Central nervous system tumors

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ABSTRACT

Central nervous system (CNS) tumors represent one of the most prevalent groups of neoplasms in the pediatric population. Recent advances in molecular biology and neuro-oncology have led to continuous updates in the classification of these tumors, which poses significant diagnostic challenges, particularly in low- and middle-income countries, with limited access to advanced diagnostic tools. The therapeutic approach varies according to tumor subtype, often requiring complex and resource-intensive protocols. One such strategy involves the use of high-dose chemotherapy followed by autologous stem cell rescue, which has shown promise in improving outcomes for select pediatric patients with CNS tumors. However, implementation of this therapy in countries like Brazil faces logistical, financial, and clinical practice challenges. This article aimed to provide a brief overview and suggestions to use high-dose chemotherapy with autologous stem cell transplantation in the treatment of pediatric CNS tumors. We discussed practical considerations for patient selection, and conditioning regimens. Our objectives were to optimize and guide current practices by proposing strategies that maybe feasible in the Brazilian public and private healthcare systems.

Keywords: Central Nervous System Tumors. Pediatrics. Children. High Dose Chemotherapy. Autologus Stem Cell Transplant.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

The 2021 fifth edition of the World Health Organization (WHO) classification for pediatric central nervous system (CNS) tumors introduced significant changes by integrating histological, molecular, anatomical, and clinical data[1–3].

Pediatric gliomas were separated from adult types and subdivided into categories such as low-grade, high-grade, and circumscribed astrocytic gliomas[2,4]. New entities were recognized, and nomenclature was updated to reflect molecular alterations[1,5]. Ependymomas are now classified by anatomical site and molecular profile, with key markers including ZFTA and *YAP1* fusions for supratentorial tumors, PFA/PFB subtypes for posterior

fossa, and *MYCN* amplification for spinal tumors[4,6,7]. Embryonal tumors, notably medulloblastomas, are now grouped into four molecular subtypes with prognostic implications[8,9]. The embryonal tumor with multilayered rosettes (ETMR—with C19MC amplification) and the atypical teratoid/rhabdoid tumors (linked to SMARCB1 loss) are aggressive tumors affecting younger children[8,10].

CNS germ cell tumors are split into germinomas and non-germinomatous germ cell tumors (NGGCTs), based on histological and molecular characteristics[11–13]. Germinomas have excellent outcomes with radiotherapy (RT) and exhibit features like KIT gene activation and isochromosome 12p[13]. NGGCTs, including teratomas and yolk sac tumors, require aggressive treatment and may benefit from immunotherapy due to PD-L1/PD-1 expression[11–13]. Choroid plexus carcinoma, a grade III tumor, remains challenging due to its aggressiveness and recurrence rate. Total surgical resection improves outcomes, with adjuvant RDT and chemotherapy often required[14]. The 2021 WHO classification reinforces the role of molecular diagnostics in guiding therapy and research inclusion[6,14,15].

In Brazil, the SOBOPE CNS Tumors Group and the Molecular Biology and Pathology Department of Santa Marcelina Hospital, supported by Tucca, provide nationwide support for review pathology and molecular diagnosis and therapeutic planning, promoting equity in pediatric neuro-oncology.

Other national institutions, including the Ribeirão Preto Medical School of the Universidade of São Paulo and the Barretos Cancer Hospital, have developed simplified, low-cost laboratory tools aimed at the accurate diagnosis and molecular classification of medulloblastoma subgroups. These tests are offered within clinical research settings and are also extended to support patient care in these institutions through Brazil's public healthcare system (SUS)[16,17].

GLIOMAS

The use of high dose chemotherapy (HDC) autologous stem cell transplant (ASCT) for malignant astrocytomas and gliomas or even diffuse pontine gliomas has not demonstrated a survival advantage or disease control over conventional therapy and has been linked to higher treatment-related toxicity. Additionally, etoposide and thiotepa followed by ASCT in pediatric high-grade gliomas have shown no significant benefits in the disease control[18–22].

EPENDYMOMA

Ependymoma is the third most common pediatric brain tumor, typically arising in the infratentorial region (60–70%), in which complete resection is challenging, and metastatic risk is higher. Supratentorial tumors, if fully resected, often have better outcomes and may not need further treatment. The standard remains surgery followed by RDT, which offers the best survival rates[23,24]. Attempts to replace or delay RDT with chemotherapy—especially in younger children—have shown limited success. High dose chemotherapy (HDC) with ASCT has not achieved sustained remission without radiation[25].

