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Iodine-131-meta-iodobenzylguanidine therapy for patients with newly diagnosed high-risk neuroblastoma (Review)

Kraal KCJM, van Dalen EC, Tytgat GAM, Van Eck-Smit BLF

Kraal KCJM, van Dalen EC, Tytgat GAM, Van Eck-Smit BLF.
Iodine-131-meta-iodobenzylguanidine therapy for patients with newly diagnosed high-risk neuroblastoma.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD010349.
DOI: 10.1002/14651858.CD010349.pub2.

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[Intervention Review]

Iodine-131-meta-iodobenzylguanidine therapy for patients with newly diagnosed high-risk neuroblastoma

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Editorial group: Cochrane Childhood Cancer Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Kraal KCJM, van Dalen EC, Tytgat GAM, Van Eck-Smit BLF. Iodine-131-meta-iodobenzylguanidine therapy for patients with newly diagnosed high-risk neuroblastoma. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD010349. DOI: 10.1002/14651858.CD010349.pub2.

ABSTRACT

Background

Patients with newly diagnosed high-risk (HR) neuroblastoma (NBL) still have a poor outcome, despite multi-modality intensive therapy. This poor outcome necessitates the search for new therapies, such as treatment with ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG).

Objectives

To assess the efficacy and adverse effects of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL.

Search methods

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library 2016, Issue 3), MEDLINE (PubMed) (1945 to 25 April 2016) and Embase (Ovid) (1980 to 25 April 2016). In addition, we handsearched reference lists of relevant articles and reviews. We also assessed the conference proceedings of the International Society for Paediatric Oncology, Advances in Neuroblastoma Research and the American Society of Clinical Oncology; all from 2010 up to and including 2015. We scanned the International Standard Randomized Controlled Trial Number (ISRCTN) Register (www.isrctn.com) and the National Institutes of Health Register for ongoing trials (www.clinicaltrials.gov) on 13 April 2016.

Selection criteria

Randomised controlled trials (RCTs), controlled clinical trials (CCTs), non-randomised single-arm trials with historical controls and cohort studies examining the efficacy of ^{131}I-MIBG therapy in 10 or more patients with newly diagnosed HR NBL.

Data collection and analysis

Two review authors independently performed the study selection, risk of bias assessment and data extraction.

Main results

We identified two eligible cohort studies including 60 children with newly diagnosed HR NBL. All studies had methodological limitations, with regard to both internal (risk of bias) and external validity. As the studies were not comparable with regard to prognostic factors and treatment (and often used different outcome definitions), pooling of results was not possible. In one study, the objective response rate (ORR) was 73% after surgery; the median overall survival was 15 months (95% confidence interval (CI) 7 to 23); five-year overall survival was 14.6%; median event-free survival was 10 months (95% CI 7 to 13); and five-year event-free survival was 12.2%. In the other study, the ORR was 56% after myeloablative therapy and autologous stem cell transplantation; 10-year overall survival was 6.25%; and event-free

survival was not reported. With regard to short-term adverse effects, one study showed a prevalence of 2% (95% CI 0% to 13%; best-case scenario) for death due to myelosuppression. After the first cycle of ^{131}I-MIBG therapy in one study, platelet toxicity occurred in 38% (95% CI 18% to 61%), neutrophil toxicity in 50% (95% CI 28% to 72%) and haemoglobin toxicity in 69% (95% CI 44% to 86%); after the second cycle this was 60% (95% CI 36% to 80%) for platelets and neutrophils and 53% (95% CI 30% to 75%) for haemoglobin. In one study, the prevalence of hepatic toxicity during or within four weeks after last the MIBG treatment was 0% (95% CI 0% to 9%; best-case scenario). Neither study reported cardiovascular toxicity and sialoadenitis. One study assessed long-term adverse events in some of the children: there was elevated plasma thyroid-stimulating hormone in 45% (95% CI 27% to 65%) of children; in all children, free T4 was within the age-related normal range (0%, 95% CI 0% to 15%). There were no secondary malignancies observed (0%, 95% CI 0% to 9%), but only five children survived more than four years.

Authors' conclusions

We identified no RCTs or CCTs comparing the effectiveness of treatment including ^{131}I-MIBG therapy versus treatment not including ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL. We found two small observational studies including chilren. They had high risk of bias, and not all relevant outcome results were available. Based on the currently available evidence, we cannot make recommendations for the use of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL in clinical practice. More high-quality research is needed.

PLAIN LANGUAGE SUMMARY

Iodine-131-meta-iodobenzylguanidine therapy for patients with newly diagnosed high-risk neuroblastoma

Review question

We reviewed the evidence of the effectiveness and side effects of ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) therapy in patients with newly diagnosed high-risk (HR) neuroblastoma (NBL).

Background

NBL is a rare solid cancer that develops from special nerves cells. Patients with newly diagnosed HR NBL have a poor outcome, despite intensive treatments such as high-dose chemotherapy to kill the cancer and surgery. This poor outcome needs research to look for new therapies, such as treatment with ^{131}I-MIBG, which is a type of targeted radiotherapy (radiation directed at the cancer without causing too much damage to surrounding area).

Study characteristics

The evidence is current to April 2016.

We found two cohort studies (where a group of people (the cohort) is followed over time, to examine different treatments received and subsequent outcomes) looking at ^{131}I-MIBG treatment in 60 children with newly diagnosed HR NBL.

Key results

The studies were not comparable with regard to the children, the ways they were treated and the ways the different outcomes were defined and so it was impossible to combine the results in an analysis. Not all relevant outcome results were available.

The percentages of children whose cancer reduced or disappeared after treatment (response rate) were 56% and 73% in the two studies, but survival was still poor: overall survival (length of time that the child remained alive) was about 15 months, event-free survival (time during which there were no objective signs of tumor recurrence) was about 10 months. Overall survival five years after treatment was 14.6%, and after 10 years was 12.2%.

With regard to short-term side effects, there were some low blood cell counts. There was no liver toxicity. The studies did not report on heart problems and infections of the salivary glands. One study assessed long-term side effects in some of the children: there was some evidence of thyroid (a gland in the neck) problems, which was brief in three children, but remained high in seven children, of whom five were prescribed medicine. There were no secondary cancers (where a different type of cancer has returned following the original cancer).

Based on the currently available evidence, we cannot make recommendations for the use of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL in clinical practice. More high-quality research is needed before definite conclusions can be made.

Quality of the evidence

All studies had problems relating to quality of the evidence.

BACKGROUND

Description of the condition

Neuroblastoma (NBL) is the most common extracranial solid tumour of childhood, derived from the sympathetic nervous system (Gurney 1996). The median age of diagnosis is 18 months. According to the International Neuroblastoma Staging System (INSS), NBL is classified into stages 1 to 4, with a special stage termed 4S. Children with stage 4 NBL present with metastatic disease at diagnosis, mainly involving lymph nodes and bone marrow. Traditionally, the defining characteristics of high-risk NBL included an age of more than one year, metastatic disease, unfavourable Shimada histology and *MYCN* amplification (Bernstein 1992; Shimada 1995; Shimada 1999). In recent years, an age cut-off of 18 months was discovered and implemented for pretreatment risk stratification, as opposed to the traditional cut-off of one year (Cohn 2009). However, most currently published studies use the old definition. Current high-risk treatment consists of intensive multi-agent chemotherapy induction (Peinemann 2015a), extensive surgical resection of the primary tumour, external beam irradiation of residual primary tumour, myeloablative chemotherapy (Yalçin 2015), and maintenance with differentiation and immunotherapy (Peinemann 2015b).

Despite this very intensive treatment, children with advanced-stage high-risk NBL still have a poor prognosis; the five-year overall survival rate of HR NBL in the Children's Oncology Group in the era between 2005 and 2010 is now 50% + 0.02 standard error (Pinto 2015). This poor outcome necessitates the search for new therapies (Matthay 1999; Simon 2011).

Description of the intervention

The majority of NBL tumours accumulate meta-iodobenzylguanidine (MIBG). When radiolabelled with ^{123}iodine, MIBG can be used for imaging and when labelled with ^{131}iodine it can be used as a form of targeted radiotherapy (Bleeker 2015; Hattner 1984; Suc 1996). In various studies around the world, the radiopharmaceutical ^{131}I-MIBG has been shown to have a significant antitumour effect against NBL (Hutchinson 1991; Klingebiel 1991a; Klingebiel 1991b; Lashford 1992; Lumbroso 1991; Matthay 1998; Matthay 2007; Simon 2011; Voute 1991). More than 95% of NBL tumours are able to accumulate ^{131}I-MIBG actively (Leung 1997). Given the unsatisfactory results of high-intensity induction chemotherapy it is rational to add ^{131}I-MIBG, as a 'targeted radiotherapy' to the treatment of HR NBL.

Extensive experience exists with ^{131}I-MIBG treatment of children with NBL. Hoefnagel and colleagues reported the value of ^{131}I-MIBG in the detection of NBL (Hoefnagel 1985). In the following years, it became clear that there was also a role for therapeutic use of ^{131}I-MIBG. Initially ^{131}I-MIBG therapy was given to children with recurrent NBL (Matthay 1998; Matthay 2001). After some time, a second group was included, that is, children with residual disease after chemotherapy and surgery. From these studies, it became clear that the most prominent response was obtained in children with a large tumour burden at the time of ^{131}I-MIBG treatment (Matthay 1998; Matthay 2001). This finding has served as the basis for a study performed in Amsterdam, with the objectives to document response in untreated children with stage 4 or non-operable stage 3 disease, and to further characterise the adverse effects of ^{131}I-MIBG treatment. The study was closed in 1999. In summary, ^{131}I-MIBG therapy has a very high response rate at induction of children with HR NBL and can be combined with induction chemotherapy followed by mega-therapy and autologous stem cell transplantation (ASCT). In this study, the chemotherapy was not dose intense and since then we have learned that dose intense chemotherapy results in better outcomes (De Kraker 2008). The current Dutch Children's Oncology Group high-risk NBL 2009 treatment protocol combines upfront ^{131}I-MIBG with induction chemotherapy followed by mega-therapy and ASCT. Matthay and colleagues reported in 2009 the results of a phase I study in children with refractory or relapsed HR NBL. It showed that closely spaced infusions of ^{131}I-MIBG can be administered safely using ASCT without dose-limiting non-haematological toxicity and with rapid and reliable reconstitution of haematopoiesis (Matthay 2009a).

