assessment when interpreting the results of the review.

Measures of treatment effect

For time-to-event data, such as survival, we extracted the hazard ratio (HR) and its standard error or confidence interval (CI) from trial reports; if these were not reported, then we attempted to estimate the log (HR) and its standard error using the methods of Parmar 1998 and Tierney 2007.

For dichotomous outcomes (e.g. response, adverse events, and treatment-related mortality), we planned to extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR). This was not applicable, as no such outcomes were addressed in the single included study.

For continuous outcomes (e.g. quality of life measures), we planned to extract the final value or change from baseline and corresponding standard deviation of the outcome of interest, and the number of participants assessed at endpoint in each treatment arm at the end of follow-up. We planned to analyse and present continuous data as mean difference (MD) provided all the results were measured on the same scale (e.g. length of hospital stay). If this was not the case (e.g. pain or quality of life), we planned to use the standardised mean difference (SMD). This was not applicable as no such outcomes were addressed in the single included study.

Dealing with missing data

We conformed to Cochrane's principal options for dealing with missing data (Higgins 2011b). If data were missing, or if only imputed data were reported, we planned to contact trial authors to request data on the outcomes for participants who were assessed. The single included study did not report the randomised toxicity data separately from the non-randomised toxicity data (ANBL0032), therefore we could not include the pooled data in the review. If the study included an analysis of the randomised toxicity data only, then we could include the results in our review. We thus emailed Alice Yu, the principal investigator of the study, asking if she could send us the results of the separate analysis.

When relevant data regarding study selection, data extraction, and 'Risk of bias' assessment were missing, we attempted to contact the study authors to retrieve the missing data. The study titled 'High risk neuroblastoma study 1.7 of SIOP-Europe (SIOPEN)', which is registered at ClinicalTrials.gov (clinicaltrials.gov/ct2/show/NCT01704716), includes four different randomisation procedures. The so-called R4 randomisation includes retinoic acid and anti-GD2 antibody and is described at ClinicalTrials.gov as "isotretinoin and ch14.18/CHO, with or without aldesleukin (IL-2)". We were unsure of the exact study design. We emailed Ruth Ladenstein, principal investigator of the study, to clarify eligibility. She promptly responded that participants in both arms received the anti-GD2 antibody "ch14.18/CHO". Because there was no arm without anti-GD2 antibody, we excluded references associated with this study.

Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which we analysed all participants in the groups to which they had been assigned. If this was not possible, we would report this. The single included study conducted an intention-to-treat analysis.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials that cannot be ascribed to sampling variation (I^2 statistic) (Higgins 2003), and, if possible, by sensitivity analyses. If there was evidence of substantial heterogeneity, we planned to investigate and report the possible reasons for it. We considered an I^2 statistic greater than 50% as indicative of substantial heterogeneity. This was not applicable as only one study was included in the review.

Assessment of reporting biases

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

Data synthesis

We analysed data using Review Manager 5 (RevMan 2014). This was done by one review author and checked by another review author. If sufficient, clinically similar studies were available, we planned to pool their results in meta-analyses if comparable outcome definitions were used. Otherwise, we planned to present the results descriptively. If any trials had multiple treatment groups, we planned to divide the 'shared' comparison group into the number of treatment groups, and treat comparisons between each treatment group and the split comparison group as independent comparisons. Random-effects models with inverse variance weighting were used for all meta-analyses (DerSimonian 1986). Not all planned methods were applicable as only one study was included in the review. In cases with zero events in one group, we calculated P values using Fisher's exact test (Social Science Statistics 2018).

For each comparison, we used GRADEpro GDT software to prepare a 'Summary of findings' table in which we presented the following outcomes: overall survival, treatment-related mortality, progression-free survival, event-free survival, early toxicity, late non-haematological toxicity, and health-related quality of life (GRADEpro GDT 2015). For each outcome, two review authors independently assessed the quality of the evidence by using the five GRADE considerations, that is study limitations, inconsistency, indirectness, imprecision, and publication bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Sensitivity analysis

For all outcomes for which pooling was possible, we planned to perform sensitivity analyses for all 'Risk of bias' criteria separately. We planned to exclude studies with a high risk of bias and studies for which the risk of bias was unclear in sensitivity analyses, and compare the results of studies with a low risk of bias with the results of all available studies. We planned to perform sensitivity analyses only when at least two studies with a low risk of bias remained in the analyses. This was not applicable as only one study was included in the review.

RESULTS

Description of studies

Results of the search

Running the searches in the electronic databases CENTRAL, MEDLINE, and Embase yielded a total of 734 distinct references. We identified one reference through searching the ongoing trials registries and two references through searching the Advances in Neuroblastoma Research (ANR) congress proceedings (Figure 1). Scanning the reference lists of relevant studies and asking experts in the field did not result in any additional references.

Following initial screening of the titles, abstracts, or both, we excluded 685 references that clearly did not meet our inclusion criteria. We assessed the 52 remaining references in full, of which seven fulfilled our inclusion criteria and were thus eligible for inclusion in the review, and 45 were excluded with reasons (Characteristics of excluded studies). One full-text article was associated with one included study (ANBL0032). Five conference proceedings and one ClinicalTrials.gov record were also associated with this study (ANBL0032); however, as it is understood that information provided in conference proceedings often differs substantially from information provided in subsequent full-text publications (Yoon 2012), we did not include these results in our analyses. An overview of reference and study selection is provided in Figure 1.

Included studies

Details of the characteristics of the single included study, ANBL0032, are provided in the Characteristics of included studies table.

Design

We judged the single included study, ANBL0032, to be a randomised, prospective, parallel, controlled clinical trial. The study enrolled participants from 2001 to 2009.

Sample sizes

ANBL0032 randomised 226 participants with high-risk neuroblastoma after high-dose chemotherapy (HDCT) followed by autologous haematopoietic stem cell transplantation (HSCT) to dinutuximab-containing immunotherapy (N = 113) or standard therapy (N = 113).

Setting

ANBL0032 was conducted as a multicentre study in 166 centres mainly in the USA, some in Canada, and a few in Australia.

Participants

ANBL0032 included people with high-risk neuroblastoma who had a complete, very good, or partial response after HDCT followed by autologous HSCT. Subsequently, patients with progressive disease were not included. The majority of participants were classified as stage 4 of the International Neuroblastoma Staging System (INSS). The Characteristics of included studies table shows a considerable clinical heterogeneity among the participants of the study with respect to response before autologous HSCT, INSS stage, and *MYCN*

status. A proportion of 23% (52 of 226) had partial response before autologous HSCT; 20% (45 of 226) had INSS stage 2, 3, 4S, or unknown; and 54% (123 of 226) had tumour *MYCN* status amplified or unknown.

Interventions

ANBL0032 randomised 113 participants to the dinutuximab-containing immunotherapy group. The treatment of participants in the dinutuximab-containing immunotherapy group consisted of isotretinoin + dinutuximab (a distinct type of anti-GD2 antibody) + granulocyte-macrophage colony-stimulating factor (GM-CSF) + interleukin-2 scheduled in 6 cycles with a total duration of 24 weeks (see Characteristics of included studies). ANBL0032 randomised 113 participants to the standard therapy group. The treatment of participants in the standard therapy group consisted of isotretinoin scheduled in 6 cycles with a total duration of 24 weeks (see Characteristics of included studies).

