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Review

A Review of Newer Pathophysiological Insights into Pediatric Brain Tumors: Revisiting Maintenance and Metronomic Chemotherapy in Resource-Limited Settings

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Abstract

Pediatric brain tumors remain a leading cause of morbidity and mortality worldwide, with management in developing countries particularly constrained by limited healthcare resources. This review highlights emerging concepts in tumor biology, particularly the roles of the tumor microenvironment (TME) and cancer stem cells (CSCs), which are increasingly recognized as critical drivers of tumor progression and therapy resistance. We summarize current evidence linking these biological mechanisms with therapeutic strategies, emphasizing practical and cost-effective approaches such as metronomic chemotherapy, maintenance chemotherapy, and intrathecal therapy delivered into the cerebrospinal fluid (CSF). While molecular targeted therapies and immunotherapies offer promise; their high costs limit accessibility in low-resource settings. Nevertheless, carefully tailored use may provide long-term benefits. By integrating pathophysiological insights with pragmatic treatment strategies, this review provides a biologically grounded and clinically applicable framework for oncologists practicing in low-resource environments.

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1. INTRODUCTION

Primary brain tumors represent the most common solid malignancies in children,
accounting for a significant proportion of pediatric solid malignancies.
Up to 80% of new cases occur in middle-income countries, where patients face major barriers to care due to limited infrastructure and restricted access to advanced therapeutics [1-3]. Financial constraints often exacerbate delays in diagnosis and treatment, underscoring the urgent need for alternative, practical, and resource-adapted treatment strategies. Integrating insights from tumor biology with feasible therapeutic approaches may offer cost-effective and clinically relevant management options in such settings.

2. SEARCH STRATEGY

A literature search was performed to identify relevant studies on pediatric brain tumors, tumor microenvironment (TME), cancer stem cells (CSCs), maintenance chemotherapy, metronomic chemotherapy, and cerebrospinal fluid (CSF)-directed therapies. Electronic databases including PubMed, Scopus, and Google Scholar were searched for articles published between January 2000 and March 2026. Search terms included combinations of "pediatric brain tumors," "medulloblastoma," "ependymoma," "glioma," "metronomic chemotherapy," "maintenance chemotherapy," "tumor microenvironment," "cancer stem cells," "intrathecal therapy," "intraventricular therapy," and "resource-limited settings." Priority was given to systematic reviews, clinical trials, landmark studies, and recent publications with direct relevance to pediatric neuro-oncology. Articles focusing exclusively on adult tumors or lacking clinical or biological relevance to the scope of this review were excluded. Additional references were identified through manual screening of cited literature. Although the primary search focused on publications from 2000 onward, selected seminal studies published before 2000 were also included when they provided important historical context or established foundational concepts relevant to maintenance therapy, CNS-directed treatment, and pediatric neuro-oncology.

3. LITERATURE REVIEW

The evolution of pediatric neuro-oncology has transitioned from aggressive, localized treatment toward a more comprehensive, biology-driven approach. Historically, the management of pediatric brain tumors borrowed heavily from the success of "Total Therapy" in childhood leukemia. The concept of maintenance therapy, pioneered by Donald Pinkel in the 1960s, established that long-term, low-intensity treatment is essential to eradicate minimal residual disease (MRD) that survives initial induction [4, 5]. While this paradigm revolutionized hematological malignancies, its systematic application in solid Central Nervous System (CNS) tumors remained limited for decades due to the unique pharmacological challenges of the blood-brain barrier (BBB).
The "pharmacological sanctuary" of the central nervous system led to the development of CSF-directed therapies. A landmark in this field was the invention of the Ommaya reservoir (1963), which shifted the focus from reactive treatment of symptomatic leptomeningeal disease to proactive CNS prophylaxis. Early studies in the 1970s and 1980s confirmed that without direct CSF intervention, a significant percentage of patients with embryonal tumors would suffer CNS relapse despite systemic remission [5, 6].
In the last two decades, the focus of the literature has shifted toward the Tumor Microenvironment (TME) and Cancer Stem Cells (CSCs) as the primary drivers of therapy resistance [7, 8]. Recent evidence suggests that conventional high-dose chemotherapy often fails to penetrate the protective niches of CSCs, leading to the late relapses commonly seen in medulloblastoma and Atypical Teratoid/Rhabdoid Tumor (AT/RT). This biological insight has revitalized interest in metronomic chemotherapy—a term coined in the early 2000s to describe frequent, low-dose drug administration [9]. Unlike maximum tolerated dose (MTD) regimens, the metronomic approach focuses on anti-angiogenesis and immune modulation [10, 11]
Despite these advancements, a significant gap exists in the literature regarding the implementation of these biological strategies in low-resource settings. While high-income countries have moved toward expensive molecular-targeted therapies, the feasibility of maintenance and metronomic protocols as "essential oncology" in developing nations remains under-explored. Current research often overlooks the pragmatic necessity of these low-cost interventions, which this review aims to synthesize by linking the historical foundations of maintenance therapy with modern TME-targeted strategies.

