REVIEW ARTICLE

Therapeutic Innovation in Pediatric Neuroblastoma: Age and Stage-Specific Strategies from Prenatal to Early Childhood-A Review Article

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ABSTRACT

Neuroblastoma is one of the most common pediatric cancers, predominantly affecting young children. Despite progress in initial treatments, high-risk cases remain challenging due to frequent relapse or resistance, with long-term survival for relapsed or refractory neuroblastoma below 20%. This highlights an urgent need for novel therapies. Emerging approaches such as GD2-targeted immunotherapy with monoclonal antibodies like dinutuximab, CAR-T cell therapy, 131I-MIBG and Lutetium-177-Dotatate radionuclide treatments, metronomic chemotherapy, oncolytic virotherapy, and tailored chemotherapy are showing promise, with autologous stem cell transplantation (ASCT) becoming integral to multimodal regimens. However, challenges persist, including treatment-related toxicity, tumor resistance, and the logistical limitations of personalized medicine. The future of neuroblastoma treatment lies in exploiting genomic profiling, biomarkers, and combinatorial strategies like immunotherapy paired with radionuclide therapy. Rigorous clinical trials will be key to refining these innovations and establishing protocols for widespread use. In summary, advancements in therapy offer hope, yet achieving durable remissions and improved survival still demands intensive research innovation to address current gaps and resistance mechanisms in this complex pediatric malignancy.

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Introduction

Neuroblastoma is the most prevalent extracranial malignant solid tumor in childhood, originating from primitive neural crest affecting infants and young children (1). It accounts for approximately 8-10% of all childhood malignancies and contributes to nearly 15% of cancer-related deaths in children (2). The disease shows significant clinical and biological diversity, resulting in varied treatment responses. While some neuroblastomas spontaneously regress or differentiate without treatment, others can be highly aggressive and metastatic despite intensive multi-treatment efforts.

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This divergence demands personalized therapeutic approaches and highlights the need for continuous research and innovation in pediatric oncology.

Neuroblastoma displays diverse clinical presentations and is categorized into low, intermediate, and high-risk groups. About half of cases fall into the high-risk category. In patients with non-high-risk disease, the response to standard treatments such as low-intensity chemotherapy and surgery is generally very favorable, with a 5-year survival rate exceeding 90% (3). While high-risk neuroblastoma historically carries a poor prognosis, advances in treatments including chemotherapy, surgery, radiation, stem cell transplantation (SCT), and immunotherapy have improved outcomes, with approximately 50% of affected children now achieving long-term survival. Even with an initial response to therapy, the relapse rate in this group can reach up to 60% and unfortunately, once relapse occurs, the overall survival rate drops below 20% (4). Given that standard treatments for relapsed/refractory neuroblastoma typically achieve limited success, with low survival rates after relapse, there is an urgent need to introduce novel therapeutic approaches. The objective of this review is to provide a summary of treatment of neuroblastoma along with a comprehensive review of the literature on modern and innovative treatments for relapsed/refractory neuroblastoma.

Risk stratifications and staging systems

The biological and clinical diversity in neuroblastoma requires identifying various prognostic factors to guide treatment and predict outcomes. Key determinants include clinical aspects like tumor stage and age at diagnosis, along with tumor biologic features such as histopathology and DNA ploidy. Cytogenetic abnormalities, particularly MYCN amplification and chromosomal changes are also crucial. Serum tumor markers and molecular biomarkers further aid in risk stratification and prognosis (5).

Accordingly, Patients are classified into low, intermediate, or high-risk groups based on a thorough assessment of clinical and biological factors. The Children's Oncology Group (COG) initially used the International Neuroblastoma Staging System (INSS) for risk stratification, considering age at diagnosis, tumor stage, INPC histopathology, DNA ploidy, and MYCN oncogene amplification. These criteria guide treatment planning and have improved outcomes in pediatric neuroblastoma (5, 6) (Table-2 and 3). In 2005, the “International Neuroblastoma Risk Group (INRG) classification and staging system” replaced the INSS system. INRGSS prioritizes preoperative radiological assessments [image-defined risk factors (IDRFs)] to better distinguish between low- and high-risk tumors. This staging system improves risk assessment by integrating seven prognostic factors including: tumor stage, patient age, histology, MYCN oncogene status, chromosome 11q aberration, and DNA ploidy. This framework improves diagnostic precision, standardizes the treatment plan and enhances patient outcomes (7, 8). In 2021, the COG revised neuroblastoma risk classification by incorporating segmental chromosomal aberrations (SCAs) into the INRGSS (9). SCAs associated with poor outcomes include 1p and 11q deletions as well as 1q, 2p, and 17q gains. These abnormalities, often associated with advanced disease and age over 18 months, are crucial for risk stratification and treatment planning (10).

Treatment of Low- and Intermediate-Risk Neuroblastoma

Non-high-risk neuroblastoma account for about 50% of newly diagnosed patients. These patients typically present with localized or metastatic disease in infants with tumors that lack MYCN amplification. Treatment strategies in non-high-risk neuroblastoma are individualized based on risk group and clinical presentation and include a) Observing very low-risk cases, b) Employing surgery alone, or c) Combining surgery with moderate-dose chemotherapy in selected patients. In summary, outcomes are highly favorable, emphasizing the critical role of personalized care guided by disease characteristics and symptom severity (2, 11).

Prenatal adrenal neuroblastoma (very low risk), identified as small adrenal masses detected before birth or up to six months of age, carries an extremely favorable prognosis without surgical or chemotherapeutic intervention. Monitoring these infants with ultrasound (without biopsy) every 6 to 8 weeks is recommended until the mass resolves spontaneously or grows significantly necessitating surgical resection (11, 12). Occasionally, these patients may progress to stage 4S, but they can be observed as long as they remain asymptomatic, with a 90-100% survival rate, since commonly experience spontaneous disease regression due to having favorable biological features such as "near triploidy" or "1p36 expression" (12, 13). However, infants under 3 months with severe hepatomegaly, liver dysfunction, or respiratory distress require emergency treatment, as mortality is high without prompt chemotherapy (14). Spontaneous regression typically occurs in tumors with near-triploid chromosome numbers, absence of MYCN amplification, lack of 1p LOH, expression of the neurotrophin receptor TrkA and H-Ras protein (12).

If localized adrenal tumor does not regress or progressively grows, surgery serves as the definitive

treatment (12). The recent COG ANBL1232 study (NCT02176967) also recommends avoiding surgery for small, localized adrenal tumors in asymptomatic children under 12 months detected incidentally via ultrasound, with further decisions made if growth occurs (15). Growing tumors are often curable with surgery alone, while relapses are manageable with chemotherapy. Infants who undergo tumor resection can be monitored with ultrasound or CT scans every 3 months for the first year and every 6 months for up to 2 years. Distant metastasis rarely occurs even after incomplete resection. Chemotherapy is recommended in case of relapse or destructive effects on organs such as spinal cord compression or respiratory problems (16).

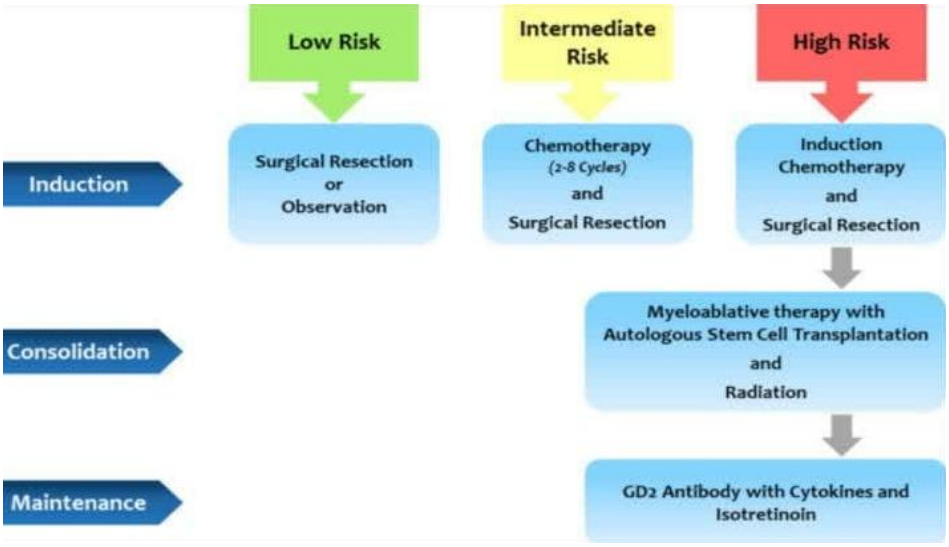

Figure 1: Treatment stages in neuroblastoma based on risk groups (2).

Treatment for intermediate-risk neuroblastoma involves moderate-dose chemotherapy and surgical resection. Considering the tumor's clinical and genetic characteristics, treatment intensity has been reduced in recent years. The COG A3961 study divided intermediate-risk patients into two groups: a) favorable biology (favorable histology and DNA index >1), receiving 4 chemotherapy cycles, and b) unfavorable biology (unfavorable histology, DNA index <1, or both), receiving 8 cycles. Overall survival was 96% in both groups with the appropriate cycle number. Recent trends increasingly recommend reducing chemotherapy intensity and extensive surgery in infants under 18 months with localized tumors and favorable biology (17).

High-Risk Neuroblastomas

Treatment of patients with high-risk neuroblastoma is divided into three phases: 1) Induction: Chemotherapy and surgery, 2) Consolidation: Myeloablative chemotherapy, ASCT, and radiotherapy, 3) post-consolidation (maintenance): Isotretinoin and Immunotherapy (Figure-1). The total upfront treatment duration is approximately 18 months (18). Treatment stages in neuroblastoma according to the risk stratification is shown in figure-1.