Primary outcome

ANBL0032 reported the following outcomes regarded as primary outcomes by the present Cochrane Review and compliant with the inclusion criteria of the present review.

- Overall survival

Secondary outcomes

ANBL0032 reported the following outcomes regarded as secondary outcomes by the present Cochrane Review and compliant with the inclusion criteria of the present review.

- Event-free survival

ANBL0032 did not report progression-free survival, late non-haematological toxicity, or health-related quality of life.

Excluded studies

We excluded 45 of 52 evaluated full-text articles (Figure 1). We determined the reasons for exclusion as follows.

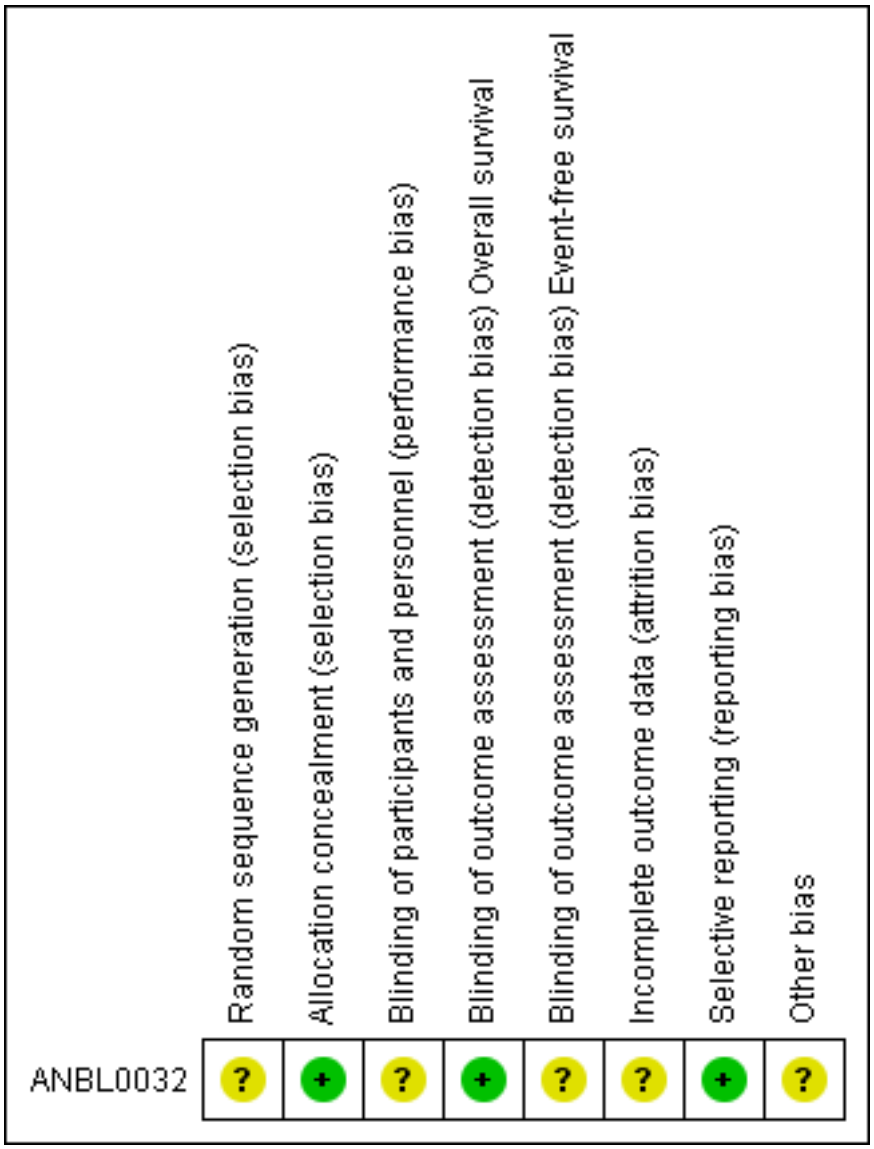
- Not population of interest: high-risk neuroblastoma (N = 0)
- Not intervention of interest: anti-GD2 antibody-containing immunotherapy (N = 4)
- Not comparator of interest: standard therapy (N = 22)
- Not outcome of interest (N = 0)
- Not study design of interest (N = 19)

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

Risk of bias in included studies

Details of each item of the 'Risk of bias' tool for the included study are provided in the the 'Risk of bias' table in Characteristics of included studies. An overview is provided in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The method of random sequence generation appeared to be conditional. We do not know if the condition applied and had any effect. We judged ANBL0032 as having an unclear risk of bias for random sequence generation. We assumed that the allocation concealment was provided by the remote system. We judged this study as having a low risk of bias for allocation concealment. Overall we judged ANBL0032 as having an unclear risk of selection bias.

Blinding

Blinding of participants and physicians and nurses was not reported. We judged ANBL0032 as having an unclear risk of performance bias. Blinding of outcome assessors was not reported, but that is not relevant for the outcome overall survival. We judged the outcome overall survival as having a low risk of detection bias. However, blinding of outcome assessors may be relevant for the outcome event-free survival. We judged the outcome event-free survival as having an unclear risk of detection bias.

Incomplete outcome data

In the dinutuximab-containing immunotherapy arm, 5% (6 of 113) of randomised participants did not receive the assigned intervention, and 31% (35 of 113) did not complete the entire assigned intervention. In the standard therapy arm, 6% (7 of 113) of randomised participants did not receive the assigned intervention, and 27% (30 of 113) did not complete the entire assigned intervention. The authors stated that they performed intention-to-treat analyses, but provided no additional information. We judged this study as having an unclear risk of attrition bias.

Selective reporting

We did not identify signs of selective reporting when comparing the outcomes and methods of the publication with those of published protocol items at ClinicalTrials.gov. We judged ANBL0032 as having a low risk of reporting bias.

Other potential sources of bias

We judged ANBL0032 as having an unclear risk of other bias. A full explanation can be found in the 'Risk of bias' table in Characteristics of included studies.

Effects of interventions

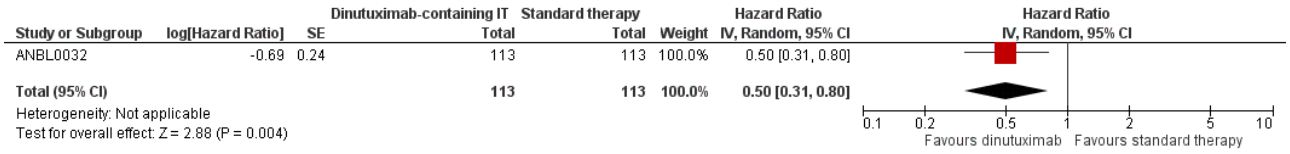
See: **Summary of findings for the main comparison** Dinutuximab-containing immunotherapy compared to standard therapy for people with high-risk neuroblastoma pre-treated with autologous hematopoietic stem cell transplantation

Primary outcomes

Overall survival

In the study ANBL0032, the results on overall survival favoured the dinutuximab-containing immunotherapy group. We estimated a hazard ratio (HR) of 0.50 (95% confidence interval (CI) 0.31 to 0.80; P = 0.004) (Analysis 1.1; Figure 3) by replicating the survival functions shown in Figure 2B of the article Yu 2010 using all available data. There were 113 participants in the dinutuximab-containing immunotherapy group and 113 participants in the standard therapy group. The study authors limited the statistical testing at the time point of 2 years and estimated an overall survival of 86% (standard error +/- 4) in the dinutuximab-containing immunotherapy group and an overall survival of 75% (standard error +/- 5) in the standard therapy group, resulting in a P value of 0.02. We judged the quality of the evidence to be moderate (see the Summary of findings for the main comparison).