4. TUMOR BIOLOGY AND RESISTANCE MECHANISMS

Pediatric embryonal brain tumors arise from primitive neural progenitor cells and predominantly affect infants and young children [12]. These highly invasive neoplasms present with overlapping histopathological features,

complicating accurate diagnosis and therapeutic planning [13]. Major subtypes include medulloblastoma (MB), atypical teratoid/rhabdoid tumor (AT/RT), neuroblastoma (NB), ganglioneuroblastoma (GNB), embryonal tumor with multilayered rosettes (ETMR), and embryonal tumor, not otherwise specified (NOS) [14].

5. CANCER STEM CELLS (CSCS)

A key driver of treatment resistance and recurrence is the subpopulation of cancer stem cells (CSCs). These cells possess self-renewal and tumor-propagating capabilities, and exhibit resistance to conventional chemotherapy and radiotherapy [15, 16]. Pediatric brain tumor CSCs typically arise from neural progenitors or dedifferentiated tumor cells and are protected within specialized niches in the tumor microenvironment. Current evidence suggests that no single therapeutic strategy, including maintenance or metronomic chemotherapy, can completely eradicate CSCs. However, these strategies may contribute to CSC modulation and microenvironmental control when used as part of multimodal regimens.

6. TUMOR MICROENVIRONMENT (TME)

The tumor microenvironment (TME) consists of stromal cells, immune populations, soluble factors, and extracellular matrix components that collectively support tumor growth and survival [17, 18].

Interactions within the TME not only promote local invasion but also protect CSCs and suppress effective antitumor immunity. In pediatric patients, developmental immune tolerance may further influence responses and treatment-related toxicities. These insights highlight the need for therapeutic strategies that target both tumor cells and their supportive microenvironment **(Fig .1)**.

7. LINKING BIOLOGY TO THERAPY

Understanding the biology of CSCs and the TME provides a rationale for prolonged, low-intensity interventions such as maintenance chemotherapy and CSF-directed therapies. These approaches may help control minimal residual disease, delay relapse, and offer feasible treatment options in resource-limited settings, particularly when advanced targeted therapies are inaccessible.

7.1. Maintenance Chemotherapy

Maintenance therapy involves the prolonged administration of low-dose chemotherapy following an initial intensive treatment phase. The main goal is to suppress residual disease, reduce relapse risk, and target cancer stem cells (CSCs) while minimizing toxicity [19].

Key principles include:

- Drug selection: Preference for agents with long-term safety, oral bioavailability, high compliance, and low resistance risk.
- Immunomodulation: Low-dose regimens can restore immune balance, particularly enhancing NK and B cell activity [20].
- Applicability: Maintenance therapy is especially useful in embryonal tumors such as medulloblastoma, but has limited benefit in adult-type solid tumors [21].

Clinical evidence supports low-dose vinorelbine plus cyclophosphamide regimens in high-risk rhabdomyosarcoma (RMS) and brain tumors, particularly in situations where high-dose chemotherapy with stem cell rescue is not feasible [22, 23]. Treatment duration usually ranges from 6 to 24 months, depending on tumor biology and patient tolerance [24].

For slow-growing glial neoplasms, targeted therapies or surgical approaches remain preferred. However, in resource-limited contexts where such strategies are inaccessible or unaffordable, metronomic chemotherapy may provide a viable alternative.

7.2. Metronomic Chemotherapy

Metronomic therapy refers to the frequent, continuous administration of low-dose chemotherapy without extended breaks. Unlike conventional regimens, its primary targets are the tumor microenvironment and tumor-associated angiogenesis rather than rapidly dividing tumor cells [25, 26] **(Fig. 2)**.

