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Immunotherapy targeting glicolipid antigen (GD2) expressed on neuroblastoma tumour cells. Review of literature

Konrad Gawin
Central Clinical Hospital of the Medical University of Łódź
Ul. Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0007-2242-4356
konrad.gawin1@icloud.com

Anita Ignasiak
Central Clinical Hospital of the Medical University of Łódź
ul. Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0000-2917-0263
anitaignasiak@interia.pl

Wiktoria Zawiślak
Dr Karol Jonscher Municipal Medical Center,
Ul. Milionowa 14, 93-113 Łódź
https://orcid.org/0009-0009-2028-8885
zawiślak.wiktoria@gmail.com

Kacper Rychlica
The Nicolaus Copernicus Provincial Multispecialty Center for Oncology and Traumatology in Łódź
ul. Pabianicka 62 93-513 Łódź
https://orcid.org/0009-0003-6103-6234
kacperychlica@gmail.com

Michał Cisowski
Central Clinical Hospital of the Medical University of Łódź
ul. Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0005-3977-8244
michał.cisowski@stud.umed.lodz.pl

Maria Dąbrowska
J. Struś Multispecialist Municipal Hospital in Poznań
ul. Szwajcarska 3, 61-285 Poznań
https://orcid.org/0009-0005-6115-0701
marysia-dabrowska1@wp.pl

Jolanta Cholewińska-Rychlica
The Nicolaus Copernicus Provincial Multispecialty Center for Oncology and Traumatology in Łódź
ul. Pabianicka 62 93-513 Łódź
https://orcid.org/0009-0002-8254-4994
jcholewinska224@gmail.com

Paulina Madura
Independent Public Healthcare Institution MSWiA in Łódź
ul. Północna 42, 91-425 Łódź
https://orcid.org/0009-0008-2141-5279
paulinamadura00@gmail.com

Daria Mrozik-Gałecka
Independent Public Healthcare Institution MSWiA in Łódź
ul. Północna 42, 91-425 Łódź
https://orcid.org/0009-0002-2853-5560
daria.mrozik99@gmail.com

Corresponding author:
Konrad Gawin, konrad.gawin1@icloud.com

Abstract

Neuroblastoma is the most common extracranial solid tumor of childhood and accounts for approximately 15% of pediatric cancer-related mortality. Despite advances in multimodal therapy, outcomes for patients with high-risk disease remain unsatisfactory, with long-term survival rates below 50%. Disialoganglioside GD2, highly expressed on neuroblastoma cells, has become a key therapeutic target enabling the development of monoclonal antibodies such as dinutuximab beta and naxitamab. Anti-GD2 antibodies exert antitumor activity through complement activation, antibody-dependent cellular cytotoxicity, and antibody-dependent phagocytosis, mechanisms that can be further enhanced by cytokines including IL-2 and GM-CSF. Clinical studies demonstrate that immunotherapy incorporating anti-GD2 antibodies significantly improves event-free and overall survival compared with standard isotretinoin maintenance, although treatment is frequently limited by severe neuropathic pain and other adverse reactions. Recent findings highlight the potential of copper chelation as an adjuvant strategy. Additionally, naxitamab-based chemoimmunotherapy shows promising activity in patients with refractory or minimal residual disease. This review summarizes the current landscape of GD2-directed immunotherapy, supportive approaches such as ketamine-based analgesia, and emerging synergistic strategies, including copper chelation, that may further optimize therapeutic outcomes in high-risk neuroblastoma.

Material and methods: A literature review of articles and studies published from 2011 to 2025 using the PubMed database. The following keywords were used: neuroblastoma, dinutuximab, natuximab, immunotherapy, glicolipid antigen, high risk neuroblastoma, anti-GD2, copper chelation, cuproptosis.