How the intervention might work

^{131}I-MIBG is a radiopharmaceutical; it is a radio-labelled molecule similar to noradrenaline which can be taken up by NBL tissue (Hattner 1984). When NBL has taken up the ^{131}I-MIBG (gamma and beta emitting isotope), its beta particles will irradiate neighbouring tissue with a median range of 1 cm causing cell death by double-strand DNA breaks and damage to lipid bilayers (Hutchinson 1991; Matthay 2007).

Why it is important to do this review

At the moment, the prognosis for patients with HR NBL is still very poor. Relapses remain common, despite the achievement of a complete clinical remission after induction therapy. The place of ^{131}I-MIBG in newly diagnosed HR NBL treatment is not yet well established.

OBJECTIVES

To assess the efficacy and adverse effects of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs), controlled clinical trials (CCTs), non-randomised single-arm trials with historical controls and cohort studies examining the efficacy of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL. We excluded cross-sectional studies, case-reports and case series (i.e. a series of non-consecutive participants). We defined a cohort study as one in which a group of consecutive participants treated for HR NBL was followed from the time of diagnosis. The described study could be the original cohort or a subgroup of the original cohort based on well-defined inclusion criteria.

We excluded studies including fewer than 10 patients.

Types of participants

Patients with newly diagnosed HR NBL. The defining characteristics of HR NBL include an age of more than one year, regional or metastatic disease, unfavourable Shimada histology or *MYCN*

amplification. We excluded patients with esthesioneuroblastoma or newly diagnosed patients who received prior chemotherapy (or both). If studies included both eligible and non-eligible participants, the results of eligible patients should have been separately available in order to be included in the review.

Types of interventions

^{131}I-MIBG therapy.

Types of outcome measures

Primary outcomes

- Response as measured by the International Neuroblastoma Response Criteria (INRC) (Brodeur 1993).
- Overall survival (as defined in the original study).
- Event-free survival, defined as the time span that follows therapy during which there are no objective signs of recurrence or other events (as defined in the original study).
- Adverse events, as defined in the original studies. We particularly looked at haematological, cardiovascular and hepatic problems, and sialoadenitis as short-term events. Long-term events were thyroid dysfunction and secondary malignancies.

Secondary outcomes

- Dose intensity after ^{131}I-MIBG treatment: the actual administered amount of ^{131}I-MIBG in mega Becquerel/milliCurie (MBq/mCi).
- Time span of delivering chemotherapy induction treatment after ^{131}I-MIBG therapy.
- Yield of peripheral stem cell collection during harvest sessions (defined as the mean number of collected autologous haematopoietic stem cells).
- Number of successful peripheral stem cell harvests (defined as more than 2×10^6/kg autologous haematopoietic stem cells).
- Number of peripheral stem cell harvest sessions necessary to obtain a sufficient amount of autologous haematopoietic stem cells (i.e. more than 2×10^6/kg autologous haematopoietic stem cells).
- Percentage of patients in which bone marrow harvest was performed
- Stem cell engraftment defined as the time to haematopoietic recovery after myeloablative chemotherapy and ASCT were measured for each of the haematopoietic cell lineages.

Stem cell harvest could have taken place at any stage of the treatment protocols (i.e. before or after ^{131}I-MIBG therapy).

Search methods for identification of studies

We imposed no language restrictions.

Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2016, Issue 3), MEDLINE in PubMed (from 1945 to 25 April 2016) and Embase in Ovid (from 1980 to 25 April 2016). The appendices show the search strategies for the different electronic databases (using a combination of controlled vocabulary and text words; Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We located information about trials not registered in CENTRAL, MEDLINE or Embase, either published or unpublished, by searching the reference lists of relevant articles and review articles. We handsearched the conference proceedings of the International Society for Paediatric Oncology, Advances in Neuroblastoma Research and the American Society of Clinical Oncology published from 2010 up to and including 2015. We scanned the International Standard Randomized Controlled Trial Number (ISRCTN) Register (www.isrctn.com) and the National Institutes of Health Register for ongoing trials (www.clinicaltrials.gov); both registers were searched on 13 April 2016 using this search strategy: (131I-MIBG OR 131I-meta-iodobenzylguanidine) AND neuroblastoma.

Data collection and analysis

Selection of studies

Two authors independently selected studies meeting the inclusion criteria. We resolved discrepancies by consensus. If this was not possible, a third-party arbitrator resolved the issue. We obtained in full-text any study which seemed to meet the inclusion criteria based on the title or abstract (or both) for closer inspection. We clearly stated details of reasons for exclusion of any study considered for this review (see Characteristics of excluded studies table). We included a flow chart of the selection of studies in the review (Figure 1).

Data extraction and management

Two authors independently performed data extraction using standardised data extraction forms. We resolved discrepancies between authors by discussion. We extracted the following data.

- Study characteristics, including:
  - design;
  - number of patients enrolled in the study;
  - number of patients fulfilling the predefined inclusion criteria.
- Participants characteristics, including:
  - gender;
  - age at time of diagnosis (range, mean, median, or a combination of these);
  - stage of disease according to the INSS;
  - tumour biology and genetic aberrations (*MYCN* amplified and loss of heterozygosity chromosome 1P);
  - tumour localisation (primary and metastasis).
- Interventions, including:
  - schedule of ^{131}I-MIBG treatment and total amount of ^{131}I-MIBG administered (in MBq/mCi);
  - additive (radio-sensitising) therapeutics (dose and schedule) during ^{131}I-MIBG treatment and chemotherapy schedules thereafter.
- Outcome measures (as described above).
- Length of follow-up.

Assessment of risk of bias in included studies

Two authors independently performed the assessment of risk of bias of the included studies. If we had identified RCTs and CCTs we would have used the risk of bias items as described in the module of Cochrane Childhood Cancer (Kremer 2012), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The assessment of risk of bias in observational studies was based on previously described checklists according to Evidence-Based Medicine Criteria (Grimes 2002; Laupacis 1994). See Table 1 for the definitions of the different risk of bias criteria. For attrition bias, detection bias and outcome reporting bias (i.e. biases that can be assessed for each outcome separately), we only assessed the risk of bias for the primary outcomes. The risk of bias in included studies was taken into account in the interpretation of the review's results. We resolved discrepancies between authors by consensus.

Measures of treatment effect

If a control group had been available, we would have analysed dichotomous variables using risk ratios (RRs); continuous outcomes using mean differences (MDs) and survival using hazard ratios (HRs). We would have used the Parmar's method if HRs had not been explicitly presented in the study (Parmar 1998). However, as all included studies did not have a control group, we used the prevalence (and corresponding 95% confidence intervals (CI)) to analyse tumour response and adverse effects; we summarised other outcomes descriptively.

Dealing with missing data

When relevant data regarding study selection were missing, we contacted the study authors to retrieve the missing data. If RCTs or CCTs had been included, we would have extracted data by the allocated intervention, irrespective of compliance with the allocated intervention, in order to allow an intention-to-treat analysis. If this was not possible, we would have stated this and we would have performed an 'as treated' analysis.

Assessment of heterogeneity

As pooling of results was not possible, assessment of heterogeneity was not applicable. Otherwise, we would have assessed heterogeneity both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, that is, the I^2 statistic. In the absence of significant heterogeneity (I^2 less than 50%) (Higgins 2011), we would have used a fixed-effect model for the estimation of treatment effects. Otherwise, we would have explored possible reasons for the occurrence of heterogeneity and we would have taken appropriate measures.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the Assessment of risk of bias in included studies section, we would have assessed reporting bias by constructing a funnel plot when there would have been a sufficient number of included studies (that is at least 10 studies included in a meta-analysis). When there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (Higgins 2011). As pooling of results was not possible, this was not applicable.

Data synthesis

We entered data into Cochrane's statistical software, Review Manager 5 (RevMan 2014), and undertook analyses according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included outcome measures only if it was the intention of the study to perform the necessary assessments in all participants (i.e. not only optional or only performed in some centres). We performed pooling of results only if studies were comparable with regard to important prognostic factors (i.e. age, stage according to INSS (bone marrow involvement), *MYCN* amplification and loss of chromosome 1P), treatment and used outcome definitions. Different study designs were taken into account in the analyses. Studies for which pooling of results was not possible were summarised descriptively. We used the Wilson method to calculate the corresponding 95% CIs of the prevalences. As this was not possible in Review Manager 5, we used a different tool (EpiTools epidemiological calculators).

Sensitivity analysis

For all outcomes for which pooling was possible, we would have performed sensitivity analyses for all risk of bias criteria separately. We would have excluded studies with a high risk of bias and studies for which the risk of bias was unclear and compared the results of studies with a low risk of bias with the results of all available studies. As pooling of results was not possible, this was not applicable.