Figure 3. Forest plot of comparison: 1 Intervention (dinutuximab-containing immunotherapy) versus comparator (standard therapy), outcome: 1.1 Overall survival. CI: confidence interval; dinutuximab: dinutuximab-containing immunotherapy; IV: inverse variance (statistical method); log: logarithm; P: P value of overall effect; Random: random-effects (analysis method); SE: standard error (standard deviation of the sampling distribution of a statistic)



Treatment-related mortality

In the study ANBL0032, data from randomised participants were mixed with data from non-randomised participants. Separate data from randomised participants were not available, so this outcome could not be assessed.

Secondary outcomes

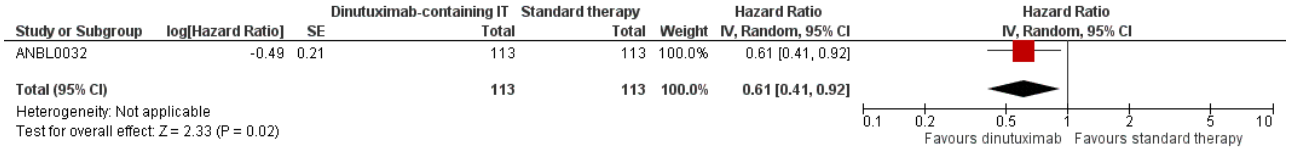
Progression-free survival

In the study ANBL0032, progression-free survival was not reported as a separate endpoint.

Event-free survival

In the study ANBL0032, the results on event-free survival also favoured the dinutuximab-containing immunotherapy group. We estimated an HR of 0.61 (95% CI 0.41 to 0.92; P = 0.020) (Analysis 1.2; Figure 4) by replicating the survival functions shown in Figure 2A of the article Yu 2010 using all available data. There were 113 participants in the dinutuximab-containing immunotherapy group and 113 participants in the standard therapy group. The study authors limited the statistical testing at the time point of 2 years and estimated an event-free survival of 66% (standard error +/- 5) in the dinutuximab-containing immunotherapy arm and an event-free survival of 46% (standard error +/- 5) in the standard therapy group, resulting in a P value of 0.01. We judged the quality of the evidence to be moderate (see the Summary of findings for the main comparison).

Figure 4. Forest plot of comparison: 1 Intervention (dinutuximab-containing immunotherapy) versus comparator (standard therapy), outcome: 1.2 Event-free survival. CI: confidence interval; dinutuximab: dinutuximab-containing immunotherapy; IV: inverse variance (statistical method); log: logarithm; P: P value of overall effect; Random: random-effects (analysis method); SE: standard error (standard deviation of the sampling distribution of a statistic)



Early toxicity

In the study ANBL0032, data from randomised participants were mixed with data from non-randomised participants. Separate data from randomised participants were not available, so this outcome could not be assessed.

Late non-haematological toxicity

In the study ANBL0032, late non-haematological toxicity was not reported as a separate endpoint.

Health-related quality of life

In the study ANBL0032, health-related quality of life was not reported as a separate endpoint.

DISCUSSION

Summary of main results

The present Cochrane Review evaluated the current state of evidence on the efficacy of anti-GD2 antibody-containing immunotherapy versus standard therapy in people diagnosed with high-risk neuroblastoma and pre-treated with HDCT followed by autologous HSCT (see Summary of findings for the main comparison).

We identified a single randomised controlled trial that included 226 participants with high-risk neuroblastoma who were randomised to receive either dinutuximab-containing immunotherapy (N = 113) or standard therapy (N = 113) after pre-treatment with HDCT followed by autologous HSCT (ANBL0032). The primary objective of ANBL0032 "was an intention-to-treat comparison of event-free survival in the two treatment groups".

The results for our primary outcome of overall survival favoured the dinutuximab-containing immunotherapy group (HR 0.50, 95% CI 0.31 to 0.80; P = 0.004; moderate-quality evidence). The results for our secondary outcome of event-free survival also favoured the dinutuximab-containing immunotherapy group (HR 0.61, 95% CI 0.41 to 0.92; P = 0.020; moderate-quality evidence). We calculated the HRs using the complete follow-up period of the trial by replicating the survival functions shown in the relevant figures of the article by Yu 2010.

The results on treatment-related mortality and early toxicity were not reported separately for randomised participants and thus were not included in the present review. No data were available for progression-free survival, late non-haematological toxicity, and health-related quality of life.

Overall completeness and applicability of evidence

The inclusion of a single study, ANBL0032, in the present review limits the inferences we can make from the extracted data.

Participants were treated in the time period from 2001 to 2009 (ANBL0032). The applicability of these data to current clinical practice might be partially restricted, as medical knowledge and terms of health care have progressed and changed since then.

We could not extract and include data on treatment-related mortality, progression-free survival, early toxicity, late non-haematological toxicity, and health-related quality of life. As a result, we could not make any conclusions regarding those outcomes, which are important for clinical practice.

We only included randomised controlled trials, since it is widely recognised that this is the only study design that can be used to obtain unbiased evidence on the use of different treatment options, provided that the design and execution of the randomised controlled trials are adequate. However, even though randomised controlled trials are the highest level of evidence, it should be noted that data from non-randomised studies are available and can be helpful in evaluating adverse events (Peinemann 2015a).

Regarding the evaluation of treatment-related mortality and early toxicity, the authors of ANBL0032 did not report randomised and non-randomised data separately. We asked Alice Yu of the Children's Oncology Group, the principal investigator of the included study, for the provision of separate data from randomised participants. In a kind reply Alice Yu told us that the policy of the Children's Oncology Group is that sharing of unpublished data is not permitted. We therefore could not include the data in the results section of the present review, but available data on randomised and non-randomised participants combined are presented in Table 5 (data from 137 people in the dinutuximab-containing immunotherapy group: 113 randomised and 25 non-randomised, data of one person either randomised or non-randomised could not be evaluated, and data from 108 of 113 randomised people in the control group). Alice Yu also commented "[...]that there appear to be no significant difference in toxicities between those in CR (complete response) and those with biopsy proven small residual disease". The possible risk of bias from the non-randomised data should be kept in mind.

Eligibility requirements for the included study were high-risk neuroblastoma, achievement of at least a partial response at the time of evaluation before autologous stem-cell transplantation, autologous stem-cell transplantation performed within 9 months after the initiation of induction therapy, enrolment between day 50 and day 100 after the final autologous stem-cell transplantation, and absence of progressive disease. This means that a considerable number of patients with high-risk neuroblastoma were not treated with dinutuximab-containing immunotherapy, and for those patients the effect of anti-GD2 antibody-containing immunotherapy remains unclear.

