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MOLECULAR MECHANISMS AND CLINICAL POSSIBILITIES OF IMMUNOTHERAPY FOR NEUROBLASTOMA IN CHILDREN

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ABSTRACT

The review examines the current state of immunotherapy for high-risk neuroblastoma and other GD2-positive tumors in children against the background of persistent limitations of standard multimodal treatment and a high relapse rate. Particular attention is paid to practical issues of selecting a therapeutic platform and managing patients, since treatment tolerability and feasibility often determine the actual clinical effect. It is shown that the inclusion of anti-GD2 therapy in maintenance and relapse protocols is associated with improved survival outcomes; however, it is accompanied by a typical toxicity profile, including neuropathic pain, fever, hypersensitivity reactions, capillary leak syndrome, and infectious complications, which often affects treatment completion and requires protocol-based supportive care. The prospects for expanding indications and developing GD2-CAR-T/CAR-NK/NKT platforms are discussed separately, along with the significance of response biomarkers, including GD2 expression, effector immune parameters, and FCGR variants, as a basis for more accurate patient stratification and optimization of therapeutic strategies.

KEYWORDS: neuroblastoma; GD2; anti-GD2 antibodies; dinutuximab beta; naxitamab; toxicity; capillary leak syndrome; neuropathic pain; CAR-T; CAR-NK; response biomarkers.

INTRODUCTION

In recent years, immunotherapy has become one of the most dynamic areas in pediatric oncology, changing the understanding of the possibilities for controlling the tumor process. This is especially evident in embryonal solid tumors, where traditional regimens often reach the limits of tolerability. This review focuses on clinically applicable approaches and unresolved issues. According to WHO estimates, approximately 400,000 cases of cancer are diagnosed annually worldwide in children and adolescents aged 0–19 years [1]. In Russia, according to specialized reports and official oncology service platforms, approximately 3,000–4,000 new cases of malignant neoplasms are registered in children each year, which corresponds to roughly 12–17 cases per 100,000 children [2].

Neuroblastoma is one of the leading solid tumors of childhood and accounts for a significant share of pediatric cancer incidence. In countries with well-developed cancer registration systems, the incidence of neuroblastoma is usually estimated at approximately 11–13 cases per 1 million children under 15 years of age, with the highest rates occurring during the first year of life [1]. Russian estimates cited in materials from federal centers and specialized sources indicate approximately 300–350 new cases of neuroblastoma annually [2]. The clinical problem is determined by the fact that the disease is often detected at advanced stages, and a substantial proportion of patients belong to the high-risk group at initial presentation [3–5]. Even with multimodal treatment, including chemotherapy, surgery, radiation therapy, and high-dose therapy with autologous transplantation, long-term outcomes in the high-risk group remain limited, while the risk of relapse remains high. Against this background, GD2, which is widely expressed on neuroblastoma cells and several other neuroectodermal tumors, has become established as a key therapeutic target [6]. In this review, GD2-directed therapy is considered as a spectrum of antibody-based strategies, including dinutuximab/dinutuximab beta and naxitamab, as well as cellular platforms, including GD2-CAR-T and CAR-NK/NKT, combined regimens, and approaches to stratification based on response biomarkers.

The introduction of anti-GD2 antibodies into maintenance therapy has improved survival outcomes and has become part of standard approaches in leading treatment protocols [8]. However, the clinical cost of effectiveness is considerable: pain syndrome, neuropathy, vascular reactions, and other complications often require treatment interruptions, dose adjustments, and complex supportive care. In addition to toxicity, questions remain regarding the optimal duration and combinations of therapy, criteria for patient selection, and the role of new platforms, ranging from bispecific antibodies to GD2-directed cellular products [12]. The studies conducted to date have significantly advanced the field, but have not provided definitive answers on how to simultaneously increase efficacy and reduce treatment burden, especially in children with refractory or relapsed disease [11]. In this regard, the relevance of the topic is determined by the need for an integrated comparison of evidence and practical limitations.

The aim of this review is to summarize the current state of immunotherapy for neuroblastoma and other GD2-positive tumors in children, systematize data on efficacy and safety, and identify the most promising directions for expanding indications.

The literature search was performed in PubMed/MedLine, Scopus, and eLIBRARY using the keywords “neuroblastoma”, “GD2”, “dinutuximab beta”, “naxitamab”, “CAR-T”, “CAR-NK”, and “toxicity” for the period 2020–2026. Clinical studies, systematic reviews, and practical guidelines were included in the review, with priority given to publications containing DOI/PMID identifiers.

GD2-Positive Tumors and Prerequisites for Immunotherapy

Osteosarcoma and rhabdomyosarcoma in children remain the most common bone and soft tissue sarcomas, and in some cases their classification as a GD2-positive phenotype is discussed as a clinically significant subgroup [13–15]. Current treatment regimens are based on surgery, chemotherapy, and, when indicated, radiation therapy, and remission can often be achieved in localized disease. However, in metastatic disease and in high-risk patients, the prognosis remains poorer, while relapses in formally localized disease continue to be a significant problem [16]. Therefore, the search for new targets should not be viewed as an “addition to the standard,” but as a necessity if a sustained antitumor effect is to be achieved.

GD2 is important in this context because it acts as a tumor-associated antigen: its high expression is typical of neuroblastoma, it is detected in a number of pediatric sarcomas, and it has been described in some aggressive central nervous system tumors, including diffuse midline gliomas with the H3K27M mutation [18]. This forms the basis for immunotherapy: with limited GD2 expression in normal tissues, there is a possibility of more precise targeting, whether through anti-GD2 antibodies or cellular approaches. CAR-T therapy has already demonstrated high efficacy in hematologic malignancies, and this experience has inevitably become an argument for transferring the technology to solid tumors in children. For GD2-positive tumors, the logic of CAR-T therapy is particularly straightforward: modified T cells acquire a receptor that recognizes the antigen on the surface of the tumor cell, after which directed cytotoxicity is triggered and the potential for long-term disease control is formed [20]. However, it is precisely in solid tumors that major limitations become apparent: poor penetration of cells into tumor tissue, limited in vivo persistence, an immunosuppressive microenvironment, and heterogeneity of antigen expression, due to which the target may partially “disappear” [22].