7.2.1. Mechanisms of Action

1. **Anti-angiogenic activity:** Continuous low-dose therapy inhibits new blood vessel formation, restricting tumor growth.
2. **Immunomodulation:** Metronomic schedules reduce regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), enhancing cytotoxic $CD8^+$ T-cells and NK-cell activity [27, 28].
3. **Targeting cancer stem cells (CSCs):** Preclinical studies show reduced CSC populations, leading to decreased recurrence risk [29].
4. **Augmentation of immunogenic cell death:** By promoting dendritic cell maturation and Damage-Associated Molecular Patterns (DAMP) recognition, metronomic regimens can synergize with immune-based approaches such as cancer vaccines [30, 31].

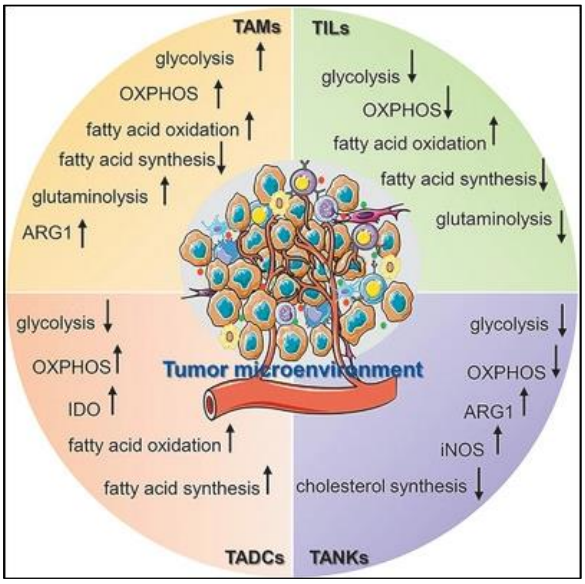

Figure 1. TME and its Active Elements [44].

7.1.2. Clinical Application

In pediatric medulloblastoma and ependymoma, metronomic regimens are increasingly used after conventional therapy or when autologous transplantation is not possible [32, 33]. Their affordability, oral administration, and limited supportive care requirements make them particularly attractive in low- and middle-income countries (LMICs). **Table 1** summarizes commonly used protocols, including MEMMAT-like combinations, vinblastine-based regimens, and oral etoposide schedules.

7.3. CSF-Directed Therapy

The blood–brain barrier (BBB) and blood–CSF barrier severely restrict systemic drug penetration, thereby necessitating direct intrathecal (IT) or intraventricular (IVT) delivery of cytotoxic or targeted agents [36, 37].

7.3.1. Standard Intrathecal Chemotherapy

Commonly used agents include methotrexate (MTX) and thiotepa, administered via lumbar puncture or Ommaya reservoir. Intraventricular delivery is preferred due to more uniform drug distribution and fewer procedural complications.

7.3.2. Targeted Intrathecal Therapies

- CAR-NK cells: Effective in CNS leukemia relapse with low neurotoxicity.
- Rituximab: Feasible for CNS lymphoma, even in resource-limited settings.
- Nitrosoureas (ACNU, MCNU): Used in resistant medulloblastoma; repeated boluses are discouraged.

While intrathecal rituximab and CAR-NK therapies may represent future therapeutic options, their practical applicability in LMICs is currently constrained by substantial economic and infrastructural barriers, including drug cost, cold-chain requirements, and limited access to advanced cellular manufacturing platforms. Consequently, broader implementation in resource-limited settings requires further development of decentralized and cost-adapted production models.

7.3.3. Pharmacokinetic Considerations

Optimizing CSF drug delivery requires precise pharmacokinetic (PK) monitoring. The area under the concentration-time curve (AUC) of MTX in ventricular CSF is considered one of the most reliable indicators of therapeutic exposure. However, interpatient variability in MTX clearance and peak levels after intralumbar administration complicates dosing.

Intrathecal co-administration of probenecid increases CSF AUC by ~3.2-fold, decreases clearance, and reduces neurotoxicity, whereas IV administration shows no significant effect [38, 39].

PK-guided dosing strategies are critical to personalize therapy, maximize efficacy, and minimize adverse effects.