Induction Phase

The induction phase is critical, as resistant clones persisting at end of induction often lead to treatment resistance and relapse. Current North American regimens include vincristine, doxorubicin, cyclophosphamide, cisplatin, and etoposide. The COG incorporates topotecan in the first two cycles, with a 6-cycle regimen: cyclophosphamide and topotecan in cycles 1-2, cisplatin and etoposide in cycles 3 and 5, and cyclophosphamide, vincristine, and doxorubicin in cycles 4 and 6 (1). The SIOPEN group employs the rapid COJEC regimen, consisting of 8 cycles of cyclophosphamide, vincristine, carboplatin, etoposide, and cisplatin administered every 10-14 days (19). No significant differences in patient response or toxicity have been observed between COJEC and COG regimens (19). Children achieving complete remission or good partial response after induction proceed to high-dose chemotherapy followed by ASCT. Stem cells are harvested during induction after cycle 2 in COG protocols and cycle 8 in COJEC from peripheral blood or bone marrow. Despite modern strategies, over 60% of high-risk patients are resistant to first-line treatments or relapse despite an initial response.

A multicenter SIOPEN HR-NBL-1 study treated patients with poor induction responses with two TVD cycles (topotecan, vincristine, doxorubicin) to improve

metastatic responses (Figure-2). Patients received topotecan (1.5 mg/m²/day for 5 days), vincristine (1 mg/m²/day), and doxorubicin (22.5 mg/m²/day for 2 days). Responses were assessed using CT, MRI, MIBG, and bone marrow morphology. Overall, 36.5% achieved complete or partial metastatic responses, demonstrating efficacy of TVD regimen in enhancing remission rates in poor COJEC responders (20). Following the induction phase, surgery is another key component of treatment and is typically performed at the end or near the end of the induction phase. Resection is usually recommended after 4-6 cycles of induction therapy. In stage 4 or metastatic tumors, complete surgical resection has not shown a significant impact on survival. In other words, in these patients, chemotherapy prior to surgery plays a significant role in the success of future tumor resection and, consequently, in improving patient survival. Therefore, in metastatic high-risk patients, surgical complications must be carefully considered and resection should not be performed at the expense of damaging vital structures (18).

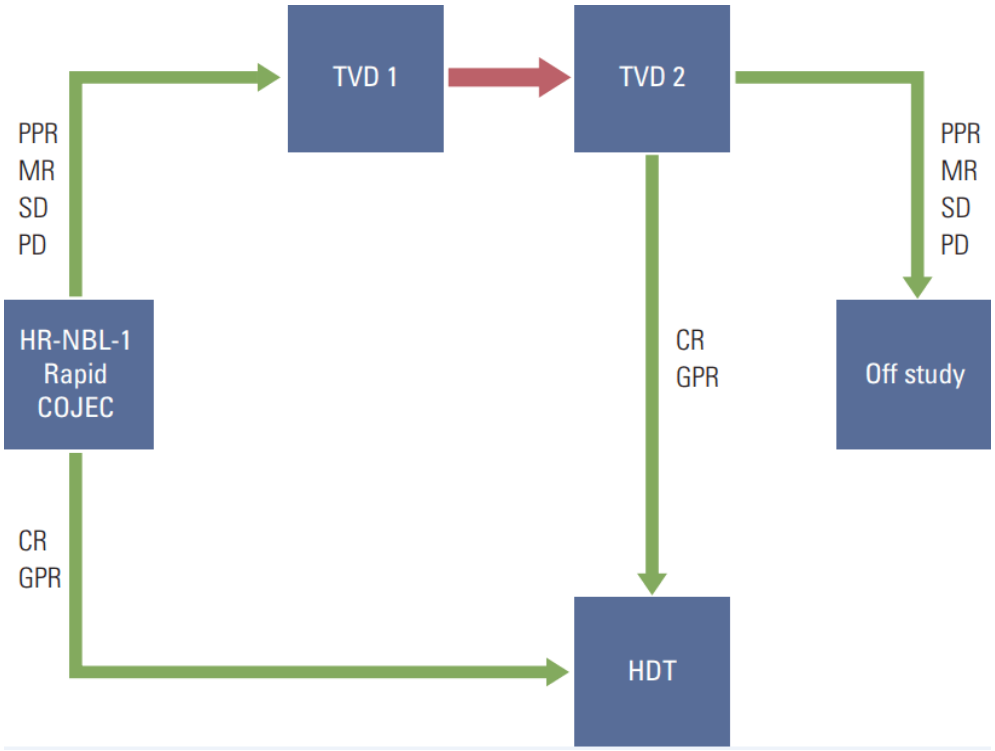

Figure 2: TVD regimen in the HR-NBL-1 protocol: PPR: Poor partial response, MR: Mixed response, SD: Stable disease, PD: Progressive disease, CR: Complete response, GPR: Good partial response (20).

As mentioned, there are conflicting recommendations regarding the necessity of complete resection for optimal local control. The NB97 protocol by the Germans showed that the extent of tumor resection (after induction therapy) in metastatic patients over 18 months did not affect patient survival (21). Another study found that tumor resection at the end of induction in the group with a poor response to induction did not impact EFS compared to those who did not undergo surgery and complete resection. Overall, metastatic relapses play a more determining and important role in the final prognosis than the extent of initial tumor resection (22).

In addition to surgery, radiotherapy is another key component in local control. Radiotherapy has no place in low-risk patients. In high-risk patients, radiotherapy is typically administered after the completion of the consolidation phase. In a study where 30 patients received radiotherapy with doses of 24-30 Gy to the primary site and 24 Gy to metastatic sites, tumor control was achieved in 84% of primary tumors and 74% of metastases. Overall, the number of MIBG-avid sites after the completion of the induction phase is a significant factor in patient prognosis (23). Various techniques such as intensity-modulated radiation therapy (IMRT) have been employed to reduce radiation exposure to healthy tissues. Proton beam therapy (PBT) reduces the side effects of radiotherapy by minimizing damage to healthy tissues. One of the advantages of PBT is its use in younger children and better protection of adjacent sensitive tissues. However, its use in children with neuroblastoma is very limited due to its high cost and the scarcity of centers offering it (24).

Consolidation Phase

The consolidation phase aims to eliminate residual disease at the end of induction. This phase includes myeloablative chemotherapy followed by ASCT. In one study evaluating the efficacy of SCT in treating high-risk neuroblastoma, a significant improvement in survival was observed in those who received high-dose chemotherapy and transplantation. Additionally, tandem transplantation with different conditioning regimens can be used in high-risk neuroblastoma, which in some cases has been associated with better survival outcomes. Stem cells are typically harvested after 2-3 cycles of induction. Although there is considerable debate regarding the source of cells used for transplantation, peripheral blood is preferred due to easier collection, higher yield, lower likelihood of tumor cell contamination, and faster recovery. Recently, a single-center study on high-risk patients suggested that even myeloablative treatments and ASCT might not improve patient survival, and in such cases, immunotherapy with anti-GD2 antibodies may be effective in improving outcomes in the post-consolidation phase. Therefore, the ideal treatment regimen in the consolidation phase remains a topic of discussion and future studies (25). As mentioned, radiotherapy to the primary tumor bed and residual involved (metastatic) sites from the end of induction is typically administered after recovery from SCT and plays a significant role in local disease control (26).

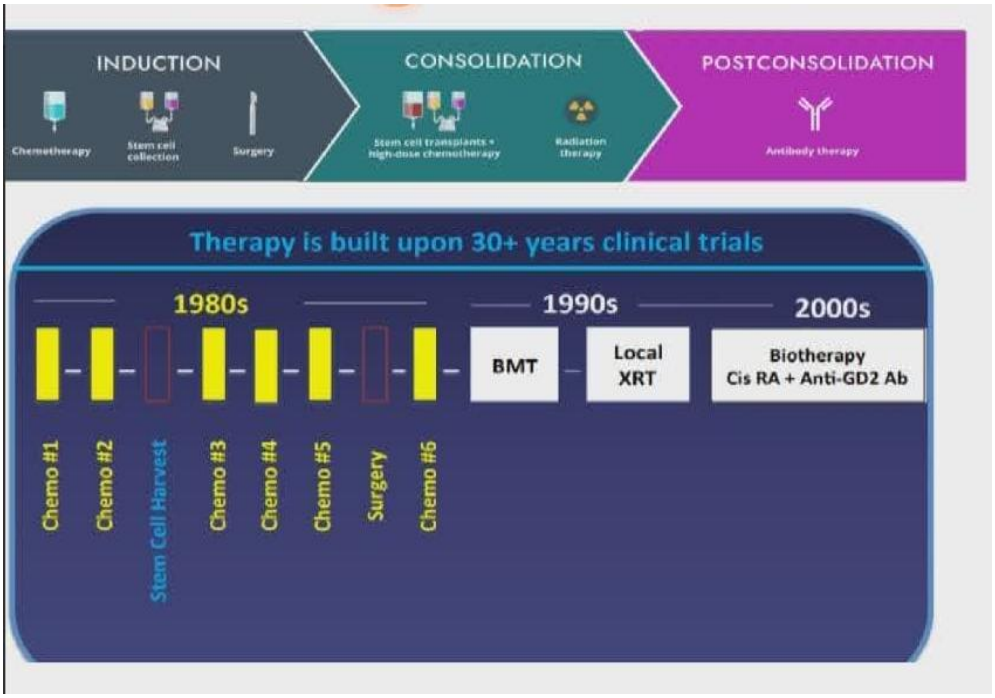

Figure 3: Overview of treatment stages in high-risk neuroblastoma and its evolution over the past four decades (27).