In high-risk neuroblastoma, the clinical value of the GD2-directed approach is supported by findings showing that, in several studies, the addition of anti-GD2 immunotherapy to maintenance treatment was associated with improved survival outcomes, for example, 2-year EFS of 66% versus 46%, 2-year OS of 86% versus 75%, as well as an increase in 5-year OS from 50% to 64% in individual protocols [9]. In diffuse midline gliomas with H3K27M, where median overall survival is usually close to 11 months and 5-year survival remains below 1%, an early-phase clinical study used GD2-CAR-T intravenously at two dose levels, from one to three million cells per kilogram after lymphodepleting therapy. Patients who responded then received repeated administrations into the ventricular system of the CNS with dose escalation, which was accompanied by tumor regressions and manageable, although frequent, inflammatory neurotoxicity [14–16].

Considering the contribution of individual authors, it can be noted that Paina O.V. et al. demonstrated that immunotherapeutic approaches in infants with acute lymphoblastic leukemia after haploidentical hematopoietic stem cell transplantation are clinically feasible, meaning that they can be applied even in the most vulnerable age group. The work of Shpakova D.V., in turn, collected and systematized clinical data on CAR-T therapy in children with ALL, focusing primarily on two practical issues — relapse risk and toxicity — without which the assessment of cellular therapy efficacy remains incomplete. Finally, the results of Zsigrai E. et al. complemented the discussion of solid tumors by showing that anti-GD2 immunotherapy in high-risk neuroblastoma is already used in real clinical practice; however, according to data from individual centers, outcomes may vary considerably. In this regard, the GD2 target will be further considered as a tumor-associated antigen, including the specific features of its expression, clinical significance, and factors that may limit the effectiveness of targeted immunotherapy.

GD2 Target: Expression, Significance, and Limitations

In pediatric oncology, GD2 is regarded as a tumor-associated antigen with practical value for solid tumors, especially in cases where standard regimens provide limited disease control [24]. This is particularly evident in certain pediatric central nervous system tumors, where GD2 is detected quite frequently and therefore becomes the basis for new therapeutic approaches that have already moved beyond purely preclinical studies.

Before discussing treatment, GD2 must be correctly identified in the tumor material. In practice, immunohistochemistry, flow cytometry, and molecular imaging methods are most often used, relying on increased antigen expression in a number of tumors [25]. Here, not only the sensitivity of the method is critical, but also the comparability of results between laboratories, since the decision on targeted therapy in a child must be as well-grounded as possible [28]. Therefore, Table

1 considers the main limitations associated with the GD2 target, indicating which tumors are characterized by its expression, how it varies, which methods confirm it, and which factors may reduce the expected effectiveness of therapy.

Table 1 — GD2-Directed Therapy: Features of Target Expression and Limitations by Nosology

Nosology / context	GD2 expression (typical)	Clinical significance	Verification in practice / research	GD2-directed approaches	Limitations and risks affecting efficacy	Key sources
Neuroblastoma: high-risk; relapsed/refractory disease	Usually high surface expression; antigen density may vary after therapy	The most "validated" GD2 target in pediatrics; anti-GD2 therapy is included in maintenance treatment and R/R regimens	IHC of tumor tissue; flow cytometry, including bone marrow; investigational molecular imaging	mAbs: dinutuximab/dinutuximab beta; naxitamab + GM-CSF; CAR-T in clinical studies	Neuropathic pain and other on-target effects; immune toxicities in combinations; heterogeneity/antigen escape; immunosuppressive microenvironment	Mora J. et al.
Diffuse midline glioma with H3K27M mutation, DMG/DIPG	Often high expression in tumor tissue; intratumoral heterogeneity is possible	One of the main reasons for interest in GD2-CAR-T in pediatric CNS tumors; early clinical signals of activity are being discussed	IHC/immunophenotyping of biopsy material; investigational approaches using CSF/images	GD2-CAR-T in early-phase trials; systemic and local delivery options	Risk of inflammatory neurotoxicity; difficulty of CNS delivery and edema; limited tissue volume for testing; barrier conditions of the brain microenvironment	DuBois S.G. et al.
Medulloblastoma	Expression has been described in some cases; may be uneven	Potential target for precision immunotherapy; more likely to be used in research and subgroup selection	IHC; flow cytometry when cellular material is available; investigational molecular panels	Antibodies/conjugates in research; CAR-T mainly in preclinical or early-phase studies	Heterogeneous expression; delivery problems across the BBB; risk of damage to normal nervous tissue with high CNS expression	Abdurashidova R.R. et al.
Pediatric ependymoma	Variable expression; data usually come from small series	Considered a promising target, but requiring strict patient selection by expression level	IHC; investigational marker panels	Antibody and cellular approaches in research	Low/unstable expression in some patients; CNS microenvironment and barriers; limited clinical data	Davis K.L. et al.
Osteosarcoma	GD2 positivity is often focal and heterogeneous; antigen density may be insufficient	Considered a subgroup for GD2-directed strategies, mainly cellular approaches; precise stratification is important	IHC; flow cytometry of cell lines/biopsies; investigational assessment of antigen density	GD2-CAR-T in early studies; combinations to increase expression, including investigational epigenetic approaches	Low GD2 density in some tumors; poor cellular infiltration into solid tumor tissue; immunosuppressive microenvironment; metastatic niches	K.M. Borokshinova et al.
Rhabdomyosarcoma	Expression is possible, but often heterogeneo	Target for research and potential expansion of	IHC; flow cytometry when cellular	CAR-T / antibodies, mainly	Heterogeneous expression; risk of antigen loss under	Wieczorek A. et al.

	us; likely depends on subtype	immunotherapy in selected GD2-positive cases	material is available	investigational directions	therapeutic pressure; immunosuppression in the TME	
Retinoblastoma	Expression has been described; data are limited and depend on the method used	Potential target, especially in resistant forms; strict toxicity risk assessment is required	IHC; investigational molecular methods	Antibody and cellular approaches in research	Limited clinical data; safety concerns for normal ocular structures and nervous tissue; delivery challenges	Del Bufalo F. et al.