Results

Clinical studies consistently demonstrate that anti-GD2 monoclonal antibodies improve outcomes in high-risk neuroblastoma, particularly when combined with GM-CSF and IL-2. Dinutuximab beta improves 5-year event-free survival by about 15%, with predictable toxicities primarily involving neuropathic pain. Naxitamab shows strong activity in relapsed or refractory disease, especially when introduced early or used as consolidation in minimal residual disease,

achieving 3-year overall survival rates up to 82%. Chemo-immunotherapy regimens combining naxitamab with irinotecan, temozolomide, and GM-CSF yield complete remission rates up to 47% in primary refractory neuroblastoma, but efficacy significantly declines when therapy is started late. Preclinical data indicate that copper chelation enhances the immune response and increases the effectiveness of anti-GD2 antibodies by reducing PD-L1 expression and promoting infiltration of cytotoxic immune cells. The most common adverse events associated with anti-GD2 therapy include pain, hypersensitivity reactions, hemodynamic instability, and capillary leak syndrome. In cases of severe, treatment-limiting pain, ketamine is an effective option that improves tolerability and reduces respiratory or cardiovascular complications.

Conclusion

Over the past two decades, the discovery of monoclonal antibodies that target neuroblastoma-specific surface antigens, known as gangliosides, and their subsequent clinical application have significantly improved the prognosis of patients with high-risk neuroblastoma. Most studies indicate that adding anti-GD2 therapy to standard treatment enhances short- and mid-term event-free and overall survival rates; however, its long-term efficacy still requires confirmation. Treatment with dinutuximab and naxitamab is more effective when combined with Interleukin-2 and GM-CSF. Clinical toxicity of immunotherapy in neuroblastoma is a significant problem but it can be successfully managed in most cases.

Keywords: neuroblastoma, dinutuximab, natuximab, immunotherapy, glicolipid, antigen, high risk neuroblastoma, anti-GD2, copper chelation, cuproptosis

Introduction

Neuroblastoma is a solid tumour originates from neural crest- derived cells which underwent a defective differentiation due to genetic and epigenetic mutations and impairments. (Ponzoni et al. 2022) [1]. On average, children are diagnosed with neuroblastoma at around 1 to 2 years of age (Mora J et al. 2025) [2]. This disease accounts for about 15% of cancer- related mortality of children. Although the overall 5-year relative survival rate has risen to around 80%, outcomes differ markedly across risk groups. For children diagnosed with high-risk neuroblastoma, the 5-year survival rate reaches only about 60% even under the most favorable circumstances. (Mora J et al. 2025) [2]. High-risk disease is associated with a much poorer prognosis despite intensive chemotherapy and surgical intervention. High-risk status is typically assigned when metastatic spread is present in children older than 18 months, or when amplification of the

MYCN oncogene is detected, regardless of the patient's age. In sharp contrast neuroblastomas classified as low or intermediate risk generally carry a very favorable outlook after therapy, and certain tumors may even undergo spontaneous regression. (Lee AC et al. 2023) [4].

A diagnosis of high-risk neuroblastoma required one of the following:

1. Being 18 months or older with stage IV metastatic disease;
2. Being 18 months or older with stage III disease plus MYCN amplification;
3. Being under 18 months with stage III or IV disease and MYCN amplification. (Lee AC et al. 2023) [4]

Heterogeneity in genetics and morphology of neuroblastomas significantly limits ways of treatment and their efficacy. While survival for patients with low- and intermediate-risk neuroblastoma approaches 100%, the 5-year survival rate for those with high-risk disease remains below 50% (Zafar et al. 2021) [3]. Most neuroblastoma tumors arise in the abdomen (Qian X et al. 2025) [5].