For example, about 10% (25 of 251) of high-risk neuroblastoma patients with residual disease were excluded from the randomisation and assigned non-randomly to receive dinutuximab-containing immunotherapy. Studies applying iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy as diagnostic have shown that patients with residual disease are associated with a poorer survival than those without residual disease (Decarolis 2013; Ladenstein 2018). It would thus have been nice to also have had separate results on adverse events for randomised and non-randomised participants. Another example is the requirement for patients to be in complete remission, very good partial remission, or partial remission before transplantation. The presence of these different options in both treatment groups is comparable, but the prognosis is different: the authors estimated a 2-year overall survival of 67% in the partial-response group, 83% in the very good partial-response group, and 86% in the complete-response group. It would thus also have been nice to have had separate data for these different groups.

With regard to overall survival and event-free survival, we stated in the Effects of interventions section that the study authors limited the statistical testing at the time point of two years. We think that it is appropriate to consider all information provided by Kaplan-Meier survival functions (Liu 2007; Logan 2008). We therefore believe that the estimation of a hazard ratio and the application of a log-rank test meet this presumption. A statistical test at a fixed point in time

does not take into account all available survival data. As the authors did not provide hazard ratios, we re-enacted the survival functions and complemented an estimate of the concerning hazard ratio.

Our search of the conference proceedings identified an abstract, Yu 2014, associated with ANBL0032. This abstract provided updated data on event-free survival, and as opposed to the original publication the difference between the treatment groups was no longer statistically significant: "The updated EFS (event-free survival) (± standard error) for immunotherapy was 67±4%(2-year) and 59±5%(4-year) versus 51±5%(2-year) and 48±5%(4-year) for isotretinoin alone (p= 0.11)." We did not include the data in the results section of the present review as we did not identify a corresponding full-text publication. It is understood that information provided in conference proceedings often differs substantially from that provided in subsequent full-text articles (Yoon 2012). If a full-text article is published, we will consider it in a future update of the present review.

Quality of the evidence

We judged there to be a low risk of detection bias for overall survival and of reporting bias and did not make any judgements of high risk of bias. Nevertheless, the risk of bias for most outcomes of the single included study was difficult to assess, in part due to lack of reporting. We judged there to be an unclear risk of selection bias, performance bias, detection bias, attrition bias (for outcomes other than overall survival), and other bias. We therefore could not rule out those potential biases. However, this is currently the best available evidence from randomised controlled trials comparing the efficacy of dinutuximab versus standard therapy in people with high-risk neuroblastoma pre-treated with HDCT followed by autologous HSCT.

The unclear risk of other bias resulted from the following inconsistencies: "The study was designed to enroll 386 randomly assigned patients, for a statistical power of 80% with a two-sided log-rank test at a level of 0.05 (or a one-sided test at a level of 0.025) to detect an absolute difference of 15 percentage points between the two groups in the 3-year estimate of event-free survival (50% in the standard-therapy group vs. 65% in the immunotherapy group). Early stopping was considered if a significant difference between the two groups was found or if the conditional power fell below 20%. The relative risk of an event was calculated for standard therapy as compared with immunotherapy on the basis of the 3-year estimate of event-free survival. The COG data and safety monitoring committee determined that the study met the criteria for early stopping of the randomization, on the basis of the superiority of immunotherapy over standard therapy with regard to event-free survival." At the time of early stopping, about 59% (226 of 386) of planned eligible patients were enrolled and randomly assigned to a treatment group, and about 61% (83 of 137) of the expected events were documented. The question might arise what would be the result if the study had included all planned people. It also may be questioned if the characteristics of people who were enrolled early and were included in the study differed from the characteristics of people who were planned to be enrolled later and were not included due to the early stopping.

Our GRADE assessment of the quality of the evidence based on the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) judged the quality of the evidence for the outcomes for which data were available as moderate. We downgraded for study limitations, as risk of bias could not be ruled out. We did not downgrade for imprecision. The evidence is based on a single study, but the measured effect on survival was large and the confidence interval below no effect (see Summary of findings for the main comparison).

We want to acknowledge the tremendous achievement of all contributors to the included randomised controlled trial in view of the many challenges associated with the realisation of the study, such as the rarity of the disease and the length of time for enrolment.

Potential biases in the review process

One of the strengths of this systematic review is the broadness of the search strategy such that study retrieval bias is very unlikely. Nevertheless, there remains a slight possibility that an unknown number of studies were not registered and not published. Duplicate publication bias is very unlikely because we searched for follow-up papers of a single study in order to ensure that we included the updated version, and we excluded secondary analyses of registers or databases, which may use data that have been published previously by individual contributing study centres. Overall, the possibility that reporting bias is present appears to be small.

AUTHORS' CONCLUSIONS

Implications for practice

We identified a single randomised controlled trial (RCT) that evaluated dinutuximab-containing immunotherapy versus standard therapy in people with high-risk neuroblastoma pre-treated with high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation. The difference in overall survival and event-free survival was statistically significant in favour of the dinutuximab-containing immunotherapy group. We judged the quality of the evidence to be moderate. We could not extract and report randomised data on adverse events, progression-free survival, late non-haematological toxicity, and health-related quality of life. More research concerning those outcomes, especially adverse effects, is needed.

Implications for research

Future trials on the use of anti-GD2 antibody-containing immunotherapy for people with high-risk neuroblastoma should be RCTs focusing on overall survival, early adverse events, and quality of life. Randomised data should be reported separately. Randomised controlled trials should be performed in homogeneous study populations (e.g. stage of disease) and have a long-term follow-up. The number of included participants should be sufficient to obtain the power needed for the results to be reliable. Different risk groups, using the most recent definitions, should be taken into account. For example, potential subgroups of patients may benefit from anti-GD2 antibody-containing immunotherapy. Various types of antibodies different from dinutuximab may be investigated in RCTs. Furthermore, long-term follow-up studies investigating late adverse events should be performed. However, we are aware that the international neuroblastoma community has decided that a new RCT comparing postconsolidation immunotherapy with and without anti-GD2 antibodies is not required (Elliott 2017; Park 2013; Simon 2017; Yu 2010).