Note: IHC — immunohistochemistry; BBB — blood-brain barrier; TME — tumor microenvironment. The terms “high,” “variable,” and “focal” reflect the typical pattern of expression according to literature data and clinical series.

Therapeutic platforms for GD2 can be conditionally divided into antibody-based and cellular approaches. Monoclonal antibodies against GD2 act not only by binding to the tumor cell, but also by recruiting immune effector mechanisms, including antibody-dependent cell-mediated cytotoxicity. The contribution of Mora J. et al. is important because they clinically evaluated the combination of naxitamab with GM-CSF in relapsed/refractory high-risk neuroblastoma, strengthening the rationale for anti-GD2 therapy as a clinically applicable approach. The work of DuBois S.G. et al., presented within the Paediatric Strategy Forum, complements this at a more systemic level: the authors described the requirements for developing GD2-targeted drugs in children and adolescents that must be met in order to make the transition from concept to medicine realistic.

GD2-CAR-T therapy appears conceptually simple: modified T cells acquire a receptor that recognizes GD2 and then exert directed cytotoxicity. However, this is where the limitations of both the target and the tumor as a biological environment become especially evident: difficulty of cellular penetration into the tumor, unstable persistence, an immunosuppressive microenvironment, and heterogeneous antigen expression, due to which some tumor cells may escape therapeutic pressure. A useful practical emphasis is provided by the work of Abdurashidova R.R. et al., which discusses bridge therapy before CAR-T in non-Hodgkin lymphomas: the logic of disease control before cellular product infusion is transferable to solid tumors as well, since the “window” between preparation and infusion often requires an active clinical strategy.

Finally, the limitations of GD2 are also related to the biology of the antigen itself. GD2 belongs to glycosphingolipids; its synthesis is determined by the activity of enzymatic pathways, and the enhancement of these pathways in tumor cells may support the malignant phenotype and influence prognosis. At the same time, GD2 is not completely tumor-specific: it is present in nervous tissue and in small amounts in peripheral nerves and melanocytes, which creates a risk of on-target/off-tumor effects and requires careful selection of doses, regimens, and monitoring. Therefore, GD2-directed approaches are increasingly considered today within combined regimens aimed at simultaneously enhancing the antitumor effect and weakening the influence of the microenvironment, while maintaining an acceptable safety profile and real feasibility of clinical studies in children.

Anti-GD2 Antibodies in Neuroblastoma

In clinical practice, anti-GD2 therapy is regarded as a key component of the post-consolidation stage in high-risk patients, while the issue of optimal supportive care and administration regimen directly affects the feasibility of completing treatment. Some randomized data have shown that intensifying the regimen with IL-2 may increase toxicity without an obvious improvement in outcomes, which supports the use of more “sparing” supportive schemes [18]. Neuroblastoma is one of the most common extracranial solid tumors of childhood, and before the introduction of intensive multimodal programs, overall survival in high-risk patients remained extremely low. The emergence of anti-GD2 antibodies changed the logic of the post-consolidation stage: the inclusion of dinutuximab beta in complex treatment is associated with an increase in 5-year event-free survival to 56.6% and 5-year overall survival to 73.2% in high-risk children [25]. For a long time, the key clinical question was not only the presence of an antitumor effect, but also how to reduce the severity of expected adverse events, primarily pain syndrome, while preserving therapeutic activity.

Against this background, the contribution of Dinikina Yu.V. and Belogurova M.B. is indicative: in their review on the personalization of therapy in pediatric oncology, they consistently substantiated the need to select treatment according to targets and biomarkers, which in the case of neuroblastoma essentially supports the GD2-oriented strategy as biologically justified. The practical aspect of anti-GD2 efficacy in first-line maintenance therapy was further expanded by Yu X. et al., who presented observational data on the use of dinutuximab beta in high-risk patients in China. Gong Z.Q. et al. occupied a separate niche by retrospectively evaluating an extended-course option of dinutuximab beta in combination with chemotherapy in patients with relapsed or refractory neuroblastoma, thereby focusing attention on therapeutic tactics for the most difficult patient group.

Even early studies of antibodies from the ch14.18 family showed that the severity of toxicity depends considerably on the infusion rate, which became one of the arguments for revising infusion regimens. This logic led to prolonged dinutuximab beta infusion schemes, in which the total course dose is distributed over a continuous 10-day infusion, with treatment combined with isotretinoin and, in some protocols, interleukin-2 [26]. Pharmacokinetic observations with this regimen indicated that antibody concentrations sufficient for antitumor activity persist even before the beginning of the next cycle, indirectly confirming sustained exposure throughout the course of therapy. SIOPEN group materials showed that the addition of interleukin-2 at a reduced dose did not improve 2-year survival outcomes compared with the regimen without

interleukin-2, but was associated with a higher frequency of fever and pain syndrome. Therefore, prolonged infusions combined with isotretinoin are considered a rational basis for post-consolidation therapy [29].