In the past, subsequent treatments have produced response rates of around 30%, with long-term overall survival remaining below 50%. Immunotherapy is still a hot topic in oncology. Various types of immunotherapy exist, and they can be classified into categories according to their mechanisms of action: cytokines (for example interferon), monoclonal antibodies, such as anti-CD20, anti-EGFR, anti-VEGF and anti-GD2, immune cellular therapy, including cytokine-induced killer cells, dendritic cells, natural killer cells and chimeric antigen receptor T (CAR-T) cells, immune checkpoint inhibitors, including programmed cell death 1 (PD-1), programmed cell death ligand 1 (PDL-1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors and bioengineered oncolytic viruses or bacteria. (Chan G.C.-F et al. 2022) [6].

Glycolipid antigen

Gangliosides are glycosphingolipids that contain sialic acid residues, and they are found throughout in all vertebrate tissues and cell types. Notably, the more structurally complex gangliosides are highly concentrated in nervous tissue across species, where they are thought to contribute significantly to neural development and neural function. In contrast, certain ganglioside species show selective overexpression in specific malignancies, which has led to their classification as cancer-associated carbohydrate antigens. Among these, GD3 and GD2 are particularly prominent, as they serve both as biomarkers of tumors arising from

neuroectodermal lineages and as targets for immunotherapeutic strategies, including monoclonal antibody–based treatments (Yesmin F et al. 2021) [7]. Disialoganglioside GD2 contributes to oncogenesis and the acquisition of aggressive tumor traits by promoting cellular proliferation, motility, migration, adhesion, and invasiveness in a tumor-type–dependent manner. These biological roles provide a strong therapeutic rationale for targeting GD2, driving the development of anti-GD2 monoclonal antibodies and a range of other GD2-directed treatment strategies (Nazha B et al. 2020) [8]. GD2 is expressed not only by neuroblastoma but also by many of neuroectodermal and epithelial origin, such as melanoma, glioma, retinoblastoma, medulloblastoma, small-cell lung cancer, breast cancer, sarcoma, bladder cancer, colorectal cancer, and prostate cancer. GD2 can be detected on normal central and peripheral nervous system cells (melanocytes, lymphocytes, dendritic cells, and mesenchymal stem cells). However, GD2 levels are markedly elevated in malignant cells compared with normal tissues, making it an attractive target not only for therapeutic intervention but also for diagnostic applications and prognostic evaluation (Philippova J et al. 2024) [9].

Anti- cancer effect of monoclonal antibodies

Neuroblastoma tumour cells are infiltrated by macrophages. Antibodies (anti-GD2) cause complementary activation by the C1q-antibody interaction, which leads to lysis of neoplasm cells. Another important mechanism is antibody-dependent cellular cytotoxicity (ADCC), which functions through the activation of natural killer (NK) cells via Fc receptors, mainly FcγRIIIA. These receptors on NK cells bind to the Fc part of the anti-GD2 antibody, initiating the release of cytotoxic substances such as perforins and granzymes that destroy the target cells. Most experts consider this process to be the primary way in which anti-GD2 antibodies exert their anti-neuroblastoma effects. The last important anti- cancer mechanism is antibody-dependent phagocytosis. Macrophages are activated by monoclonal antibodies via Fc receptors. This leads to the facilitated phagocytosis of neoplasm cells. There are certain polymorphisms of macrophages, which are associated with better progression- free survival of patients being treated with anti-GD2. Moreover, according to some researches, the role of calreticulin is also valid. This protein enhances the phagocytosis of macrophages. Anti- GD2 increase expression of calreticulin on neuroblastoma cells (Chan G.C.-F et al. 2022) [6].

hu3F8 vs. ch14.18

There are various forms of anti-GD2. They differ in affinity to the GD2 receptor, half-life and potential side effects. For example, hu3F8 has higher affinity to the GD2, but shorter half-life than Ch14.18 form. In contrary, Ch14.18 antibody tend to have lower affinity and cytotoxic potency and longer half-life. Ch14.18K332A form was invented to lower side effect in form of complement lysis-induced pain. This resulted in absence of complement- dependent cellular toxicity of this form. However, Ch14.18K332A has greater antibody-dependent cellular cytotoxicity (ADCC) than other bioengineered form of anti-GD2. Evaluated differences significantly influence the treatment of patients and need to be expanded in the future (Chan G.C.-F et al. 2022) [6].

