Hematopoietic stem cell transplantation for neuroblastoma

Carla Nolasco Monteiro Breviglieri[1*], Nathália da Silva Halley Neves[2], Mariana Bohns Michalowski[3,4], Augusto Oliveira Silva[5], Patrícia Shimoda Ikeuti[6], Ainá Henriques Melgaço[7], Simone de Castro Resende Franco[6], Cláudio Galvão de Castro Júnior[8,9], Adriana Seber[1,10]

1. Hospital Samaritano de São Paulo – São Paulo (SP), Brazil.
2. Hospital Israelita Albert Einstein – São Paulo (SP), Brazil.
3. Universidade Federal do Rio Grande do Sul – Porto Alegre (RS), Brazil.
4. Hospital de Clínicas de Porto Alegre – Porto Alegre (RS), Brazil.
5. Hospital Pequeno Príncipe – Curitiba (PR), Brazil.
6. Hospital da Criança de Brasília José Alencar – Brasília (DF), Brazil.
7. Complexo Hospitalar de Niterói – Niterói (RJ), Brazil.
8. Hemacore – São José dos Campos (SP), Brazil.
9. Certo – Guaratinguetá (SP), Brazil.
10. Grupo de Apoio ao Adolescente e à Criança com Câncer – São Paulo (SP), Brazil.

***Corresponding author:** canolasco@gmail.com

Section editor: Fernando Barroso Duarte

Received: Sept. 14, 2025 • **Accepted:** Nov. 14, 2025

ABSTRACT

High-risk neuroblastoma requires intensive multimodal therapy, and autologous hematopoietic stem cell transplantation (auto-HCT) remains a key component of consolidation treatment. This consensus document updates the 2021 Brazilian recommendations for neuroblastoma transplantation, focusing on indications, eligibility criteria, conditioning regimens, and the role of single versus tandem auto-HCT. Post-transplant consolidation strategies, including radiotherapy, isotretinoin, and anti-GD2 immunotherapy, as well as transplant-related toxicities and follow-up, are reviewed. The role of transplantation in relapsed or refractory disease is also addressed. These recommendations aim to support standardized, evidence-based management of children with high-risk neuroblastoma in the Brazilian setting.

Keywords: Neuroblastoma. Stem Cell Transplantation. High-risk Disease. Pediatric. Consensus.

INTRODUCTION

Neuroblastomas are a heterogeneous group of tumors with significant clinical and biological variability, influencing their prognosis, and treatment. They are the most common extracranial solid tumor in pediatrics, accounting for 8–10% of all childhood cancers and 15% of pediatric oncology-related mortality. Approximately half of the cases present as high-risk disease, requiring intensive multimodal therapy[1].

Standard treatment for high-risk neuroblastoma (HR-NB) includes induction chemotherapy, surgical resection, and consolidation with autologous hematopoietic stem cell transplantation (auto-HCT), followed by radiotherapy and maintenance therapy with isotretinoin and anti-GD2 immunotherapy and eflornithine (DFMO). Auto-HCT plays a crucial role in reducing relapse risk, a major challenge in NB management[2]. Immunotherapy has improved survival, but there is currently no sufficient scientific evidence to support its use instead of HCT.

Emerging approaches, such as anti-GD2 CAR-T cell therapy, have shown promising results for neuroblastoma but remain unavailable in Brazil[3]. Given the high relapse rate and associated mortality, strict adherence to current treatment protocols is essential. This document updates the recommendations published in the 2021 Brazilian Society of Cell Therapy and Bone Marrow Transplantation (SBTMO) neuroblastoma transplant consensus[4] and expands on them.

The following sections focus on the consolidation phase of treatment, including auto-HCT and maintenance strategies.

INDICATIONS FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Auto-HCT is a standard first-line consolidation therapy following induction chemotherapy and tumor resection for HR-NB, typically defined as age ≥ 18 months with metastatic disease or *MYCN* gene amplification.