Post-Consolidation or Maintenance Phase

Patients with high-risk neuroblastoma are typically candidates for maintenance therapy after completing induction, surgical resection, myeloablative chemotherapy, ASCT, and radiotherapy (Figure-3). While many patients achieve complete remission with the above treatments, relapse remains a serious issue, indicating that residual disease is a significant risk factor for relapse in neuroblastoma. In an effort to prevent relapse, isotretinoin is used in the maintenance phase. However, it appears to have no impact on overall survival. Isotretinoin is a non-cytotoxic treatment that aids in the maturation of neuroblastoma cells, reducing proliferation and promoting differentiation of tumor cells (27).

Immunotherapy

Recent progress in treating high-risk neuroblastoma highlights key role of immunotherapy in sustaining remission after consolidation. Central to this approach are monoclonal antibodies, particularly those targeting GD2; a surface antigen abundant on neuroblastoma cells, but rare in normal tissues, making it an ideal therapeutic target. Since the late 1990s, the GD2-specific antibody ch14.18 has demonstrated notable anti-tumor activity while sparing healthy tissue. Integrating GD2-targeted therapies into maintenance regimens shows promise for improving long-term outcomes (28).

Dinutuximab, also known as Unituxin (ch14.18) or Anti-GD2, is a chimeric mouse-human monoclonal

antibody that binds to GD2 on the surface of tumor cells. Its activity is enhanced when combined with GM-CSF or interleukin-2. In two phase 1 studies, ch14.18 was evaluated in combination with GM-CSF, interleukin-2, and isotretinoin after transplantation, paving the way for the phase 3 study by the Children's Oncology Group (ANBL0032). This study compares the outcomes of immunotherapy with dinutuximab plus GM-CSF, interleukin-2, and isotretinoin versus isotretinoin alone in 226 children with high-risk neuroblastoma after transplantation. Patients in one group received oral isotretinoin (six 28-day cycles, 14 days per cycle at 160 mg/m²/day divided into two doses) alone. In the other group, patients received dinutuximab (25 mg/m²/day for 4 consecutive days over five 4-week cycles) along with interleukin-2 (in cycles 2 and 4, continuous infusion for 4 days in the first week at 3×10^6 units/m²/day and 4 days in the second week at 4.5×10^6 units/m²/day) and GM-CSF (in cycles 1, 3, and 5 at 250 µg/m²/day for 14 days, starting 3 days before dinutuximab). Additionally, during the last 2 weeks of each of the five cycles and in the sixth cycle, they received isotretinoin alone at 160 mg/m²/day. The three-year survival was 63% in the group receiving dinutuximab with interleukin-2, GM-CSF and isotretinoin, compared to 46% in the group treated with isotretinoin alone. The five-year survival was also clearly higher in the group receiving immunotherapy (29). Based on these results, the U.S. FDA approved dinutuximab in 2015 for the treatment of high-risk neuroblastoma in children (30). Similarly, following a phase III study by SIOPEN, Europe approved dinutuximab in 2017 (31).

Based on these findings, the standard treatment for high-risk neuroblastoma in the maintenance phase includes isotretinoin plus dinutuximab and cytokines. The treatment in Europe differs slightly from that in North America. In Europe, a different antibody called dinutuximab beta is used along with isotretinoin. Dinutuximab beta (tradename Qarziba®) is administered only with interleukin-2 and not with GM-CSF. The results of the studies have shown no evidence that adding subcutaneous interleukin-2 to dinutuximab beta improves outcomes in patients with high-risk neuroblastoma, and the combination was associated with more toxicity than dinutuximab alone. Therefore, until trial results are available, dinutuximab beta and isotretinoin, without interleukin-2, are considered the current standard combination in Europe (32).

Naxitamab or hu3F8, marketed under the name Danyelza® (Naxitamab-gqg), is a humanized monoclonal antibody that specifically targets GD2, a surface marker presents on neuroblastoma cells (33). Approved by the FDA in 2020, this treatment is used alongside GM-CSF to manage relapsed/refractory neuroblastoma in patients aged one or older, with the disease only in the bone and bone marrow (34).

Relapsed/Refractory Neuroblastoma

As mentioned, up to 60% of high-risk patients experience relapse, and 5-year survival after relapse is ultimately 20%. It should be noted that there is no specific protocol or optimal treatment for relapse, and decisions are made for each patient based on their condition. In children over 18 months at diagnosis, survival after relapse is 8%, and in those with MYCN gene amplification, survival drops to less than 5% (34). The time to first relapse is significantly correlated with survival rate (1). The Children's Cancer and Leukemia Group (CCLG) has a subgroup that deals with neuroblastoma treatment. In 2015, based on the latest available treatments at that time, this group provided treatment protocols for high-risk patients and those with resistant/relapsed disease (Table-1) (34).

Patients with refractory disease appear to benefit more than those with relapsed disease. Some of these regimens have been taken forward to front-line therapy; for example topotecan-cyclophosphamide is now used at induction by COG following the promising results of a non-randomized pilot study (12). However, none of these regimens have been evaluated in randomized Phase II trials, leaving efficacy and toxicity comparisons unclear (35).

The CCLG suggests enrolling patients with relapsed neuroblastoma in clinical trials. A tumor re-biopsy is recommended at relapse at either the primary or metastatic sites due to possible genetic changes. It is recommended to test these tumors for ALK mutations or amplifications. If detected, consider ALK-directed therapies. ALK mutations occur in about 10% of neuroblastoma cases, with a higher rate after relapse. (36, 37).

Although chemotherapy is not necessarily a prerequisite for starting re-induction, and treatment with radionuclides and targeted radiotherapy can be started from the beginning as re-induction. If the patient responds well to re-induction treatment and has not previously received myeloablative treatments, myeloablative treatments can be used as a consolidation phase, or after re-induction, targeted radiotherapy can be used as a consolidation phase. Then, isotretinoin or immunotherapy can be used if they have not previously received Anti-GD2. Patients with multiple relapses (second relapse, etc.) should be enrolled in clinical trials (38).

Treatments for Relapse Before Myeloablative Therapy

Induction Phase

In patients who experience relapse or disease progression despite receiving the high-risk protocol before receiving the myeloablative regimen, re-induction with protocols such as BEACON-Neuroblastoma, TVD, temozolomide alone, topotecan-temozolomide, or irinotecan-temozolomide is recommended. The choice of treatment regimen at this stage depends on the patient's family decision, previous treatments, drug toxicities, and the feasibility of administration based on the patient's vascular access. The patient is evaluated after receiving 2 courses, and if acceptable responses are achieved (complete or partial response or stable disease), 4-6 courses of induction treatment can be continued (34, 38).

Table 1: Chemotherapy regimens in relapsed or refractory neuroblastoma (34).

Regimen (Reference)	Collaborative group		Responses (No. patients)	Response Rate (%)		Comments
				CR +PR	SD	
Temozolomide (13)	UKCCSG/ SFOP		5/25 CR, VGPR, PR 7/25 SD/NR 3/25 MR	20%	40% (SD/NR/MR)	TMZ 200 mg/m^2/d x 5 days every 28 days
Irinotecan (14)	SFOP/ UKCCSG		0/37 CR, PR 5/37 SD	0%	13%	IRI 600 mg/m^2, every 3 weeks
Temozolomide/ Irinotecan (15,16)	MSKCC		3/39 CR,PR, 5/39 SD	7.7%	12.8%	5-day courses of IRI 50 mg/m^2 and TMZ 150 mg/m^2 (oral) every 3 to 4 weeks
	COG		8/55 CR, PR 29/55 SD	15%	53%	IRI (10 mg/m^2/dose 5 days a week for 2 weeks) and TMZ (100 mg/m^2/dose for 5 days) every 3 weeks
Temozolomide/ oral Irinotecan (Phase I) (17)	NANT		1/14 CR 5/14 SD	7%	36%	TMZ 100-75 mg/m^2/day for 5 days plus IRI 30-60 mg/m^2 for 5 days a week for 2 weeks in a 3-week course
Topotecan/ Temozolomide (18,19)	ITCC		3/38 CR, 6/38 PR, 4/38 MR, 17/38 SD (best response)	18%	55%	TPT 0.75 mg/m^2/d days 1 to 5, TMZ 150 mg/m^2/d day1 to 5, every 4 weeks
Topotecan/ Vincristine/ Doxorubicin (20)	SIOPEN		16/25 CR, PR 4/25 SD	64%	16%	already in HR-NBL1 for doses see appendix)
Topotecan/ cyclophosphamide vs. topotecan alone (12)	COG	TPT/ CYCL	24/87 CR, PR 15/87 MR	27.5%	17% (MR)	improved PFS (p=0.08) [TPT 0.75 mg/m^2 and CYC 250 mg/m^2] versus [daily 5-day TPT 2 mg/m^2]
		TPT	17/89 CR, PR 12/89 MR	19%	13.5% (MR)	
Topotecan/ etoposide (21)	GPOH		17/36 (CR, PR) SD n/a	47%	n/a	TPT (schedule A: 1.0 mg/m^2/d days 1 to 5, B: 0.7 mg/m^2/d days 1 to 7, and C: 1.0 mg/m^2/d days 1 to 7) followed by VP-16 (100 mg/m^2/d days 8 to 10) every 4 weeks

Consolidation Phase

If there is a response to re-induction, the patient should subsequently receive radiotherapy with I131-MIBG or Lutetium-177-Dotatate, depending on previous treatments, patient condition, and previous toxicities. Treatment with Lutetium-177-Dotatate is a new therapeutic method. Before treatment with Lutetium-Dotatate, patients must show Gallium-68 octreoscan. It should be noted that, unlike MIBG

therapy, treatment with Lu-Dotatate does not require stem cells (39).

Myeloablative Chemotherapy Phase

After radiotherapy, high-dose chemotherapy with busulfan/melphalan followed by SCT is recommended (if stem cells are available) (18, 34).