Matthay 2016 reviewed advances in therapy for patients with high-risk disease and indicated that new approaches including targeting the noradrenaline transporter and others may be candidates for future improvements in survival and long-term quality of life. Bosse 2016 reviewed neuroblastoma genetics and genomics and its possibilities in improved prognostication and potential therapeutic opportunities. Morgenstern 2016 evaluated prognostic factors in patients with stage 4 neuroblastoma that may be especially important in the context of new therapies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

ANBL0032

Methods	Setting • Multicentre study enrolling participants from 166 institutions • Located mainly in the USA, some in Canada, and a few in Australia Duration of enrolment • 18 October 2001 to 13 January 2009 Randomisation • "Patients with high-risk neuroblastoma who had a response to induction therapy and stem-cell transplantation were randomly assigned, in a 1:1 ratio" • "Randomization occurred at the time of enrollment and was stratified on the basis of factors thought to potentially affect the post-transplantation outcome: the response before autologous stem-cell transplantation, induction-therapy protocol, number of transplantations of autologous stem cells, and purged versus nonpurged stem-cell infusion." • "Stratified permuted blocks were used for randomization. Procedurally this was accomplished by the COG Remote Data Entry (RDE1) system. The treatment group was assigned in real-time based on the balance existing at that time within 'blocks', where blocks in this case were the study strata. The block size, or 'margin' was set (margin=2 within each stratum) prior to the activation of the study. In this RDE approach, the treatment group assignment is random until such time as a margin within a stratum is exceeded, and only then does the method become deterministic. Once a randomized treatment group assignment was made for a given patient, that patient's treatment group was never changed for any reason." Follow-up time • "Median follow-up after randomization in patients alive without an event was 2.0 years (5 days to 6.5 years) and 2.1 years (4 days to 6.9 years) for the ch14-18-containing immunotherapy group and the standard therapy group, respectively." • The follow-up time regarding all randomised participants is unclear, as it is only reported for participants alive and without an event.
Participants	Eligibility criteria

ANBL0032 *(Continued)*

- "Eligible patients had high-risk neuroblastoma, defined strictly by the Children's Oncology Group (COG), Maris 2007, and confirmed by means of review of clinical, pathological, and biologic features by the COG Neuroblastoma Biology Study Committee and local institutions, before study enrollment." Other eligibility requirements were:
  - an age at diagnosis of under 31 years;
  - completion of induction therapy, autologous stem-cell transplantation, and radiotherapy;
  - achievement of at least a partial response at the time of evaluation before autologous stem-cell transplantation;
  - autologous stem-cell transplantation performed within 9 months after the initiation of induction therapy;
  - enrolment between day 50 and day 100 after the final autologous stem-cell transplantation;
  - absence of progressive disease; and
  - adequate organ function and a life expectancy of at least 2 months.

"An additional eligibility criterion enforced early on in the study was the requirement for enrollment in the COG biology study (ANBL00B1)."

Number of participants enrolled in each group:

- Dinutuximab-containing immunotherapy group: N = 113
- Standard therapy group: N = 113

Age, dinutuximab-containing immunotherapy group versus standard therapy group (N):

- < 18 months: 4 versus 4
- >= 18 months: 109 versus 109

Stage: International Neuroblastoma Staging System (INSS); dinutuximab-containing immunotherapy group versus standard therapy group (N):

- Stage 2: 4 versus 0
- Stage 3: 10 versus 16
- Stage 4S: 2 versus 0
- Stage 4: 89 versus 92
- Unknown: 8 versus 5

Comorbidity: the authors reported important findings associated with neuroblastoma, such as tumour *MYCN* status, tumour histologic features, and tumour ploidy; other disease entities were not reported.

Tumour *MYCN* status; dinutuximab-containing immunotherapy group versus standard therapy group (N):

- Not amplified: 52 versus 51
- Amplified: 36 versus 45
- Unknown: 25 versus 17

Tumour histologic features; dinutuximab-containing immunotherapy group versus standard therapy group (N):

- Favourable: 4 versus 5
- Unfavourable: 68 versus 81
- Unknown: 41 versus 27

Tumour ploidy; dinutuximab-containing immunotherapy group versus standard therapy group (N):

- Hyperdiploid: 49 versus 48
- Diploid: 35 versus 46
- Unknown: 29 versus 19

Previous treatment; treatment prior to enrolling in this study (as described in the Supplemental Explanatory Material of the paper):

ANBL0032 *(Continued)*

- During the first 6 years of this study, the majority of participants received induction and myeloablative therapy per the COG A3973 protocol.
  - This consisted of an induction regimen with 4 cycles of cyclophosphamide, doxorubicin, vincristine, interspersed with 2 cycles of cisplatin and etoposide, and surgical resection of residual disease.
  - This was followed by a conditioning regimen with carboplatin, etoposide, and melphalan (CEM) for ASCT.
- Since 2008, most participants have received therapy per COG ANBL0532, which was activated in November 2007.
  - This consists of the same induction therapy as A3973, except for substituting 2 cycles of dose-intensive cyclophosphamide and topotecan for the initial 2 cycles of the A3973 induction.
  - Following induction therapy, participants are randomised to either 1 myeloablative consolidation with CEM or 2 myeloablative consolidations. For the latter, the first conditioning regimen is thiotepa plus cyclophosphamide, and the second is the standard CEM regimen.
- After ASCT, all participants received local irradiation before enrolling into this ANBL0032 study.

Response before ASCT; dinutuximab-containing immunotherapy group versus standard therapy group (N):

- Complete response: 40 versus 38
- Very good partial response: 47 versus 49
- Partial response: 26 versus 26

Number of ASCTs; dinutuximab-containing immunotherapy group versus standard therapy group (N):

- 1: 107 versus 102
- 2: 6 versus 11

Interventions

The cumulative total dose participants received was not mentioned. We calculated these figures by using the treatment schedule information reported in the article.

Treatment:

- Number of groups: 2
- Type of intervention:
  - Dinutuximab-containing immunotherapy group: 6 cycles of isotretinoin and 5 concomitant cycles of dinutuximab (also known as ch14.18 antibody) in combination with alternating GM-CSF and interleukin-2
  - Standard therapy group: 6 cycles of isotretinoin

Dinutuximab-containing immunotherapy group: 6 cycles * 28 days = 168 days

- Isotretinoin: 6 cycles * 14 days * 160 mg/m^2 per day = 13,440 mg/m^2 total dose
- Dinutuximab: 5 cycles * 4 days * 25 mg/m^2 per day = 500 mg/m^2 total dose
- GM-CSF (in cycle 1, 3, and 5, starting 3 days before dinutuximab): 3 cycles * 14 days * 250 ug/m^2 per day = 10,500 ug/m^2 total dose
- Interleukin-2 (in cycle 2 and 4, concurrent with dinutuximab): 2 cycles * 4 days * 3.0 x 10^6 IU/m^2 per day + 2 cycles * 4 days * 4.5 x 10^6 IU/m^2 per day = 60.0 x 10^6 IU/m^2 total dose

Standard therapy group: 6 cycles * 28 days = 168 days

- Isotretinoin: 6 cycles * 14 days * 160 mg/m^2 per day = 13,440 mg/m^2 total dose

The following information describes deviations from the study protocol:

- Dinutuximab-containing immunotherapy group: 5% (6 of 113) randomised participants did not receive the assigned intervention, and 31% (35 of 113) did not complete the entire assigned intervention
- Standard therapy arm: 6% (7 of 113) randomised participants did not receive the assigned intervention, and 27% (30 of 113) did not complete the entire assigned intervention