The best outcomes are seen when transplantation is performed in remission[5,6]. Therefore, every effort should be made to deepen response prior to transplant, including the use of ALK inhibitors (*e.g.*, lorlatinib) in patients with *ALK* mutations and chemotherapy combined with anti-GD2 immunotherapy (chemoimmunotherapy) in those who fail to achieve a complete or very good partial response after induction[7].

Auto-HCT may also be considered in patients with relapses after treatment, following reinduction therapy[8].

Patients may undergo one or two consecutive HCT, depending on the recommendations of the protocol followed[8].

Table 1 summarizes the current transplant recommendations for HR-NB, and Table 2 the eligibility criteria for autologous transplant.

Table 1. Stem cell transplantation recommendations for neuroblastoma.

Neuroblastoma	Autologous	Allogenic
First line high-risk treatment	Yes	No
Responding relapse disease	Yes	Clinical option
Mobilization failure or bone marrow residual disease	-	Clinical option

Source: Elaborated by the authors.

Table 2. Eligibility criteria for autologous transplant.

Elegibility criteria
No progressive disease (tumor increased by > 25% or new lesions)
Minimum of 2×10^6 CD34+ cells/kg per hematopoietic stem cell transplantation, ideally > 3–5 $\times 10^6$ CD34+ cells/kg*
No uncontrolled infection
Chemoimmunotherapy is the preferred treatment for persistent bone marrow involvement. If complete remission is not feasible, but other sites of disease remain stable, allogeneic transplantation may be considered, also including mobilization failure.

*Additional cells (2×10^6 CD34+ cell/kg) may be frozen for potential future needs (*e.g.*, metaiodobenzylguanidine therapy). Source: Elaborated by the authors.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION MODALITIES AND RECOMMENDATIONS

Currently, there are two strategies to HCT: single or tandem HCT. The Children's Oncology Group (COG) demonstrated that tandem HCT using thiotepa/cyclophosphamide followed by a second HCT with carboplatin/etoposide/melphalan (CEM) 6–10 weeks later resulted in improved event-free survival (EFS) compared to single auto-HCT with CEM, when used after the COG induction regimen[9].

However, for single auto-HCT, the International Society of Paediatric Oncology Europe Neuroblastoma Group

(SIOPEN) conducted a randomized study comparing busulfan/melphalan (BuMel) *versus* CEM after induction with rapid COJEC. The study showed improved EFS with BuMel compared to CEM[5]. It is not yet know whether one BuMel is equal or inferior to tandem.

The COG launched a multi-arm study (COG ANBL1531) in which all groups received tandem HCT, except for one arm, which received single auto-HCT with BuMel[10]. This single-arm cohort was discontinued due to toxicity.

Meanwhile, SIOPEN has conducted VERITAS trial, that evaluates thiotepa HCT *versus* metaiodobenzylguanidine (MIBG) therapeutic before one BuMel HCT in patients with inadequate response to induction[11].

These ongoing studies aim to refine consolidation strategies and optimize long-term survival outcomes for HR-NB patients.

While COG studies have demonstrated the superiority of tandem transplantation and SIOPEN is actively evaluating tandem-based strategies, it remains essential to follow the consolidation approach established by the patient's treatment protocol[9,12].

In Brazil, the Neuroblastoma Group continues to recommend single auto-HCT with BuMel. With the national commercialization of thiotepa, tandem transplants have become a feasible option and may be adopted following institutional discussion.

The suggested conditioning regimens are presented in Table 3.

Table 3. Suggested conditioning regimen***.