Combination Therapy: Chemoimmunotherapy and New Approaches

Chemoimmunotherapy in high-risk neuroblastoma is a combined approach in which an anti-GD2 antibody, most often dinutuximab beta, is administered alongside chemotherapy in order to simultaneously enhance the cytostatic effect on the tumor and engage immune effector mechanisms through GD2 binding. This format is especially relevant in relapse or disease progression, when chemotherapy alone is usually insufficient and there may be no time to enroll the patient in a clinical trial. In European programs, this logic is implemented in temozolomide-based combinations, including regimens with topotecan, while efficacy is monitored according to standard response criteria, with regular assessment every two cycles using CT/MRI, MIBG scanning, and, when necessary, PET and bone marrow examination [36]. Figure 1 shows the management algorithm: confirmation of progression, early initiation of therapy, monitoring every two cycles, and selection of the next step. As data on chemoimmunotherapy in neuroblastoma continue to accumulate, a similar logic is beginning to be discussed for other GD2-positive nosologies, primarily sarcomas, where a balance is required between the intensity of the cytostatic component and the tolerability of the immune component. This makes preliminary verification of the target and unification of response criteria especially important.

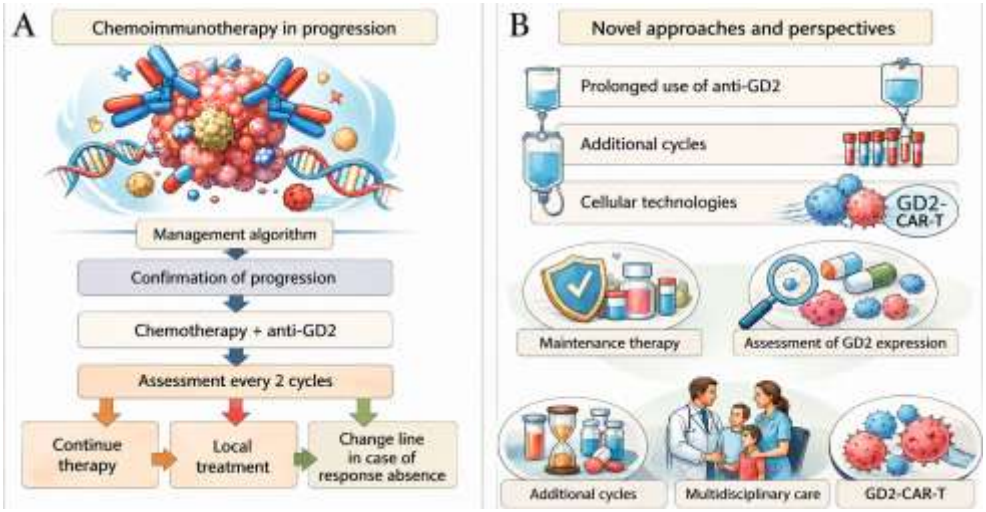

Figure 1. Combination Therapy in High-Risk Neuroblastoma: Chemoimmunotherapy and Promising Approaches.

It is practically important that the results of chemoimmunotherapy in real clinical practice may be comparable across different chemotherapy "backbones," but patients' baseline status differs substantially and directly affects treatment outcomes [35]. Combinations with topotecan and cyclophosphamide are often prescribed after failure of temozolomide-containing regimens; therefore, expected responses and the duration of disease control should be interpreted with regard to prior resistance. Weaker responses in local relapses within the primary tumor area are also noted, which emphasizes the need to plan local methods, such as surgery or radiation therapy, in advance as part of the strategy rather than as a "reserve" option [19].

New approaches within chemoimmunotherapy are primarily related to optimizing treatment duration and sequencing: it remains under discussion whether a limited number of cycles is sufficient and how to manage patients with stable disease but without complete remission after completing the course. Options for continuation include additional cycles, transition to maintenance therapy, or use as a "bridge" to cellular technologies, including GD2-directed CAR-T. At the same time, protocols increasingly require measurement of GD2 expression before retreatment and at progression [22]. Safety remains a key part of assessment: toxicity combines complications of cytostatic agents and effects of GD2-directed therapy, including neuropathic pain, fever, and manifestations of increased vascular permeability. Therefore, the goal of current regimens is to ensure reproducibility and manageability, rather than simply to "soften" treatment.

Toxicity of Anti-GD2 Therapy: Profile and Management of Complications

The clinical efficacy of anti-GD2 therapy in high-risk neuroblastoma is accompanied by a predictable spectrum of adverse events, which essentially represents the "cost" of improved survival and requires a systematic approach to the prevention and treatment of complications. The most typical manifestations of toxicity during dinutuximab beta therapy include severe pain, fever, hypersensitivity reactions, and capillary leak syndrome. These events often become limiting factors for treatment intensity and completion in real clinical practice.

For example, data from the study by Hoshi Y. et al. show that even with high feasibility of maintenance anti-GD2 immunotherapy, toxicity remains the main limitation, primarily pain, fever, and catheter-associated infections. Across 124 treatment courses, 310 episodes of grade ≥3 adverse events and 33 grade 4 episodes were recorded in 19 of 26 patients; bloodstream infections related to central venous access occurred in 81% of patients, and 4 episodes required intensive care treatment. At the level of the evidence base, the overall safety profile and practical applicability of anti-GD2 therapy were further clarified in the review by Mohd A.B. et al., while Wieczorek et al. contributed real-world data on maintenance therapy with dinutuximab beta in the first-line setting and in relapsed/refractory disease, showing that the complication

profile and requirements for supportive care persist beyond clinical trials. These figures directly define the practical priorities for complication management: protocol-based analgesia, early assessment of fever with exclusion of sepsis, and strict measures for the prevention and control of central line infections. Complementing the toxicity profile, randomized data on dinutuximab beta show that the addition of subcutaneous IL-2 worsens tolerability and reduces completion of the assigned regimen, 62% versus 87% without IL-2, without a convincing efficacy benefit, with 3-year EFS of 56% versus 60%. All this emphasizes that intensification of immunostimulation may increase toxic burden and complicate management without proportionally improving clinical outcomes. In practical terms, these data mean that key decisions about treatment continuation are often determined not only by oncological response, but also by the team's ability to control pain, fever, and central venous access complications. Therefore, clinical recommendations for adverse event management effectively become part of the standard of care rather than an optional addition to therapy.

If specific complications are considered, neuropathic pain during anti-GD2 therapy requires not merely "symptomatic" treatment, but protocol-based management, including premedication, timely use of an opioid component, adjuvant therapy, and assessment of response using pain scales, since pain most often determines the need to slow the infusion or reduce the dose. Fever and inflammatory reactions, especially against the background of IL-2, are important because they may mask an infectious process; therefore, the practical approach includes parallel assessment for sepsis, central line monitoring, and a low threshold for early initiation of antibacterial therapy when clinically indicated.

Capillary leak syndrome and hemodynamic instability are among the most clinically significant complications: large series have described fatal outcomes associated with CLS and infection-associated ARDS; therefore, monitoring of circulating blood volume, urine output, body weight, and early infusion support should be integrated into each treatment course. As a comparable example within the class of anti-GD2 agents, data on naxitamab show that even with clinically meaningful activity in patients with residual disease in bone and bone marrow, the toxicity profile remains "vascular-pain" in nature: grade 3 adverse events included hypotension in 58% and pain in 54%, meaning that the leading risks recur regardless of the specific antibody used.

Considering the contribution of individual authors to understanding the clinical field, it should be noted that organizational accessibility of therapy and the quality of complication management may influence real-world outcomes. Against this background, the toxicity of anti-GD2 therapy appears not as a secondary detail, but as a mandatory condition for the safe implementation of targeted technologies.

Prospects: Expansion of Indications, CAR-T/NK, and Response Biomarkers

The prospects for the development of GD2-directed approaches are currently shaped not only by the accumulated experience in high-risk neuroblastoma, but also by the expansion of indications to other GD2-positive tumors, where the need for new therapeutic options remains substantial. At the same time, movement toward broader application inevitably depends on the balance between efficacy and tolerability: first-generation antibodies are associated with predictable complications, while cellular platforms still raise important questions regarding the controllability of inflammatory reactions and the reproducibility of response. Within this framework, optimization of antibody administration regimens, including prolonged infusions, is becoming increasingly important, alongside the parallel development of GD2-CAR-T, CAR-NK, and CAR-NKT technologies, which may potentially enhance the cytotoxic component and reduce some off-tumor effects. Against this background, response biomarkers are becoming not an additional element, but a key tool: the efficacy of anti-GD2 treatment is largely determined by the activity of the effector arm, primarily NK cells, the ability to implement ADCC, and the specific features of interaction between the Fc fragment of the antibody and Fcγ receptors, including FCGR polymorphisms, which may alter the "strength" of the immune response.

In practical terms, this means a transition toward more precise patient stratification based on a combination of parameters: the level and heterogeneity of GD2 expression, immune profile, including NK and monocyte components, FCGR genotype, and drug exposure indicators. These parameters can guide the choice of the optimal platform, whether antibody therapy, CAR-T, or CAR-NK/NKT, as well as the required supportive care. At the same time, expansion of indications requires standardization of methods for confirming GD2 positivity and consideration of interlesional variability; otherwise, some patients may enter therapy without a sufficient "target," which would distort the assessment of outcomes. Thus, the further development of this field can be described as a transition from proven efficacy in neuroblastoma to a broader oncological niche, where success will be determined by accurate patient selection, choice of technology, and a pre-established system for toxicity control.

CONCLUSION

This study reviewed the key directions determining the further evolution of GD2-directed therapy, including expansion of indications, development of cellular platforms, and the role of response biomarkers. The findings substantiate the need for a standardized approach to assessing the target and the patient's immune status before treatment initiation, as well as to monitoring tolerability throughout the course. The presented analysis may serve as a basis for further refinement of patient selection criteria and for the development of practical algorithms for therapy support in clinical settings.

REFERENCES

1. World Health Organization. Childhood cancer: Fact sheet. World Health Organization website. 10.03.2026. URL: https://www.who.int/news-room/fact-sheets/detail/cancer-in-children (accessed: 25.03.2026).

2. Russian Children's Clinical Hospital. For the Youngest: How Russia Fights Childhood Cancer. RCC X website. 15.02.2025. URL: https://rdkb.ru/about/news/smi-o-nas/za-samykh-malenkikh-kak-v-rossii-boryutsya-s-detskim-rakom/ (accessed: 25.03.2026).

3. Borokshinova K.M., Kuleva S.A., Baldueva I.A., Nekhaeva T.L., Novik A.V., Emelyanova N.V., Mikhailova E.A., Khabarova R.I., Senchurov E.M., Gumbatova E.D., Sakhautdinov G.A., Semenova Yu.K. “Results of Active Immunotherapy in Children with Solid Tumors.” Problems in Oncology, vol. 69, no. 3S, 2023, pp. 254–255.
4. Paina O.V. et al. Immunotherapy of acute lymphoblastic leukemia in infants using blinatumomab and donor lymphocyte infusion after haploidentical hematopoietic stem cell transplantation. Pediatric Hematology/Oncology and Immunopathology. 2022;21(4):53–59. DOI: 10.24287/1726-1708-2022-21-4-53-59
5. Shpakova D.V. “Overcoming Relapses and Toxicity: Analysis of Clinical Experience with CAR-T Therapy in Children with ALL.” Bulletin of Science, vol. 5-1, no. 6(87), 2025, pp. 945–955.
6. Abdurashidova R.R., Mangasarova Ya.K., Sadreeva A.A., Akezheva K.A., Belkina D.S., Bogolyubova A.V., Aleshina O.A. “Bridge Therapy before CAR-T in Non-Hodgkin Lymphomas: Necessity and Impact on Outcomes.” Oncohematology, vol. 20, no. 4, 2025, pp. 63–75. doi:10.17650/1818-8346-2025-20-4-63-75
7. Popova M.O., Markelov V.V. “CAR-T: From Idea to Application.” Oncohematology, vol. 19, no. 3, 2024, pp. 185–198. doi:10.17650/1818-8346-2024-19-3-185-198
8. Murtuzaliev Sh.M., Salakheeva E.Yu., Kardovskaya S.A., et al. Cardiovascular Toxicity of CAR T-Cell Therapy: A Literature Review. Clinical Oncohematology. 2024;17(4):404–414. doi: 10.21320/2500-2139-2024-17-4-404-414
9. Gribkova I.V. “Immune Checkpoint Inhibitors in Tumor Diseases of the Blood System in Children.” Oncohematology, vol. 18, no. 2, 2023, pp. 25–34.
10. Melnikov M.E., Kuleva S.A., Kondratyev G.V., Vasilyeva M.M., Savelyeva O.E. “Mechanisms of Cytotoxicity of Passive Anti-GD2 Immunotherapy in Pediatric Tumors.” Advances in Molecular Oncology, vol. 12, no. 2, 2025, pp. 47–57. doi:10.17650/2313-805X-2025-12-2-47-57
11. Babakhanova N.N., Ibragimova S.Z., Matkarimova D.S., Boboev K.T. “Experience with Blinatumomab in Acute Lymphoblastic Leukemia in Children: A Clinical Case.” Bulletin of Hematology, vol. 19, no. 1, 2023, pp. 29–31.
12. Dinikina Yu.V., Belogurova M.B. “Possibilities of Therapy Personalization in Pediatric Oncology: A Literature Review.” Russian Journal of Pediatric Hematology and Oncology, no. 4, 2021, pp. 71–80.
13. Queudeville M., Ebinger M. Blinatumomab in Pediatric Acute Lymphoblastic Leukemia — From Salvage to First-Line Therapy: A Systematic Review. J Clin Med. 2021 Jun 8;10(12):2544. doi: 10.3390/jcm10122544. PMID: 34201368; PMCID: PMC8230017.
14. Zsigrai E., Barna S., Gaál Z., Macsi L., Szegedi I., Petrás M., Kiss C. Single-Center Cohort of Pediatric Patients with High-Risk Neuroblastoma Receiving Immunotherapy. Cancers. 2025;17(11):1824. https://doi.org/10.3390/cancers17111824
15. Challagundla K.B., Ansari K.M., Pandey M.K. Editorial: Immunotherapy: Up-to-Date Progress in Childhood and Hematological Malignancies. Front. Oncol. 2025;15:1584101. doi: 10.3389/fonc.2025.1584101
16. Zhao W., Yang P., Qin J., Huang C., Fan H., Jin M., Duan C., Wu Y., Wang X., Cui C., Su Y. Efficacy and Safety of Dinutuximab Beta Combined with GM-CSF and Isotretinoin ± Chemotherapy as First-Line Maintenance Treatment for Pediatric High-Risk Neuroblastoma in China. Front. Oncol. 2026;16:1765578. doi: 10.3389/fonc.2026.1765578
17. Ni X., Li Z., Li X., Zhang X., Bai G., Liu Y., et al. Socioeconomic Inequalities in Cancer Incidence and Access to Health Services among Children and Adolescents in China: A Cross-Sectional Study. Lancet. 2022;400:1020–1032. doi:10.1016/S0140-6736(22)01541-0
18. Pediatric Oncology Committee, Chinese Anti-Cancer Association; Oncology Group, Chinese Association of Pediatric Surgeons. Expert Consensus on Diagnosing and Treating Neuroblastoma in Children: CCCG-NB-2021. Chin J Pediatr Surg. 2022;43:588–598. doi:10.3760/cma.j.cn421158-20211227-00638
19. Olgun N., Cecen E., Ince D., Kizmazoglu D., Baysal B., Onal A., et al. Dinutuximab Beta plus Conventional Chemotherapy for Relapsed/Refractory High-Risk Neuroblastoma: A Single-Center Experience. Front Oncol. 2022;12:1041443. doi:10.3389/fonc.2022.1041443
20. Kennedy P.T., Zannoupa D., Son M.H., Dahal L.N., Woolley J.F. Neuroblastoma: An Ongoing Cold Front for Cancer Immunotherapy. J Immunother Cancer. 2023;11:e007798. doi:10.1136/jitc-2023-007798
21. Wieczorek A., Zaniewska-Tekieli A., Ehlert K., Pawinska-Wasikowska K., Balwierz W., Lode H. Dinutuximab Beta Combined with Chemotherapy in Patients with Relapsed or Refractory Neuroblastoma. Front Oncol. 2023;13:1082771. doi:10.3389/fonc.2023.1082771
22. Balaguer J., García H., Hladun R., Márquez V.C., Pérez A.V. Recent Evidence-Based Clinical Guide for the Use of Dinutuximab Beta in Pediatric Patients with Neuroblastoma. Target Oncol. 2023;18:77–93. doi:10.1007/s11523-022-00930-w
23. Mao C., Poimenidou M., Craig B.T. Current Knowledge and Perspectives of Immunotherapies for Neuroblastoma. Cancers (Basel). 2024;16(16):2865. doi:10.3390/cancers16162865
24. Żebrowska U., Balwierz W., Wechowski J., Wieczorek A. Survival Benefit of Myeloablative Therapy with Autologous Stem Cell Transplantation in High-Risk Neuroblastoma: A Systematic Literature Review. Target Oncol. 2024;19:143–159. doi:10.1007/s11523-024-01033-4
25. Mora J., Chan G.C.F., Morgenstern D.A., Amoroso L., Nysom K., Faber J., et al. The Anti-GD2 Monoclonal Antibody Naxitamab plus GM-CSF for Relapsed or Refractory High-Risk Neuroblastoma: A Phase 2 Clinical Trial. Nat Commun. 2025;16(1):1636. doi:10.1038/s41467-025-56619-x
26. DuBois S.G., Moreno L., Bagatell R., Cheung N.K., Gray J.C., Locatelli F., et al. Paediatric Strategy Forum for Medicinal Product Development of Agents Targeting GD2 Ganglioside in Children and Adolescents with Cancer. Eur J Cancer. 2025;231:116093. doi:10.1016/j.ejca.2025.116093

27. Simon T., Thole T., Castelli S., Timmermann B., Jazmati D., Schwarz R., et al. GPOH Guidelines for Diagnosis and First-Line Treatment of Patients with Neuroblastic Tumors, Update 2025. Klin Padiatr. 2025;237:117–140. doi:10.1055/a-2556-4302
28. National Comprehensive Cancer Network. Neuroblastoma. NCCN Clinical Practice Guidelines in Oncology. Version 1.2025. Plymouth Meeting, PA: NCCN; 2025 [cited 2025 Dec 10]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1520
29. Yu X., Kang S., Ge J., Wang J. A Clinical Observational Study of Dinutuximab Beta as First-Line Maintenance Treatment for Patients with High-Risk Neuroblastoma in China. BMC Pediatr. 2025;25:203. doi:10.1186/s12887-025-05568-x
30. Gong Z.Q., Kang S.Y., Bai C.F., Li Y., Yu X.D., Shang K., et al. Extended Cycles of Anti-GD2 Antibody Dinutuximab Beta Treatment Combined with Chemotherapy in Patients with Relapsed or Refractory Neuroblastoma: A Retrospective Study. Oncol Lett. 2025;31:85. doi:10.3892/ol.2025.15438
31. Gray J.C., Weston R., Owens C., Canete A., Gambart M., De Wilde B., et al. Dinutuximab Beta Added to Temozolomide-Based Chemotherapy for Children with Relapsed and Refractory Neuroblastoma: Results of the ITCC-SIOPEN BEACON Immuno Phase II Trial. J Clin Oncol. 2026;44(3):176–187. doi:10.1200/JCO-25-01868
32. Irwin M.S., Naranjo A., Zhang F.F., Cohn S.L., London W.B., Gastier-Foster J.M., et al. Revised Neuroblastoma Risk Classification System. J Clin Oncol. 2021;39:3229–3241.
33. Pasqualini C., Rubino J., Brard C., Cassard L., André N., Rondof W., et al. Phase II and Biomarker Study of Programmed Cell Death Protein 1 Inhibitor Nivolumab and Metronomic Cyclophosphamide in Paediatric Relapsed/Refractory Solid Tumours: Arm G of AcSe-ESMART, a Trial of the European Innovative Therapies for Children with Cancer Consortium. Eur J Cancer. 2021;150:53–62.
34. Davis K.L., Fox E., Isikwei E., Reid J.M., Liu X., Minard C.G., et al. A Phase I/II Trial of Nivolumab plus Ipilimumab in Children and Young Adults with Relapsed/Refractory Solid Tumors: A Children's Oncology Group Study ADVL1412. Clin Cancer Res. 2022;28:5088–5097.
35. Qiu B., Matthay K.K. Advancing Therapy for Neuroblastoma. Nat Rev Clin Oncol. 2022;19:515–533.
36. Del Bufalo F., De Angelis B., Caruana I., Del Baldo G., De Ioris M.A., Serra A., et al. GD2-CART01 for Relapsed or Refractory High-Risk Neuroblastoma. N Engl J Med. 2023;388:1284–1295.
37. Siebert N., Zumpe M., Schwencke C.H., Biskupski S., Troschke-Meurer S., Leopold J., et al. Combined Blockade of TIGIT and PD-L1 Enhances Anti-Neuroblastoma Efficacy of GD2-Directed Immunotherapy with Dinutuximab Beta. Cancers (Basel). 2023;15:3317.
38. Mohd A.B., Mohd O.B., Alabdallat Y.J., Al Dwairy S.Y., Ghannam R.A., Hanaqtah B.M., et al. Safety and Efficacy of Dinutuximab in the Treatment of Neuroblastoma: A Review. J Res Med Sci. 2023;28:71.
39. Wieczorek A., Żebrowska U., Ussowicz M., Sokół A., Stypińska M., Dembowska-Bagińska B., et al. Dinutuximab Beta Maintenance Therapy in Patients with High-Risk Neuroblastoma in First-Line and Refractory/Relapsed Settings — Real-World Data. J Clin Med. 2023;12:5252.
40. Lode H.N., Ladenstein R., Troschke-Meurer S., Struppe L., Siebert N., Zumpe M., et al. Effect and Tolerance of N5 and N6 Chemotherapy Cycles in Combination with Dinutuximab Beta in Relapsed High-Risk Neuroblastoma Patients Who Failed at Least One Second-Line Therapy. Cancers (Basel). 2023;15:3364.
41. Troschke-Meurer S., Zumpe M., Meißner L., Siebert N., Grabarczyk P., Forkel H., et al. Chemotherapeutics Used for High-Risk Neuroblastoma Therapy Improve the Efficacy of Anti-GD2 Antibody Dinutuximab Beta in Preclinical Spheroid Models. Cancers (Basel). 2023;15:904.
42. Campbell K., Siegel D.A., Umaretiya P.J., Dai S., Heczey A., Lupo P.J., et al. A Comprehensive Analysis of Neuroblastoma Incidence, Survival, and Racial and Ethnic Disparities from 2001 to 2019. Pediatr Blood Cancer. 2024;71:e30732.
43. Hoshi Y., Enokida T., Tamura S., Nakashima T., Okano S., Fujisawa T., et al. Efficacy of Anti-PD-1 Monotherapy for Recurrent or Metastatic Olfactory Neuroblastoma. Front Oncol. 2024;14:1379013.
44. Barone G., Barry A., Bautista F., Brichard B., Defachelles A.S., Herd F., Manzitti C., Reinhardt D., Rubio P.M., Wieczorek A., van Noesel M.M. Managing Adverse Events Associated with Dinutuximab Beta Treatment in Patients with High-Risk Neuroblastoma: Practical Guidance. Paediatr Drugs. 2021 Nov;23(6):537–548. doi: 10.1007/s40272-021-00469-9. PMID: 34541620; PMCID: PMC8563639.
45. Blom T., Lurvink R., Aleven L., Mensink M., Wolfs T., Dierselhuis M., van Eijkelenburg N., Kraal K., van Noesel M., van Grotel M., Tytgat G. Treatment-Related Toxicities during Anti-GD2 Immunotherapy in High-Risk Neuroblastoma Patients. Front Oncol. 2021 Feb 17;10:601076. doi: 10.3389/fonc.2020.601076. PMID: 33680926; PMCID: PMC7925836.
46. Herriage T., Rawwas J., Sterman A., Hennen E., Bevers E. Naxitamab for Relapsed/Refractory Neuroblastoma. J Pediatr Hematol Oncol Nurs. 2026 Feb 19:27527530251410910. doi: 10.1177/27527530251410910. PMID: 41712415.
47. Kushner B.H., Modak S., White C., Basu E.M., Roberts S.S., Mauguen A., Cheung N.V. A Phase II Trial of Naxitamab plus Stepped-Up Dosing of GM-CSF for Patients with High-Risk Neuroblastoma in Second or Later Complete Remission. Int J Cancer. 2026 Feb 11. doi: 10.1002/ijc.70374. PMID: 41670398.
48. Zhang K., Wang Z., He J., Lu L., Wang W., Yang A., Xie H., Huang L., Huang Y., Zhang K., Jiang M., Wei R. Advances in T Cell-Based Immunotherapy for Osteosarcoma. Front. Immunol. 2026;17:1769847. doi: 10.3389/fimmu.2026.1769847
49. Yu A.L., Gilman A.L., Ozkaynak M.F., et al. Long-Term Follow-Up of a Phase III Study of ch14.18 (Dinutuximab) + Cytokine Immunotherapy in Children with High-Risk Neuroblastoma: COG Study ANBL0032. Clin Cancer Res. 2021;27(8):2179–2189. doi:10.1158/1078-0432.CCR-20-3909