The role of Interleukin- 2 and GM-CSF

Antibody-dependent cell-mediated cytotoxicity, which involves various effector cells, can be enhanced by specific cytokines such as GM-CSF and interleukin-2. These cytokines independently boost the populations of granulocytes or macrophages and natural killer cells, respectively, thereby strengthening their ch14.18-mediated antibody-dependent cytotoxic activity. Moreover, GM-CSF promotes the regeneration of bone marrow following myelosuppressive or bone-marrow–injuring treatments (Mora J et al. 2025) [2].

Example of a trial evaluating anti-GD2 therapy was the German NB97 study. This was a non-randomised cohort investigation in which children older than one year with stage 4 neuroblastoma received six courses of ch14.18 as part of their maintenance regimen. A comparison group of 69 patients—who did not receive ch14.18 because of parental refusal or other circumstances—served as controls. No cytokines were co-administered. Reported nine-year event-free and overall survival rates were 41% and 46%, respectively. While overall survival was significantly higher in the anti-GD2 group than in the control group ($p = 0.019$), event-free survival did not differ. These findings imply that anti-GD2 therapy without cytokine support during the maintenance period may be insufficient to achieve an optimal immunologic effect (Chan G.C.-F et al. 2022) [6]. However, The SIOPEN later carried out a multicentre, phase III randomized trial evaluating maintenance therapy with dinutuximab beta, administered either alone or together with subcutaneous IL-2. Participants first completed induction chemotherapy (Rapid COJEC or N7), proceeded to high-dose therapy with autologous PBSCT

rescue, and subsequently received focal radiotherapy to the primary tumor site. For the maintenance phase, patients were randomly allocated to dinutuximab beta monotherapy or to dinutuximab beta combined with IL-2. IL-2 was administered at a relatively high dose—twice the amount used in the COG protocol. Three-year event-free survival did not differ significantly between the monotherapy and combination groups. Grade 3–4 hypersensitivity reactions were the most frequent serious adverse event, occurring in 10% of those receiving dinutuximab beta alone and rising to 20% with the addition of IL-2. The investigators concluded that IL-2 did not enhance outcomes in high-risk neuroblastoma and instead increased treatment-related toxicity. Some commentators suggested that the lack of benefit could be attributed to the particularly high IL-2 dosing used in this study (Chan G.C.-F et al. 2022) [6].

Another study evaluating the anti-GD2 antibody 3F8 (murine) reported its findings as well. A total of 169 children with stage 4 neuroblastoma—who had achieved either complete remission or a very good partial response following intensive chemotherapy, with or without autologous stem-cell transplantation—were treated with 3F8 in combination with GM-CSF. The patients were assigned to three treatment strategies**:** Group A (n = 43) received 3F8 alone**,** Group B (n = 41) received 3F8 together with intravenous GM-CSF, Group C (n = 57) received 3F8 with subcutaneous GM-CSF. In addition, 28 children classified as ultra-high-risk were treated using the group C approach. Five-year progression-free survival rates were 44%**,** 56%**,** and 62% for groups A, B, and C, respectively (p = 0.018). Overall survival over the same timeframe followed a similar pattern, reaching 49%**,** 61%**,** and 81% for the three regimens (p = 0.003). Among the ultra-high-risk patients, the 5-year PFS and OS were 36% and 75%, respectively—remarkably strong outcomes for this particularly challenging subgroup. Overall, these results suggest that combining anti-GD2 therapy with subcutaneous GM-CSF may offer the most favorable therapeutic benefit (Chan G.C.-F et al. 2022) [6].

The role of copper chelation

Since neuroblastomas possess a strongly immunosuppressive tumor microenvironment, it is now believed that combination therapies stand a better chance of restoring the antitumor immune activity required for an effective response to anti-GD2 treatment.