Maintenance Phase

Children who achieve acceptable responses after myeloablative therapy receive immunotherapy including Anti-GD2 antibody with or without IL-2 (18). In case of multiple relapses and lack of response to the above, the next options are: receiving re-induction regimens as described above, MIBG therapy or LuDO (if they have octreotide uptake on scanning), or enrolling in clinical trials, or oral etoposide (50 mg/m²/day, for 21 days, every 28 days), or symptomatic treatments are recommended (Figure-4)(18).

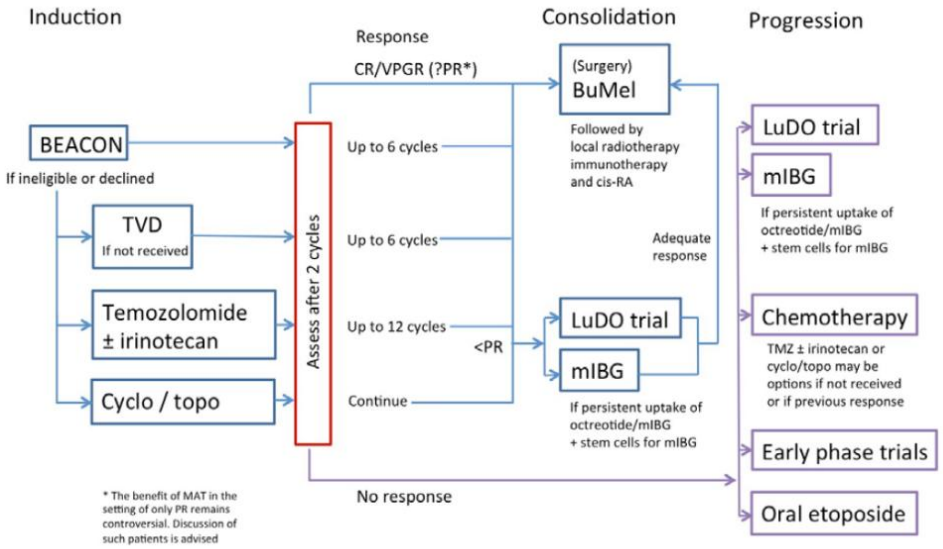

Figure 4: Protocols for relapse before myeloablative therapy (34).

Treatments for Relapse After Myeloablative Therapy (MAT)

Induction Phase

Various options exist for addressing relapse after MAT, tailored to individualized needs, among them are BEACON-Neuroblastoma protocol, Topotecan-Cyclophosphamide, Topotecan-Vincristine-Doxorubicin, Irinotecan-Temozolomide, Topotecan-Temozolomide, and Temozolomide alone (200 mg/m²/day), which is known for its low toxicity, though no alternative has proven superior. Treatment choice relies on family preferences, previous patient treatments, drug toxicities, and treatment administration viability relating to patient vascular access. After two treatment courses, the patient's response is assessed. If satisfactory, treatment can continue for 4-6 courses, with a strong recommendation for consolidation after six courses. Regular cardiac monitoring every two courses ensures patient safety throughout the process (18).

Consolidation Phase

If an acceptable response is achieved after completing re-induction (with any of the above protocols, 6-12 courses for temozolomide-based regimens and 4-6 courses for TVD regimen), targeted radiotherapy should be administered, which is most effective in controlling soft tissue and bone disease but not in widespread bone marrow involvement. Additionally, targeted radiotherapy is not a suitable option for CNS involvement (18, 34). In this group of patients, there is no evidence that the patient benefits from repeat myeloablative therapy and SCT, unless the relapse is late and after 5 years, and the patient previously received only melphalan. Studies conducted to date on haploidentical transplantation have not shown favorable results or improved survival.

Maintenance Phase

Children who achieve acceptable responses or have stable disease after induction and consolidation are candidates for immunotherapy, which includes infusion of dinutuximab with or without IL-2. As of 2015, when the CCLG published this information,

patients who had previously received Anti-GD2 were not candidates for re-administration at the time of relapse. In case of multiple relapses and lack of response, the patient either enters clinical trials or receives oral etoposide (50 mg/m²/day, for 21 days, every 28 days), or only symptomatic treatments are recommended (Figure-5) (18, 34).

In recent years, the use of targeted therapies based on monoclonal antibodies such as dinutuximab and naxitamab, combined with chemotherapy, has led to improved therapeutic responses (33, 40). Furthermore, multiple studies have demonstrated that radiotherapy with 131I-MIBG in patients with resistant neuroblastoma increases progression-free survival and reduces tumor size (29, 41, 42).

Another treatment option is administration of metronomic therapy in relapsed/refractory patients (43). Some of these patients achieve a normal quality of life with this approach. While the upper limit of metronomic therapy remains unknown, some patients experience a cancer-free life three to four years after discontinuing treatment, though others relapse.

A new modern treatment under investigation is oncolytic virus therapy. Viruses are genomically modified to selectively target and replicate in tumor cells. The death of these cells, in addition to destroying the tumor, enhances therapeutic effects by activating anti-cancer immune responses. Preliminary results from human trials indicate the safety and relative efficacy of this method in pediatric refractory neuroblastoma (44). In a case report, injection of an adenovirus resulted in a 70% reduction in the child's abdominal mass (45).

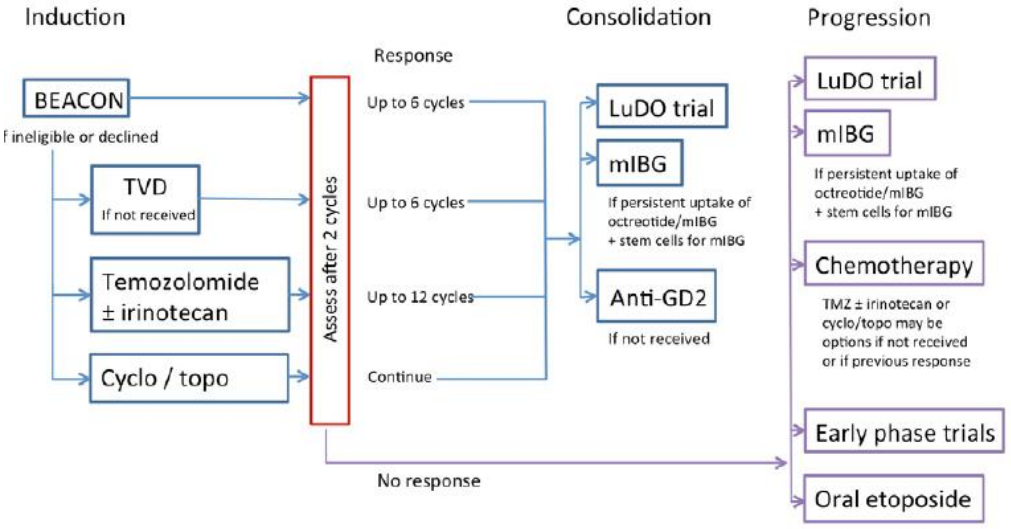

Figure 5: Protocols for relapse after myeloablative therapy 18,34).

The Turkish Pediatric Oncology Group assessed the combination of dinutuximab beta and chemotherapy in 19 patients with relapsed or refractory neuroblastoma initially treated under the NB 2009 protocol. The focus was on patients without remission at primary or metastatic sites. Various chemotherapy regimens were used alongside dinutuximab beta, including irinotecan and temozolomide (days 0-4), and combinations like vincristine + topotecan + temozolomide, etoposide + topotecan + temozolomide, carboplatin + etoposide + temozolomide, and ifosfamide + carboplatin + etoposide. Dinutuximab beta was administered as a 10 mg/m²/day continuous infusion for 10 days over 2 to 14 cycles, repeating every 28 days. Evaluations were performed every 2-3 cycles; 63% showed positive response: six complete, six partial. Two patients remained stable, while five experienced disease progression after 2-4 cycles. Common toxicities included leukopenia, thrombocytopenia, hypertransaminasemia, fever, rash, and capillary leak syndrome. The combination therapy improved response rates for relapsed or refractory neuroblastoma (46). In this study, treatment with dinutuximab in the maintenance phase (after transplantation) increased survival by about 20%.

In a study, dinutuximab was included in the protocol for high-risk neuroblastoma since 2018. Seven patients who had received induction, consolidation, radiotherapy, and ASCT, received dinutuximab (10 mg/m²/day intravenously for 10 days

in five 28-day cycles) along with isotretinoin (160 mg/m²/day for 14 days per cycle for six cycles) in the maintenance phase. The use of corticosteroids, immunosuppressive drugs, and IVIG was prohibited from 2 weeks before to 2 weeks after receiving dinutuximab. Four patients remained in complete remission (40). Currently, in many European countries, dinutuximab alongside isotretinoin is included in the standard treatment protocol for neuroblastoma in the maintenance phase.

The SIOPEN group investigated the effects of adding dinutuximab beta to the phase 2 BEACON-Neuroblastoma study for children with relapsed or refractory neuroblastoma, aiming to see if combining Anti-GD2 with chemotherapy improves antitumor activity over chemotherapy alone. Study participants were split into two groups: one receiving chemotherapy only (temozolomide and topotecan), and the other combining chemotherapy with dinutuximab beta. Dinutuximab was offered as a 7-day infusion (10 mg/m²/24 hours) along with chemotherapy. The study included 22 patients on chemotherapy alone and 43 on the combination treatment. Major outcomes focused on achieving partial or complete responses in the first six treatment rounds. The objective response rate was 18% with chemotherapy alone, whereas the combined therapy had a 35% rate, with one-year survival rates showing significant improvement over the chemotherapy-only group. These results highlight the potential benefits of integrating dinutuximab beta with a temozolomide regimen (47).