50. Mora J., Castaneda A., Gorostegui M., et al. Naxitamab Combined with Granulocyte-Macrophage Colony-Stimulating Factor as Consolidation for High-Risk Neuroblastoma Patients in Complete Remission. Pediatr Blood Cancer. 2021;68(10):e29121. doi:10.1002/pbc.29121
51. Cheung I.Y., Cheung N.V., Modak S., et al. Survival Impact of Anti-GD2 Antibody Response in a Phase II Ganglioside Vaccine Trial among Patients with High-Risk Neuroblastoma with Prior Disease Progression. J Clin Oncol. 2021;39(3):215–226. doi:10.1200/JCO.20.01892
52. Berlanga P., Pasqualini C., Potschger U., et al. Central Nervous System Relapse in High-Risk Stage 4 Neuroblastoma: The HR-NBL1/SIOPEN Trial Experience. Eur J Cancer. 2021;144:1–8. doi:10.1016/j.ejca.2020.10.020
53. Desai A.V., Gilman A.L., Ozkaynak M.F., et al. Outcomes following GD2-Directed Postconsolidation Therapy for Neuroblastoma after Cessation of Random Assignment on ANBL0032: A Report from the Children's Oncology Group. J Clin Oncol. 2022;40(35):4107–4118. doi:10.1200/JCO.21.02478
54. Flaadt T., Ladenstein R.L., Ebinger M., et al. Anti-GD2 Antibody Dinutuximab Beta and Low-Dose Interleukin 2 after Haploidentical Stem-Cell Transplantation in Patients with Relapsed Neuroblastoma: A Multicenter, Phase I/II Trial. J Clin Oncol. 2023;41(17):3135–3148. doi:10.1200/JCO.22.01630
55. Flaadt T., Ebinger M., Schreiber M., et al. Multimodal Therapy with Consolidating Haploidentical Stem Cell Transplantation and Dinutuximab Beta for Patients with High-Risk Neuroblastoma and Central Nervous System Relapse. J Clin Med. 2023;12(19):6196. doi:10.3390/jcm12196196
56. Lode H.N., Ehlert K., Huber S., et al. Long-Term, Continuous Infusion of Single-Agent Dinutuximab Beta for Relapsed/Refractory Neuroblastoma: An Open-Label, Single-Arm, Phase 2 Study. Br J Cancer. 2023;129(11):1780–1786. doi:10.1038/s41416-023-02457-x
57. Mora J., Chan G.C.F., Morgenstern D.A., et al. Outpatient Administration of Naxitamab in Combination with Granulocyte-Macrophage Colony-Stimulating Factor in Patients with Refractory and/or Relapsed High-Risk Neuroblastoma: Management of Adverse Events. Cancer Rep. 2023;6(1):e1627. doi:10.1002/cnr2.1627
58. Kushner B.H., Modak S., Mauguen A., et al. A Phase II Trial of Naxitamab plus Stepped-Up Dosing of GM-CSF for Patients with High-Risk Neuroblastoma in First Complete Remission. Clin Cancer Res. 2025;31(10):1877–1884. doi:10.1158/1078-0432.CCR-24-3427