MEDULLOBLASTOMA

Treatment for medulloblastoma typically involves a multimodal approach, including surgery, radiation therapy, and chemotherapy. Molecular and histological classification is necessary to establish the risk groups, plus the traditional with high-risk features, such as metastatic disease (M1-M3), residual tumor post-resection (> 1.5 cm^2)[24].

Children younger than 3 or in some studies younger than 5 years old should be carefully evaluated, and if they have high-risk features, they should benefit using high-dose chemotherapy. Using this approach, they can avoid or delay radiotherapy[26,27]. The Head Start Protocols studied this patient population and provided all the base of autologous transplantation in patients with CNS tumors[27]. Table 1 summarizes the indications for autologous transplantations for patients younger than 5 years old.

Table 1. Transplant indications for patients younger than 5 years old with medulloblastoma.

Category	Details
Indications	- Metastatic disease (M1–M3): All molecular subtypes with metastatic dissemination at diagnosis are candidates for high-dose chemotherapy. - Large residual tumor (> 1.5 cm^2): Any molecular subtype with significant residual disease post-surgery should be considered for HDC with autologous stem cell transplant (ASCT) if chemosensitive.
Molecular subtype-specific indications	- Sonic Hedgehog (SHH) subtype: SHH patients with high-risk features (metastatic, residual tumor) are strong candidates for ASCT. - Group 3 and Group 4: More likely to present with metastatic disease and higher risk of relapse. High-risk Group 3/4 patients (< 5 years old) are considered for ASCT, though outcomes are less favorable than SHH. - WNT Subtype: Rare in children under 5; typically favorable prognosis with standard therapy. ASCT generally not indicated unless high-risk features are present (uncommon).
Contraindications / no indication	- Chemoresistant disease - Bulky or rapidly progressive disease - Average risk, localized, favorable subtype (*e.g.*, WNT): Children with average-risk, non-metastatic, completely resected WNT or SHH (desmoplastic/nodular) medulloblastoma with favorable molecular profile do not require ASCT.

Source: Elaborated by the authors.

Patients with late recurrence (more than two years after the end of the previous treatment) are the focus of debate and may also benefit from autologous transplantation, although not indicated in chemoresistance or bulky disease. Such unusual cases should be evaluated carefully and in an individual approach to assess the real benefit of high-dose chemotherapy[28].

A more recent paper showed the role of autologous transplantation in older patients with high-risk features. All children received postoperative induction chemotherapy (etoposide and carboplatin), followed by two high-dose thiotepa courses (600 mg/m^2) with hematological stem cell support. At the latest 45 days after the last stem cell rescue, patients received risk-adapted craniospinal radiation therapy. Maintenance treatment with temozolomide was planned to start between one and three months after the end of radiotherapy. The five-year progression free survival (PFS) was 76% (63–86), and the 5-year overall survival (OS) was 76%[29].

SUGGESTED REGIMENS AND DOSES

Thiotepa is a medication approved in 1959. It easily penetrates cerebrospinal fluid (CSF), and it has been used as part of the conditioning regimens in CNS tumors since the very first publications[27].

This medication was registered in Brazil to treat solid tumors, but since the end of the 1990 decade it was unavailable and for a long time it had to be imported. Recently, he was again registered in the Brazilian Health Regulatory Agency (ANVISA)[29] named Dipate, so it will be easier to use it.

The most common preferred and classic regimen is thiotepa + carboplatin + etoposide.

For high-risk patients in the first treatment, the publication mentioned the use of three doses of thiotepa 200 mg/m^2 from day -4 to day -2[29].

The regimen is summarized in Table 1.

EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES

There is no standard treatment for ETMR, and multiple protocols are used. These typically involve platinum and etoposide-based chemotherapy, sometimes with cyclophosphamide, vincristine, and high-dose methotrexate[32,33]. Atypical teratoid/rhabdoid tumors protocols show activity, with promising results[34]. Gross total resection (GTR), high-dose chemotherapy, and RDT were linked to better survival[34]. Better OS

in carboplatin/etoposide and high-dose chemotherapy, compared to other regimens. Complete resection, absence of metastases, and supratentorial tumors were favorable factors[35]. Intrathecal chemotherapy using methotrexate, cytarabine, etoposide, or topotecan may help control leptomeningeal spread[36]. RDT improves outcomes, but it must be used cautiously in young children due to neurocognitive risks[32,37].