RESULTS

Description of studies

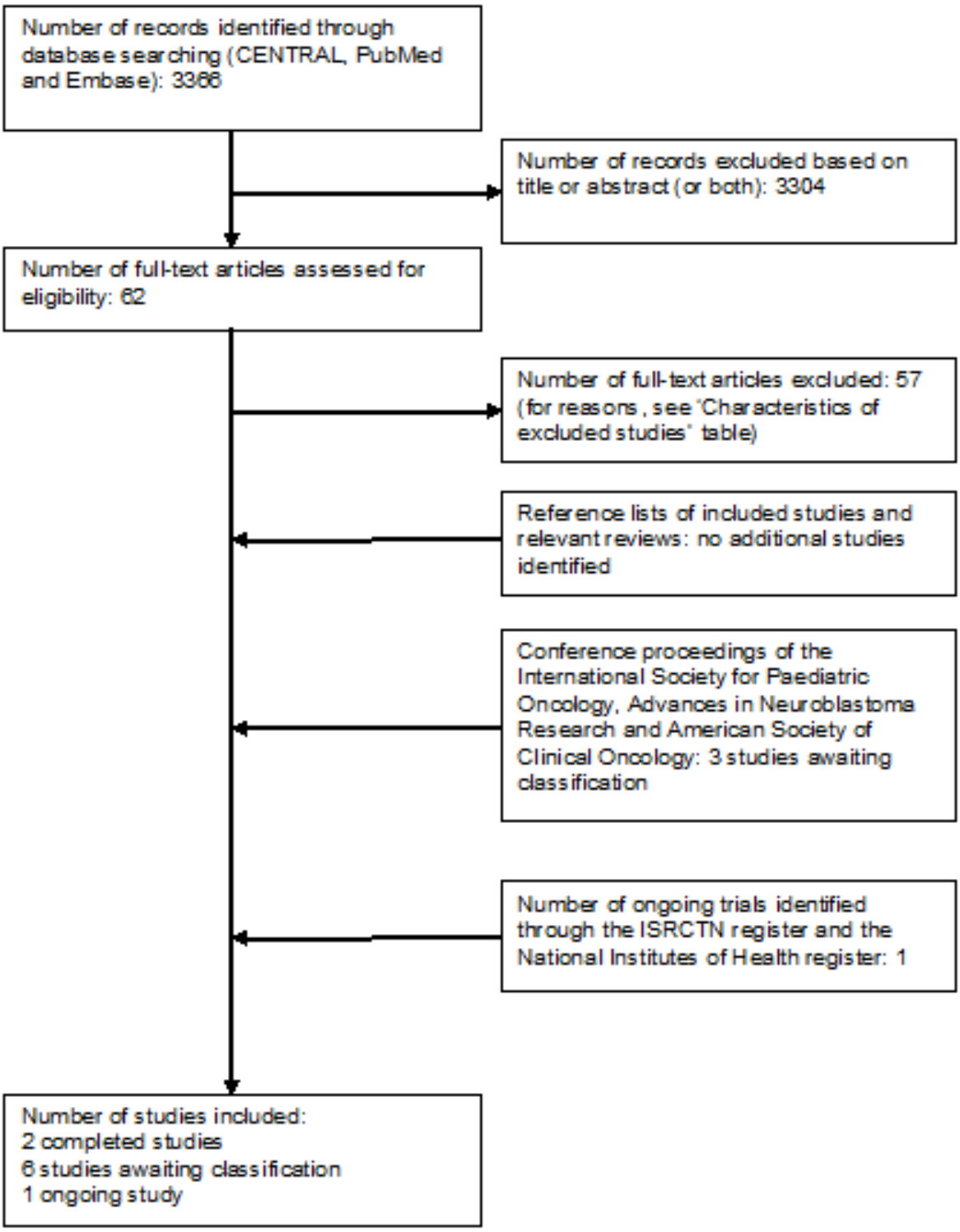
Results of the search

Running the searches in the electronic databases of CENTRAL, MEDLINE (PubMed) and EMBASE (Ovid) yielded 3366 references. Following initial screening of the titles, abstracts, or both, we excluded 3304 references which clearly did not meet all criteria for this review. We assessed the full-text of the 62 remaining references, of which two fulfilled all the criteria and were eligible for inclusion. Three articles are awaiting classification (see Characteristics of studies awaiting classification table) and the 57 excluded references are described in the Characteristics of excluded studies table.

Scanning the reference lists of the included articles and reviews did not identify any additional eligible studies. By scanning the conference proceedings we identified three additional studies (see Characteristics of studies awaiting classification table) and by scanning the ongoing trials databases we identified one possible ongoing study (see Characteristics of ongoing studies table).

In summary, two studies were eligible for inclusion in the review; six studies were awaiting classification, 57 were excluded and one was ongoing. See Figure 1 for a flow diagram of the selection of studies for this systematic review.

Figure 1. Study flow diagram



Included studies

The characteristics of the included studies are summarised below. For more detailed information, see the Characteristics of included studies table.

We identified one single-centre prospective cohort study (De Kraker 2008), and one multi-centre prospective phase II windows study (Kraal 2015), both conducted in the Netherlands. The total number of children with newly diagnosed HR NBL included in these studies

was 60. In both studies children had metastatic disease (i.e. INSS stage 4) (De Kraker 2008, Kraal 2015). Children were aged between 1 and 15.4 years at diagnosis. In one study, children received ^{131}I-MIBG single agent therapy (De Kraker 2008), while in the other study, children received ^{131}I-MIBG in combination with topotecan (Kraal 2015). For complete detailed treatment information, see the Characteristics of included studies table. None of the studies reported the length of follow-up.

Risk of bias in included studies

See the risk of bias section of the Characteristics of included studies table and Figure 2 for the exact scores per study and the support for the judgements made. We have looked both at internal and external validity.

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

Internal validity

Selection bias

For evaluating selection bias, we assessed if there was a representative study group. In both studies, the risk of selection bias was low.

Attrition bias

For evaluating attrition bias, we assessed the completeness of follow-up for the different primary outcomes. Both studies assessed response, overall survival and haematological toxicity; for the first two outcomes, the risk of attrition bias was low in both studies, for haematological toxicity, the risk of bias was low in one study (Kraal 2015), and unclear in the other study (De Kraker 2008). De Kraker 2008 also assessed event-free survival (low risk of attrition bias), hepatic toxicity (unclear risk of attrition bias), thyroid dysfunction (high risk of attrition bias) and secondary malignancies (low risk of attrition bias).

Detection bias

For evaluating detection bias, we assessed if the outcome assessors were blinded to the investigated determinant for the different primary outcomes. For overall survival, this was not applicable and therefore the risk of detection bias was low in both studies. For all other outcomes that were assessed in both studies, the risk of detection bias was unclear.

External validity

Reporting bias

In both studies, the study group was well-defined and the risk of reporting bias was low.

In both studies, the length of follow-up was not mentioned, so the risk of reporting bias was unclear.

For overall survival, the outcome is well-defined by default, so the risk of reporting bias was low in both studies. Both studies also assessed response (low risk of reporting bias in both studies) and haematological toxicity (low risk of reporting bias in Kraal 2015, unclear risk of reporting bias in De Kraker 2008). For all other primary outcomes that were assessed in both studies, the risk of reporting bias was unclear.

Overall, neither of the included studies scored good on all applicable reporting bias items.

Effects of interventions

Not all articles allowed data extraction for all endpoints (see the Characteristics of included studies table for a more detailed description of the extractable endpoints from each article).

As the studies were not comparable with regard to prognostic factors and treatment (and often used different outcome definitions), pooling of results was not possible. For response and adverse effects (both short-term and long-term), we used the Wilson method to calculate the prevalence and 95% CI; for all other outcomes, we presented results as described in the publications.

Response

De Kraker 2008 used the INRC to define response (Brodeur 1993). The objective response rate (ORR, i.e. complete response (CR), very good partial response (VGPR) or partial response (PR)) was evaluated at two different time points. After two cycles of ^{131}I-MIBG therapy, the ORR was 66% (95% CI 51% to 78%); 1/41 children had a CR and 26/41 had a PR. After surgery, the ORR was 73% (95% CI 58% to 84%); 16/41 children had a CR, 1/41 a VGPR and 13/41 a PR. For the ORRs in ^{131}I-MIBG-treated children and ^{131}I-MIBG plus chemotherapy-treated children, see Table 2.

Kraal 2015 also used the INRC to define response (Brodeur 1993). The ORR was evaluated at two different time points. After two cycles of ^{131}I-MIBG therapy plus topotecan the ORR was 56% (95% CI 33% to 77%); 1/16 children had a VGPR and 8/16 children had a PR. After myeloablative therapy and ASCT, the ORR was also 56% (95% CI 33% to 77%); 5/16 children had a CR and 4/16 children a PR.

Overall survival

De Kraker 2008 provided no definition for overall survival. The median overall survival for all 41 children was 15 months (95% CI 7 to 23) and five-year overall survival was 14.6%.

Kraal 2015 provided no definition for overall survival. The 10-year overall survival was 6.25%.

Event-free survival

De Kraker 2008 provided no definition for event-free survival. The median event-free survival for all 41 children was 10 months (95% CI 7 to 13) and five-year event-free survival was 12.2%.

Kraal 2015 did not report event-free survival.

Short-term adverse events

Haematological adverse events

De Kraker 2008 defined haematological adverse events as death due to myelosuppression. One child died 43 days after stem cell reinfusion of a cerebral bleeding while still thrombocytopenic (no definition provided); the child had received a cumulative dose of 800 mCi of MIBG. A toxic myelosuppression is highly suspective for the death. It was unclear if all children were assessed for this outcome, but the best-case scenario showed a prevalence of 2% (95% CI 0% to 13%).

Kraal 2015 defined haematological adverse events as grade 3 or 4 according to the Common Terminology Criteria Adverse Event version 3 (CTCAEv3) criteria. They assessed platelets, neutrophils and haemoglobin (Hb) at two different time points. After the first cycle of ^{131}I-MIBG therapy with topotecan, 6/16 children had grade 3 or 4 platelets (38%, 95% CI 18% to 61%), 8/16 had grade 3 or 4 neutrophils (50%, 95% CI 28% to 72%) and 11/16 had grade 3 or 4 Hb (69%, 95% CI 44% to 86%). After the second cycle of ^{131}I-MIBG therapy with topotecan 9/15 children had grade 3 or 4 platelets and grade 3 or 4 neutrophils (60%, 95% CI 36 to 80%), and 8/15 children had grade 3 or 4 Hb (53%, 95% CI 30 to 75%).

Cardiovascular adverse events

Neither De Kraker 2008 nor Kraal 2015 reported cardiovascular adverse events.

Hepatic adverse events

De Kraker 2008 defined hepatic adverse events as higher than grade 1, but no definition was provided. It was assessed during or within four weeks after last the ^{131}I-MIBG treatment. It was not clear if all participants were assessed for this outcome, but the best-case scenario showed a prevalence of 0% (95% CI 0% to 9%).