Monitoring AUC in the CSF is therefore essential for personalized dosing and optimization of therapeutic outcomes. **Figure 3** illustrates CSF circulation and drug penetration dynamics, while **Figure 4** depicts plasma concentration-time profiles of MTX and its metabolite 7-hydroxymethotrexate, along with predicted CSF penetration at different dosing levels. These data underscore how varying MTX doses influence CSF exposure and highlight the critical role of pharmacokinetic monitoring in treatment planning [40, 41].

7.3.4. Individualized Maintenance Strategies

Maintenance therapy should be personalized based on tumor type, patient age, disease dissemination, and healthcare resources.

8. DISCUSSION

This review argues that biologically informed, low-intensity maintenance strategies can partially compensate for the lack of advanced therapies in resource-limited settings. Pediatric brain tumors present significant therapeutic challenges worldwide, particularly in resource-limited settings where access to advanced diagnostics, molecular therapies, and

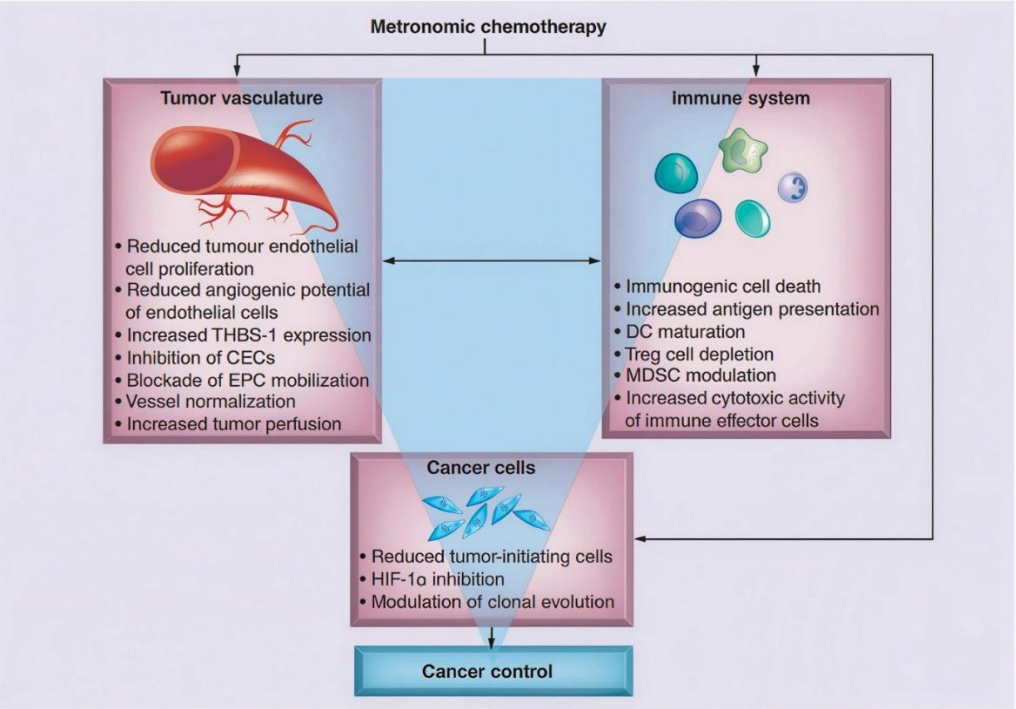

Figure 2. Metronomic chemotherapy mechanisms and participating cells stimulated in the antitumor effects of this method [45].