HDC and ASCT are indicated in patients with GTR, responsive to chemotherapy protocols in complete remission or partial remission. P-HIT trial proposed a conditioning regimen: carboplatin/etoposide (carboplatin 500 mg/m^2/24 hours, etoposide 250 mg/m^2/24 hours, each over 96 hours from day 8 to day 5) and one course of cyclophosphamide/thiotepa (cyclophosphamide 1,500 mg/m^2/1 hour infusion, thiotepa 300 mg/m^2/1 hour infusion, each day 4 to day 2). Intraventricular methotrexate (2 mg/d, on four consecutive days in parallel to the intravenous chemotherapy) for patients without signs for impaired CSF circulation may be value[35].

ATYPICAL TERATOID/RHABDOID TUMORS

Despite survival has improvement with the use of multi-modality therapies, outcomes remain suboptimal, with OS around 50%. Worse outcomes are linked to younger age (infants under 6 months old) and metastasis or synchronous tumors[38–42]. Prompt tumor resection is critical, and future directions include molecular subgroups and novel approaches[39,40].

Based in Children's Oncology Group Trial ACNS0333 results publication in the European Rhabdoid Registry 2021, HDC and ASCT are indicated in tumor responsive to chemotherapy protocol in complete remission or partial remission: TANDEM strategy with three sequential transplants, 21 days interval each. Conditioning regimen is: carboplatin 500 mg/m^2/24 hours, from day -6 to day -4; thiotepa 300 mg/m^2/1 (> 36 mo) or 10 mg/kg (< 36 mo) 1-hour infusion, each day -6 to day -4[41].

For craniospinal irradiation, according to the European Rhabdoid Registry 2021, children below the age of 18 months should only be irradiated under particular circumstances. In case of primary metastasized disease, radiotherapy may be delayed until the end of intensive chemotherapy. Age ≥ 18 months irradiated as soon as possible.

PINEALOBLASTOMA

Pinealoblastoma is an aggressive embryonal tumor of the CNS. Standard therapy for older children and adolescents includes safe surgical resection, craniospinal irradiation (CSI), and chemotherapy. In infants and younger children, the disease is more aggressive, with poorer outcomes, especially without RDT. Conventional chemotherapy by itself has shown limited efficacy in these children, with most survivors eventually requiring RDT. For older than 4 years old, the use of HDC has not significantly impacted the survival[42–46]. A subset of younger patients (less than 4 years old) with localized disease benefited from local RDT combined with HDC, reducing neurotoxicity compared to CSI[43–45]. For children under 6, treatment options include HDC with ASCT in two or three tandem cycles using thiotepa every 21–28 days, followed by delayed post-transplant CSI or focal irradiation, reducing neurotoxicity and endocrinologic complications[43].

For patients who have previously received radiation therapy, HDC with ASCT support like other embryonal CNS tumors (like medulloblastoma) is a feasible option[47,48.]

GERM CELL TUMORS

As first-line treatment, HDC with ASCT is not indicated. For recurrent germinomas, standard-dose chemotherapy and re-irradiation is preferred. HDC with ASCT is considered if re-irradiation is not feasible[49–51]. For recurrent non-germinomatous gene activation, poor prognosis, especially with alpha-fetoprotein (AFP)

secretion. Recommended approach is HDC, surgery, and RT if feasible[49,50]. Conditioning regimens for HSCT are thiotepa-based with or without platinum derivatives:

- Thiotepa 300 mg/m^2 (days 1–3) + etoposide 250 mg/m^2 (days 1–3), repeated after four weeks;
- Thiotepa 200 mg/m^2 (three days), repeated after four weeks;
- Carboplatin (AUC 7, days 1–3) + thiotepa 300 mg/m^2 (days 4–6) + etoposide 250 mg/m^2 (days 4–6);
- Carboplatin (AUC 7, days 1–3) + thiotepa 300 mg/m^2 (days 4–6) + temozolomide 150–250 mg/m^2 [52,53].

There is no data available to determine the best conditioning regimen. Carbo + thiotepa + etoposide or thiotepa + etoposide are feasible options.

CHOROID PLEXUS CARCINOMA

Genetic mutations play a crucial role in choroid plexus carcinoma (CPC) tumorigenesis, with *TP53* alterations being the most significant. *TP53* mutations are present in up to 50% of CPC cases[54–58].

Treatment of CPC is centralized on achieving GTR, as complete surgical removal is strongly associated with better outcomes. Postoperative chemotherapy is the mainstay of treatment in infants and young children, aiming to delay or avoid RDT due to its long-term neurocognitive and endocrine complications. While radiotherapy can improve survival, its role remains controversial, especially in young patients. In cases of *TP53*-mutated CPC, conventional therapies have limited effectiveness, making HDC with ASCT an alternative. One course carboplatin / TT / etoposide—head start treatment overcomes chemoresistance and demonstrated prolonged survival, particularly in patients with radically resected tumors or relapsed tumors, reinforcing the need for multimodal treatment strategies that integrate surgery, chemotherapy, and, in select cases, RDT to optimize outcomes[53,55,56].

Table 2 lists the conditioning regimens, and Table 3 summarizes the indications.

Table 2. Conditioning regimen.

Carboplatin etoposide and thiotepa[24]				
Days	**Drug**	**Route**	**Dose**	
			Patients < 12 kg	**Patients≥ 12kg**
D-9 to D-7 (three days)	Carboplatin	IV in four hours (once a day)	AUC = 7/day or maximum 16.7 mg/kg (whichever is lower)	AUC = 7/day or maximum 500 mg/m^2 (whichever is lower)
D-6 to D-4 (three days)	Thiotepa	IV in three hours (once a day)	10 mg/kg/day	300 mg/m^2/day
	Etoposide	IV in three hours immediately after TT (once a day)	8.3 mg/kg/day	250 mg/m^2/day
D-3 to D-1	Rest			
D0	PBSC infusion (48–72 h after the last dose of etoposide)			
Tandem with thiotepa[26]				
D-5 to D-3 (three days)	Thiotepa	IV in three hours (once a day)	6.6 mg/kg/day	200 mg/m^2/day
D-2 to D-1	Rest			
D 0	Peripheric blood stem cell infusion (48 after the last dose of thiotepa)			

Source: Elaborated by the authors.

Table 3. Indications for transplantation in central nervous system tumors.

	Autologous	Allogeneic	Comments
Pineoblastoma	CI	NR	
Atypical teratoid/rhabdoid tumors and embryonal tumors with multilayered rosettes	CI	NR	
Medulloblastoma high risk	CI	NR	Please read the text
Medulloblastoma younger than 5 years old	CI	NR	Please read the text
Medulloblastoma relapse	CI	NR	Special cases
Central nervous system germ cell tumor	CI	NR	
Glioblastoma multiforme	NR	NR	
Ependymoma	NR	NR	
High grade gliomas	NR	NR	
Brainstem gliomas	NR	NR	
Choroid plexus carcinoma	CI	NR	

Source: Elaborated by the authors. CI: clinically indicated; NR: generally not recommended.

CONCLUSION

High-dose chemotherapy followed by autologous stem cell transplantation represents a valuable therapeutic option for a specific subset of pediatric patients with central nervous system tumors, particularly those under five years of age with high-risk or recurrent embryonal tumors such as medulloblastoma, atypical teratoid/rhabdoid tumor, embryonal tumor with multilayered rosettes, and choroid plexus carcinoma. Despite advances in molecular classification and treatment stratification, survival rates for many high-grade or relapsed cases remain suboptimal, emphasizing the need for individualized treatment approaches and multidisciplinary coordination.

The implementation of transplant-based regimens requires careful patient selection, standardized conditioning protocols, and integration with molecular diagnostics to optimize outcomes while minimizing long-term toxicity. Thiotepa-based regimens have demonstrated consistent feasibility and efficacy across several studies and remain a cornerstone for conditioning in pediatric neuro-oncology settings.

In low- and middle-income countries, such as Brazil, expanding access to molecular diagnostics, harmonizing transplant protocols, and strengthening collaborative national networks are crucial steps to enhance equity in care and ensure that advanced therapeutic strategies like autologous transplantation can be safely and effectively incorporated into clinical practice. Ongoing multicenter cooperation and translational research will be fundamental to refining these therapeutic modalities and improving survival and quality of life in children with CNS tumors.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Zamperlini G, Klinger PHS, Zanette A, Kuwahara C, Epelman S, Seber A and Castro Junior CG. **Conception and design:** Zamperlini G, Klinger PHS, Zanette A, Kuwahara C, Epelman S, Seber A and Castro Junior CG. **Manuscript writing:** Zamperlini G, Klinger PHS, Zanette A, Kuwahara C, Epelman S, Seber A and Castro Junior CG. **Final approval:** Zamperlini G.

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