Kraal 2015 did not report hepatic adverse events.

Sialoadenitis

Neither De Kraker 2008 nor Kraal 2015 reported sialoadenitis.

Long-term adverse events

Thyroid dysfunction

De Kraker 2008 tested thyroid function in 22/41 children (54%) before or after ^{131}I-MIBG treatment. They assessed thyroid-stimulating hormone (TSH) (greater than 4.5 mU/L) and T4 (cut-off

point not provided). Children were measured at a median follow-up of 19 months (range 0.7 to 129). Ten out of 22 children had an elevated plasma TSH (45%, 95% CI 27% to 65%), which was transient in three children. It remained elevated in seven children of which five were prescribed thyroxine. In all 22 children, free T4 was within the age-related normal range (0%, 95% CI 0% to 15%).

Kraal 2015 did not report thyroid dysfunction.

Secondary malignancies

De Kraker 2008 provided no definition for secondary malignancies. None were observed (0%, 95% CI 0% to 9%), but only five children survived more than four years.

Kraal 2015 did not report secondary malignancies.

Dose intensity after ^{131}I-MIBG treatment: the actual administered amount of ^{131}I-MIBG

In De Kraker 2008, children received a cumulative dose of 350 mCi to 950 mCi (13 GBq to 35 GBq) ^{131}I-MIBG (median 500 mCi) as induction therapy.

In Kraal 2015, the administered activity was median 0.5 GBq/kg (range 0.4 to 0.6) and 14.5 mCi/kg (range 10.1 to 16.8) in the first cycle and median 0.4 GBq/kg (range 0.3 to 0.5) and 10.6 mCi/kg (range 6.9 to 12.6) in the second cycle. The cumulative administered activity was median 0.9 GBq/kg (range 0.5 to 1.1) and median 25 mCi/kg (range 14.3 to 29.4).

Time span of delivering chemotherapy induction treatment after ^{131}I-MIBG therapy

De Kraker 2008 did not report time span of delivering chemotherapy induction treatment after ^{131}I-MIBG therapy.

In Kraal 2015, the researchers aimed to give treatment at four-week intervals. The actual mean interval time between the second MIBG plus topotecan and the first VECI (vincristine, etoposide, carboplatin and ifosfamide) chemotherapy course was 30 days (range 20 to 47). The mean interval time for the subsequent VECI chemotherapy courses was 30 days (range 18 to 40) for the first course, 31 days (range 28 to 38) for the second course and 29 days (range 21 to 46) between the third and fourth course.

Stem cells

Yield of peripheral stem cell collection during harvest sessions

De Kraker 2008 did not report the mean number of collected autologous haematopoietic stem cells, but they did report the median value for the 17 children who underwent a stem cell harvest. In the first eight children, it was 11.6 × 10^4/kg colony-forming unit in culture (CFU-C) colonies (range 2.9 to 31.6), while in the subsequent nine children, the median was 4.9 × 10^6/kg CD34+ cells (range 1.2 to 17).

Kraal 2015 did report the mean number of collected stem cells for the 13 children who underwent a stem cell harvest: the mean yield of peripheral blood stem cells harvest was 2.2 × 10^6/kg (0 to 6.9) CD34+ stem cells. For the bone marrow harvest, this was 3.4 × 10^6/kg (1.0 to 9.1) CD34+ stem cells.

Number of successful peripheral stem cell harvests

De Kraker 2008 did not report the number of successful peripheral stem cell harvests.

Kraal 2015 did not provide a definition for a successful peripheral stem cell harvest, so we could not be certain it was according our prespecified definition of 2 × 10^6/kg autologous haematopoietic stem cells. They reported that peripheral blood stem cell apheresis was successful in 6/13 children (46%).

Number of peripheral stem cell harvest sessions necessary to obtain a sufficient amount of autologous haematopoietic stem cells

Neither De Kraker 2008 nor Kraal 2015 reported the number of peripheral stem cell harvest sessions necessary to obtain a sufficient amount of autologous haematopoietic stem cells.

Percentage of children in which bone marrow harvest was performed

De Kraker 2008 did not report the percentage of children in which bone marrow harvest was performed.

In Kraal 2015, 6/13 children (46%) underwent further bone marrow harvesting.

Stem cell engraftment defined as the time to haematopoietic recovery after myeloablative chemotherapy and autologous stem cell transplantation for each of the haematopoietic cell lineages

De Kraker 2008 assessed stem cell engraftment for platelets and neutrophils, but not for Hb. The median time to platelet engraftment (greater than 50 × 10^3/μL) was 47 days. The median time to neutrophil engraftment (greater than 1 × 10^3/μL) was 23 days.

Kraal 2015 also assessed stem cell engraftment for platelets and neutrophils, but not for Hb. The median time to platelet engraftment (greater than 25 × 10^9/L) was 37 days (range 14 to 74). For neutrophil engraftment (greater than 0.5 × 10^9/L), this was 21 days (range 12 to 62).

DISCUSSION

Summary of main results

Patients with newly diagnosed HR NBL still have a poor outcome, despite multi-modality intensive therapy. This poor outcome necessitates the search for new therapies, such as treatment with ^{131}I-MIBG. In this systematic review, we assessed the efficacy and adverse effects of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL.

We identified two prospective (cohort) studies investigating efficacy and toxicity of upfront ^{131}I-MIBG therapy in children with newly diagnosed HR NBL. The first study included 44 children (De Kraker 2008), the second study included 16 children (Kraal 2015). As the studies were not comparable with regard to prognostic factors and treatment (and often used different outcome definitions), pooling of results was not possible.

Both studies assessed response according to the INRC. In De Kraker 2008, the ORR was 73% after surgery. In Kraal 2015 the ORR was 56% after myeloablative therapy and ASCT.

In De Kraker 2008, median overall survival was 15 months (95% CI 7 to 23) and five-year overall survival was 14.6%. Median event-free survival was 10 months (95% CI 7 to 13) and five-year event-free survival was 12.2%. In Kraal 2015, 10-year overall survival was 6.25% and event-free survival was not reported.

With regard to short-term adverse effects, De Kraker 2008 assessed death due to myelosuppression. It was unclear if all children were assessed for this outcome, but the best-case scenario showed a prevalence of 2% (95% CI 0% to 13%). Kraal 2015 assessed platelets, neutrophils and Hb grade 3 or 4 according to the CTCAEv3 criteria. After the first cycle of ^{131}I-MIBG therapy plus topotecan there was platelet toxicity in 38% (95% CI 18% to 61%), neutrophil toxicity in 50% (95% CI 28% to 72%) and Hb toxicity in 69% (95% CI 44% to 86%). After the second cycle, this was 60% (95% CI 36% to 80%) for platelets and neutrophils and 53% (95% CI 30% to 75%) for Hb. Only De Kraker 2008 reported hepatic toxicity: it was assessed during or within four weeks after last the MIBG treatment (higher than grade 1). It was unclear if all children were assessed for this outcome, but the best-case scenario showed a prevalence of 0% (95% CI 0% to 9%). Neither study reported cardiovascular toxicity and sialoadenitis. Kraal 2015 did not look at long-term adverse events, but De Kraker 2008 reported elevated plasma TSH in 45% of the 22 assessed children (95% CI 27% to 65%); in all 22 children, the free T4 was within the age-related normal range (0%, 95% CI 0% to 15%). There were no secondary malignancies observed (0%, 95% CI 0% to 9%), but only five children survived more than four years.

With regard to dose intensity after ^{131}I-MIBG treatment, in De Kraker 2008, children received a cumulative dose of 350 mCi to 950 mCi (13 GBq to 35 GBq) ^{131}I-MIBG (median 500 miC) as induction therapy, while in Kraal 2015 the administered activity was median 0.5 GBq/kg (range 0.4 to 0.6) and 14.5 mCi/kg (range 10.1 to 16.8) in the first cycle and median 0.4 GBq/kg (range 0.3 to 0.5) and 10.6 mCi/kg (range 6.9 to 12.6) in the second cycle. The cumulative administered activity was median 0.9 GBq/kg (range 0.5 to 1.1) and median 25 mCi/kg (range 14.3 to 29.4).

Only Kraal 2015 reported time span of delivering chemotherapy induction treatment after ^{131}I-MIBG therapy, who aimed to give treatment at four-week intervals. The actual mean interval time between the second MIBG plus topotecan and the first VECI chemotherapy course was 30 days (range 20 to 47). The mean interval time for the subsequent VECI chemotherapy courses was 30 days (range 18 to 40) for the first course, 31 days (range 28 to 38) for the second course and 29 days (range 21 to 46) between the third and fourth course.

We also collected information on stem cells. De Kraker 2008 reported the median number of collected autologous haematopoietic stem cells during harvest sessions for the 17 children who underwent a stem cell harvest. In the first eight children, it was 11.6 × 10^4/kg CFU-C colonies (range 2.9 to 31.6), while in the subsequent nine children, the median was 4.9 × 10^6/kg CD34+ cells (range 1.2 to 17). Kraal 2015 reported the mean number of collected stem cells for the 13 children who underwent a stem cell harvest: the mean yield of peripheral blood stem cells harvest was 2.2 × 10^6/kg CD34+ stem cells (range 0 to 6.9). For the bone marrow harvest, this was 3.4 × 10^6/kg CD34+ stem cells (range 1.0 to 9.1). De Kraker 2008 provided no information on the number of successful stem cell harvests; Kraal 2015 reported that peripheral blood stem cell apheresis was successful in 46% of the children, but did not provide a definition. Neither study provided information on the number of peripheral stem cell harvest sessions necessary to obtain a sufficient amount of autologous haematopoietic stem cells. In Kraal 2015, 46% of children underwent bone marrow harvesting; De Kraker 2008 provided no information. Both studies reported on stem cell engraftment for platelets and neutrophils, but not for Hb. In De Kraker 2008, the median time to platelet engraftment (greater than 50 × 10^3/μL) was 47 days; the median time to neutrophil engraftment (greater than 1 × 10^3/μL) was 23 days. In Kraal 2015, the median time to platelet engraftment (greater than 25 × 10^9/L) was 37 days (range 14 to 74); for neutrophil engraftment (greater than 0.5 × 10^9/L) this was 21 days (range 12 to 62).