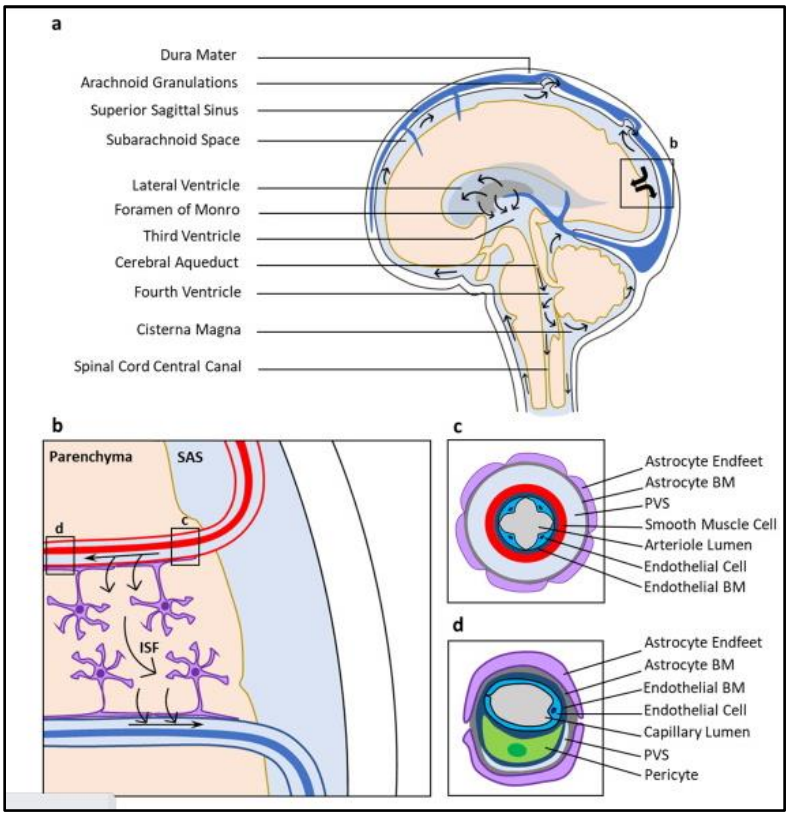

Figure 3 CSF circulation system in the brain and its connection with brain tissue [41].

high-dose chemotherapy with stem cell support is often restricted. Effective management requires balancing therapeutic efficacy with long-term safety, especially in children whose developing brains are highly vulnerable.

Cancer stem cells (CSCs) play a crucial role in therapy resistance and tumor recurrence. These cells reside in protective niches within the tumor microenvironment (TME), shielding them from cytotoxic effects and suppressing antitumor immunity. Therefore, targeting both the bulk tumor and CSC-enriched regions is critical for sustained disease control. Maintenance and metronomic chemotherapy offer low-toxicity, cost-effective approaches to modulate CSC activity and the TME. While these strategies may not completely eradicate CSCs, they can reduce relapse risk, enhance immune-mediated tumor clearance, and complement conventional high-dose therapies, particularly when autologous stem cell transplantation is not feasible [22, 33].

Table 1. **Commonly Utilized Metronomic Chemotherapy Protocols in Pediatric Central Nervous System Tumors.**

No.	Protocol Name	Drugs and Dosages	Treatment Duration & Cycles	Key Notes	Ref
1	MEMMAT-like Metronomic Chemotherapy Protocol	• Celecoxib 250 mg/m² PO BID (Days 1–43) • Etoposide 50 mg/m² PO daily (Days 1–21) • Cyclophosphamide 2.5 mg/kg PO daily (Days 22–43) • Fenofibrate 90 mg/m² PO daily (Days 1–43) • Thalidomide 6–12 mg/kg PO daily (max 800 mg/day) (Days 1–43) • Bevacizumab 10 mg/kg IV weekly (Days 15, 22, 29) • Liposomal cytarabine 25–50 mg intraventricular every 4 weeks starting Day 29	Median 16 months (continuous cycles)	Maintenance therapy for medulloblastoma, especially when autologous stem cell transplantation is not feasible.	[33]
2	Vinblastine-based Metronomic Protocol	• Vinblastine 3 mg/m² weekly (Weeks 1–7) • Methotrexate 10 mg/m² PO twice weekly (Weeks 5–7) • Celecoxib 250 mg/m² PO BID (Days 1–56) • Cyclophosphamide 30 mg/m² PO daily (Days 1–21)	8-week cycles with 2-week chemotherapy-free intervals	For medulloblastoma, PNET, neuroblastoma, and other pediatric tumors.	[34]
3	Modified 8-week Vincristine-based Metronomic Protocol	• Vincristine 1.5 mg/m² on Days 1, 8, 15, and 22 • Cyclophosphamide 25 mg/m² PO daily (Days 1–21), then twice weekly thereafter • Methotrexate 15 mg/m² (Days 21–42)	56-day (8-week) cycles; Vincristine on Weeks 1 & 5 in subsequent cycles	Suitable for pediatric brain tumors with low-dose, scheduled timing.	[34]
4	Etoposide-based Metronomic Maintenance Regimen	• Etoposide 50 mg/m² PO daily for 10 consecutive days • One-week drug-free interval between cycles	Cycles repeated over one year	Maintenance therapy for ependymoma and medulloblastoma.	[35]

Metronomic regimens exert multiple antitumor effects, including anti-angiogenesis, immunomodulation, CSC targeting, and induction of immunogenic cell death. These approaches are especially relevant in pediatric medulloblastoma, ependymoma, and other embryonal tumors, providing feasible alternatives in low- and middle-income countries (LMICs). Oral maintenance regimens and minimally invasive protocols offer a practical option that balances efficacy, safety, and accessibility, reducing the need for prolonged hospitalization.

Cerebrospinal fluid (CSF)-directed therapies, including intrathecal or intraventricular administration of methotrexate, thiotepa, and targeted biologics, are essential for managing leptomeningeal dissemination. Pharmacokinetic monitoring, particularly measurement of the area under the concentration-time curve (AUC), enables personalized dosing to optimize CNS drug exposure while minimizing neurotoxicity. Co-administration with agents such as probenecid further enhances therapeutic outcomes [38, 39]. Treatment planning should consider tumor type, age, CSF involvement, and available healthcare resources to ensure individualized, safe, and effective therapy.

9. LIMITATIONS

Despite promising clinical experiences, evidence supporting maintenance chemotherapy, metronomic chemotherapy, and CSF-directed therapies in pediatric brain tumors remains limited. Most data are derived from small cohorts, retrospective studies, or preclinical models. Tumor heterogeneity and patient variability further complicate the establishment of standardized protocols. Access to advanced therapies remains a significant barrier in LMICs, and long-term safety and efficacy data are often lacking. Therefore, larger, multicenter, prospective trials are necessary to validate these approaches, optimize dosing schedules, and evaluate long-term outcomes.

10. FUTURE DIRECTIONS

Future research should focus on developing novel targeted therapies capable of effectively penetrating the blood–brain and blood–CSF barriers, minimizing systemic toxicity while maximizing antitumor activity. Emerging immunotherapies, including CAR-NK and CAR-T cell therapies, show promise

Table 2. Intrathecal Chemotherapy Protocol Using Thiotepa in Leptomeningeal and Spinal Metastases.

Phase	Treatment Days	Dose (mg)	Route	Cycle Frequency	Number of Cycles
Induction	Days 1 and 4	10	Intrathecal or intraventricular	Weekly	8
Consolidation	Day 1	10	Intrathecal or intraventricular	Weekly (if CSF cytology negative)	4
Maintenance	Day 1	10	Intrathecal or intraventricular	Every 4 weeks	4

Table 3. Targeted Treatments in Cerebrospinal Fluid (CSF).

Treatment Type	Drug/Cell Therapy	Indication/Application	Dose and Administration	Key Notes
Intrathecal Chemotherapy	Thiotepa	Leptomeningeal/spinal mets	10 mg IT/IVT	See Table 2
Intrathecal Cell Therapy	CAR-NK cells	CNS relapse in leukemia	Direct CSF	Low neurotoxicity
Intrathecal Biologic Therapy	Rituximab	CNS lymphoma	Intrathecal	Safe in low-income countries
Intrathecal Chemotherapy	MTX, ACNU, MCNU	Resistant medulloblastoma	Intrathecal	Avoid repeated nitrosoureas

Table 4. Target Populations and Preferred Maintenance Strategies in Pediatric Brain Tumors,

Patient Population	Tumor Types	Preferred Maintenance Strategy	Rationale
Infants & Young Children	Medulloblastoma, AT/RT, ETMR	Metronomic chemotherapy, intrathecal (intra-CSF) therapy	Better tolerability; targets tumor microenvironment (TME) & cancer stem cells (CSCs)
High-risk Pediatric Patients	Rhabdomyosarcoma, recurrent medulloblastoma	Oral maintenance therapy instead of autologous stem cell transplant (SCT)	Safer long-term; preserves SCT option for relapse
Patients in LMICs	All embryonal tumors	Oral metronomic maintenance; minimal hospitalization	Low-cost, accessible, effective
Patients with CSF Dissemination	Medulloblastoma, PNET	Intrathecal methotrexate, tiotepa	Direct access to leptomeningeal metastases
Glial Tumor Patients	Low-grade glioma, High-grade glioma, Ependymoma	Vinblastine- or carboplatin-based regimens for low-grade glioma; metronomic maintenance in selected cases	Low-grade glioma may respond to vinblastine- or carboplatin-based regimens; however, high-grade glioma shows limited benefit from metronomic maintenance strategies [42, 43]

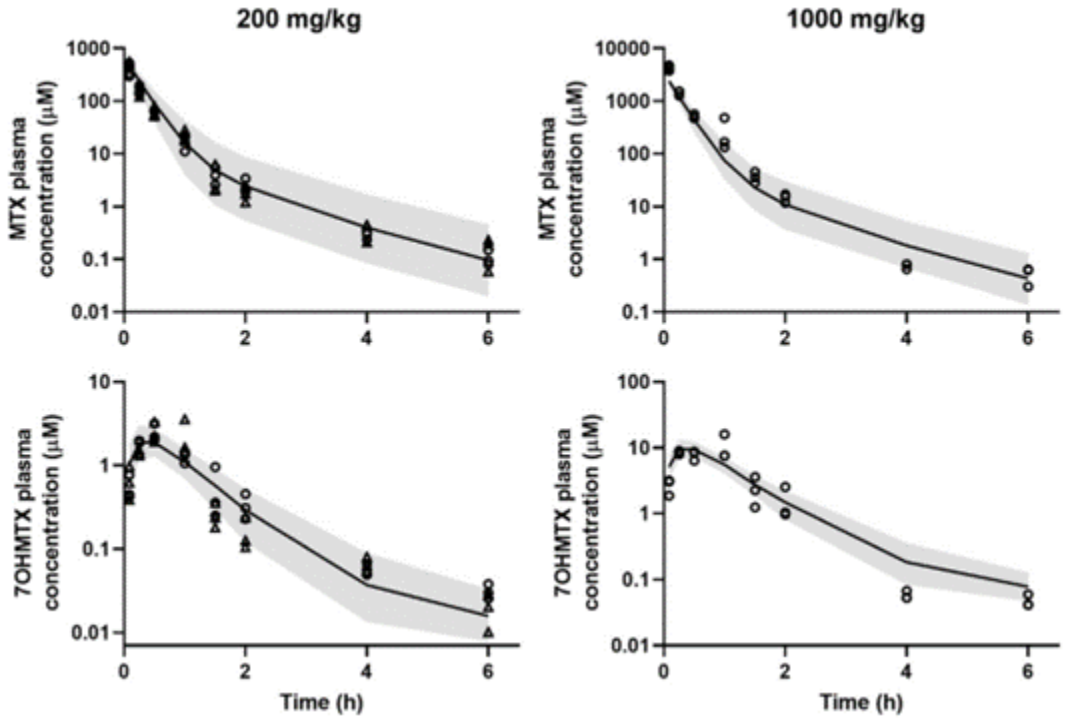

Figure 4. Plasma concentration-time profiles of MTX and 7-hydroxymethotrexate with predicted CSF penetration at 50% and 90% levels for doses of 200 mg/kg (left) and 1000 mg/kg (right) [40].

but require further evaluation across diverse populations. Optimizing drug delivery systems—such as advanced intrathecal administration techniques and pharmacologic enhancers like probenecid—may improve therapeutic outcomes. Large-scale clinical trials in LMICs are critical to validate cost-effective regimens such as metronomic chemotherapy. Integrative approaches combining systemic, intrathecal, and targeted therapies should be explored to overcome tumor resistance and improve long-term survival.

11. CLINICAL IMPLICATIONS

Effective management of pediatric brain tumors requires individualized treatment protocols that account for tumor biology, patient characteristics, and healthcare infrastructure. Maintenance strategies such as metronomic chemotherapy and CSF-directed therapies provide practical and clinically applicable options, particularly in resource-limited settings. Pharmacologic enhancers like probenecid can reduce toxicity and increase drug persistence in the CSF. Multidisciplinary collaboration among oncologists, pharmacologists, and researchers is essential to safely translate emerging therapies into clinical practice. Integrating these strategies may significantly improve survival and quality of life for pediatric patients worldwide.

12. CONCLUSION

Maintenance and metronomic chemotherapy, combined with CSF-directed interventions, represent biologically informed and pragmatic strategies for pediatric brain tumor management. By targeting CSCs, modulating the TME, and individualizing therapy through pharmacokinetic guidance, clinicians can optimize both efficacy and safety. This integrative approach underscores that scientific insights and practical considerations must work together to achieve effective, accessible, and safe neuro-oncology care for children globally.

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Declaration of interest

The authors declare no competing interests.

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