Since 2017, a medical center in Barcelona has led naxitamab research, using the immunotherapy in 864 treatment cycles for 131 patients over three years. They conducted two trials: monotherapy with naxitamab and GM-CSF, and the HITS regimen, combining naxitamab with irinotecan, temozolomide, and GM-CSF, per protocol NCT03189706. The monotherapy offers outpatient administration of naxitamab followed by GM-CSF. This experience positions the center as a leader in naxitamab studies (Figure-6). Monotherapy with naxitamab was given to patients with resistant or relapsed disease (limited to bone or bone marrow) who had partial or suboptimal responses to previous treatments, or as consolidation therapy for patients who achieved complete remission after relapse and re-treatment with chemotherapy. The second regimen, which includes chemotherapy and naxitamab, was given to resistant patients with soft tissue involvement who showed increased uptake on MIBG or PET scans (48).

Table 1. Overview of treatment regimens used at HJSD

Regimen and cycle length	Treatment and dosage	Cycle day											
		−4 to 0	1	2	3	4	5	6	7	8	9	10	11	12+
Naxitamab monotherapy[a] 28-day cycles	Naxitamab 3 mg/kg/day i.v. (9 mg/kg/cycle)		X		X		X							
	GM-CSF 500 µg/m²/day s.c.		X	X	X	X	X							
	GM-CSF 250 µg/m²/day s.c.	X												
Naxitamab chemoimmunotherapy[b,19] 21-day cycles	Naxitamab 2.25 mg/kg/day i.v. (9 mg/kg/cycle)			X		X					X		X	
	Irinotecan 50 mg/m²/day i.v. + temozolomide 150 mg/m²/day p.o.		X	X	X	X	X							
	GM-CSF 250 µg/m²/day s.c.								X	X	X	X	X	

BM, bone marrow; CR, complete response/remission; GM-CSF, granulocyte–macrophage colony-stimulating factor; HR, high risk; HSJD, Hospital Sant Joan de Déu; i.v., intravenous; MR, minor response; p.o., oral; PR, partial response; R/R, relapsed and/or refractory; s.c., subcutaneous; SD, stable disease.
[a]Naxitamab monotherapy is suggested for three groups of patients at HSJD: patients with R/R HR disease limited to bone or BM who have demonstrated PR, MR, or SD to prior therapy; or as consolidation in patients with relapsed disease who achieve a CR following latest therapy, or patients with HR disease who achieve a CR following frontline therapy.
[b]Naxitamab chemoimmunotherapy is suggested for two groups of patients at HSJD: patients with persistent soft-tissue disease; or patients who are refractory to or relapse following naxitamab monotherapy.

Figure 6: Treatment regimens including Naxitamab (48).

The HITS regimen, a combination of naxitamab with chemotherapy, is used when naxitamab alone is ineffective due to relapse or resistance. It's administered every 4 weeks for up to 5 cycles or until there's a partial or full response. If a satisfactory response is seen, subsequent treatments are scheduled every 8 weeks. Continuation of treatment is determined by the physician. Naxitamab is given as a 30-60 minute outpatient infusion.

The same group, in another study, reported the results of treatment with naxitamab in the consolidation phase in 73 children with high-risk neuroblastoma who were in first or second complete remission. Overall survival was 91% in patients in first remission, and the drug showed excellent results for consolidation in high-risk patients (33).

Molecular changes and gene mutations in neuroblastoma offer potential therapeutic pathways. ALK gene mutations occur in about 10% of sporadic and almost all familial neuroblastoma cases. Crizotinib, an ALK inhibitor, shows promise, especially alongside cyclophosphamide and topotecan. The COG is testing crizotinib in a phase 3 trial (NCT03126916) to assess its effectiveness with

standard treatments for high-risk neuroblastoma patients with ALK mutations, aiming to enhance patient outcomes (49).

Research into neuroblastoma maintenance therapies reveals promising methods to prevent relapse and enhance outcomes. Difluoromethylornithine (DFMO), an irreversibly inhibiting ornithine decarboxylase, has demonstrated potential in preliminary trials for relapsed or difficult cases. Its efficacy in remission maintenance is currently under evaluation in a phase 2 trial (NCT02139397). Additionally, a bivalent ganglioside vaccine targeting GD2 and GD3, combined with β-glucan, appears promising for sustaining remission. Further investigation is required to assess the long-term effectiveness of these strategies (50).

The Italian Medicines Agency reported positive results from a phase 1-2 clinical trial of CAR T-cell therapy targeting GD2 for children with relapsed or refractory neuroblastoma. The trial included 27 patients aged between 1 and 25, testing three dosages. The highest dose (10×10^6 cells/kg) was chosen for phase 2 due to its safety and efficacy. The study showed a 63% response rate with 9 complete and 8 partial responses. Patients on this dose had a 60% three-year survival rate. While 74% experienced cytokine release syndrome, most cases were mild, indicating that GD2-CART01 is a promising and safe treatment for high-risk patients, providing lasting tumor prevention (51).

MIBG therapy

Metaiodobenzylguanidine (MIBG) is structurally similar to norepinephrine and specifically targets neuroendocrine cells, including neuroblastoma. MIBG is taken up by 90% of neuroblastomas. Radioactive iodine-131 emits beta rays capable of destroying tumor cells. Treatment with I131-MIBG was first used in 1986 for neuroblastoma, and since then, numerous clinical trials have been conducted with I-131 MIBG in high-risk neuroblastoma patients. In fact, MIBG therapy is a low-dose radiotherapy where radioactive iodine remains in the tumor for more than 2 weeks.

In a study from Japan published in 2020, treatment outcomes and prognostic factors in high-risk neuroblastoma patients with resistant or relapsed disease who received I131-MIBG were reported. Twenty children with neuroblastoma resistant to previous conventional treatments received MIBG at doses of 444 - 666 MBq/kg. Patients were between 2.5-17 years old at the time of MIBG therapy. Patients had at least one lesion with MIBG uptake on scanning within the past 4 weeks, and arrangements for bone marrow transplantation were in place. Four days after MIBG therapy, imaging was performed to visualize the accumulation of radioactive material in tissues. Nineteen patients were evaluated. Five underwent ASCT, and 12 underwent allogeneic transplantation. Overall, 5 out of 19 patients (26%) had good and acceptable responses. One interesting finding of this study was that a time interval of less than 3 years between diagnosis and receiving MIBG was a significant prognostic factor. Overall, high-dose MIBG therapy in resistant patients improved prognosis and was not associated with serious non-hematologic side effects (41). Given the poor prognosis of high-risk neuroblastoma, multiple studies are evaluating the efficacy of MIBG treatment as a first-line therapy in these patients. In some studies, the possibility of administering MIBG simultaneously with myeloablative regimens after induction and then transplantation has been evaluated. In a retrospective, single-center study conducted in China from 2003-2019, newly diagnosed high-risk neuroblastoma patients without progressive disease after the completion of induction therapy received upfront consolidation treatment with I131-MIBG followed by myeloablative chemotherapy and HSCT (52).

In a study from Italy, 13 children over one year old with advanced neuroblastoma at diagnosis underwent MIBG and simultaneous chemotherapy during a one-month rapid induction period. In five patients, chemotherapy including vincristine, cyclophosphamide, etoposide, and cisplatin was administered in the first 10 days, and on the tenth day, they received MIBG at a dose of 150-200 mCi. Eight other patients received higher doses of MIBG on the tenth day and chemotherapy including doxorubicin, cyclophosphamide, vincristine, and cisplatin over 30 days. Disease response to this rapid induction regimen was evaluated 40 days after starting treatment. Hematologic side effects were similar in both groups. MIBG up to 16.6 mCi/kg had no side effects, even in patients with extensive bone marrow involvement. Complete response was reported in 2 patients, very good partial response in 6 patients, and partial response in 4 patients. In group 2, who received higher doses of MIBG, very good responses were observed (42).

The same group conducted another study in 2022 on 15 children over 18 months with metastatic disease. Again, the induction regimen was an intensive sequence of radiochemotherapy over one month. In this method, patients received continuous chemotherapy over one month and radiotherapy with MIBG at doses of 12-18.3 mCi/kg. During the first 10 days, vincristine, cyclophosphamide, etoposide, and cisplatin were administered. In this study, radioactive iodine at high doses of 16-18 mCi/kg was injected on

the tenth day of chemotherapy, when neutrophil and platelet counts were very low. Animal studies had shown that chemotherapy before radiotherapy protects normal tissues, including bone marrow (but not the tumor), from radiotherapy waves. In this method, the tumor is exposed to high-dose radioactive iodine continuously, while chemotherapy continues before and after for one month. Patients in this study were evaluated for response to treatment after 50 days. No non-hematologic side effects were observed in any patient. In most patients, hematologic recovery occurred within 3 weeks. The results of this intensive radio-chemotherapy protocol were very good, even better than the rapid COJEC protocol, with bone metastases cleared in 12/14 cases and bone marrow involvement in 12/13 cases. Additionally, those who received higher doses of MIBG clearly showed better responses (53).

In a prospective phase 2 study from the Netherlands, MIBG and topotecan were used as a drug that increases sensitivity to MIBG in 16 high-risk patients at diagnosis. Patients initially received 2 cycles of MIBG and topotecan (0.7 mg/m²/day for 5 days per cycle). The MIBG dose was 0.5 GBq/kg in the first cycle and 0.4 GBq/kg in the second cycle. After these two cycles, induction therapy (four courses of VECI: vincristine, teniposide, carboplatin, and ifosfamide), surgery, myeloablative therapy, and then ASCT were performed (Figure 7). Patient response was evaluated after two courses of MIBG/topotecan and also after myeloablative therapy and transplantation. The median age of patients was 2.8 years. Initial tumor response after two courses of MIBG/topotecan was 94%, and bone marrow response was 43%. Overall response after transplantation was 57%. Grade 4 hematologic toxicity was observed in 25-30%. Overall, combination treatment with MIBG/topotecan is proposed as an effective method in newly diagnosed neuroblastoma patients, provided that after induction and myeloablative chemotherapy, and in case of severe hematologic toxicities, they can receive autologous transplantation (54).

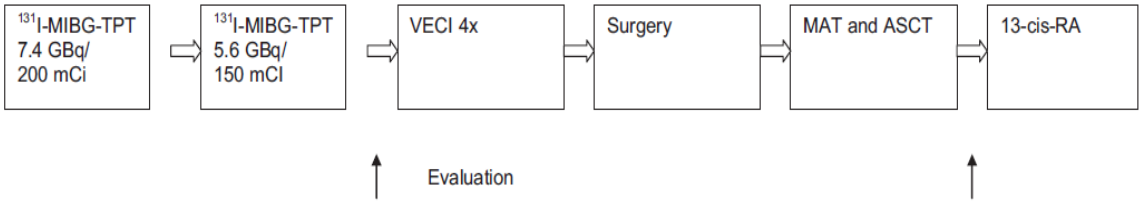

Figure 7: Phase 2 study AMRO-NB-HR-2000/01. Starting treatment for neuroblastoma with MIBG and topotecan, followed by induction, surgery, pre-transplant chemotherapy, and autologous transplantation (54).

COG designed a study (NCT01175356) for the first time to evaluate the tolerability of MIBG therapy at the end of the induction phase in high-risk neuroblastoma patients. Having MIBG-avid lesions was one of the inclusion criteria for the study. All patients were high-risk cases, and at least 4 million CD34 cells/kg had been collected from them. All patients received induction therapy consisting of 5 cycles of chemotherapy (Figure 8). According to the initial design, the first group received MIBG at a dose of 18 mCi/kg along with vincristine and irinotecan two weeks later. Then, stem cells were infused at more than 2×106 CD34 cells/kg, and five weeks later, they received a myeloablative regimen including busulfan/melphalan followed by SCT. After two patients developed severe sinusoidal obstruction syndrome, the study was modified. Patients received MIBG alone, without vincristine and irinotecan, at escalating doses of radioactive iodine at 12, 15, and 18 mCi/kg after induction, followed by the myeloablative regimen and ASCT 10 weeks later. Out of 68 patients who completed induction, 59 (86.8%) received MIBG. 82.2% of patients received MIBG and busulfan/melphalan. This study demonstrated the feasibility and tolerability of administering MIBG followed by myeloablative chemotherapy with busulfan/melphalan in children with newly diagnosed neuroblastoma, paving the way for another ongoing study using MIBG during the induction phase (55).

In a multicenter study across European countries, 32 patients with metastatic neuroblastoma were enrolled. Twenty-one children with MIBG-avid lesions on scanning received two courses of MIBG therapy within two weeks of diagnosis, before any chemotherapy, followed by the GPOH-2004 protocol and then a myeloablative regimen and autologous transplantation. The other 11 patients received chemotherapy. The aim of this study was to investigate the feasibility, toxicity, efficacy, and tolerability of MIBG. In the group receiving MIBG therapy, there was no need for stem cell support. Stem cell collection was possible in both groups, neutrophil recovery was similar in both groups, but platelet recovery was slower in the MIBG group. Overall, the results of this multicenter study confirmed the feasibility of using MIBG in the first-line treatment of metastatic patients, and it will certainly be used more

in future studies as a first-line treatment for high-risk and metastatic patients (56).

The Neuroblastoma-BEACON study, conducted under the supervision of the SIOPEN group, uses chemotherapy regimens plus bevacizumab, a monoclonal antibody against anti-angiogenesis, in relapsed/refractory neuroblastoma. Patients aged 1-21 years were enrolled and divided into four groups: temozolomide with or without bevacizumab, and irinotecan-temozolomide with or without bevacizumab. The primary objective of this study was to determine whether adding bevacizumab to chemotherapy increases antitumor activity in relapsed or refractory neuroblastoma. Courses are repeated every 3-4 weeks, and response to treatment is evaluated after 2 courses. If there is a response to treatment, patients will receive 6-12 courses (34).

In the phase 2 Neuroblastoma-BEACON study, patients were divided into three chemotherapy groups: temozolomide alone, irinotecan/temozolomide, and topotecan/temozolomide, with or without bevacizumab. The primary goal of this study was to achieve a higher overall response rate in the groups receiving bevacizumab, and this was successfully achieved in the bevacizumab groups. Overall, bevacizumab met the success criterion for achieving more acceptable responses (partial and complete responses) in this trial and had an acceptable toxicity profile (57).

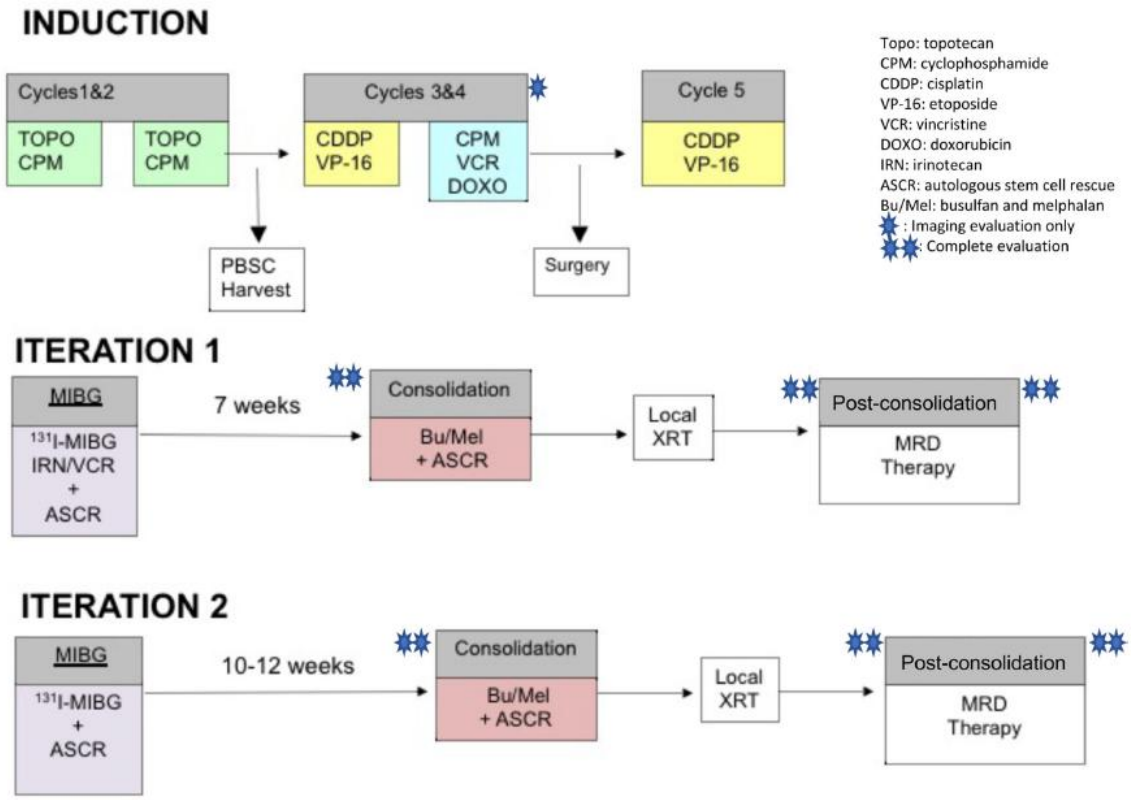

Figure 8: MIBG therapy after induction followed by myeloablative regimen and transplantation (55).

Central Nervous System Relapse in Neuroblastoma

The risk of CNS relapse after treatment for metastatic neuroblastoma is approximately 8% within 3 years. Half of these patients have isolated CNS relapse. CNS relapse can occur in the parenchyma, meninges, or both. The prognosis for CNS relapse is very poor, and there is no uniform treatment strategy for CNS relapse. Nevertheless, surgical removal of metastases, if possible, craniospinal radiotherapy, and chemotherapy can somewhat control CNS relapse. The Memorial Sloan Kettering Cancer Center has used intrathecal radioimmunotherapy after CNS relapse in a clinical trial. Currently, this intrathecal radioimmunotherapy is only performed at MSKCC as part of a clinical trial. Twenty-one patients treated with recurrent neuroblastoma metastatic to the CNS received a compartmental intrathecal antibody-based radioimmunotherapy regimen incorporating intrathecal 131I-monoclonal antibodies (MoAbs) targeting GD2 following surgery and radiation. Most patients also received outpatient craniospinal irradiation, murine anti GD2/GMCSF as immunotherapy, 13-cis-retinoic

acid and oral temozolomide for systemic control (58). Other radiotherapy methods such as Lutetium-177-Dotatate or MIBG are not recommended for CNS disease.

Proposed treatments for CNS relapse in the UK include surgery for CNS disease, craniospinal radiotherapy, and Temozolomide ± irinotecan. Patients who achieve complete or very good partial responses and have not previously received myeloablative chemotherapy can receive busulfan/melphalan followed by systemic immunotherapy with Anti-GD2 (in patients who have not previously received this drug) and isotretinoin (59). Beacon-Neuroblastoma is a treatment option when there is progressive disease after radiotherapy. However, patients with CNS metastasis are at risk of bleeding associated with bevacizumab.

Primary Refractory Neuroblastoma

Approximately 10-20% of high-risk neuroblastoma patients have primary refractory disease and are unable to achieve an acceptable response at the end of induction. Patients who have not responded well to induction therapy (rapid COJEC or N7 protocol or any induction protocol) based on INRC can receive 4-6 cycles of TVD as re-induction to meet acceptable criteria for entering the consolidation phase and receiving myeloablative therapy (as explained in previous sections). These patients can also be considered for the Beacon-Neuroblastoma protocol earlier. Patients who respond to re-induction (complete, very good, or partial response) can receive molecularly targeted radiotherapy and/or myeloablative chemotherapy in the next phase, consolidation. Such approaches may be useful in patients who have only a partial response (e.g., those who do not meet the standard criteria for myeloablative chemotherapy). After myeloablative chemotherapy, these patients should be candidates for systemic immunotherapy (dinutuximab plus interleukin-2)(34).