Overall completeness and applicability of evidence

The external validity of a study indicates how well its results can be extrapolated to individual children with newly-diagnosed HR NBL treated with ^{131}I-MIBG therapy. It includes the following items: well-defined study group, well-defined follow-up and well-defined outcome. If important information is missing, it is difficult to correctly interpret the results and extrapolate them to individual children. In both included studies, the study group was well-defined and the risk of reporting bias was low. In both studies, the length of follow-up was not mentioned, so the risk of reporting bias was unclear. Follow-up could have been too short for children to develop, for example, long-term adverse effects. For overall survival, the outcome is well-defined by default, so the risk of reporting bias was low in both studies. Both studies assessed response (low risk of reporting bias in both studies) and haematological toxicity (low risk of reporting bias in Kraal 2015; unclear risk of reporting bias in De Kraker 2008). For all other primary outcomes assessed by the included studies, the risk of reporting bias was unclear. Overall, neither of the included studies scored good on all applicable reporting bias items, on many occasions due to a lack of reporting.

In addition, the studies were performed in a different treatment era (1989 to 1999 (De Kraker 2008) and 2000 to 2003 (Kraal 2015)). Supportive care, like antibiotic use, anticancer treatments, diagnostic techniques and reporting standards have changed substantially since then, so consequently, the results may not be applicable to children who are treated in the 2010s. The overall survival reported in both included studies (five-year overall survival in De Kraker 2008 of 14.6% and 10-year overall survival in Kraal 2015 of 6.25%) is very much less than the current norm in other studies of treatment in children with newly diagnosed HR NBL. For example, Pinto 2015 found a five-year overall survival rate of 50% in the treatment era between 2005 and 2010 (Pinto 2015). This can be explained by the fact that the two included studies were carried out in different treatment era (1989 to 2003). In both studies, the ^{131}I-MIBG therapy was followed by VECI chemotherapy, which later was shown to be less effective chemotherapy than other regimens (Pearson 2008).

Supportive care, such as antibiotic use, and anticancer treatments have changed substantially within this period, so consequently, the results may not all be applicable to children who are treated in the 2010s.

It should be kept in mind that the time span of delivering chemotherapy induction treatment after ^{131}I-MIBG therapy does not only depend on the effects of ^{131}I-MIBG therapy, but, for example, also on adverse effects after chemotherapy.

The absence of reporting of either whole-body dose (which correlates with toxicity (Trieu 2016)) or tumour dose (which may correlate with response and survival (Trieu 2016)), or both, in the included studies is a major methodological flaw.

Despite all children having newly diagnosed HR NBL, in this review we used the old definition of HR NBL. Recently, the age cut-off has been changed from one year to 18 months (Cohn 2009). As a result, some included children might now be classified as having intermediate-risk disease. However, the number of children that will switch from high-risk to intermediate-risk treatment is low.

Even though RCTs provide the highest level of evidence, it should be recognised that data from non-randomised studies on the efficacy of ^{131}I-MIBG therapy in children with newly diagnosed NBL are available (Kraal 2015; De Kraker 2008). The overall response rate after two courses of ^{131}I-MIBG therapy was 66% (De Kraker 2008) and 56% (Kraal 2015). Although the results of these studies are promising, they should be interpreted with caution due to the biases associated with non-randomised study designs, in these cases, two retrospective cohort studies. A study by Park and colleagues described a lower response rate to chemotherapy of 12/31 (39%) children after two cycles of topotecan/cyclophosphamide in children with HR NBL (Park 2011).

Finally, data were not available for all outcomes of interest. As a result, we cannot draw conclusions regarding those outcomes, which are important for clinical practice.

Quality of the evidence

To adequately assess the efficacy and adverse effects of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL, the best study design - provided that the design and execution are correct - is an RCT in which the only difference between the intervention and control group is use of ^{131}I-MIBG therapy. CCTs can also provide reliable information, keeping in mind their limitations, but we found none of these. This review included other study designs, but they were associated with a high risk of bias.

The internal validity gives an indication of the bias present in a study and thus how valid the results of a certain study are. It includes the following issues: selection bias, attrition bias and detection bias. In both studies, selection bias could be ruled out. The risk of attrition bias was low for response, event-free survival, overall survival, secondary malignant disease, stem cells and, in one study (Kraal 2015), for haematological toxicity. In the other study, the risk of attrition bias was unclear for haematological toxicity and hepatic toxicity, and high for thyroid dysfunction (De Kraker 2008). Attrition bias can lead to an overestimation or underestimation of the risk of these adverse effects. The risk of detection bias was low for overall survival, but it could not be ruled out for all other assessed primary outcomes. Knowledge of prognostic factors can increase the possibility of classifying a person as having a certain outcome.

Potential biases in the review process

This systematic review used a very broad search strategy for identifying eligible studies. However, although it is unlikely that eligible studies were missed, it is never possible to completely rule out reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

We found no randomised controlled trials or controlled clinical trials comparing the effectiveness of treatment including ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) therapy versus treatment not including ^{131}I-MIBG therapy in patients with newly diagnosed high-risk (HR) neuroblastoma (NBL). We found two observational studies in children, but, besides the associated high risk of bias, results were not available for all relevant outcomes. In addition, it should be kept in mind that recently the age cut-off for high-risk disease was changed from one year to 18 months. As a result, it is possible that children with what is now classified as intermediate-risk disease were included in the high-risk groups. Based on the currently available evidence, we cannot make recommendations for the use of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL in clinical practice. At the moment, ^{131}I MIBG treatment should only be given in the context of a well-designed randomised controlled trials.

Implications for research

Prospective randomised controlled trials are essential to strengthen the evidence base on the use of ^{131}I-MIBG therapy in patients with newly diagnosed HR NBL. The studies should be performed in homogeneous study populations (e.g. stage of disease; using the most recent definitions for high-risk disease) and have a long-term follow-up. Dosimetry for ^{131}I-MIBG therapy should be incorporated into the treatment protocol. The number of included participants should be sufficient to obtain the power needed for the results to be reliable. Accurate and transparent reporting of findings will make it possible for readers to critically appraise the results of these studies.

ACKNOWLEDGEMENTS

Huib Caron was a coauthor of the protocol for this systematic review and we thank him for his valuable input. We would like to acknowledge the Editorial Base of Cochrane Childhood Cancer for their advice and support. The Editorial Base of Cochrane Childhood Cancer is funded by 'Stichting Kinderen Kankervrij' (KiKa), the Netherlands.

We would like to thank the peer reviewers for their comments.

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CHARACTERISTICS OF STUDIES

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

De Kraker 2008

Methods	Prospective cohort study. Single-centre study performed in the Netherlands. Start and end date: April 1989 and October 1999.
Participants	44 children (median age at diagnosis 2.6 years (range 1-15.4); 21 girls and 23 boys) with newly diagnosed high-risk NBL (INSS stage not explicitly mentioned, but based on the metastatic disease, deduced as stage 4). Only 41 children evaluable (age range at start treatment 1.2-15.5 years; 20 girls and 21 boys; 24 received MIBG, 17 received MIBG + chemotherapy): in 2 children, it was not feasible to start ^{131}I-MIBG therapy (1 early progression requiring immediate treatment; 1 sepsis and too unstable for MIBG treatment); in 1 child with progressive disease, parents refused further therapy after 1 MIBG infusion. 2 other children with only 1 MIBG infusion remained in the study. **Tumour biology:** NBL. **Genetics:** 10/44 (23%) *MYCN* amplification (4/24 (16%) MIBG and 6/17 (35%) MIBG + chemotherapy), 20/43 (47%; value for 1 child not available) loss of heterozygosity chromosome 1p (LOH1p) (12 (50%) MIBG and 8 (47%) MIBG + chemotherapy). **Primary tumour location:** not mentioned. **Tumour metastasis:** BM all children. **Previous treatment received:** not mentioned (but see exclusion criteria for further information). **Inclusion criteria:** children aged 1-18 years at diagnosis with high-risk, MIBG-positive NBL. **Exclusion criteria:** previous chemotherapy. Initial surgery as the only treatment modality was allowed.
Interventions	**Induction therapy:** 2 cycles of ^{131}I-MIBG single-agent therapy; if objective response occurred then third MIBG treatment (24 children); if stable disease or progression preoperative VECI chemotherapy

De Kraker 2008 *(Continued)*

	(17 children) then surgery (as soon as the surgeon felt that > 95% resection was feasible) then 4 courses of VECI chemotherapy at 4-weekly intervals then consolidation therapy 4 weeks after last VECI: HD-CT/ASCT then retinoic acid. VECI: vincristine (1.5 mg/m^2 IV on day 1), ifosfamide (3000 mg/m^2 IV over 1 hour on days 1 and 2), carboplatin (400 mg/m^2 IV in a 24-hour infusion on day 3), etoposide (150 mg/m^2 IV over 4 hours on day 4). **Consolidation therapy:** carboplatin (800 mg/m^2 IV over 6 hours on day 1), melphalan (180 mg/m^2 IV on day 3), reinfusion of BM or PBCS on day 5. **Harvest of stem cells:** during postoperative VECI courses as soon as the child was in VGPR or CR with a clear BM. After stem cell reinfusion, 13-cis-retinoic acid 160 mg/m^2 per day administered orally in 2 divided doses for 14 consecutive days in a 28-day cycle, given for 6 months, beginning 4 weeks after stem-cell reinfusion, in 14-day cycles. **^{131}I-MIBG therapy:** first infusion fixed dose 200 mCi (7.4 GBq), 2nd and all subsequent infusions 100-150 mCi (3.7-5.6 GBq) by IV 4-hour infusion. Interval between MIBG infusions 4 weeks. MIBG dosimetry not performed. **Thyroid blocking:** potassium iodide 100 mg for 14 days, beginning on day before MIBG infusion. 14 children had no surgery; 2 had only 1 MIBG infusion; 17 had stem cell transplant. No control participants.
Outcomes	*Response* (according to INRC (Brodeur 1993)). *Overall survival* (no definition provided). *Event-free survival* (no definition provided). *Toxicity:* • haematological toxicity (i.e. death due to myelosuppression; no definition provided); • hepatic (> grade 1, but no definition provided); • thyroid (based on TSH (> 4.5 mU/L) and T4 (no cut-off point provided)); • Secondary malignancies. *Dose intensity after ^{131}I-MIBG treatment* (the actual administered amount of ^{131}I-MIBG MBq/mCi). *Stem cells:* • yield of PBSC collection (median number of collected stem cells, either CFU-C colonies or CD34+ cells); • stem cell engraftment (platelets > 50 × 10^3/μL); • stem cell engraftment (neutrophils > 1 × 10^3/μL).
Notes	**Follow-up:** not mentioned, but the maximal follow-up according to the survival curves was approximately 175 months; thyroid dysfunction was assessed after a mean follow-up of 19 months (range 0.7-129). **Influence of funders:** not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	> 90% of the original cohort.