	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Observations
Single BuMel	Busulfan dose per kg* in 3 hours	Busulfan dose per kg or target AUC* in 3 hours	Busulfan dose per kg or target AUC* in 3 hours	Busulfan dose per kg or target AUC* in 3 hours	24-h interval	Melphalan 140 mg/m² in 30 min	24-h interval	PBSC Infusion (at least 2 × 10^6 CD34+ cells/kg)	Mel must be infused in 15–30 min, within 1 hour of preparation
Thiotepa-Cyclophosphamide (TT-Cy) #1 (Tandem)	Thiotepa 300 mg/m² in 2 h	Thiotepa 300 mg/m² in 2 h	Thiotepa 300 mg/m² in 2 h + Cy 1,500 mg/m² in 1 h	Cy 1,500 mg/m² in 1 h	Cy 1,500 mg/m² in 1 h	Cy 1,500 mg/m² in 1 h	24-h interval	PBSC Infusion (at least 2 × 10^6 CD34+ cells/kg)	**
Carboplatin + etoposide + melphalan (CEM) #2 (Tandem)	Mel 60 mg/m² + Eto (300 mg/m²) parallel to Carbo (375 mg/m²) over 24 h	Mel 60 mg/m² + Eto (300 mg/m²) parallel to Carbo (375 mg/m²) over 24 h	Mel 60 mg/m² + Eto (300 mg/m²) parallel to Carbo (375 mg/m²) over 24 h	Eto (300 mg/m²) parallel to Carbo (375 mg/m²) over 24 h	72-h interval			PBSC Infusion (at least 2 × 10^6 CD34+ cells/kg)	Mel must be infused in 15–30 min, within 1 hour of preparation

*Dose per kg for every-24-hour busulfan administration: < 9 kg = 4 mg/kg, 9 ≤ 16 kg = 4.8 mg/kg; 16 ≤ 23 kg = 4.4 mg/kg; 23–34 kg = 3.8 mg/kg; > 34 kg = 3.2 mg/kg. Whenever available target AUC of 4,500 µMol•min/L; **TT: Bathe patients three or four times/day. Avoid large occlusive dressing and skin creams and remove adhesive residue. Cy: hydrating at 2,500–3,000 mL/m². Mesna 300 mg/m²/dose prior to each Cy dose and then 4 and 8 h after; ***Single CEM regimen consists of Melphalan 70 mg/m² for three days (30-minute infusion), etoposide 338 mg/m² for four days (continuous infusion), and carboplatin 425 mg/m² for four days (continuous infusion); PBSC: peripheral blood stem cells. Source: adapted from Ladenstein et al.[5] and Park et al.[9].

TRANSPLANT-RELATED COMPLICATIONS

Thrombotic microangiopathy (TMA) and veno-occlusive disease (VOD) are important toxicities after auto-HCT for HR-NB, including both single and tandem transplants. Recent multicenter data show that TMA occurred in up to 23% of patients when actively screened, and VOD in up to 19%, especially after the second HCT[13,14]. Standardized definitions have been proposed for both toxicities[15,16]. Given their impact on early outcomes, consistent surveillance is essential in all HCT settings.

POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION CONSOLIDATION STRATEGIES

Radiotherapy aims to improve local control. While most relapses occur in metastatic sites, local control may enhance overall survival (OS).

Primary tumor bed irradiation:

- Recommended post-HCT, especially for incompletely resected tumors;
- Timing: no sooner than D+28 and no later than D+60, before immunotherapy;
- Dose: 21 Gy to the primary site.

Metastatic sites of irradiation:

- Persistent metastasis after induction should be irradiated, but irradiating more than 50% of the bone marrow is not recommended due to hematological toxicity;
- For diffuse bone metastases, the sites of irradiation may be guided by disease reassessment after HCT[8]I
- The role of radiotherapy in other metastatic sites remains unclear, and it is not routinely recommended in first-line treatment[17].

Isotretinoin (Roaccutan) is a standard maintenance therapy after auto-HCT, improving EFS when used for six months[18].

Start after radiotherapy, preferably between anti-GD2 cycles.

Dosage: 160 mg/m^2/day, divided into two daily doses for 14 days every 28 days repeated for six months.

Toxicity: side effects include mucocutaneous dryness, hyperlipidemia, and hepatic dysfunction, requiring monitoring.