ANBL0032 *(Continued)*

Outcomes	We included only the outcomes for which results were available from randomised data. The study reported adverse events results from mixed populations including both randomised and non-randomised participants. As separate randomised data were not available, we did not report these outcomes. Primary outcomes • Overall survival was regarded as a secondary outcome in the study: "Overall survival was defined as the time from study enrollment until death or the last contact with the patient, if death did not occur during the study." Secondary outcomes • Event-free survival was regarded as a primary outcome in the study: "For event-free survival, the time to an event was defined as the time from study enrollment (which occurred after transplantation) until the first occurrence of relapse, progressive disease, secondary cancer, or death or, if none of these events occurred, until the last contact with the patient."
Notes	• "Patients with biopsy-proven residual disease after autologous stem-cell transplantation were eligible for enrollment but not for randomization and were nonrandomly assigned to receive immunotherapy. They were excluded from the primary efficacy analysis. Previous data indicate that patients with residual disease have a poorer prognosis than those without residual disease." These patients were therefore not eligible for inclusion in the present review. • "The National Cancer Institute (NCI) was the sponsor of the study and also provided the ch14.18 monoclonal antibody. Bayer provided the GM-CSF." • "Supported by grants from the National Institutes of Health (U10-CA98543, U10-CA98413, and U10-CA29139) and the Food and Drug Administration (FD-R-002319)." • Ralph Reisfeld, author of the included study, received consulting fees and reimbursement of travel expenses from Merck Pharmaceuticals. • Paul Sondel, author of the included study, received research grant from Merck Serono and reimbursement of travel expenses from the National Childhood Cancer Foundation. • The funding source (US National Institutes of Health; US Food and Drug Administration) had no role in the design, data collection, data analysis, interpretation of the findings, or writing of the report.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Stratified permuted blocks were used for randomization. Procedurally this was accomplished by the COG Remote Data Entry (RDE1) system. The treatment group was assigned in real-time based on the balance existing at that time within “blocks”, where blocks in this case were the study strata. The block size, or “margin” was set (margin=2 within each stratum) prior to the activation of the study. In this RDE approach, the treatment group assignment is random until such time as a margin within a stratum is exceeded, and only then does the method become deterministic. Once a randomized treatment group assignment was made for a given patient, that patient’s treatment group was never changed for any reason." The method of randomisation appeared conditional. We do not know if the condition applied and had any effect. We judged risk of bias to be unclear.
Allocation concealment (selection bias)	Low risk	"Procedurally this was accomplished by the COG Remote Data Entry (RDE1) system." We assumed that the allocation concealment was provided by the remote system. We judged risk of bias to be low.

ANBL0032 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and physicians and nurses was not reported. We judged risk of bias to be unclear.
Blinding of outcome assessment (detection bias) Overall survival Overall survival	Low risk	Blinding of outcome assessors was not reported, but this is not relevant to the outcome overall survival. We judged risk of bias to be low.
Blinding of outcome assessment (detection bias) Event-free survival All outcomes	Unclear risk	Blinding of outcome assessors was not reported, and this may be relevant to the outcome event-free survival. We judged this outcome as having an unclear risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	• Dinutuximab-containing immunotherapy group: 5% (6 of 113) randomised participants did not receive the assigned intervention, and 31% (35 of 113) did not complete the entire assigned intervention • Standard therapy group: 6% (7 of 113) randomised participants did not receive the assigned intervention, and 27% (30 of 113) did not complete the entire assigned intervention • The authors stated that they performed intention-to-treat analyses, but no further information is provided. We judged risk of bias to be unclear.
Selective reporting (reporting bias)	Low risk	We did not identify any signs of selective reporting when comparing the outcomes and methods of the publication with those of published protocol items at ClinicalTrials.gov. We judged risk of bias to be low.
Other bias	Unclear risk	Interim analysis: • "With 61% of the number of expected events observed, the study met the criteria for early stopping owing to efficacy." • "As of January 13, 2009, with 226 eligible patients enrolled and randomly assigned to a treatment group (of 386 anticipated) and 83 of the expected 137 events reported (61%), the COG data and safety monitoring committee determined that the study met the criteria for early stopping of the randomization, on the basis of the superiority of immunotherapy over standard therapy with regard to event-free survival." We did not identify any baseline imbalances with respect to age, INSS stage, tumour *MYCN* status, tumour histologic features, tumour ploidy, and response before transplantation. We judged risk of bias to be unclear.

ASCT: autologous stem-cell transplantation
COG: Children's Oncology Group
GM-CSF: granulocyte-macrophage colony-stimulating factor
IU: international units

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

Study	Reason for exclusion
Berthold 2018	Not study design of interest
Cheung 1991	Not comparator of interest
Cheung 1998	Not comparator of interest
Cheung 2000	Not intervention of interest
Cheung 2012	Not study design of interest
Cheung 2014	Not comparator of interest
Chi 2009	Not comparator of interest
Diccianni 2018	Not study design of interest
Erbe 2017	Not study design of interest
Erbe 2018	Not study design of interest
Federico 2014	Not comparator of interest
Hoy 2016	Not study design of interest
Kushner 2015	Not comparator of interest
Kushner 2016	Not comparator of interest
Ladenstein 2011	Not comparator of interest
Ladenstein 2012	Not comparator of interest
Ladenstein 2013	Not comparator of interest
Ladenstein 2014a	Not comparator of interest
Ladenstein 2014b	Not comparator of interest
Ladenstein 2014c	Not comparator of interest
Ladenstein 2014d	Not comparator of interest
Ladenstein 2015	Not comparator of interest
Ladenstein 2016a	Not comparator of interest
Ladenstein 2016b	Not comparator of interest
Ladenstein 2016c	Not comparator of interest
Ladenstein 2016d	Not comparator of interest
London 2009	Not study design of interest
Marachelian 2016	Not comparator of interest

Study	Reason for exclusion
Mody 2017	Not intervention of interest
Morgenstern 2018	Not intervention of interest
Ozkaynak 2014	Not comparator of interest
Ozkaynak 2018a	Not study design of interest
Ozkaynak 2018b	Not study design of interest
Ploessl 2016	Not study design of interest
Seif 2013	Not intervention of interest
Simon 2004	Not study design of interest
Simon 2005	Not study design of interest
Simon 2009	Not study design of interest
Simon 2011a	Not study design of interest
Simon 2011b	Not study design of interest
Simon 2016	Not study design of interest
Sondel 2017	Not study design of interest
Talleur 2017	Not study design of interest
Yang 2017	Not study design of interest
Yu 1998	Not comparator of interest

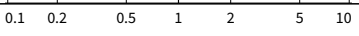
DATA AND ANALYSES

Comparison 1. Dinutuximab-containing immunotherapy versus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1	226	Hazard Ratio (Random, 95% CI)	0.50 [0.31, 0.80]
2 Event-free survival	1	226	Hazard Ratio (Random, 95% CI)	0.61 [0.41, 0.92]

Analysis 1.1. Comparison 1 Dinutuximab-containing immunotherapy versus standard therapy, Outcome 1 Overall survival.

Study or subgroup	Dinutuximab-containing IT N	Standard therapy N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
ANBL0032	113	113	-0.7 (0.24)		100%	0.5[0.31,0.8]
Total (95% CI)					**100%**	**0.5[0.31,0.8]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.88(P=0)						



Favours dinutuximab — Favours standard therapy

Analysis 1.2. Comparison 1 Dinutuximab-containing immunotherapy versus standard therapy, Outcome 2 Event-free survival.