Multiple cancers have been shown to exhibit increased intracellular copper concentrations, indicating that copper regulation represents a tumor dependency that could potentially be

targeted therapeutically (Rouaen JRC et al. 2024) [16]

It was demonstrated that copper toxicity disrupts specific mitochondrial metabolic enzymes, thereby initiating a distinct form of cell death known as cuproptosis. This newly defined, non-apoptotic pathway is driven by intracellular copper accumulation and is tightly linked to mitochondrial function. To uncover the metabolic processes underlying copper-induced cytotoxicity, the authors performed a genome-wide CRISPR-Cas9 loss-of-function screen, followed by targeted knockout studies to pinpoint the key genes involved in cuproptosis. This work introduces an entirely new perspective on regulated cell death. Notably, additional studies have reported that copper imbalance in SH-SY5Y human neuroblastoma cells can induce apoptosis through mechanisms including mitochondrial damage and oxidative stress (Tian XM et al. 2022) [18].

The anti- cancer effect of copper chelation is very complex. Firstly, copper-chelating agents have ability to suppress tumor angiogenesis. Copper plays a key role in this process, as it promotes the growth and movement of endothelial cells and influences the release of bone-marrow–derived endothelial progenitor cells that contribute to new blood vessel formation. Secondly, among the copper-binding proteins that have been identified, the transcription factor ATOX1 enhances the expression of the proliferation-related protein cyclin D1. Consequently, blocking ATOX1's ability to bind copper—without reducing extracellular copper levels—significantly impacts the proliferation of cancer cells. Moreover, higher copper concentrations in the blood have been observed in breast cancer patients with distant metastases, implying that copper may facilitate cancer cell migration and invasion, thereby enhancing their metastatic potential. Finally, a key approach in cancer immunotherapy involves blocking the interaction between the immune checkpoint molecules PD-1 and PD-L1 with targeted antibodies. Studies have shown a positive association between the copper transporter CTR1 and PD-L1 expression in neuroblastoma and glioblastoma cells. Notably, copper chelation lowers PD-L1 levels and leads to a marked rise in tumor-infiltrating lymphocytes in a syngeneic neuroblastoma mouse model. These findings suggest that copper-chelating treatments could enhance the effectiveness of PD-1/PD-L1-based immunotherapies (Baldari S et al. 2020) [17].

In neuroblastoma, it was earlier showed that the high-affinity copper transporter 1 (CTR1) is

upregulated in both patient tumor samples and preclinical models. More recently, it was found that intratumoral copper levels influence the expression of the immune checkpoint protein PD-L1. Reducing copper using chelators such as tetraethylenepentamine (TEPA) lowered PD-L1 expression in tumors, increased infiltration of $CD8^+$ cytotoxic T cells and NK cells, and improved survival outcomes. These findings encourage researchers to investigate copper chelation as a therapeutic approach capable of broadly reshaping the neuroblastoma tumor microenvironment. Copper chelation serves as an effective adjuvant approach to enhance anti-GD2 therapy in two immunocompetent preclinical neuroblastoma models. The results show that reducing copper levels beneficially shapes immune infiltration and boosts the antitumor functions of both lymphoid and myeloid cells, with a particularly strong effect on neutrophils. Reaserchers described a tumor immune-evasion mechanism in which copper sequestration impairs neutrophil function. Notably, TETA (triethylenetetramine), an FDA-approved copper chelator used for Wilson's disease, is a promising immunomodulatory agent that can be repurposed to enhance anti-GD2 therapy (Rouaen JRC et al. 2024) [16].

