Review Article

Safety and efficacy of dinutuximab in the treatment of neuroblastoma: A review

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Dinutuximab, which is a monoclonal antibody targeting GD2 expressed in neuroblasts, improves survival when included in the therapy regimen. This article reviews the importance of dinutuximab in managing neuroblastoma (NB). Dinutuximab targets high levels of GD2 expression in NB cells, thus increasing event-free survival when used in the maintenance therapy of high-risk patients with NB. Although several collaborative studies have set the standard of care for maintenance therapy, the long-term follow-up and continuous evaluation of the use of antibodies and the co-administration of other pharmacological or immunomodulatory drugs remain to be studied. Trials have shown that the use of dinutuximab for maintenance therapy can prolong the time before the first relapse and improve overall survival. However, there is uncertainty in the function of cytokines co-administered with dinutuximab, which may lead to increased toxicity without additional benefits. Recent studies on relapsed and refractory NB have shown the potential efficacy of dinutuximab. Further research is required to properly incorporate Dinutuximab in current treatment modalities.

Keywords: Dinutuximab, GD2, monoclonal antibody, neuroblastoma

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INTRODUCTION

Neuroblastoma (NB), which is a malignancy of the sympathetic nervous system, is the most prevalent extracranial solid tumor that occurs during childhood, and its clinical presentation and course vary depending on the nature of the tumor.[1] It either regresses spontaneously, particularly in children or progresses to a benign ganglioneuroma. However, in adults, even the most intensive multimodal therapy cannot prevent the continuous growth of metastatic malignancies.[2] Approximately 500 new cases of NB are recorded annually. Although 90% of NB cases are detected before the age of 5 years, 30% are diagnosed with NB during the 1st year of life, and the median age at diagnosis is 22 months.[3]

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Gangliosides, including GD2, are complex glycolipids present on the outer cell membrane as surface antigens, and only peripheral neurons, the central nervous system, and skin melanocytes express these glycolipids. Moreover, NB and melanoma, which are tumors of Neuroectodermal origin, express GD2. NB cells exhibit high GD2 expression, enzymatic activity, and GM2/GD2 synthase transcript levels. Although the function of GD2 in normal development is not fully known, it is believed to be crucial for neural tissue differentiation and repair.[4,5] Furthermore, several studies have demonstrated the involvement of GD2 in cancer cell adhesion, invasion, viability, and immune cell activation.[6]

High-risk NB responds well to monoclonal antibodies (mAbs) that target GD2. However, different anti-GD2 antibodies have various outcomes and side

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effects.[7] Dinutuximab, a mAb that targets GD2 expressed in neuroblasts, improves survival when included in the therapy regimen. Moreover, the combination of dinutuximab and chemotherapy has shown high efficacy in regressing relapsed disease.[8] The present article reviews dinutuximab and discusses its importance in managing NB.

MECHANISM OF ACTION OF DINUTUXIMAB

Most tumor-specific mAbs target antigens that are specific to the cancer type; therefore, particular cancer therapy regimens may include mAbs that bind to a cell-surface antigen that is overexpressed or expressed exclusively in certain tumors.[9] Dinutuximab targets GD2 in NB cells, attaches to NB cells, and makes them a target for the body's immune system, thus eliminating cancer cells. Furthermore, it induces the lysis of cells expressing GD2 through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and direct cytotoxicity. In addition, dinutuximab may prevent interactions between the circulating malignant cells and the extracellular matrix.[10,11]

The binding of dinutuximab triggers the following three potential effector processes to the surface of NB cells: Binding of C1q to the mAb, which induces CDC, thus leading to the activation of the complement cascade and formation of membrane attack complex that injures the membrane of the tumor cell; the recruitment of cells that express fludarabine, cyclophosphamide, and rituximab (including natural killer [NK] cells and granulocytes to mediate ADCC) and monocytes and macrophages to initiate phagocytosis; and direct cytotoxicity by the cross-linking of the mAbs, which induces apoptosis.[9]