Study or subgroup	Dinutuximab-containing IT N	Standard therapy N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
ANBL0032	113	113	-0.5 (0.21)		100%	0.61[0.41,0.92]
Total (95% CI)					**100%**	**0.61[0.41,0.92]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.33(P=0.02)						

Favours dinutuximab — Favours standard therapy

ADDITIONAL TABLES

Table 1. The International Neuroblastoma Risk Group (INRG) consensus pre-treatment classification schema

INRG stage	Age (months)	Histologic category	Grade of tumour differentiation	MYCN	11q aberration	Ploidy	Pre-treatment risk group	
							Code	Interpretation
L1/L2	-	Ganglioneuroma maturing; ganglioneuroblastoma intermixed	-	-	-	-	A	Very low
L1	-	Any, except ganglioneuroma or ganglioneuroblastoma	-	Not amplified	-	-	B	Very low
				Amplified	-	-	K	High
L2	< 18	Any, except ganglioneuroma or ganglioneuroblastoma	-	Not amplified	No	-	D	Low
					Yes	-	G	Intermediate
	≥ 18	Ganglioneuroblastoma nodular; neuroblastoma	Differentiating	Not amplified	No	-	E	Low
					Yes	-	H	Intermediate
			Poorly differentiated or undifferentiated	Not amplified	-	-	H	Intermediate
			-	Amplified	-	-	N	High
M	< 18	-	-	Not amplified	-	Hyperdiploid	F	Low
	< 12	-	-	Not amplified	-	Diploid	I	Intermediate
	12 to < 18	-	-	Not amplified	-	Diploid	J	Intermediate
	< 18	-	-	Amplified	-	-	O	High
	≥ 18	-	-	-	-	-	P	High
MS	< 18	-	-	Not amplified	No	-	C	Very low
					Yes	-	Q	High

Table 1. The International Neuroblastoma Risk Group (INRG) consensus pre-treatment classification schema *(Continued)*

	Amplified	-	-	R	High

Reference: Cohn 2009

The International Neuroblastoma Risk Group (INRG) consensus classification schema includes the criteria for INRG stage, age, histologic category, grade of tumour differentiation, *MYCN* status, presence/absence of 11q aberrations, and tumour cell ploidy. Sixteen statistically and/or clinically different pre-treatment groups of patients (lettered A through R) have been identified using these criteria. The categories are designated as very low (A, B, C), low (D, E, F), intermediate (G, H, I, J), or high (K, N, O, P, Q, R) pre-treatment risk subsets.
Abbreviations: MYCN: the official gene symbol approved by the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC), which is a short abbreviated form of the gene name 'v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog'.

Table 2. Children's Oncology Group (COG) assignment to low-, intermediate-, and high-risk group

INSS stage	Age	MYCN	INPC classification	DNA index	Risk group
1	0 to 21 y	Any	Any	Any	Low
2A/2B	< 365 d	Any	Any	Any	Low
	≥ 365 d to 21 y	Non-amplified	Any	-	Low
	≥ 365 d to 21 y	Amplified	Favourable	-	Low
	≥ 365 d to 21 y	Amplified	Unfavourable	-	High
3	< 365 d	Non-amplified	Any	Any	Intermediate
	< 365 d	Amplified	Any	Any	High
	≥ 365 d to 21 y	Non-amplified	Favourable	-	Intermediate
	≥ 365 d to 21 y	Non-amplified	Unfavourable	-	High
	≥ 365 d to 21 y	Amplified	Any	-	High
4	< 548 d	Non-amplified	Any	Any	Intermediate
	< 365 d	Amplified	Any	Any	High
	≥ 548 d to 21 y	Any	Any	-	High
4S	< 365 d	Non-amplified	Favourable	> 1	Low
	< 365 d	Non-amplified	Any	= 1	Intermediate
	< 365 d	Non-amplified	Unfavourable	Any	Intermediate
	< 365 d	Amplified	Any	Any	High

Reference: NCI PDQ 2018
DNA index: favourable > 1 (hyperdiploid) or < 1 (hypodiploid); unfavourable = 1 (diploid)
Abbreviations: d: days; INPC: International Neuroblastoma Pathology Committee (also called Shimada system); INSS: The International Neuroblastoma Staging System; MYCN: the official gene symbol approved by the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC), which is a short abbreviated form of the gene name 'v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog'; y: years

Table 3. The International Neuroblastoma Staging System (INSS)

Stage	Definition
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive)
2A	Localised tumour with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically

Table 3. The International Neuroblastoma Staging System (INSS) *(Continued)*

2B	Localised tumour with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically.
3	Unresectable unilateral tumour infiltrating across the midline,[1] with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
4S	Localised primary tumour (as defined for stages 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow[2] (limited to infants < 1 year of age)

Reference: Brodeur 1993
Note: Multifocal primary tumours (e.g. bilateral adrenal primary tumours) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript letter 'M' (e.g. 3_M).
[1]The midline is defined as the vertebral column. Tumours originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
[2]Marrow involvement in stage 4S should be minimal (i.e. < 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate). More extensive marrow involvement would be considered to be stage 4. An MIBG (metaiodobenzylguanidine) scan (if performed) should be negative in the marrow.

Table 4. Response to treatment

Response	Primary tumour	Metastatic sites
Complete response	No tumour	No tumour; catecholamines normal
Very good partial response	Decreased by 90% to 99%	No tumour; catecholamines normal; residual ^{99}Tc bone changes allowed
Partial response	Decreased by more than 50%	All measurable sites decreased by greater than 50%. Bones and bone marrow: number of positive bone sites decreased by greater than 50%; no more than one positive bone marrow site allowed
Minimal response	No new lesions; more than 50% reduction in any measurable lesion (primary or metastases) with less than 50% reduction in any other; less than 25% increase in any existing lesion	
No response	No new lesions; less than 50% reduction but less than 25% increase in any existing lesion	
Progressive disease	Any new lesion; greater than 25% increase in any measurable lesion; previous negative marrow positive for tumour	

Reference: Brodeur 1993

Table 5. Adverse events including non-randomised participants

Adverse event	Immunotherapy (N = 137)	Standard therapy (N = 108)	Risk ratio[1] (95% CI)	Fisher's exact test[2]
Adverse events statistically significantly more often in the dinutuximab-containing immunotherapy group than in the standard therapy group				