Arm T		
Days 1 - 5	Temozolomide 200 mg/m^2/d PO	Every 4 weeks
Arm BT		
Days 1 - 5	Temozolomide 200 mg/m^2/d PO	Every 4 weeks
Day 1 / Day 15	Bevacizumab 10mg/kg IV	Every 4 weeks
Arm IT		
Days 1 - 5	Temozolomide 100 mg/m^2/d PO	Every 3 weeks
Days 1 - 5	Irinotecan 50 mg/m^2/d IV	Every 3 weeks
Arm BIT		
Days1 – 5	Temozolomide 100 mg/m^2/d PO	Every 3 weeks
Days 1 - 5	Irinotecan 50 mg/m^2/d IV	Every 3 weeks
Day 1	Bevacizumab 15 mg/kg IV	Every 3 weeks

Figure 9: BEACON-Neuroblastoma trial (34).

Another Target for Radioisotope Radiotherapy

Somatostatin receptors which are expressed on the surface of neuroblastoma cells are another target for radioisotope radiotherapy. Somatostatin analogs labeled with gallium-68 are used for diagnostic scanning, and analogs (Dotatate) labeled with Lutetium-177-Dotatate are used for treatment. In fact, the Ga-68 Dotatate scan first determines whether the patient is a candidate for Lutetium-177-Dotatate therapy. The efficacy of this radioisotope therapy was first proven in adult neuroendocrine tumors under the name peptide receptor radionuclide therapy, and it was found to be well-tolerated with minimal hematologic and renal side effects. Pilot studies in children at University College London Hospitals and the Royal Children's Hospital in Melbourne, Australia, have shown that Ga-68 Dotatate PET/CT scanning is a practical method for identifying patients who can benefit from Lutetium-177-Dotatate therapy. Both centers have reported promising results from treating

children with refractory/relapsed neuroblastoma, with some cases achieving long-term remission for several years. The LuDO-N trial is a phase 2 clinical trial in children aged 18 months to 18 years, conducted by the Nordic Society of Pediatric Hematology and Oncology (NOPHO) and approved by SIOPEN. This study is still ongoing, and its results are expected to be finalized in the next 3-5 years. In this study, Lutetium-177-Dotatate is administered every 2 weeks to children with primary refractory disease or relapsed patients (60).

In a study from Iran, the potential of combination therapy with chemotherapy and Lutetium-177-Dotatate in children with relapsed/refractory metastatic neuroblastoma was evaluated. Fourteen children aged 4-9 years who were resistant to or relapsed after 131I-MIBG therapy underwent evaluation with Ga-68 Dotatate PET/CT scanning, which showed intense Ga-68 Dotatate uptake in 10 out of 14 patients (71.4%). The average number of lesions in patients was 2 (range 1-13). Five patients received Lutetium-177-Dotatate therapy. Patient responses were classified based on imaging findings as complete response, partial response, stable disease, and progressive disease. After each isotope therapy cycle, laboratory tests were performed to evaluate hematologic, renal, and hepatic tests. The time interval between the start of the first cycle and the last follow-up or death was calculated as overall survival. In total, 19 cycles and approximately 66.4 GBq of Lutetium-177-Dotatate were administered. Of these 5 patients, 2 initially showed complete response but relapsed a few months later, 1 patient showed partial response, and 2 patients showed progressive disease. Overall survival in these patients was estimated at 14.5 months (61). The authors' opinion is that in cases of relapse before myeloablative therapy or refractory disease, if the desired response is not achieved after two rounds of re-induction treatment, metronomic therapy should be started. Concurrently, Lutetium-177-Dotatate or MIBG therapy should also be performed (the timing of Lutetium-177-Dotatate or MIBG therapy should be coordinated with the metronomic therapy schedule).

Paraneoplastic neurological syndromes (PNS): OMAS syndrome

Paraneoplastic neurological syndromes are defined as neurological syndromes that are mainly immune-mediated. This broad definition may lead to misconception that any neurological syndrome in the setting of neuroblastoma might be considered as PNS. The detection of onconeural antibodies has been very helpful in indicating the existence of the tumor and defining a given neurological syndrome as paraneoplastic (62). Diagnosis of paraneoplastic syndromes may result in early detection and treatment of the neuroblastoma and can reduce the neurological damage that is the major source of morbidity in children with successfully treated tumors. Opsoclonus-Myoclonus-Ataxia Syndrome (OMAS) is the most common paraneoplastic syndrome in neuroblastoma which is often associated with more favorable outcome. Treatment is largely predicated on immune suppression, but there is limited evidence to indicate an optimal regimen. Besides begining induction chemotherapy, immunosuppressive treatments including adrenocorticotropic hormone (ACTH) or corticosteroids, plasmapheresis, IV immunoglobulin (IVIg), and rituximab or cyclophosphamide have been used as upfront to manage symptoms of the patient (63).

Low-Dose Metronomic Therapy

Minimal residual disease is primarily due to tumor-initiating cells in the primary site or metastases. Additionally, primary or secondary drug resistance may develop following cytotoxic chemotherapy. In metronomic chemotherapy, cytotoxic drugs are administered at low doses continuously without interruption. One of the therapeutic goals in low-dose metronomic therapy is to prevent angiogenesis. In metronomic therapy, unlike standard chemotherapy regimens that involve intensive courses every 3 to 4 weeks, low-dose continuous chemotherapy inhibits angiogenesis, thereby halting tumor growth. Additionally, metronomic therapy can overcome drug resistance caused by chemotherapy. Metronomic chemotherapy may be administered as monotherapy (e.g., daily oral cyclophosphamide) or as drug cocktails. Interestingly, the idea of metronomic therapy was proposed to maintain the disease in a stable state, but it has led to promising results in increasing patient survival (Table-2 and 3).

Among cytotoxic drugs, vinblastine, cyclophosphamide, and etoposide have anti-angiogenic properties (43). Another finding in this tumor is the presence of tumor-associated macrophages, which can either promote tumor growth or exhibit anti-tumor properties due to cytokines and the environment. Another characteristic of metronomic therapies is stimulating the immune system against tumor cells. Cyclooxygenase-2 enzyme expression is increased in neuroblastoma. Celecoxib, an inhibitor of this enzyme, converts macrophages to anti-tumor types and directly inhibits tumor growth (43).

Various articles have highlighted the role of vinblastine in neuroblastoma (64). Studies have shown that rapamycin, an mTOR inhibitor with

immunosuppressive activity can inhibit angiogenesis and prevents the proliferation of human neuroblastoma cells in laboratory conditions. Laboratory and clinical studies have examined the anti-angiogenic effects of low-dose vinblastine and rapamycin in neuroblastoma and concluded that their combination has synergistic effects (65). In a study on 21 children with neuroblastoma with bone metastases, oral cyclophosphamide (25 mg/m²/day) plus zoledronic acid was administered in multiple cycles of 2-4 mg/m² every 28 days. In about half of the patients, the disease remained stable, and acceptable clinical responses were achieved (66). A Four -drug regimen has been reported in a study from France (Figure 10). It included 8-week cycles including: vinblastine 3 mg/m² weekly (weeks 1-7), cyclophosphamide 30 mg/m²/day (days 1-21), methotrexate 10 mg/m² (days 21-42, twice a week), and celecoxib 100-400 mg twice daily (days 1-56), followed by a 2-week rest. Interestingly, no hair loss or alopecia was observed in these patients. Nausea and vomiting were not severe, and the most important side effect was hematologic toxicity. However, there was no significant difference in time to disease progression compared to those who received other metronomic regimens. At last follow-up, 43% of patients were alive (67).

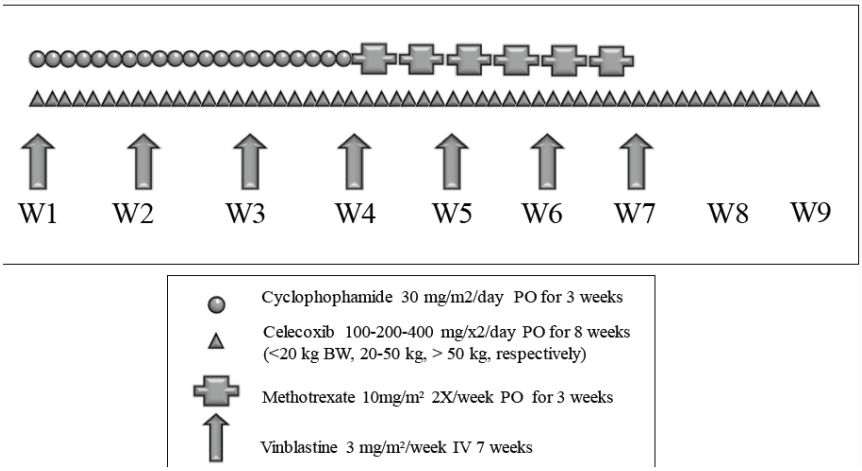

Figure 10: 4-drug oral metronomic regimen (67).

Table 2: Oral metronomic regimens including cyclophosphamide, vinorelbine, etoposide, and/or topotecan, and celecoxib after induction, surgery, and radiotherapy (68).