De Kraker 2008 *(Continued)*

Complete follow-up assessment (attrition bias): response	Low risk	Response assessed for > 90% of the study group of interest.
Complete follow-up assessment (attrition bias): event-free survival	Low risk	Event-free survival assessed for > 90% of the study group of interest.
Complete follow-up assessment (attrition bias): overall survival	Low risk	Overall survival assessed for > 90% of the study group of interest.
Complete follow-up assessment (attrition bias): haematological toxicity	Unclear risk	Not mentioned.
Complete follow-up assessment (attrition bias): hepatic toxicity	Unclear risk	Not mentioned.
Complete follow-up assessment (attrition bias): thyroid dysfunction	High risk	Thyroid dysfunction only assessed in 50% of the study group of interest.
Complete follow-up assessment (attrition bias): secondary malignancies	Low risk	Secondary malignancies were assessed in > 90% of the study group of interest.
Blinded outcome assessor (detection bias): overall survival	Low risk	Blinding of outcome assessor not applicable for overall survival.
Blinded outcome assessor (detection bias): all other primary outcomes	Unclear risk	Not mentioned.
Well-defined study group (reporting bias)	Low risk	All necessary items (see Table 1) provided.
Well-defined follow-up (reporting bias)	Unclear risk	Length of follow-up not mentioned.
Well-defined outcome (reporting bias): response and overall survival	Low risk	Outcome definition provided for response, not applicable for overall survival.
Well-defined outcome (reporting bias): haematological toxicity	Unclear risk	No outcome definition provided.
Well-defined outcome (reporting bias): all other evaluated primary outcomes	Unclear risk	No outcome definition provided.

Kraal 2015

Methods	Prospective phase II windows study. Multi-centre study performed in the Netherlands (2 centres). Start and end date: March 2000 and August 2003.
Participants	16 children (median age at diagnosis 2.8 years (range 1.6-8.3); age at start treatment not mentioned; 10 boys and 6 girls) with newly diagnosed HR NBL (INSS stage not explicitly mentioned, but based on the metastatic disease, deduced as stage 4). **Tumour biology:** NBL. **Genetics:** 8/14 (57%; value for 2 children not available) *MYCN* amplification, 6/15 (40%; value for 1 child not available) loss of heterozygosity chromosome 1p (LOH1p), *MYCN* amplification and LOH1p 6/14 (43%; value for 2 children not available). **Primary tumour location:** 15/16 (94%) abdominal and 1/16 (6%) thoraco-abdominal. **Tumour metastasis:** 16/16 (100%) BM, 4/16 (25%) lymph node and 1/16 (6%) pleura. **Previous treatment received:** none (no prior cancer treatment was allowed). **Inclusion criteria:** histologically confirmed HR NBL, no prior cancer treatment, a non-complicated clinical condition which allowed for a 5-day radioprotective isolation for ^{131}I-MIBG treatment, aged 0-16 years at diagnosis, signed and dated informed consent. **Exclusion criteria:** not conform inclusion criteria stated above.
Interventions	**Upfront treatment:** 2 cycles of ^{131}I-MIBG therapy + topotecan (16 children) then 4 courses of VECI chemotherapy at 4 week intervals (15 children) then surgery (12 children; optimal timing of surgery was discussed when the distant metastases were inactive and the tumour operable) then myeloablative therapy/ASCT (9 children) then 13 cis retinoic acid (13 children). Topotecan: daily 1-hour infusion of topotecan 0.7 mg/m^2 IV for 5 days after MIBG therapy. VECI: vincristine (1.5 mg/m^2 IV on day 1), ifosfamide (3000 mg/m^2 IV on days 1 and 2), carboplatin (400 mg/m^2 IV on day 3), etoposide (150 mg/m^2 IV on day 4). **Harvest of stem cells:** PBSC harvesting took place after the first VECI course if the BM was clear; if not successful this was repeated after the next course. **Myeloablative therapy:** carboplatin (800 mg/m^2 on day -3) and melphalan (180 mg/m^2 IV on day -1), ASCT on day 0. 13-cis-retinoic acid 160 mg/m^2 in 2 doses for 2 weeks followed by 2 weeks' rest (6 cycles). **^{131} I-MIBG therapy:** first dose 7.4 GBq/200 mCi and second dose 5.6 GBq/150 mCi. Interval between MIBG infusions 4 weeks. MIBG dosimetry not performed. **Thyroid blocking:** not reported. 4 children had no surgery; 1 had only 1 MIBG infusion; 9 had stem cell transplant. No control participants.
Outcomes	*Response* (according to INRC (Brodeur 1993)). *Overall survival* (no definition provided). *Toxicity:* • haematological toxicity: platelets, Hb, neutrophils (grade 3 and 4 according to CTCAEv3).

Kraal 2015 *(Continued)*

	Dose intensity after ^{131}I-MIBG treatment (defined as the actual administered amount of ^{131}I-MIBG MBq/mCi). *Time span of delivering chemotherapy induction treatment after ^{131}I-MIBG therapy.* *Stem cells:* • yield of PBSC collection (mean number of collected CD34+ stem cells); • number of successful PBSC harvest (no definition provided); • percentage of children in which BM harvest was performed; • stem cell engraftment (platelets > 25 × 10^9/L); • stem cell engraftment (neutrophils > 0.5 × 10^9/L).
Notes	**Follow-up:** not mentioned, but maximal length of follow-up 10 years. **Influence of funders:** not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	All eligible consecutive participants.
Complete follow-up assessment (attrition bias): response	Low risk	Response assessed for > 90% of the study group of interest.
Complete follow-up assessment (attrition bias): overall survival	Low risk	Overall survival assessed for > 90% of the study group of interest.
Complete follow-up assessment (attrition bias): haematological toxicity	Low risk	Haematological toxicity assessed for > 90% of the study group of interest.
Blinded outcome assessor (detection bias): overall survival	Low risk	Blinding of outcome assessor not applicable for overall survival.
Blinded outcome assessor (detection bias): all other primary outcomes	Unclear risk	Not mentioned.
Well-defined study group (reporting bias)	Low risk	All necessary items (see Table 1) provided.
Well-defined follow-up (reporting bias)	Unclear risk	Length of follow-up not mentioned.
Well-defined outcome (reporting bias): response and overall survival	Low risk	Outcome definition provided for response, not applicable for overall survival.
Well-defined outcome (reporting bias): haematological toxicity	Low risk	Outcome definition provided.

ASCT: autologous stem cell transplantation; BM: bone marrow; CFU-C: colony-forming unit culture; CR: complete response; CTCAEv3: Common Terminology Criteria for Adverse Events version 3 (publication date: 9 August 2006); Hb: haemoglobin; HDCT: high-dose chemotherapy; HR: high risk; INRC: International Neuroblastoma Response Criteria; INSS: International Neuroblastoma Staging System; IV: intravenous; LOH1p: loss of heterozygosity chromosome 1p; MBq/mCi: megaBecquerel/milliCurie; MIBG: meta-iodobenzylguanidine; NBL: neuroblastoma; PBSC: peripheral blood stem cell; TSH: thyroid-stimulating hormone; VECI: vincristine, etoposide, carboplatin and ifosfamide; VGPR: very good partial response.

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

Study	Reason for exclusion
Bleeker 2009	Unclear number of patients with HR NBL.
Bleeker 2013	Unclear number of patients with HR NBL.
Brans 2002	< 10 patients with HR NBL.
Brendel 1989	Case reports.
Claudiani 1988	< 10 patients with MIBG therapy.
Clement 2013	Unclear if they are newly diagnosed or patients with HR NBL, or both.
Clement 2015	Unclear if they are newly diagnosed or patients with HR NBL, or both.
Corbett 1991	< 10 patients with HR NBL.
De Kraker 1995	Included all stages, no separate analysis for patients with HR NBL.
Edeling 1986	< 10 patients with HR NBL.
El-Sabban 2013	Unclear number of patients with HR NBL.
Garaventa 1995	Unclear number of patients.
Garaventa 2003	Unclear if they were patients with HR NBL.
Gerrard 1987	Case report.
Hartmann 1988	Not MIBG therapy.
Hoefnagel 1987	Unclear number of patients with HR NB.
Hoefnagel 1988	Unclear number of patients with HR NBL.
Hoefnagel 1991	< 10 patients with HR NBL.
Hoefnagel 1994	Unclear if they were patienst with HR NBL.
Hoefnagel 1995	Included all stages, no separate analysis for patients with HR NBL.
Klingebiel 1991	Unclear number of patients with HR NBL.
Klingebiel 1994	< 10 patients with HR NBL.
Klingebiel 1998	Prior chemotherapy before MIBG therapy.