Anti-GD2 maintenance therapy post-HCT improves overall (73.2 *versus* 56.6%) and EFS (56.6 *versus* 46.1%) compared to isotretinoin alone[6]. In Brazil, the use of betadinutuximabe has been approved by the Brazilian Health Regulatory Agency and was incorporated into the public health system by the National Committee for Health Technology Incorporation as maintenance post-HCT, but it does not have financial mechanism yet as of March 2025.

Start on D+60–90 days after HCT.

Dosage:

- Betadinutuximabe: 10 mg/m^2/day, continuous infusion for 10 days or 20 mg/m^2/day in 8-hour infusion for five days, every 35 days, for five cycles.

Toxicity and management:

- Neuropathic pain is common, decreasing with subsequent cycles. Gabapentin (starting three days before infusion) plus opioids and analgesics is effective for pain control;
- Severe reactions (allergic responses, systemic inflammatory response syndrome) require clinical management;
- The first cycle under intensive care unit supervision is recommended, with subsequent cycles in a standard ward if clinically stable.

Following anti-GD2 therapy, DFMO maintenance for two years improved four-year EFS from 72 to 84%[19]. Its implementation in Brazil is not available yet.

RELAPSE AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Patients who relapse after auto-HCT if respond well to salvage therapy, particularly chemoimmunotherapy, may still be eligible for a second consolidation with autologous or allogeneic HCT[20]. Maintenance immunotherapy may also be considered.

ALLOGENEIC TRANSPLANT IN NEUROBLASTOMA

Allogeneic hematopoietic stem cell transplantation (allo-HCT) may be an option if mobilization fails or in relapsed/refractory cases[21–23].

Conditioning regimens (*e.g.*, Flu-Thio-Mel or Bu-Flu-Mel), graft-*versus*-host disease prophylaxis (*e.g.*, calcineurin inhibitors with PTCy or CSA + MTX), and post-transplant immune modulation (*e.g.*, donor lymphocyte infusions) can be used[21,24]. KIR reactive donors may offer increased graft *versus* tumor effect[25].

Combining haploidentical HCT with anti-GD2 therapy has shown encouraging results[21,24]. Post-transplant immunotherapy, including anti-GD2 agents, CAR-T cells, and NK cell infusion, offers promise, especially in relapsed cases, though access and side effects remain obstacles[26]. Ongoing research aims to refine these strategies and define their role in treatment.

FOLLOW-UP SCHEDULE

Follow-up should ideally include physical examination and catecholamine measurements (VMA and HVA) every three months during the first year, every six months until year 5, and annually thereafter. Cross-sectional and functional imaging is recommended at three, six, 12, 18, 24, and 36 months after the end of therapy, and later as clinically indicated[27].

Long-term follow-up of at least five years is advised. Special attention should be given to the risk of thyroid dysfunction in patients who received MIBG therapy[28].

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data are presented in the article.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Breviglieri CNM, Neves NSH, Michalowski MB, Silva AO, Ikeuti PS, Melgaço AH, Franco SCR, Castro Júnior CG and Seber A. **Conception and design:** Breviglieri CNM, Neves NSH, Michalowski MB, Silva AO, Ikeuti PS, Melgaço AH, Franco SCR, Castro Júnior CG and Seber A. **Analysis and interpretation of data:** Breviglieri CNM, Neves NSH, Michalowski MB, Silva AO, Ikeuti PS, Melgaço AH, Franco SCR, Castro Júnior CG and Seber A. **Technical procedures:** Breviglieri CNM, Neves NSH, Michalowski MB, Silva AO, Ikeuti PS, Melgaço AH, Franco SCR, Castro Júnior CG and Seber A. **Statistics analysis:** Breviglieri CNM, Neves NSH, Michalowski MB, Silva AO, Ikeuti PS, Melgaço AH, Franco SCR, Castro Júnior CG and Seber A. **Manuscript writing:** Breviglieri CNM, Neves NSH, Michalowski MB, Silva AO, Ikeuti PS, Melgaço AH, Franco SCR, Castro Júnior CG and Seber A. **Final approval:** Breviglieri CNM.

FUNDING

Not applicable.

ACKNOWLEDGEMENTS

Not applicable.

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