Chemotherapy Regimens	Drugs Dosage and Administration
Induction Chemotherapy:	
CAV (Cycle 1, 3, 5, and 7)	Cyclophosphamide (CTX) 1 g/m^2, iv drip for 0.5 h, d1–2 Mesna 330 mg/m^2 0, 4, and 8 h after CTX, iv, d1–2 Vincristine 1.5 mg/m^2, iv, d1 Pirarubicin 50 mg/m^2, iv, d1
VIP (Cycle 2, 4, 6, and 8)	Cisplatin 25 mg/m^2, iv drip for 3 h, d1–4 Etoposide 100 mg/m^2, iv drip for 3 h, d1–4 Ifosfamide (IFO) 1.5 g/m^2, iv drip for 3 h, d1–4 Mesna 300 mg/m^2, iv 0, 4, 8 h after IFO, d1–4
Second-line chemotherapy:	
VIT	Vincristine 1.5 mg/m^2, iv, d1 Irinotecan 50 mg/m^2, iv drip for 1.5 h, d1–5 Temozolomide 100 mg/m^2, po, d1–5
Maintenance therapy:	
Oral metronomic anti-angiogenic agents	At months 1, 3, 5, 7, 9, and 11: Cyclophosphamide 25–50 mg/m^2, po, d1–30 Vinorelbine 40 mg/m^2, po, qw × 3 Etoposide 25 mg/m^2, po, d1–21 Celecoxib 200 mg/m^2, po, bid d1–30 At months 2, 4, 6, 8, 10, and 12: Cyclophosphamide 25-50 mg/m^2, po, d1–30 Vinorelbine 40 mg/m^2, po, qw × 3 Topotecan [a] 1.4 mg/m^2, po, d1–5 Celecoxib 200 mg/m^2, po, bid d1–30

[a]: Since December 2017, topotecan has been discontinued due to no oral topotecan supply; NB: neuroblastoma; CAV: cyclophosphamide, pirarubicin, and vincristine; iv: intravenous injection; VIP: etoposide, ifosfamide, and cisplatin; po: oral administration; VIT: vincristine, irinotecan, and temozolomide.

In a study from China, 217 high-risk neuroblastoma patients received 8 cycles of induction with CAV(cyclophosphamide, pirarubicin, vincristine) and VIP (etoposide, ifosfamide, cisplatin) every 3 weeks alternately, surgery after four to six cycles of chemotherapy, and local radiotherapy, followed by low-dose metronomic maintenance therapy. These patients were reluctant or unable to undergo ASCT or receive anti GD2. All patients received local radiotherapy of 25-30 Gy after surgery. Then, patients who achieved complete remission, very good partial response, and partial response (CR/VGPR/PR) were placed on oral metronomic therapy with cyclophosphamide, vinorelbine, etoposide, and/or topotecan, and celecoxib) for 1 year. 185 patients (85%) had CR/VGPR/PR, and among 167 stage 4 patients who received metronomic therapy, the 3-year survival was 42%, and overall survival was 71% (68).

Table 3: Overview of metronomic therapies in neuroblastoma patients (43).

Patient population/disease setting	Phase of study	Regimen	Number of study patients	Number of neuroblastoma patients	Evidence of response in neuroblastoma patients	Reference
Neuroblastoma refractory or relapsed	Phase 1/2	Oral etoposide 50 mg/m² d1–21, 7days rest. Then repeat	20	20	Refractory: 1 /4 CR; 3 /4 SD Asymptomatic relapses: 2 /5 PR; 3 /5 SD Progression: 0 /11 responses	Kushner BH et al. 1999 J Clin Oncol 17:3221–5
Various recurrent pediatric tumors	Phase 1/2	Oral celecoxib 250 mg/m²xd, vinblastine 1 mg/m² 3x/wk i.v. or oral cyclophosphamide 30 mg/m²xd. Then repeat	33	3	Not reported	Stempak D et al. 2006 J Pediatr Hematol Oncol 28:720–8
Various recurrent pediatric tumors	Phase 1/2	Oral celecoxib 200 mg/m²xd d1–78, oral etoposide 25 mg/m²xd d1–21, oral temozolomide 60 mg/m²xd d36–77, isotretinoin 100 mg/m²xd d1–14, 29–42, 57–70. Then repeat	22	4	2 /4 VGPR, 1 /4 SD, 1 /4 PROG	Sterba J et al. 2006 Onkologie 29:308–13
Various recurrent pediatric tumors	Phase 1/2	Oral etoposide 25 mg/m²xd d1–14, oral cyclophosphamide 25 mg/m²xd d15–28, oral celecoxib 100–400 mg/d d1–28	17	1	1/1 PROG	André N et al. 2008 Clin Therapeutics 30: 1336–40
Various refractory pediatric tumors	Phase 1/2	Vincristine 1.5 mg/m² 1x/wk i.v. d1–22 cycle 1 and 2x/cycle following cycles, oral cyclophosphamide 25 mg/m²xd d1–21, oral methotrexate 15 mg/m² 2x/wk during d21–42	12	1	1/1 PROG	Fousseyni T et al. 2011 J Pediatr Hematol Oncol 33:31–4
Neuroblastoma refractory or relapsed	Phase 1/2	Zoledronic acid i.v. every 28 days in escalating doses, oral cyclophosphamide 25 mg/m²xd cont.	21	21	1 /21 PR, 9 /21 SD, 10 /21 PROG, 1 /21 not evaluable	Russell HV et al. 2011 Pediatr Blood Cancer 57:275–82
Various refractory pediatric tumors	Phase 1/2	Vinblastine 3 mg/m² 1x/wk wk 1–7, oral cyclophosphamide 30 mg/m²xd d1–21,oral methotrexate 10 mg/m² 2x/wk d21–42, oral celecoxib 100–400 mg/d d1–56	16	1	1/1 PROG	André N et al. 2011 Oncotarget 2:960–5
Various recurrent pediatric tumors	Phase 2	COMBAT I-III schedules combining variously oral temozolomide 30–60 mg/m²xd d36–77, oral etoposide 25 mg/m²xd d1–21 or d1–35, oral celecoxib 200–400 mg/m²xd d1–77 or 1–78, oral cholecalciferol 300kU/m²xd d1, oral vitamin D3 1,500 U/m²xd d1–78, oral fenofibrate 100 mg/m²xd d1–78, isotretinoin 100 mg/m²xd d1–14, 29–42, 57–70, bevacizumab i.v. 10 mg/kg every 14 days	74	11	1/11 VGPR for >12 months, 1/11 PR for 63 months,8/11 temporary responses or SD, 1/11 PROG	Zapletalova D et al. 2012 Oncology 82:249–60.
Various relapsed or refractory pediatric tumors	Phase 2	Vinorelbine 25–30 mg/m²xd i.v. d1,8,15, oral cyclophosphamide 25 mg/m²xd d1–28. Then repeat without rest.	117	16	1/16 PR,1 /16 SD, 13/16 PROG	Minard-Colin V et al. 2012 Eur J Cancer 48:2409–16
Various refractory pediatric tumors	Phase 2	Oral methotrexate 15 mg/m² 2x/wk weeks 5–7, oral cyclophosphamide 30 mg/m²xd d1–21, vincristine 1.5 mg/m² i.v. 1x/wk weeks 1,2,3,4,9,13, oral valproic acid 200 mg/kgxd cont. wk1–15	7	1	1/1 PR	Traore F et al. 2013 Indian J Cancer 50:250–3
Various relapsed or refractory pediatric tumors and leukemias	Phase 2	Oral thalidomide 3 mg/kg start and weekly increase by 50 mg as tolerated to 24 mg/kg (maximum 1,000 mg/d), oral celecoxib <20kg 2x100 mg/d, 20–50kg 2x200 mg/d, >50kg 2x400 mg/d, oral fenofibrate 90 mg/m²xd,oral etopside 35–50 mg/mxd d1–21 alternated with oral cyclophosphamide 2,5 mg/kgxd (maximum 100 mg) d1–21. Repeat up to 27 wk	97	3	2 /3 SD, 1 /3 PROG	Robison NJ et al. 2014 Pediatr Blood Cancer 61:636–42

Note. CR = complete remission; d = day; i.v. = intravenously; PR = partial remission; PROG = progressive disease; SD = stable disease; VGPR = very good partial remission; wk = week.

Metronomic

therapy with oral cytotoxic drugs (cyclophosphamide 50 mg/m²/day and etoposide 50 mg/m²/day for 21 days) alternating with daily valproic acid 15 mg/kg/day and celecoxib 250 mg/m², twice daily has been reported in six cases of neuroblastoma (69).

In a study published in 2017, 20 children with relapsed neuroblastoma and 3 with refractory disease

were treated with metronomic therapy consisting of cyclophosphamide, etoposide, vinblastine, and celecoxib for 2 years. The metronomic regimen included 4 cycles of celecoxib 200 mg/m² twice daily, cyclophosphamide 25 mg/m²/day, etoposide 25 mg/m²/day on days 1 to 21 alternating monthly with vinblastine 3 mg/m² every 14 days. The results in the metronomic group were similar to those in the group that received standard chemotherapy with low toxicity and outpatient treatment (43).

In Conclusion

The treatment of relapsed/refractory neuroblastoma remains one of the greatest challenges in pediatric oncology despite significant advances in the recent years. Drug resistance in relapsed patients, toxicity of new treatments, limited access to advanced therapeutic technologies, and high treatment costs are serious barriers to the implementation of the new methods. Therefore, there is a need for larger multicenter clinical trials to investigate the efficacy and safety of novel therapeutic methods, including immunotherapy, and targeted radiotherapy with 131I-MIBG and CAR-T cell therapy. Additionally, focusing on genomic and molecular studies to identify factors involved in drug resistance and the use of personalized medicine can be an important step toward increasing survival and reducing relapse rates in patients with refractory neuroblastoma.

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None

Author's Contribution

Samin Alavi data analysis, supervised the entire research process

Ali Aminasnafi, Alireza Jenabzade assisted in the study design

Conflict of interest

None

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