Study	Reason for exclusion
Kosmin 2012	Unclear if they were patients with HR NBL.
Lashford 1990	Unclear if they were patients with HR NBL.
Mastrangelo 1987	Editorial, no primary data.
Mastrangelo 1991	Case report.
Mastrangelo 2001	Unclear if they were patients with HR NBL.
Mastrangelo 2011	No separate analysis for patients with HR NBL; prior chemotherapy before MIBG therapy.
Matthay 2009b	Relapsed/refractory patients.
McEwan 1986	No participant data, biochemical analysis.
Mitjavila 1989	< 10 patients with HR NBL.
Monsieurs 2001	Unclear if they were patients with HR NBL.
Mussa 1987	Diagnostic MIBG scan.
O'Donoghue 1991	< 10 patients with HR NBL.
Picco 1995	Unclear if they were patients with HR NBL.
Rachh 2011	< 10 patients with HR NBL.
Schoot 2009a	< 10 patients with HR NBL.
Schoot 2009b	< 10 patients with HR NBL.
Shapiro 1991	Unclear number of patients with HR NBL.
Sudbrock 2010	Unclear number of patients with HR NBL.
Sutton 1982	Unclear number of patients with HR NBL.
Sze 2013	< 10 patients with HR NBL.
Teszler 2013	Editorial.
Van Hasselt 1996	Includes all stages, no separate analysis for patients with HR NBL.
Van Santen 2002	No outcome parameters mentioned as included in the eligibility criteria of this review.
Van Santen 2005	Includes all stages, no separate analysis for patients with HR NBL.
Van Santen 2012	Unclear if they were patients with newly diagnosed or HR NBL, or both.
Van Santen 2013	Includes all stages, no separate analysis for patients with HR NBL.
Vitale 2012	Includes all stages, no separate analysis for patients with HR NBL.
Voute 1985	Unclear number of patients with HR NBL.

Study	Reason for exclusion
Voute 1987a	Unclear number of patients with HR NBL.
Voute 1987b	Unclear number of patients with HR NBL.
Voute 1988a	Unclear number of patients with HR NBL.
Voute 1988b	Unclear number of patients with HR NBL.
Voute 1991	Includes all stages, no separate analysis for patients with HR NBL.
Wong 2013	Patients with refractory NBL.

HR: high risk; NBL: neuroblastoma; MIBG: meta-iodobenzylguanidine.
It should be noted that the list of excluded studies is not exhaustive, and that other valid reasons for exclusion may also exist.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Hamidieh 2014

Methods	Single-centre study.
Participants	13 children (mean age at diagnosis 42.5 months (range 17-65) and mean (± SD) age at transplantation 60.2 ± 21.3 months (range 34-92)) with HR NBL and MIBG avid lesions.
Interventions	Therapeutic ^{131}I- MIBG therapy (12 mCi/kg) followed by myeloablative therapy (etoposide 1200 mg/m^2, carboplatin 1500 mg/m^2 and melphalan 210 mg/m^2) and ASCT. After ASCT, all children received cis-retinoic acid.
Outcomes	Median time to neutrophil engraftment after ASCT was 10 days (range 9-13) and median platelet engraftment was 13 days (range 10-20). None of the children failed to engraft after ASCT. In studied children, 3-year overall survival (mean ± SD) was 66 ± 21% while 3-year EFS was 53 ± 20%.
Notes	This study has not been published in full text (as of 16 May 2016), but has been published as an abstract for Bone Marrow Transplantation meeting.

Kraal 2012

Methods	Multi-centre pilot study.
Participants	Children with HR NBL.
Interventions	2 cycles of upfront ^{131}I-MIBG therapy. Of the 33 evaluable children, 16 (48%) received 2 cycles of upfront ^{131}I-MIBG therapy (group A), 17 (51%) children were treated without upfront ^{131}I-MIBG therapy (group B; insufficient MIBG uptake, weak clinical condition and hypertension) and 2 children were excluded (they received prior chemotherapy).
Outcomes	^{131}I-MIBG therapy within 2 weeks from diagnosis was feasible in all children eligible for ^{131}I-MIBG therapy. Interval between subsequent N5/N6 chemotherapy courses was similar in both groups (22-30 days). There was no serious haematological toxicity. Stem cell harvest after ^{131}I-MIBG therapy was undisturbed and did not compromise high-dose chemotherapy with ASCT treatment. Response analysis (follow-up 1 January 2005 to 1 January 2012) showed an effect of 2 ^{131}I-MIBG courses in 10/15 (67%) children (1 missing) after 3 times N5/N6 of 15/16 (94%) and at follow-up of 13/16 (81%).

Kraal 2012 *(Continued)*

Notes	This study has not been published in full text (as of 16 May 2016), but was presented at the Advances in Neuroblastoma Research conference 2012.

Leung 2011

Methods	Retrospective chart review.
Participants	15 children (median age 3.6 years) with stage 4 (HR) disease with ^{131}I-MIBG-avid lesions at initial diagnosis.
Interventions	All children received ^{131}I-MIBG therapy (14 had 1 infusion; 1 had 2 infusions). 14 ^{131}I-MIBG-therapies were administered as part of the conditioning regimen for HSCT. Lugol's solution was given for thyroid protection. For ^{131}I-MIBG therapy administered as curative treatment, the dose range was 9-12.9 mCi/kg, with median dose of 12 mCi/kg. Carboplatin, etoposide and melphalan was given 7-10 days after MIBG treatment as conditioning for HSCT.
Outcomes	At a median follow-up of 1.2 years (range 0 to 7), 5/14 children receiving therapeutic ^{131}I-MIBG treatment relapsed (36%) and 4 of them died (7%). The estimated 2-year overall survival was 12.8% and EFS was 15.3%. 6 children (43%) developed primary hypothyroidism with elevation of TSH at 5 months to 1 year after treatment and 3 required thyroxine replacement. No child experienced liver derangement immediately after ^{131}I-MIBG treatment.
Notes	Overlap in children with Leung 2013 is very likely. This study has not been published in full text (as of 16 May 2016), but was presented at the Société International Oncologie et Pediatrie (International Society of Paediatric Oncology) conference 2011.

Leung 2013

Methods	Retrospective chart review.
Participants	22 children (median age 2.9 years) with stage 4 (HR) NBL with MIBG avid lesions at diagnosis.
Interventions	All children received ^{131}I-MIBG therapy. 21 ^{131}I-MIBG therapies were administered as part of the conditioning regimen for HSCT. The median dose of ^{131}I-MIBG administered for curative treatment was 12 mCi/kg (range 5.8 to 12.9). Lugol's solution was given for thyroid protection.
Outcomes	At a median follow-up of 1.2 years (range 0 to 9), 12/21 (57%) children receiving therapeutic ^{131}I-MIBG treatment relapsed and 8 of them died (38%). The estimated 2-years overall survival (mean ± SD) was 66.1 ± 12.5%. Among 15 children who had evaluable thyroid function result, 9 (60%) developed primary hypothyroidism with elevation of TSH at 0.3-2.9 years' post-treatment and 4 required thyroxine replacement. No children experienced liver derangement.
Notes	Overlap in participants with Leung 2011 was very likely.

Leung 2013 *(Continued)*

	This study has not been published in full text (as of 16 May 2016), but has been presented at the Société International Oncologie et Pediatrie (International Society of Paediatric Oncology) conference 2013.

López-Aguilar 2003

Methods	Cohort study.
Participants	Children with newly diagnosed NBL stage III and IV; not mentioned if they all had HR disease.
Interventions	Chemotherapy (cisplatin, epirubicin, etoposide, ifosfamide), massive doses of ^{131}I-MIBG and surgical ablation of the remaining tumour were possible.
Outcomes	Not reported for the children treated with MIBG.
Notes	We are currently awaiting the translation of this article from Spanish. Based on the currently available information it is unclear whether this study fulfils the inclusion criteria for this review.

Nakajo 1987

Methods	Unclear.
Participants	Participants with pheochromocytoma and NBL; no further information available.
Interventions	^{131}I-MIBG; no further information available.
Outcomes	Unclear.
Notes	Article in Japanese. We were unable to obtain a copy of this article. Based on the currently available information it is unclear whether this study fulfils the inclusion criteria for this review.

ASCT: autologous stem cell transplantation; EFS: event-free survival; HR: high risk; HSCT: haematopoietic stem cell transplantation; MIBG: meta-iodobenzylguanidine; NBL: neuroblastoma; SD: standard deviation; TSH: thyroid-stimulating hormone.

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

NCT01175356

Trial name or title	Induction Therapy Including ^{131}I-MIBG and Chemotherapy in Treating Patients with Newly Diagnosed High-risk Neuroblastoma Undergoing Stem Cell Transplant, Radiation Therapy, and Maintenance Therapy with Isotretinoin.
Methods	Interventional study.
Participants	Patients with newly diagnosed neuroblastoma or ganglioneuroblastoma stage 4 disease according to International Neuroblastoma Staging System.
Interventions	^{131}I-MIBG therapy followed by myeloablative busulfan/melphalan.
Outcomes	Response, event-free survival and adverse effects.
Starting date	October 2010.

NCT01175356 *(Continued)*

Contact information	Children's Oncology Group; principal investigator: Brian Weiss, MD.
Notes	No full-text publication as of 22 May 2016.

MIBG: meta-iodobenzylguanidine.

ADDITIONAL TABLES

Table 1. Risk of bias criteria for observational studies

	Internal validity	External validity
Study group	**Selection bias** (representative: yes/no): If the described study group consisted of > 90% of patients with HR NBL treated with ^{131}I-MIBG included in the original cohort *Or* If it was a random sample of these patients with respect to important prognostic factors (i.e. age, stage according to INSS (bone marrow involvement), *MYCN* amplification and loss of chromosome 1p), type of disease (i.e. newly diagnosed, relapsed, refractory) and cancer treatment.	**Reporting bias** (well-defined: yes/no): If the mean, median or range of the cumulative ^{131}I-MIBG dose was mentioned *And* When it was described what other treatment (including the received doses) was given.
Follow-up	**Attrition bias** (adequate: yes/no): If the outcome was assessed for > 90% of the study group of interest (++) *Or* If the outcome was assessed for 60-90% of the study group of interest (+).	**Reporting bias** (well-defined: yes/no): If the length of follow-up was mentioned.
Outcome	**Detection bias** (blind: yes/no): If the outcome assessors were blinded to the investigated determinant.	**Reporting bias** (well-defined: yes/no): If the outcome definition was provided.