PHARMACOKINETICS

Dinutuximab is administered intravenously at a dose of 17.5–25 mg/m^2 every 10–12 h daily,[12] and the infusion rate is maintained at 50% for 30 min. The rate gradually should be increased as tolerated to a maximum of 1.75 mg.[12] However, the patient's vital signs should be examined every 15 min during the 1st h and then hourly until the infusion is completed.[12] Dinutuximab is a protein, i.e., broken down into small amino acids by a proteolytic enzyme. According to population pharmacokinetic (PPK) analysis, the estimated half-life of dinutuximab is 5.1–7.5 days among adults and 2.8–10 days among children.[13] Moreover, the absorption rate of dinutuximab is not affected by age, race, sex, or medication. Instead, human anti-chimeric antibodies increase dinutuximab clearance by 60%.[13] Dinutuximab does not cross the blood–brain barrier. Its volume of distribution is 0.4 L/kg or 5.4–7.2 L. Its rate of clearance is approximately fourfold higher in children than adults and appears to be age-dependent; the clearance is 0.5 L/(day·m^2) and 0.21–0.6 L/day or 2 L/(day·m^2) among adults and children, respectively.[14]

The immune system components of the patient interact with dinutuximab to exert its anticancer effects. Dinutuximab destroys NB cells by attaching to the tumor cell surface and initiating an immunological response through antibody-dependent cellular cytotoxicity. However, many patients show reduced complement components (C3, C4) during the treatment course because of excessive consumption.[14]

THERAPEUTIC EFFICACY

The children oncology group conducted a phase 3 trial for 3 years on 226 children with NB,[15] which were divided into two groups. Group 1 comprised 113 patients who were administered an oral retinoid drug, namely, isotretinoin (13-cis-retinoic acid). Group 2 comprised the remaining 113 patients who received dinutuximab antibody therapy combined with 2 immune-boosting compounds, interleukin-2 (IL-2), and granulocyte–macrophage colony-stimulating factor (GM-CSF).[16] After 3 years, results showed that the combination of dinutuximab and immunotherapy was more effective than isotretinoin alone.[15,16] Similar results were reported by Keyel and Reynolds.[15] Another study revealed that 63% of the participating patients survived the disease and were free of tumor growth; however, 46% of patients treated with isotretinoin survived the disease.[17] In addition, a clinical trial using dinutuximab showed a higher overall survival advantage than isotretinoin.[16] Dinutuximab decreased the risk of death by 46%, 33%, and 38% after two, three, and 5 years, respectively.[17] Dinutuximab combination therapy led to improved outcomes compared to standard therapy in patients with high-risk NB.

TOLERANCE AND SAFETY

The children's oncology group conducted a dose escalation study of dinutuximab and revealed that the starting dose for a 4-day cycle was 25 mg/day.[18] However, a 28-day cycle of Dinutuximab (17.5 mg/[m^2·day]) was administered in combination with multiple drugs.[18] GM-CSF administration was started 2 days before dinutuximab at a dose of 250 mg/day for 14 days. IL-2 (4.5 MIU/[m^2·day]) was administered during the 2nd week along with Dinutuximab; during the final 14 days, isotretinoin (80 mg/m^2 twice daily) was administered.[16] Although 23% of the patients reported a new onset of capillary leak syndrome, it was more common in those who had received dinutuximab and IL-2 therapy than in those who had received dinutuximab and GM-CSF.[19]

Conversely, the Cooperative German NB trials of dinutuximab monotherapy recorded capillary leak syndrome in one–two patients, thus indicating that it is less frequent in monotherapy than in combination therapy.[19] Moreover, Dinutuximab administration often resulted in neuropathic pain. However, numerous trials have revealed that morphine can be used for symptom management in case of infusion reactions and neuropathy.[16] The most frequent serious adverse effects reported with dinutuximab therapy are thrombocytopenia, neutropenia, urticaria, lymphopenia, and anemia, among others[16,19] [Figure 1].

Several preventive techniques for some of these adverse effects include infusion rate reduction, interruption, permanent discontinuation, monitoring peripheral blood count, and administering intravenous hydration and analgesics.[16-19] However, dinutuximab recipients must be evaluated for proper hematological and renal functions before each cycle of dinutuximab administration to reduce adverse effects and infusion reactions.[19] Notably, the safety profile for dinutuximab therapy has been established on the basis of patients with high-risk NB who participated in the ANBL0032 study and received dinutuximab as a part of antibody treatment.[17]

DINUTUXIMAB IN THE MANAGEMENT OF HIGH-RISK NEUROBLASTOMA

The multimodal therapy regimen used in treating NB, including chemotherapy, radiation therapy, isotretinoin, autologous hematopoietic stem cell transplantation (HSCT), and surgery, may be effective in reducing the tumor. However, this treatment regimen is not entirely efficient for removing the tumor. The few remaining cells result in tumor regrowth and resistance to other therapies, and dinutuximab administration is required to remove these remnant tumor cells and avoid relapse.[9]

The Food and Drug Administration has recently approved dinutuximab therapy for patients with high-risk NB. However, this is only applicable to patients who partially respond to the initial multimodal therapy.[20] A retrospective study was conducted at the Children's Hematology and Oncology Clinic in Bratislava, Slovakia, to assess the efficacy of dinutuximab in treating high-risk NB, and seven patients had dinutuximab included in their treatment regimen. The study showed that the left retroperitoneum was the primary tumor site in four of the seven patients; six of the seven patients experienced metastasis; and the most common metastatic sites were the bone marrow, skeleton, and lymph nodes.

After completing multimodal therapy, the patients were administered a continuous infusion of dinutuximab at 10 mg/m^2 for 10 days. The patients received medication for over five 28-day cycles. Isotretinoin was also administered with dinutuximab (160 mg/m^2/day) as a differentiation therapy instead of including it in the initial multimodal therapy. After receiving dinutuximab, four patients experienced complete remission, and three showed an outstanding partial response and received additional therapy. The first patient received metaiodobenzylguanidine with concomitant topotecan and showed a good response without complete remission, whereas the second patient was administered iobenguane and concomitant topotecan with additional peripheral blood stem cell treatment and he/she experienced complete remission. The third patient received proton beam therapy and showed complete remission of the tumor.[21]

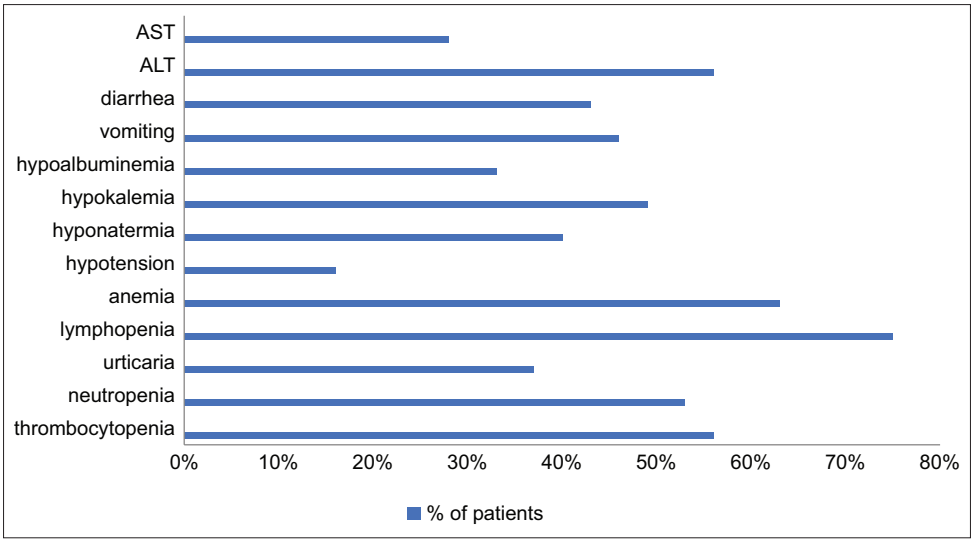

Figure 1: Adverse reaction in patients receiving Dinutuximab treatment. AST = Aspartate transaminase; ALT = Alanine transaminase

DINUTUXIMAB IN THE TREATMENT REGIMEN/ COMBINATIONS

As mentioned previously, dinutuximab is administered to patients who partially respond to the initial multimodal therapy, and it is administered as a continuous infusion for over 10 days at a daily dose of 10 mg/m^2. However, dinutuximab is not recommended as a monotherapy, and its administration is advised with other substances, including IL-2.[22] The presence of cytokines in the tumor causes a reduction in the toxicity caused by systemic cytokines.

Furthermore, they activate the immune system in the tumor environment.[23] Dinutuximab is administered as a continuous infusion for 5 days at a daily dose of 20 mg/mL^2.[22] However, if it is administered along with IL-2, the dose must be adjusted. Furthermore, dinutuximab can be combined with other immunotoxins, which help deliver bacterially and plant toxins into the tumor cells by binding with specific molecules on the tumor cell surface and gaining entry through endocytosis, followed by the release of toxins into the cell, ultimately causing tumor cell death.[24]

DINUTUXIMAB WITH NEUROSURGERY

In a study involving three children diagnosed with high-risk NB, dinutuximab was administered at least once preoperatively in all three patients. According to the final examination outcomes, these three patients showed complete recovery from NB[25] [Table 1].

POTENTIAL MECHANISMS OF RESISTANCE TO DINUTUXIMAB

Despite the significant clinical benefits of dinutuximab reported on anti-GD2 in patients with NB, 40% of the patients experience relapse or resistance to treatment.[15,26] Moreover, the molecular mechanisms underlying differences in response and treatment resistance remain unknown. However, some potential mechanisms include the following:

Small extracellular vesicles

Small extracellular vesicles (sEVs) are small lipid bilayer-bound vesicles that are released from the surface of myriad cells and are crucial in mediating intercellular communication. *Trichinella Spiralis* extracellular vesicles from cancer cells can evidently promote tumor progression and metastasis, neoangiogenesis, chemoresistance, and immune suppression.[26-28]

The role of sEVs in inducing resistance to anti-GD2 immunotherapy and the modulation of the cancer microenvironment was investigated in a 9464D-GD2 mouse model. The study reported novel results that can enhance our understanding of the mechanism of resistance; the authors proposed tsEV secretion inhibitor drugs as subsidizer adjunct drugs to dinutuximab. They reported that NB-derived sEVs promoted resistance to dinutuximab by suppressing and infiltrating the mobilization of dinutuximab-induced NK cells and decreasing cell maturation. Furthermore, extracellular vesicles increase the number of tumor-associated macrophages. To apply these results to obtain clinical benefits, they treated the mice with tipifarnib with or without dinutuximab and revealed that tipifarnib plus dinutuximab treatment exhibited a reduction in tumor volume and weight, and the antitumor effect of both was synergistic.[29]

Effector immune cells

The mechanism of dinutuximab largely relies on NK cells,[30-32] myeloid cells,[30-32] the repertoire of killer-cell immunoglobulin-like receptors (KIRs), and KIR ligands expressed in patients with NB.[33-36] Therefore, factors underlying the resistance mechanism may either be a lack of sufficient affinity between Fc receptor-dependent killing of GD2 and/or modulation in the tumor microenvironment

Table 1: Demonstrates the effect of dinutuximab when administered pre- and post-surgery

Patient	Primary tumor	Metastasis	Before surgery	After surgery	Result
2-year-old girl diagnosed with neuroblastoma stage 4	Left adrenal gland	Multiple pelvic and abdominal lymph nodes Central nervous system Bone marrow	In order Eight cycles of COJEC A cycle of dinutuximab (10 mg/m^2 daily for 10 days) Two cycles of TVD	In order One cycle of TVD One cycle of dinutuxmab (10 mg/m^2 daily for 10 days) BuMel, ASCT Four cycles of dinutuximab	Full recovery (examined 19 months posttherapy)
8-month-old boy diagnosed with neuroblastoma stage 4	Left adrenal gland	Para-aortic and para-abdominal lymph nodes	In order Eight cycles of COJEC A cycle of dinutuximab (10 mg/m^2 daily for 10 days)	In order One cycle of dinutuxmab (10 mg/m^2 daily for 10 days) BuMel, ASCT	Full recovery (examined 11 months' post therapy)
2-year-old girl diagnosed with neuroblastoma stage 4	Left adrenal gland	Mandible cervical and tonsillar lymph nodes Bone marrow involvement	In order Seven cycles of COJEC Three cycles of irinotecan/ temozolomide and dinutuximab	BuMel, ASCT	Full recovery (examined 12 months posttherapy

TVD=Topotecan, vincristine, and doxorubicin; ASCT=Autologous stem cell transplant; BuMel=Busulfan/melphalan; COJEC=Cisplatin, carboplatin, cyclophosphamide, vincristine, and etoposide

that counteracts the capability of the immune effectors to stimulate ADCC formation.[37]

Keyel *et al*. showed the intelligible role of immune effector cell genotype diversity in modulating the response of dinutuximab by variation in the amount of NK cell-activating ligand expression; the balance between the activity and inhibitory KIR signals; and factors that inhibit NK cell cytotoxicity, including transforming growth factor beta 1, Fc gamma receptors, and macrophage polarization.[15]

GD2 expression density

The limited expression of the disialoganglioside GD2 subtype in as high as 12% of patients with NB highlights the possibility of its contribution to treatment failure.[38] This suggests a correlation between the density and percentage of GD2 expression, response rate to treatment, and even relapse.[39] Tumor DNA sequencing and defining the levels of GD2 expression will help identify responders as early as possible, thus leading to the avoidance of toxicities by the drug and the modification or development of new treatment approaches.

Antidrug antibody

The development of antidrug antibodies has been reported in many studies and has been identified as a potential mechanism of resistance to rituximab. This finding prompted efforts to develop anti-GD2 mAbs that utilize a chimeric version of mAb 14.G2a to form ch14.18 and avoid the challenge of withholding the drug for several months before a repeat antibody injection.[40] In addition, these antidrug antibodies help reduce serum levels in patients with NB and hasten antibody clearance, which can compromise clinical efficacy.[14,41] However, the prognostic effect of antidrug antibodies (anti-GD2) on patients' responses and outcomes remains unclear. Further investigation is required to identify whether it represents an anti-idiotypic network that can enhance antitumor activity or is an indirect antitumor response of the patient.[42-44]

Future directions

Currently, the standard therapeutic protocol to manage NB is an intensive multiagent therapy starting from maximal surgical resection and adjuvant chemotherapy for low- and intermediate-risk groups to an aggressive multimodality approach, including neoadjuvant and adjuvant high-dose chemotherapy, surgical resection, autologous HSCT, and radiation therapy, for patients with high-risk NB.[45,46]

The combination of chemotherapy with ch14.18 (dinutuximab) has demonstrated promising outcomes. However, other preclinical studies are warranted to increase the efficacy of dinutuximab and to identify novel critical biological approaches to overcome its resistance and toxicity. For instance, many studies have emphasized the critical function of incorporating tumor DNA sequencing, genetic analysis, and immune monitoring during therapy in the clinical management of patients to guide the most effective treatment and provide the patient with an optimal quality of life with minimal adverse effects and toxicities.[26,47]

Recently, the therapeutic application of sEVs has been proposed, which brings hope for new potential cancer diagnostic biomarkers, treatment delivery, and choice of treatment, as well as in understanding the molecular mechanisms underlying cancer predisposition and environmental interactions preceding resistance.[29,48]

Different approaches to increase the effectiveness of dinutuximab include positive outcomes when combined with irinotecan and temozolomide[15,49,50] and galunisertib (an inhibitor of transforming growth factor β receptor 1), which increases dinutuximab activity by blocking transforming growth factor β1, thus leading to enhanced NK cell toxicity.[49,50] Previous preclinical studies examined the combination of dinutuximab with fenretinide, a synthetic derivative of Vitamin A, and have shown beneficial effects.[49,50] In addition, complementary advantages are conferred by engaging invariant NK T cells and NK cells.[30,51]

Few clinical trials have used adjuvant immunotherapy with vaccines containing NB-associated antigens (GD2 and GD3) to induce host anti-ganglioside antibodies through stimulation of B-cells to produce anti-GD2 and anti-GD3. In a phase I trial, Kushner *et al*. reported that there was no delayed or acute toxicity in patients receiving all seven protocol injections. The drug was safe and encouraged serological responses with minimal residual disease responses.[52] Other preclinical studies and clinical trials of vaccines in adults have shown that immunogenicity is significantly augmented.[53-55]

Targeted immunotherapy with time may have lower efficacy because resistance is developed frequently. Considering that GD2 may be associated with neural tissue differentiation and repair,[4,5] finding new approaches to interfere with GD2 may be beneficial. Targeting the specific gene promoter sites of the genes responsible for this antigen or even interfering with its transcription can be significant. Furthermore, if the GD2 gene silencer and promoter sites are targeted, the expression of the protein will also be altered. These approaches will not only neutralize GD2 but also prevent its transcription, which would affect the translation of the protein. However, the disruption of normal tissue repair in tumor cells can lead to a new outbreak of NB.

CONCLUSION

The anti-GD2 antibody dinutuximab targets the high levels of GD2 expression in NB cells, thus improving the event-free survival for this deadly condition when used to treat patients with high-risk NB. The efficacy of dinutuximab in other therapeutic stages or in patients who have experienced relapse or are resistant to treatment is still being studied. Although several cooperative studies have made dinutuximab the standard of treatment for maintenance therapy, long-term follow-ups and continuous assessment concerning the duration of antibody usage and co-administration of other pharmacologic or immune-modulatory drugs remain under research. Many trials have shown that using dinutuximab for maintenance treatment can extend the time before the first relapse and increase overall survival. Uncertainty surrounds the function of cytokines that are given together with dinutuximab because this approach may lead to increased toxicity without added benefits; however, recent studies on relapsed and refractory NB have shown potential effectiveness. Therefore, further research is required to incorporate dinutuximab into existing therapy modalities.

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Conflicts of interest
There are no conflicts of interest.

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