Dinutuximab beta

Dinutuximab beta is a chimeric human/mouse IgG1 antibody (ch14.18) produced using Chinese hamster ovary cells. It specifically targets the GD2 disialoganglioside. This chimeric monoclonal antibody attaches to the disialoganglioside GD2 and activates complement (Yu AL et al. 2021) [10]. The European Medicines Agency (EMA) has approved this therapy for the treatment of high-risk neuroblastoma in patients aged 12 months and older who have achieved at least a partial response to induction chemotherapy and have undergone myeloablative therapy followed by stem cell transplantation. Dinutuximab is diluted in solution of NaCl and albumin and administered to patients in five cycles. Every cycle last 35 days. It can be administered as an eight-hour infusion during the first five days of each treatment cycle, or as a continuous infusion over the initial 10 days. The highest plasma concentration is achieved on the final day of the infusion period. Its relatively long half-life (8 days) makes it crucial to check full blood constituency and kidneys and liver function before every administration of the drug (Aust Prescr 2020) [11].

In the maintenance, treatment with the anti-GD2 antibody dinutuximab, either combined with

interleukin-2 (IL-2) and GM-CSF or administered without cytokine co-therapy, has been associated with roughly a 15% improvement in 5-year event-free survival (Lode HN et al. 2023) [12].

The role of immunotherapy in contrary to the standard treatment

About 50% of patients suffer from the high-risk phenotype of neuroblastoma. This results in widespread metastasis and inferior prognosis despite multimodal therapy. The standard treatment for high-risk neuroblastoma includes myeloablative therapy with stem-cell rescue, followed by isotretinoin therapy to target minimal residual disease (Lode HN et al. 2023) [12]. The Children's Oncology Group (COG) carried out the first prospective randomized study evaluating chemoimmunotherapy incorporating an anti-GD2 antibody in relapsed or refractory neuroblastoma. In this trial, the combination of dinutuximab and GM-CSF with irinotecan and temozolomide produced an objective response rate—complete or partial—of 41.5% (Lode HN et al. 2023) [12].

Moreover, the study aimed to evaluate whether the addition of ch14.18 (Dinutuximab beta), GM-CSF, and interleukin-2 to standard isotretinoin therapy following intensive multimodal treatment could improve outcomes in patients with high-risk neuroblastoma is going to be reviewed.

Patients with high-risk neuroblastoma who responded to induction therapy and stem-cell transplantation were randomly assigned, in a 1:1 ratio, to receive either standard therapy (six cycles of isotretinoin) or immunotherapy (six cycles of isotretinoin combined with five concurrent cycles of ch14.18 administered with alternating GM-CSF and interleukin-2) (Yu AL et al. 2010) [10].

Event-free survival and overall survival were evaluated and compared. The median follow-up period was 2.1 years. Immunotherapy demonstrated superiority over standard therapy in terms of event-free survival (66 ± 5% vs. 46 ± 5% at 2 years, $P = 0.01$) and overall survival (86 ± 4% vs. 75 ± 5% at 2 years, $P = 0.02$). Clinical evidence shows that ch14.18, a monoclonal antibody targeting the tumor-associated disialoganglioside GD2, is active against neuroblastoma, and that its efficacy increases when administered in combination with granulocyte–macrophage colony-stimulating factor (GM-CSF) or interleukin-2 (IL-2) (Yu AL et al. 2010) [10].

Clinical toxicities associated with the dinutuximab beta immunotherapy

Reported adverse effects specific to the immunotherapy were neuropathic pain (52% of the tested group)- most frequent, especially abdomen pain, hypertension (18% of the tested group), capillary leak syndrome (23% of the tested group)- more frequent during the cycles with interleukin- 2, hypersensivity reaction- also more frequent during the cycles with interleukin-2 (25% of the tested group). Such reactions may result from symptoms and signs associated with both the toxic effects of interleukin-2 and hypersensitivity related to the antibody (Yu AL et al. 2010) [10].

Naxitamab

Naxitamab (humanized 3F8; hu3F8), is a monoclonal antibody designed to recognize the disialoganglioside GD2. In 2020, the U.S. Food and Drug Administration (FDA) approved its use, in combination with granulocyte–macrophage colony-stimulating factor (GM-CSF), to treat pediatric and adult patients with relapsed or refractory high-risk neuroblastoma with metastasis limited to the bone or bone marrow (Castañeda A, et al. 2022). This approval was supported by findings from two single-arm studies, NCT03363373 and NCT01757626, in which patients were treated with naxitamab plus GM-CSF. In NCT03363373, 45% of the 22 participants achieved an objective response, with 23% maintaining their response for at least six months. In NCT01757626, 34% of the 38 patients responded, and 23% experienced responses that persisted for six months or longer (Furman WL. 2021) [14].

This study aims to review an article that provides a concise, practice-oriented overview of the clinical experience with naxitamab at the Sant Joan de Déu Children's Hospital in Barcelona, Spain.

Between June 2017 and May 2020, a total of 131 patients underwent 864 cycles of naxitamab treatment, administered either through compassionate use programs or as part of clinical trials. Naxitamab was administered to patients as monotherapy (with GM-CSF) or as chemoimmunotherapy (naxitamab with irinotecan and temozolamide) (Castañeda A, et al. 2022) [13].

Monotherapy is for patients with high risk disease limited to bone marrow or bone who present partial response, minor response, or stable disease to prior therapy or as a consolidation to

patients with complete remission (Castañeda A, et al. 2022) [13].

Chemoimmunotherapy, incorporating the use of hu3F8, irinotecan, temozolamide and GM-CSF, is currently under investigation as a potential treatment option for patients with disease resistant to conventional chemotherapy. Patients who continue to have the disease—identified by MIBG avidity or uptake on PET/CT scans—receive treatment with naxitamab-based chemoimmunotherapy. This treatment approach is also used for patients whose disease does not respond to, or returns after, naxitamab monotherapy (Castañeda A, et al. 2022) [13].

Among 73 patients with high-risk neuroblastoma in either first or second complete remission who received naxitamab as consolidation therapy, the three-year event-free survival rate was 58%, while overall survival at three years reached 82%. Overall survival was determined from the initiation of immunotherapy until death, whereas event- free survival incorporated disease progression, relapse, or the occurrence of a secondary malignancy as events. Patients treated in first complete remission demonstrated a significantly better three-year event free survival compared with those in second complete remission (74% vs. 19%; P= 0.0029). However, the difference in three-year overall survival between the two groups did not reach statistical significance (91.6% vs. 66.1%; P = 0.18) (Castañeda A, et al. 2022) [13].

Another study which is going to be cited in this review evaluated the combination of humanized anti-GD2 mAb naxitamab (Hu3F8), irinotecan, temozolomide, and sargramostim (GM-CSF) against primary resistant high risk neuroblastoma. Each chemo-immunotherapy cycle consisted of irinotecan combined with temozolomide. Naxitamab was administered intravenously over 30–60 minutes, depending on tolerance, on days 2, 4, 9, and 11, while GM-CSF was given subcutaneously on days 6–10. The cycles were repeated every 4 weeks. The findings indicate that this regimen achieves a complete remission rate of 47% in primary refractory high-risk neuroblastoma patients when initiated promptly after an assessment confirms the absence of complete remission. In this early-treatment group, the three-year overall survival reached an encouraging 84.8% and the event- free survival was 54.4%, closely matching recent outcomes reported for patients who attained their first complete remission following standard induction therapy (three-year overall survival of 81% and event-free survival of 57%). These data suggest that established chemo-refractory disease can be overcome by introducing naxitamab to rescue chemotherapy early in the disease course. These findings emphasize the importance of introducing naxitamab early during induction to counteract chemotherapy resistance. In

contrast, using this regimen in patients with long-standing refractory disease is far less effective, indicating that deep, entrenched multi-drug resistance undermines the potential synergy between naxitamab-induced antibody-dependent cellular cytotoxicity (ADCC) and chemotherapeutic agents (Muñoz JP et al. 2023) [15].

Clinical toxicities associated with the naxitamab immunotherapy

Clinical toxicities concerned 50% of the tested patients. Most frequent adverse events during naxitamab therapy are going to be overview. Most of them were rewardingly treated with premedication before infusions of hu3F8, supporting medications and actions. Side effects involved: skin problems (erythema, pruritus), hypotension, hypertension, bronchospasm, edema of tongue, apnea, laryngitis, post infusion pain, nausea and anxiety (Castañeda A, et al. 2022) [13].

The role of ketamine

Pain is a known and common adverse effect of immunotherapy, with grade 3 pain reported in 65% of patients in clinical trials of naxitamab and 51% in trials of dinutuximab (Qian X et al. 2025). Severe pain is a dose-limiting adverse effect of anti-GD2 monoclonal antibody therapy, often emerging during the infusion. Although opioids are the standard treatment for this infusion-related pain, their efficacy can be incomplete, and their use may lead to undesirable effects such as hypotension, hypoventilation or decreased responsiveness (Castañeda A, et al. 2022) [13].

Activation of the NR2B subunit of the N-methyl-D-aspartate (NMDA) receptor has been implicated in the pain mechanism triggered by GD2 targeting. This understanding has prompted exploration of ketamine, an NMDA receptor antagonist, as a potential non-opioid alternative for controlling acute pain associated with naxitamab when conventional analgesics are insufficient. When administered at subanesthetic doses, ketamine generally does not worsen hypotension and may even counteract it slightly by promoting catecholamine release. Between June 2017 and March 2020, a total of 115 patients at Sant Joan de Déu Children's Hospital in Barcelona underwent treatment, of whom 21 (18%) required ketamine-based pain control. The main reasons for introducing ketamine were uncontrolled pain in 7 patients, episodes of apnea in 6, complex allergic reactions that might have been worsened by opioid use in 4, and persistent

hypotension unresponsive to standard management in another 4. Among these patients, 19 (90%) were able to complete their scheduled naxitamab therapy in the outpatient clinic. Two very young children (1–2 years old) experienced apnea within minutes of the first infusion under the ketamine protocol and were subsequently withdrawn from further naxitamab treatment. According to caregiver feedback, the ketamine regimen did not appear to interfere with patients' usual daily functioning once each treatment cycle had concluded. (Castañeda A, et al. 2022) [13].

Severe pain as an adverse effect was also managed with ketamine at the Children's Hospital of Fudan University in China. Their study reveals that pain is one of the most frequent complication. Patients experiencing pain were first given naxitamab with hydromorphone and midazolam for sedation, but this combination caused notable adverse effects, including hypoventilation and low blood pressure. Consequently, the analgesic regimen was changed to esketamine with midazolam, since esketamine's sympathomimetic properties reduce the likelihood of hypotension. However, substantial improvement in hypotension was not achieved, likely due to the influence of midazolam. As a result, throughout the study, most patients enrolled in the program were no longer sedated with midazolam, which corresponded with fewer cases of severe hypotension or hypoxemia. Still, uncooperative patients continued to receive esketamine plus midazolam. Overall, fentanyl or esketamine served as the main analgesic agents (Qian X et al. 2025) [5].

Author's contribution

Project administration: Wiktoria Zawiślak, Michał Cisowski, Maria Dąbrowska, Konrad Gawin

Formal analysis: Wiktoria Zawiślak, Anita Ignasiak, Michał Cisowski

Writing (rough preparation): Maria Dąbrowska, Jolanta Cholewińska-Rychlica, Kacper Rychlica. Paulina Madura

Software: Wiktoria Zawiślak, Jolanta Cholewińska-Rychlica

Supervision: Anita Ignasiak, Kacper Rychlica, Daria Mrozik- Gałecka

Check: Maria Dąbrowska, Paulina Madura, Konrad Gawin

Conceptualization: Daria Mrozik-Gałecka, Anita Ignasiak, Paulina Madura, Konrad Gawin

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