HR: high risk; INSS: International Neuroblastoma Staging System; MIBG: meta-iodobenzylguanidine; NBL: neuroblastoma.

Table 2. Objective response rate for children treated with ^{131}I-MIBG only and ^{131}I-MIBG plus chemotherapy

Treatment	ORR (95% CI) before surgery	ORR (95% CI) after surgery
^{131}I-MIBG only (24 children)	79% (60% to 91%)	92% (74% to 98%)
^{131}I-MIBG and chemotherapy (17 children)	35% (17% to 59%)	47% (26% to 69%)

CI: confidence interval; MIBG: meta-iodobenzylguanidine; ORR: objective response rate.

APPENDICES

Appendix 1. Search strategy for CENTRAL (the Cochrane Library)

1. For 'Neuroblastoma' the following text words were used:

neuroblastoma OR neuroblastomas OR neuroblast* OR ganglioneuroblastoma OR ganglioneuroblastomas OR neuroepithelioma OR neuroepitheliomas OR Peripheral Primitive Neuroectodermal Tumors OR Peripheral Primitive Neuroectodermal Neoplasm OR Primitive Neuroectodermal Tumor, Extracranial OR Neuroectodermal Tumor, Peripheral OR Neuroectodermal Tumors, Peripheral OR Peripheral Neuroectodermal Tumor OR Peripheral Neuroectodermal Tumors OR Tumor, Peripheral Neuroectodermal OR Tumors, Peripheral Neuroectodermal OR pPNET OR PNET OR PNET* OR Peripheral Primitive Neuroectodermal Tumor OR Extracranial Primitive Neuroectodermal Tumor OR Extracranial Primitive Neuroectodermal Tumors OR Neuroectodermal Neoplasm, Peripheral Primitive OR Neuroectodermal Tumor, Peripheral Primitive

2. For '^{131}I-meta-iodobenzylguanidine' the following text words were used:

131I-Meta-iodobenzylguanidine or 131I-MIBG or 131I-metaiodobenzylguanidine or Iodine-131 Metaiodobenzylguanidine or Iobenguane (131I) or (3-Iodo- (131I) benzyl) guanidine OR iodine-131-metaiodobenzylguanidine or 131I-MIBG therapy or I-metaiodobenzylguanidine or I-131-MIBG or I-131-Metaiodobenzylguanidine or (131) I-MIBG or (131) I-metaiodobenzylguanidine or (MIBG and (treatment or therapy)) OR 3-Iodobenzylguanidine

Final search 1 AND 2

The search was performed in title, abstract or keywords

[* = zero or more characters]

Appendix 2. Search strategy for MEDLINE (PubMed)

1. For 'Neuroblastoma' the following MeSH headings and text words were used:

neuroblastoma OR neuroblastomas OR neuroblast* OR ganglioneuroblastoma OR ganglioneuroblastomas OR neuroepithelioma OR neuroepitheliomas OR (Peripheral Primitive Neuroectodermal Tumors OR Peripheral Primitive Neuroectodermal Neoplasm OR Primitive Neuroectodermal Tumor, Extracranial OR Neuroectodermal Tumor, Peripheral OR Neuroectodermal Tumors, Peripheral OR Peripheral Neuroectodermal Tumor OR Peripheral Neuroectodermal Tumors OR Tumor, Peripheral Neuroectodermal OR Tumors, Peripheral Neuroectodermal) OR (pPNET OR PNET OR PNET*) OR Peripheral Primitive Neuroectodermal Tumor OR Extracranial Primitive Neuroectodermal Tumor OR Extracranial Primitive Neuroectodermal Tumors OR Neuroectodermal Neoplasm, Peripheral Primitive OR Neuroectodermal Tumor, Peripheral Primitive

2. For '^{131}I-meta-iodobenzylguanidine' the following MeSH headings and text words were used:

(131I-Meta-iodobenzylguanidine OR 131I-MIBG OR 131I-metaiodobenzylguanidine OR Iodine-131 Metaiodobenzylguanidine OR Iobenguane (131I) OR (3-Iodo-(131I)benzyl)guanidine OR Iodine Radioisotopes/therapeutic use OR 3-Iodobenzylguanidine/therapeutic use) OR (iodine-131-metaiodobenzylguanidine OR 131I-MIBG therapy OR I-metaiodobenzylguanidine OR I-131-MIBG OR I-131-Metaiodobenzylguanidine OR (131) I-MIBG OR 3-Iodobenzylguanidine[mh] OR (131) I-metaiodobenzylguanidine OR (MIBG AND (treatment OR therapy)))

Final search 1 AND 2

[* = zero or more characters]

Appendix 3. Search strategy for Embase (Ovid)

1. For 'Neuroblastoma' the following Emtree terms and text words were used:

a. exp neuroblastoma/
b. (neuroblastoma or neuroblastomas or neuroblast$).mp.
c. (ganglioneuroblastoma or ganglioneuroblastomas or ganglioneuroblast$).mp.
d. (neuroepithelioma or neuroepitheliomas or neuroepitheliom$).mp.
e. exp neuroectoderm tumor/ or (peripheral primitive neuroectodermal tumors or peripheral primitive neuroectodermal tumours).mp.
f. (peripheral primitive neuroectodermal neoplasm or peripheral primitive neuroectodermal neoplasms).mp.
g. (peripheral neuroectodermal tumor or peripheral neuroectodermal tumors or peripheral neuroectodermal tumour or peripheral neuroectodermal tumours).mp.
h. (pPNET or PNET or PNET$).mp.

i. (peripheral primitive neuroectodermal tumor or peripheral primitive neuroectodermal tumour).mp.
j. (extracranial primitive neuroectodermal tumor or extracranial primitive neuroectodermal tumors or extracranial primitive neuroectodermal tumour or extracranial primitive neuroectodermal tumours).mp.
k. or/1-10

2. For '^{131}I-meta-iodobenzylguanidine' the following Emtree terms and text words were used:

a. exp "(3 iodobenzyl)guanidine i 131"/ or 131I-Meta-iodobenzylguanidine.mp.
b. 131I-MIBG.mp.
c. 131I-metaiodobenzylguanidine.mp.
d. Iodine-131 Metaiodobenzylguanidine.mp.
e. Iobenguane 131I.mp.
f. "(3 iodobenzyl)guanidine"/
g. Iodine Radioisotopes.mp. or exp radioactive iodine/
h. radiopharmaceutical agent/ad, dt
i. 131I-MIBG therapy.mp.
j. I-metaiodobenzylguanidine.mp.
k. (I-131-MIBG or I-131-Metaiodobenzylguanidine or 131-I-MIBG).mp.
l. 3-Iodobenzylguanidine.mp.
m. 131-I-metaiodobenzylguanidine.mp.
n. (MIBG and (treatment or therapy)).mp.
o. or/1-14

Final search 1 AND 2

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; / = Emtree term; $=zero or more characters; ad=drug administration; dt=drug therapy]

CONTRIBUTIONS OF AUTHORS

KK designed the study and wrote the protocol; identified the studies meeting the inclusion criteria (both by initial screening and thereafter); searched for unpublished and ongoing studies; performed the data extraction and risk of bias assessment of the included studies; interpreted the results; wrote and revised the manuscript.

ED designed the study and critically reviewed the protocol; identified studies meeting the inclusion criteria and searched for ongoing studies; acted as a third-party arbitrator for study selection; performed the data extraction and risk of bias assessment of the included studies; analysed the data and contributed to the interpretation of the results; wrote the manuscript and critically reviewed the manuscript.

GT critically reviewed the protocol; identified studies meeting the inclusion criteria; contributed to the interpretation of the results and critically reviewed the manuscript.

BES critically reviewed the protocol; identified studies meeting the inclusion criteria; contributed to the interpretation of the results and critically reviewed the manuscript.

DECLARATIONS OF INTEREST

Some of the authors of this systematic review were also authors of the included studies: KK, BES and GT are authors of Kraal 2015, and BES is also an author of De Kraker 2008.

SOURCES OF SUPPORT

Internal sources

- Cochrane Netherlands, Netherlands.

  Training

External sources

- Stichting Kinderen Kankervrij (KiKa), Netherlands.
- Koningin Wilhelmina Fonds (KWF), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol was written for newly diagnosed, relapsed and refractory HR NBL (Kraal 2013). Since then, we decided that it would be preferable to prepare separate reviews for newly diagnosed and relapsed/refractory disease. This review focused on newly diagnosed disease.

As recommended by Cochrane Childhood Cancer, we classified the outcome "Toxicity and adverse effects" as a primary outcome instead of a secondary outcome to comply with the MECIR standards.

The protocol stated that when relevant data regarding data extraction and risk of bias assessment were missing, we would attempt to contact the study authors to retrieve the missing data. This was not done. In addition, in consultation with Cochrane Childhood Cancer, we restricted the risk of bias assessment of observational studies to the primary outcomes for attrition bias, detection bias and outcome reporting bias (i.e. biases that can be assessed for each outcome separately).

Data synthesis: after the publication of our protocol, Cochrane Childhood Cancer changed its policy regarding the calculation of prevalences and the corresponding 95% confidence intervals. So instead of using the generic inverse variance function of Review Manager 5 to calculate the 95% confidence intervals we were advised to use the Wilson method. As this was not possible in Review Manager 5 we used the EpiTools epidemiological calculators.

INDEX TERMS

Medical Subject Headings (MeSH)

3-Iodobenzylguanidine [adverse effects] [*therapeutic use]; Antineoplastic Agents [adverse effects] [therapeutic use]; Bone Marrow [radiation effects]; Hematologic Diseases [chemically induced] [therapy]; Hematopoietic Stem Cell Transplantation; Neuroblastoma [*radiotherapy]; Observational Studies as Topic; Radiopharmaceuticals [adverse effects] [*therapeutic use]; Thyroid Diseases [chemically induced]; Topotecan [adverse effects] [therapeutic use]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant