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ADIS DRUG EVALUATION

Dinutuximab: A Review in High-Risk Neuroblastoma

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Abstract Dinutuximab (ch14.18; Unituxin™) is a chimeric human–mouse monoclonal antibody that binds to the glycolipid antigen disialoganglioside, which is highly expressed on the surface of neuroblastoma cells. This intravenous drug is approved in the EU and USA as combination therapy with granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-2 and isotretinoin for the postconsolidation treatment of patients with high-risk neuroblastoma. In a multinational, phase III study in this patient population, event-free survival (EFS) benefits with the dinutuximab-containing regimen versus isotretinoin alone were observed at the time of the primary ($p = 0.0115$) and confirmatory ($p = 0.0330$) efficacy analyses, although the observed p-value for the between-group difference in EFS for the primary efficacy analysis did not cross the prespecified boundary for statistical significance ($p < 0.0108$). Significant and sustained (5 years) overall survival benefits were seen with the dinutuximab-containing regimen versus isotretinoin alone. Despite pretreatment with analgesics, antihistamines and antipyretics, serious adverse reactions have been reported with the dinutuximab-containing regimen, with infusion reactions and neuropathy prompting the US FDA to issue boxed warnings. Dinutuximab administered in combination with GM-CSF, IL-2 and isotretinoin represents an important advance in the postconsolidation treatment of patients with high-risk neuroblastoma, with its benefits outweighing its risks in a patient population with a poor prognosis and limited therapeutic options.

Dinutuximab: clinical considerations
First therapy approved specifically for the treatment of high-risk neuroblastoma
Monoclonal antibody that binds to the glycolipid antigen disialoganglioside (which is highly expressed on neuroblastoma cells), inducing cell lysis
Although the dinutuximab-containing regimen did not reach the threshold for statistical significance for EFS, it was associated with significant and sustained (5 years) overall survival benefits compared with isotretinoin alone
The dinutuximab-containing regimen was associated with serious adverse reactions, with two (infusion reactions and neuropathy) prompting the US FDA to issue boxed warnings

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1 Introduction

Neuroblastoma is the most common extracranial solid tumour of childhood [1, 2]. Incidence peaks between infancy and 4 years, with a median age at diagnosis of 23 months [1, 2]. High-risk disease is present in half of all patients diagnosed with neuroblastoma and is typically associated with aggressive biological features (e.g. MYCN oncogene amplification)

and bone or bone marrow metastases [1, 3]. The prognosis for such patients is poor, with a 5-year survival rate of less than 30 % [1, 4].

The treatment strategy for high-risk neuroblastoma consists of three phases: induction (chemotherapy and surgical resection), consolidation [high-dose chemotherapy with autologous stem-cell transplantation (ASCT) and irradiation] and postconsolidation (maintenance therapy) [4]. Postconsolidation therapy is used to treat potential minimal residual disease [4]. On the basis of a previous study [5], isotretinoin was considered the standard-of-care treatment, with targeted immunotherapy a recent addition to the postconsolidation armamentarium for high-risk neuroblastoma [2, 4]. Specifically, monoclonal antibodies target the glycolipid antigen disialoganglioside (GD2), which is highly expressed on neuroblastoma cells, inducing tumour cell apoptosis via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [1, 4]. Moreover, a stronger ADCC response to antibody therapy can be elicited by the concomitant administration of cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-2, which stimulate the natural antitumour activity of the immune system [1].

This article provides a narrative review of pharmacological, therapeutic efficacy and tolerability data relevant to the intravenous use of the GD2-binding monoclonal antibody dinutuximab (ch14.18; Unituxin™) when administered in combination with GM-CSF, IL-2 and isotretinoin in patients with high-risk neuroblastoma. The amount of antibody in the dinutuximab product evaluated in the clinical studies discussed in this article was calculated using a theoretical extinction coefficient (molar absorptivity) of 1.00 [6]. However, the actual extinction coefficient of 1.41 was subsequently used to calculate the amount of antibody in the current manufactured product. Thus, the dosage of dinutuximab differs between the product administered in the clinical studies (25 mg/m^2/day) and the recommended dosage of the manufactured product (17.5 mg/m^2/day; Sect. 6); however, the amount of antibody in both products is identical [6]. Indeed, in a population pharmacokinetic (PPK) analysis (discussed in Sect. 3), bioequivalent systemic exposure was demonstrated between these two products at the 17.5 and 25 mg/m^2/day dosages [7].

2 Pharmacodynamic Properties of Dinutuximab

Dinutuximab is a chimeric human–mouse monoclonal antibody produced in a murine myeloma cell that binds to GD2, which is highly expressed on the surface of neuroblastoma cells and minimally expressed on the surface of normal human neurons, peripheral pain fibres and skin melanocytes [2, 8, 9]. GD2 assists in the attachment of tumour cells to the extracellular matrix [1], with the binding of dinutuximab to GD2 inducing cell lysis via ADCC and CDC [9]. According to preclinical studies, the binding of dinutuximab to the GD2 antigen located on the surface of myelin and/or peripheral nerve fibres may mediate the induction of mechanical allodynia, resulting in dinutuximab-induced neuropathic pain [8, 9]. See Sect. 5 for further discussion of dinutuximab tolerability.

In vitro, dinutuximab has been shown to bind to human neuroblastoma cells, and to more effectively mediate their lysis with human effector cells [e.g. granulocytes and natural killer cells within the peripheral blood mononuclear cell (PBMC) population] compared with 14.G2a (dinutuximab's murine counterpart) [10]. Granulocytes were found to be more effective than PBMCs in lysing neuroblastoma cells, with dinutuximab-mediated lysis enhanced with the addition of GM-CSF [10]. Moreover, in vivo, dinutuximab, either alone or in combination with IL-2, partially inhibited tumour growth in mice [8]. Such enhancements in ADCC activity rationalized combining GM-CSF and IL-2 with dinutuximab in clinical studies [8].

The antitumour effects of dinutuximab regimens have also been observed in four phase I studies [11–14] and two phase III studies [15–17] in patients with neuroblastoma (see Sect. 4 for a discussion of the phase III data).

As with other therapeutic proteins, dinutuximab recipients may develop anti-dinutuximab antibodies [9]. In the nonrandomized portion of ANBL0032 and in ANBL0931, 18 % of 284 patients and 13 % of 103 patients, respectively, developed anti-dinutuximab antibodies. Among those patients who tested positive for anti-dinutuximab binding antibodies, 3.6 % in both studies had neutralizing antibodies. However, this incidence may not be reliable owing to assay limitations [9].

3 Pharmacokinetic Properties of Dinutuximab

The pharmacokinetics of dinutuximab are best described by a two-compartment model, as assessed by a PPK analysis of data from a study in 27 children (aged 1–9 years) with high-risk neuroblastoma [2, 9]. In this study, patients received up to five cycles of intravenous dinutuximab (administered at dosages of 17.5 or 25 mg/m^2/day depending on the manufacturer) for 4 days every 4 weeks, in combination with GM-CSF, IL-2 and isotretinoin [2, 9]. The mean observed maximum plasma concentration of dinutuximab following the fourth infusion was 11.5 μg/mL [8, 9]. According to the PPK analysis, the estimated geometric mean volume of distribution at steady state is 5.2 L [8].

Biotransformation studies have not yet been performed; however, dinutuximab is expected to be degraded by ubiquitous proteolytic enzymes to small peptides and individual amino acids [8]. According to the PPK analysis, the estimated geometric mean clearance is 0.025 L/h (and increased with body size) and the estimated mean terminal half-life is 10 days [8].

According to another PPK analysis of data from four clinical studies, the disposition of dinutuximab does not appear to be altered by age, race, sex, concomitant medications (GM-CSF, IL-2) or the presence of capillary leak syndrome or renal or hepatic impairment [2, 8]. However, the presence of human anti-chimeric antibodies appears to increase the clearance of dinutuximab by approximately 60 % [8].

4 Therapeutic Efficacy of Dinutuximab

A phase I dose-escalation study [13] in patients with neuroblastoma was conducted to determine the maximum tolerated dosage of dinutuximab when administered in combination with GM-CSF, IL-2 and isotretinoin. On the basis of findings from this study, dinutuximab 25 mg/m^2/day for 4 days was selected for further clinical evaluation [13].

The efficacy of a dinutuximab-containing regimen has been evaluated in patients with high-risk neuroblastoma participating in an open-label, multinational phase III study (NCT00026312; ANBL0032) [15] and a noncomparative, multicentre, phase III study (NCT01041638; ANBL0931) [available as an abstract] [16, 17]. ANBL0931 is primarily designed to evaluate the safety and tolerability of dinutuximab [16, 17]. Both studies enrolled patients (aged <31 years [15]) who had completed induction therapy, ASCT (within 9 months following the initiation of induction therapy) and radiotherapy and had achieved at least a partial response, and were absent of progressive disease [15–17]. In ANBL0032, the assignment of patients to randomized (1:1) treatment arms (dinutuximab-containing regimen or standard therapy with isotretinoin alone; see Table 1 for treatment regimen details) was stratified by factors thought to potentially affect post-transplantation outcome (e.g. response before ASCT, number of ASCTs and purged vs. non-purged stem-cell infusion) [15]. Of note, patients with biopsy-proven residual disease following ASCT ($n=25$) were eligible for enrolment, but not randomization, and received the dinutuximab-containing regimen [15]. Baseline characteristics did not significantly differ between the randomized treatment groups; 96 % of patients were aged ≥18 months and 85 % had International Neuroblastoma Staging System (INSS) stage 4 disease [15]. In ANBL0931, the dinutuximab-containing regimen was administered as per ANBL0032 [16, 17].

4.1 ANBL0032

Event-free survival (EFS; primary endpoint) and overall survival were evaluated at a prespecified interim analysis (hereafter referred to as the primary efficacy analysis) conducted after 83 events (corresponding to 61 % of the prespecified total of 137 events) [2, 15], with the results published in Yu et al. [15]. Randomization was terminated following this analysis, with ongoing and additional patients receiving the dinutuximab-containing regimen in what is hereafter referred to as the nonrandomized portion of ANBL0032 [18]. Owing to corruption of the raw datasets used for the primary efficacy analysis, a subsequent confirmatory efficacy analysis was conducted after 94 events (corresponding to 69 % of the prespecified total of 137 events) and used for the EU and US approval process [2, 18]. Two follow-up efficacy analyses (at 3 and 5 years) were also conducted [2]. Efficacy analyses were conducted in the intent-to-treat population [2].

The dinutuximab-containing regimen was associated with improvements in EFS, corresponding to a 43 and 36 % reduction in the risk of relapse, progression, secondary malignancy or death relative to isotretinoin alone, at the time of the primary ($p=0.0115$) and confirmatory ($p=0.0330$) efficacy analyses (Table 1) [2, 8]. However, the observed p-value of 0.0115 for the between-group difference in EFS for the primary efficacy analysis did not cross the prespecified boundary for statistical significance ($p<0.0108$) [8]. At the time of the primary and confirmatory efficacy analyses, median EFS duration had not yet been reached in the dinutuximab-containing regimen group, but was 1.92 years (primary efficacy analysis) and 1.95 years (confirmatory efficacy analysis) in the isotretinoin alone group [18]. A 31 % numerical reduction in the risk of relapse, progression, secondary malignancy or death was observed with the dinutuximab-containing regimen versus isotretinoin alone at the time of the first follow-up analysis (Table 1) [2]. At this timepoint, median EFS duration had not yet been reached in the dinutuximab-containing regimen group, but was 3.22 years in the isotretinoin alone group [18].

Compared with isotretinoin alone, the dinutuximab-containing regimen was associated with significant and sustained overall survival benefits, reducing the risk of death by 46 % at 2 years, 43 % at 3 years and 38 % at 5 years (Table 1) [2]. At 2 and 3 years' follow-up, the median overall survival duration with the dinutuximab-containing regimen had not yet been reached; the median overall survival duration with isotretinoin alone was 3.88 years and had not yet been reached, respectively [18].

4.1.1 Subgroup Analyses

In neuroblastoma, age at diagnosis of >18 months, INSS stage 4 disease and MYCN oncogene amplification are

Table 1 Efficacy of the dinutuximab-containing regimen versus isotretinoin alone in patients with high-risk neuroblastoma in the ANBL0032 study [2, 8, 9, 15]

Endpoint (% of pts) [timepoint]	DIN-containing regimen[a,b]	Isotretinoin[b,c]	Hazard ratio (95 % CI)
Event-free survival[d,e]			
Primary efficacy analysis [2 years]	66.3	46.4	0.57 (0.37–0.89)[f]
Confirmatory analysis [2 years]	65.6	48.1	0.64 (0.43–0.97)[f]
First follow-up analysis [3 years]	62.8	50.9	0.69 (0.47–1.01)
Overall survival[e]			
Primary efficacy analysis [2 years]	86.2	74.5	0.52 (0.30–0.92)*
Confirmatory analysis [2 years]	85.4	75.3	0.54 (0.32–0.92)*
First follow-up analysis [3 years]	79.5	67.3	0.57 (0.36–0.89)*
Second follow-up analysis [5 years]	74.2	57.0	0.62 (0.40–0.96)*

DIN dinutuximab, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *IL* interleukin, *IV* intravenous, *PO* oral, *pts* patients, *SC* subcutaneous

* $p < 0.05$ vs. isotretinoin

[a] IV DIN 25 mg/m^2 /day for 4 days for the first five of six 4-week cycles plus IV or SC GM-CSF 250 μg/m^2 /day for 14 days in cycles 1, 3 and 5 plus IV IL-2 3.0 x 10^6 IU/m^2 /day for days 1–4 and 4.5 x 10^6 IU/m^2 /day for days 8–11 in cycles 2 and 4 plus PO isotretinoin 160 mg/m^2 /day for 14 days in cycles 1–6. During the first five cycles, pts were pretreated with analgesics, antihistamines and antipyretics

[b] For each treatment group, $n = 113$ (primary and confirmatory analyses) and 114 (first and second follow-up analyses)

[c] PO isotretinoin 160 mg/m^2 /day for 14 days in cycles 1–6

[d] Primary endpoint

[e] Event-free survival was defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy or death; overall survival was defined as the time from enrolment until death

[f] The observed p-value of 0.0115 for the primary efficacy analysis did not cross the prespecified boundary for statistical significance ($p < 0.0108$); the observed p-value for the confirmatory efficacy analysis was 0.0330

associated with a poorer prognosis than age at diagnosis of <12 months, INSS stage 2a, 3 or 4s disease and MYCN non-amplification [2]. DNA diploidy, an unfavourable tumour histology and a partial response prior to ASCT are also expected to be associated with a poorer prognosis [2]. Hazard ratios (HRs) for EFS and overall survival favoured the dinutuximab-containing regimen over isotretinoin alone in most prespecified subgroups, including patient age at enrolment, INSS stage, pre-ASCT response and tumour histology, at the time of the confirmatory efficacy analysis (with these findings generally supported by the primary efficacy analysis [19]) [2]. However, in some instances the benefit did not reach significance, including in patients with DNA hyperploidy and those who had received a purged stem cell transplant (both favourable prognostic factors) [2]. Moreover, in patients with INSS stage 4 disease (i.e. the subgroup accounting for the majority of the patient population), a significant ($p = 0.04$) benefit with the dinutuximab-containing regimen over isotretinoin alone for EFS was observed in the confirmatory analysis [HR at 2 years 0.64 (95 % CI 0.42–0.99)], but not in the first follow-up analysis. For overall survival, a significant ($p = 0.0149$) benefit was observed in the first follow-up analysis [HR at 3 years 0.55 (95 % CI 0.34–0.90)], but not in the confirmatory analysis [2].

4.2 ANBL0931

The 2-year EFS and overall survival rates following the dinutuximab-containing regimen ($n = 105$) were 74 and 84 % [16].

5 Tolerability and Safety of Dinutuximab

Discussion in this section focuses on data from the primary safety analysis of ANBL0032 derived from the US prescribing information [9]. Unless otherwise specified, adverse reactions were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [9].

Adverse reactions were the most common reason for patients to discontinue the dinutuximab-containing regimen (whereas isotretinoin alone was most commonly discontinued because of disease progression) [19 % of 134 and 17 % of 106 patients] [9]. The most common (incidence ≥50 %) adverse reactions (all grades) observed following therapy with the dinutuximab-containing regimen were pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatraemia, increased alanine aminotransferase levels and anaemia [9]. However, it should be noted that

grade 1 or 2 adverse reactions were collected sporadically (as the protocol instructed investigators not to report grade 1 or 2 adverse reactions [18]). The most common grade 3 or higher (i.e. severe) adverse reactions are presented in Fig. 1. Other grade 3 or higher adverse events of interest include peripheral neuropathy, which occurred in 3 % of patients receiving the dinutuximab-containing regimen and 0 % of patients receiving isotretinoin [9]. One grade 5 adverse reaction was reported (acute capillary leak syndrome in the setting of an IL-2 overdose) [9, 18]. It is worth noting that while the overall incidence of the most severe adverse reactions in the dinutuximab-containing regimen group were generally similar regardless of whether GM-CSF or IL-2 was administered, severe pain occurred numerically more frequently during cycles with GM-CSF (i.e. cycles 1, 3 and 5) than during those with IL-2 (i.e. cycles 2 and 4) [43 % of 134 patients and 35 % of 127 patients] [9, 20]. Moreover, severe pyrexia (37 vs. 10 %), capillary leak syndrome (20 vs. 11 %), infusion-related reactions (20 vs. 10 %), hypotension (16 vs. 5 %) and diarrhoea (13 vs. 6 %) occurred numerically more frequently during cycles with IL-2 than during those with GM-CSF [9, 20].

The most frequently reported (≥5 % of patients) serious adverse reactions observed with the dinutuximab-containing regimen were infections, infusion reactions, hypokalaemia, hypotension, pain, pyrexia and capillary leak syndrome [9]. The US prescribing information for dinutuximab carries a boxed warning regarding infusion reactions and also neuropathy (Sect. 6) [9].

The tolerability profile of the dinutuximab-containing regimen in the randomized portion of ANBL0032 was generally similar to that observed in the nonrandomized portion (i.e. following the termination of randomization) [$n = 783$] of ANBL0032, and in ANBL0931 ($n = 104$) [9]. For instance, in ANBL0931, serious adverse events were reported in 99 % of patients, with lymphopenia (75 %), pyrexia (66 %), anaemia (63 %), thrombocytopenia (56 %), neutropenia (53 %), hypokalaemia (49 %), pain (44 %) and hyponatraemia (40 %) being the most common (incidence ≥40 %) [17].

6 Dosage and Administration of Dinutuximab

Intravenous dinutuximab is indicated as combination therapy with intravenous or subcutaneous GM-CSF, intravenous IL-2 and oral isotretinoin for the treatment of high-risk neuroblastoma in the EU [8] and the USA [9]. In the EU, it is approved for use in patients aged 1–17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT [8]. In the USA, it is approved for use in paediatric patients who have previously received first-line multi-agent, multimodality therapy and achieved at least a partial response [9].

The recommended dosage of dinutuximab is 17.5 mg/m^2/day administered as an intravenous infusion over 10–20 h for 4 consecutive days for a maximum of five cycles [8, 9]. The infusion should be initiated at a rate of 0.875 mg/m^2/h over 30 min; the rate should then be increased, as tolerated, to 1.75 mg/m^2/h [8, 9].

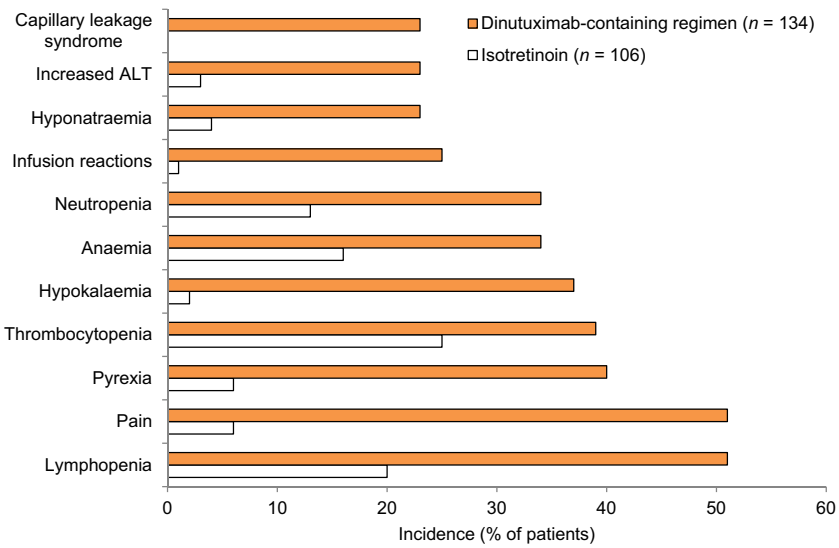

Fig. 1 Grade 3 or higher adverse reactions occurring in >20 % of patients and with a >5 % higher incidence in the dinutuximab-containing regimen group than the isotretinoin alone group in patients with high-risk neuroblastoma in the ANBL0032 study [9]. *ALT* alanine aminotransferase

The US prescribing information carries a boxed warning regarding infusion reactions and neuropathy in patients receiving dinutuximab, with interruptions in therapy recommended for severe infusion reactions and discontinuations of therapy recommended for anaphylaxis, moderate to severe peripheral motor neuropathy, severe sensory neuropathy or severe unresponsive pain [9].

Local prescribing information should be consulted for detailed information regarding contraindications, the dosing schedule, other events for which dosage interruptions and/or reductions are recommended, potential drug interactions, preparation and administration procedures, pretreatment recommendations, use in special patient populations and other warnings and precautions.

7 Current Status of Dinutuximab in the Management of High-Risk Neuroblastoma

Immunotherapy administered in combination with cytokines and isotretinoin is now considered part of the standard of care treatment for patients with high-risk neuroblastoma [4], with the monoclonal antibody dinutuximab the first therapy approved specifically for this patient population [21]. Its approval was primarily based on an open-label, multinational phase III study (Sect. 4). EFS benefits were obtained with the dinutuximab-containing regimen over isotretinoin alone at the time of the primary ($p = 0.0115$) and confirmatory ($p = 0.0330$) efficacy analyses, reflecting a 43 and 36 % reduction in the risk of relapse, progression, secondary malignancy or death. However, the observed p-value for the between-group difference in EFS for the primary efficacy analysis did not cross the prespecified boundary for statistical significance ($p < 0.0108$). Significant and sustained (5 years) overall survival benefits were seen with the dinutuximab-containing regimen versus isotretinoin alone, with EFS and overall survival rates generally favouring the dinutuximab-containing regimen over isotretinoin alone in most prespecified subgroups.

Despite pretreatment with analgesics, antihistamines and antipyretics [2], serious adverse reactions have been reported with the dinutuximab-containing regimen (Sect. 5), with two (infusions reactions and neuropathy) prompting the US FDA to issue boxed warnings (Sect. 6). Of note, the presence of infusion reactions (associated with dinutuximab and the cytokines) and (cytokine-mediated) capillary leak syndrome were expected, as was neuropathy, given that mechanical allodynia is thought to be induced by dinutuximab (Sect. 2) [15]. Adverse reactions should be managed by interrupting the infusion, reducing the infusion rate, dose reduction or treatment discontinuation of dinutuximab, GM-CSF and/or IL-2 [8, 9]. However, both the European Medicines Agency [2] and the US FDA [20] have concluded that the benefits of dinutuximab outweighs the risks.

Although beyond the scope of the review, it is worth noting that dinutuximab is a current focus of interest in an upcoming clinical study in recurrent osteosarcoma (NCT02484443). Other anti-GD2 antibodies are also currently under evaluation in the clinical setting, including ch14.18/CHO, a chimeric human–mouse GD2-binding monoclonal antibody produced in Chinese hamster ovary (CHO) cells (unlike dinutuximab, which is produced in a murine myeloma cell) [17].

In conclusion, current evidence suggests that dinutuximab administered in combination with GM-CSF, IL-2 and isotretinoin represents an important advance in the postconsolidation treatment of patients with high-risk neuroblastoma, with its benefits outweighing its risks in a patient population with a poor prognosis and limited therapeutic options.

Data selection sources: Relevant medical literature (including published and unpublished data) on dinutuximab was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 19 January 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Dinutuximab, Unituxin, ch14.18, neuroblastoma.
Study selection: Studies in patients with neuroblastoma who received dinutuximab. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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