Table 5. Adverse events including non-randomised participants *(Continued)*

Any toxic effect of grade 3 or 4[3]	94% (129 of 137)	63% (68 of 108)	1.50 (1.29, 1.74)	-
Neuropathic pain	52% (71 of 137)	6% (6 of 108)	9.33 (4.22, 20.64)	-
Hypotension	18% (24 of 137)	0	-	P < 0.001
Hypoxia	13% (18 of 137)	2% (2 of 108)	7.09 (1.68, 29.91)	-
Fever without neutropenia	39% (53 of 137)	6% (6 of 108)	6.96 (3.11, 15.59)	-
Acute capillary leak syndrome	23% (31 of 137)	0	-	P < 0.001
Hypersensitivity reaction	25% (34 of 137)	1% (1 of 108)	26.80 (3.73, 192.68)	-
Urticaria	13% (18 of 137)	0	-	P = 0
Infection (any)	39% (54 of 137)	22% (24 of 108)	1.77 (1.18, 2.67)	-
Diarrhoea	13% (18 of 137)	1% (1 of 108)	14.19 (1.92, 104.62)	-
Hyponatraemia	23% (31 of 137)	4% (4 of 108)	6.11 (2.22, 16.78)	-
Hypokalaemia	35% (48 of 137)	2% (2 of 108)	18.92 (4.70, 76.10)	-
Abnormal ALT[4]	31% (31 of 137)	3% (3 of 108)	8.15 (2.56, 25.93)	-
Abnormal AST[4]	10% (14 of 137)	0	-	P < 0.001
Difference in adverse events between dinutuximab-containing immunotherapy group and standard therapy group not statistically significant				
Hypercalcaemia	5% (7 of 137)	6% (6 of 108)	0.92 (0.32, 2.66)	-
Serum sickness	1% (1 of 137)	0	-	P = 1
Ocular symptoms	0	1% (1 of 108)	-	P = 0.4408
Seizure	1% (1 of 137)	1% (1 of 108)	1.00 (0.06, 15.83)	-
CNS cortical symptom[5]	4% (5 of 137)	0	-	P = 0.0687
Infection, catheter related	13% (18 of 137)	7% (7 of 108)	2.03 (0.88, 4.68)	-
Nausea	3% (4 of 137)	1% (1 of 108)	3.15 (0.36, 27.80)	-
Vomiting	6% (8 of 137)	3% (3 of 108)	2.10 (0.57, 7.73)	-
Treatment-related mortality[6]	1% (1 of 137)	0	-	P = 1

[1]We calculated risk ratios using Review Manager 5 software (RevMan 2014).
[2]In cases with zero events in one group, we calculated P values using Fisher's exact test (Social Science Statistics 2018).
[3]Toxic effects of grade 3 or 4 according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE V3) (NCI CTCAE 2018).

[4]Grade 3 elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were defined as levels that were 5 to 20 times the upper limit of the normal range, and grade 4 elevations were levels that were more than 20 times the upper limit of the normal range.
[5]Central nervous system (CNS) cortical symptoms were encephalopathy, confusion, and psychosis.
[6]Treatment-related mortality: one event due to an interleukin-2 overdose.
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; CNS: central nervous system; N: number of participants
Bold typeface indicates that the result of the statistical test showed the adverse events were statistically significantly more often in the dinutuximab-containing immunotherapy group than in the standard therapy group.

APPENDICES

Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **Anti-GD2** we used the following text words:

monoclonal antibodies or ganglioside or ganglioside* or immunotherapy or anti gd2 or ch14 18 or dinutuximab or unituxin or 3f8

2. For **Neuroblastoma** we used the following text words:

neuroblastoma or neuroblastomas or neuroblast* or ganglioneuroblastoma or ganglioneuroblastomas or ganglioneuroblast* or neuroepithelioma or neuroepitheliomas or neuroepitheliom* or esthesioneuroblastoma or esthesioneuroblastomas or esthesioneuroblastom* or schwannian

Final search 1 and 2

[*=zero or many characters]

We performed the search in title, abstract or keywords.

Appendix 2. Search strategy for MEDLINE (PubMed)

1. For **Anti-GD2** we used the following MeSH headings and text words:

“antibodies, monoclonal/therapeutic use”[mh] OR “gangliosides/therapeutic use”[mh] OR immunotherapy/methods[mh] OR anti gd2[tiab] OR ch14 18 OR ganglioside* OR dinutuximab OR unituxin OR 3f8

2. For **Neuroblastoma** we used the following MeSH headings and text words:

neuroblastoma OR neuroblastomas OR neuroblast* OR ganglioneuroblastoma OR ganglioneuroblastomas OR ganglioneuroblast* OR neuroepithelioma OR neuroepitheliomas OR neuroepitheliom* OR esthesioneuroblastoma OR esthesioneuroblastomas OR esthesioneuroblastom* OR schwannian

3. For **RCTs/CCTs** we used the following MeSH headings and text words according to Lefebvre 2011:

(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh])

Final search 1 and 2 and 3

[*=zero or more characters; mh=MeSH term; tiab=title or abstract; sh=subheading; pt=publication type; RCT = randomized controlled trial; CCT = controlled clinical trial]

Appendix 3. Search strategy for Embase (Ovid)

1. For **Anti-GD2** we used the following Emtree terms and text words:

1. exp monoclonal antibody/
2. exp ganglioside/
3. exp immunotherapy/ or exp cancer immunotherapy/
4. anti gd2.mp. or exp ganglioside antibody/
5. ch14 18.mp. or exp dinutuximab/ or 3F8.mp.
6. (ganglioside$ or dinutuximab or unituxin).mp.
7. or/1-6

2. For **Neuroblastoma** we used the following Emtree terms and text words:

1 exp neuroblastoma/
2 (neuroblastoma or neuroblastomas or neuroblast$).mp.
3 (ganglioneuroblastoma or ganglioneuroblastomas or ganglioneuroblast$).mp.
4 (neuroepithelioma or neuroepitheliomas or neuroepitheliom$).mp.
5 exp esthesioneuroblastoma/
6 (esthesioneuroblastoma or esthesioneuroblastomas or esthesioneuroblastoma$).mp.
7 schwannian.mp.
8 or/1-7

3. For **RCTs/CCTs** we used the following Emtree terms and text words:

1. Randomized Controlled Trial/
2. Controlled Clinical Trial/
3. (randomized or randomised).ti,ab.
4. placebo.ti,ab.
5. randomly.ti,ab.
6. trial.ti,ab.7. groups.ti,ab.
8. drug therapy.sh.
9. or/1-8
10. animals/ not human/
11. 9 not 10

Final search 1 and 2 and 3

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title, abstract; / = Emtree term; $=zero or many characters ; RCT = randomized controlled trial; CCT = controlled clinical trial]

CONTRIBUTIONS OF AUTHORS

All authors approved the final version of the review.

FP: concept, selecting studies, extracting and analysing data, interpretation of results, GRADE assessment, and primary manuscript preparation.

ECVD: extracting and analysing data, interpretation of results, GRADE assessment, and manuscript review.

HE: selecting studies, extraction of toxicity data, interpretation of results, and manuscript review.

GAMT: providing a clinical perspective, interpretation of results, and manuscript review.

DECLARATIONS OF INTEREST

FP: no conflicts of interest

ECVD: no conflicts of interest

HE: no conflicts of interest

GAMT: no conflicts of interest

SOURCES OF SUPPORT

Internal sources

- University of Cologne, Germany.

  Provision of the full texts of articles

External sources

- Stichting Kinderen Kankervrij (KiKa), Netherlands.

  The salary of ECVD is paid by KiKa; KiKa was not involved in the design and execution of this Cochrane Review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included the outcomes overall survival and event-free survival data in the review, although the definitions for these outcomes differed from the ones in our protocol. Otherwise important information could have been missed. We did not use a data extraction form specifically designed for the review.

We clarified the description of the types of interventions. The intervention group is now presented as 'anti-GD2 antibody-containing immunotherapy' (formerly 'addition of anti-GD2'). We specified the comparator group as 'standard therapy' (formerly 'the same treatment but no addition of anti-GD2').

INDEX TERMS

Medical Subject Headings (MeSH)

*Hematopoietic Stem Cell Transplantation; Antibodies, Monoclonal [*therapeutic use]; Consolidation Chemotherapy; Disease-Free Survival; Immunologic Factors [therapeutic use]; Immunotherapy; Neuroblastoma [immunology] [mortality] [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans