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ONCOLOGY: RESEARCH ARTICLE

Treatment of pediatric high-grade central nervous system tumors with high-dose methotrexate in combination with multiagent chemotherapy: A single-institution experience

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Abstract

Background: Effective treatment for pediatric embryonal brain tumors includes dose-intensive multiagent chemotherapy (DIMAC) followed by high-dose chemotherapy with stem cell rescue (HDCSCR). Use of repeated cycles of DIMAC including high-dose methotrexate (HDMTX) without HDCSCR has not been described.

Procedure: We retrospectively reviewed the responses/toxicities in 13 patients (aged 2-155 months, median 22 months) with central nervous system (CNS) tumors (atypical teratoid rhabdoid tumors, CNS embryonal tumors not otherwise specified, pineoblastoma, embryonal tumor with multilayered rosettes, and CNS sarcoma) treated over a 12-year period with repeated cycles of HDMTX followed by etoposide, cisplatin, cyclophosphamide, and vincristine.

Results: Six patients (46.2%) had disseminated disease at presentation and five (38.5%) had gross total resection. A total of 64 courses of therapy were administered with a median of five courses per patient. Eight patients (61.5%) received radiation therapy (one at relapse). By completion of therapy, 11 patients (84.6%) achieved a response (six complete, five partial). Six of the 13 patients (46.2%) remain alive with a median follow-up of 48 months (6-146). Acute toxicities included fever/neutropenia (70.3%), bacteremia (15.6%), and grade 3 mucositis (18.8%). Long-term complications included learning disability, seizure disorder, and brain necrosis, without treatment-related deaths.

Abbreviations: ANC, absolute neutrophil count; ATRT, atypical teratoid rhabdoid tumor; CCG, Children's Cancer Group; CNS, central nervous system; COG, Children's Oncology Group; CR, complete response; CSI, craniospinal irradiation; DIMAC, dose-intensive multiagent chemotherapy; ETMR, embryonal tumor with multilayered rosettes; GTR, gross total resection; HDCSCR, high-dose chemotherapy with stem cell rescue; HDMTX, high-dose methotrexate; NOS, not otherwise specified; PD, progressive disease; PNET, primitive neuroectodermal tumor; PR, partial response; RT, radiation therapy; SD, stable disease; SPNET, supratentorial primitive neuroectodermal tumor; STR, subtotal resection.

Conclusions: DIMAC with HDMTX without HDCSCR may be an effective treatment option for selected patients with embryonal or high-grade CNS tumors.

KEYWORDS
ATRT, high-dose chemotherapy, high-dose methotrexate, medulloblastoma, PNET, stem cell rescue

1 | INTRODUCTION

Central nervous system (CNS) tumors are the most common solid malignancy of childhood and the leading cause of cancer-related mortality in children.[1] Survival rates for subsets of patients have improved with the addition of radiation therapy (RT) and/or chemotherapy. Craniospinal irradiation (CSI) in children less than 36 months is avoided due to its deleterious effects on the CNS, making treatment of malignant tumors in this age group challenging.[2] Embryonal tumors, which include medulloblastoma, embryonal tumor with multilayered rosettes (ETMR), pineoblastoma; embryonal tumor not otherwise specified (NOS), and atypical teratoid rhabdoid tumors (ATRT), are the most common brain tumors in children under 36 months, and all are aggressive malignancies that have a tendency to disseminate throughout the CNS.[3] These high-grade tumors often recur due to resistance to multiple treatment modalities including surgical resection, chemotherapy, and radiosurgery.[3] This is especially true for infants and very young children. Standard-dose chemotherapy regimens have had only a modest impact on survival.[4,5]

Multiagent chemotherapy including high-dose methotrexate (HDMTX) followed by high-dose chemotherapy with autologous hematopoietic stem cell rescue (HDCSCR) has been shown to be effective for the treatment of embryonal CNS tumors in several small studies and case series.[6–8] These protocols typically include two to five induction cycles of dose-intensified chemotherapy followed by one to three cycles of HDCSCR.[9] Acute toxicities of HDCSCR include prolonged cytopenias with risk for life-threatening infections, pulmonary and/or cardiac toxicity, and thrombotic microangiopathy.[10,11] Specifically, pediatric survivors of stem cell transplant have high rates of pulmonary complications,[12] hypertension,[13] and neurosensory deficits.[14] Further, HDCSCR is a highly specialized procedure often requiring management at a pediatric stem cell transplant center, creating a barrier to treatment for many patients.

The use of repeated cycles of dose-intensified multiagent chemotherapy including HDMTX without subsequent stem cell transplant has not been described. We adopted such a treatment strategy at our institution for select patients who were poor candidates for HDCSCR or whose families did not want to receive HDCSCR. The regimen included HDMTX followed by etoposide, cisplatin, cyclophosphamide, and vincristine. Involved field RT was used except in very young patients. CSI was reserved for older patients with disseminated disease. This retrospective study reports the responses and toxicities to this treatment regimen in 13 patients diagnosed with a high-grade CNS tumor treated over a 12-year period at Children's of Alabama in Birmingham, Alabama.

2 | METHODS

A retrospective review, approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB)-approved protocol (160512004) compliant with guidelines set forth by the NIH, was performed; all patients treated for embryonal CNS tumors between 2003 and 2015 were identified and included in the study if they were treated with at least two cycles of HDMTX and multiagent chemotherapy, but did not receive HDCSCR. Chemotherapy consisted of HDMTX and vincristine on day 1, followed by etoposide on days A, B, and C, cyclophosphamide on days A and B and cisplatin on day C (Figure 1). Day A started when the methotrexate level was < 0.1 μM. Leucovorin was administered starting at 24 hours after methotrexate infusion and given at a dose of 10 mg/m^2 every 6 hours until the methotrexate level reached < 0.1 μM. Mesna was given at 100% of the daily cyclophosphamide dose on days A and B for bladder protection. Vincristine was again given on days 8 and 15 of each cycle. Filgrastim at a dose of 5 μg/kg/day was started the day after completion of day C chemotherapy. Once the absolute neutrophil count (ANC) recovered to > 1000/μL off Filgrastim and platelets were $> 100{,}000$/μL (day 22 or later), the next cycle of chemotherapy was initiated. RT summaries (dose, treatment field, and timing) were reviewed and tabulated. Radiologic response was measured at the end of chemotherapy. SigmaPlot v12.0 (Systat Software) was used to generate overall survival (OS) and progression-free survival (PFS) Kaplan-Meier curves.

3 | RESULTS

Histologically confirmed diagnoses included CNS sarcoma, ATRT, CNS embryonal tumor NOS, pineoblastoma, medulloblastoma, spinal-embryonal tumor NOS, and ETMR (Table 1). The median age at diagnosis was 22 months (range, 2-155 months). Primary tumor location was supratentorial in eight patients, infratentorial in four patients (one ATRT, one ETMR, two medulloblastoma), and an intramedullary spinal tumor (from thoracic vertebral level 10 to lumbar level 2) in one patient. At the time of diagnosis, six patients (46.2%) had disseminated disease. Only five patients (38.5%) achieved upfront gross total resection of their primary tumor, six patients (46.2%) received subtotal resection, and two patients (15.4%) received biopsy only. Eight patients (61.5%) received RT. A total of 64 cycles of chemotherapy was administered with a median of five courses of chemotherapy per patient. Of the eight patients who did not have an upfront gross total resection, five (62.5%) achieved a response (three complete, two partial) to the chemotherapy. Figure 2 shows the dramatic response

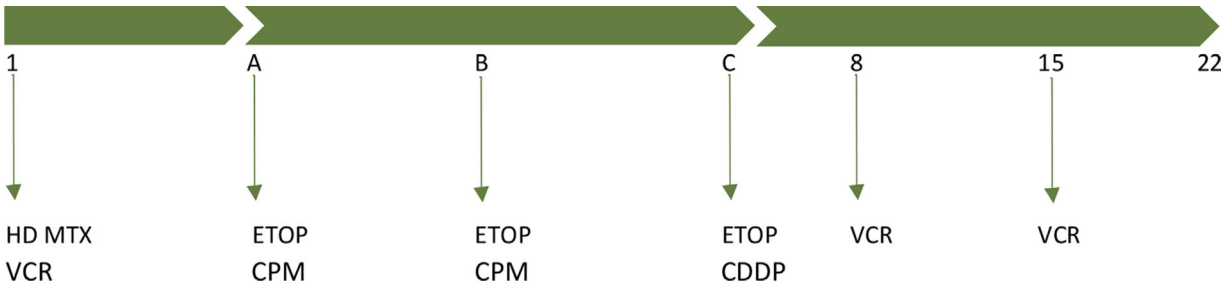

FIGURE 1 Chemotherapy design schema. HD MTX, high-dose methotrexate 8 g/m^2/day; VCR, vincristine 1.5 mg/m^2/day (0.05 mg/kg/day if < 36 months of age); ETOP, etoposide 75 mg/m^2/day (2.5 mg/kg/day if < 36 months of age); CMP, cyclophosphamide 1.8 g/m^2/day (60 mg/kg/day if < 36 months of age); CDDP, cisplatin 105 mg/m^2/day (3.4 mg/kg/day if < 36 months of age)

TABLE 1 Clinical features, treatment, and outcomes

Patient	Age at diagnosis (months)	Histology	Disseminated disease at diagnosis	Upfront resection	Radiation	# of cycles	Disease response at end of therapy	Outcome	Time to follow-up (months)
1	155	CNS sarcoma (NRSTS)	No	Biopsy only	59.4 Gy + 12 Gy gamma knife	6	PR	Alive	130
2	25	ATRT	No	GTR	50.4 Gy	6	CR	Alive	146
3	2	Embryonal tumor NOS	No	STR	No	6	CR	Alive	117
4	3	ATRT	No	GTR	No	5	CR	DOD	12
5	37	Pineoblastoma	Yes	STR	50.4 Gy (23.4 Gy CSI)	5	CR	Alive	95
6	26	ATRT	Yes	STR	50.4 Gy	3	PD	DOD	8
7	3	Gliosarcoma	No	Biopsy only	No	5	PR (CR after second resection)	Alive	57
8	11	Embryonal tumor NOS	No	GTR	At relapse, only 2 fractions delivered	4	PD	DOD	6
9	32	Medulloblastoma[a]	Yes	STR	54 Gy (36 Gy CSI)	5	PR	DOD	14
10	34	Embryonal tumor NOS	Yes	GTR	54 Gy (36 Gy CSI)	5	CR	Alive	48
11	16	ETMR	Yes	STR	No	4	PD	DOD	6
12	22	Medulloblastoma[b]	Yes	STR	No	5	PR	DWD	137
13	55	Embryonal tumor NOS-spinal	No	GTR	45 Gy	5	CR	DOD	30

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CR, complete response; CSI, craniospinal irradiation; DOD, dead of disease; DWD, dead without disease; ETMR, embryonal tumor with multilayered rosettes; GTR, gross total resection; NOS, not otherwise specified; NRSTS, non-rhabdomyosarcoma soft-tissue sarcoma; PD, progressive disease; PR, partial response; SD, stable disease; STR, subtotal resection.

[a]Molecular classification was not possible secondary to myogenic and melanocytic differentiation.

[b]Histology was desmoplastic/nodular and molecular classification was Sonic Hedgehog, p53 wild-type.

of a patient with gliosarcoma (patient 7 on Table 1) that received only biopsy with minimal debulking of tumor, followed by rapid growth prior to initiation of chemotherapy. This response was observed after five cycles of chemotherapy and the patient was able to achieve a complete response (CR) after second look surgery. Six of the 13 patients (46.2%) are currently alive (Figure 3) with a median follow-up of 48 months (range, 6-146 months; Table 1). Of the six long-term survivors, two received only focal RT (two and three months of age at diagnosis) and two did not receive any RT. Six patients died of disease, whereas one patient with very poor functional status died of sepsis without evidence of disease approximately 11 years after completion of all chemotherapy. Toxicities during therapy included fever and neutropenia (70.3% of courses), bacteremia (15.6%), and grade 3 mucositis (18.8%). No treatment-related deaths occurred as the one death from sepsis was > 11 years after completion of chemotherapy. Delays for count recovery or toxicity were frequent, with an average length of time between cycles of 35 days. Long-term toxicities from the disease and/or therapies in survivors included seizure disorders in three (50%) and at least mild developmental delays and learning difficulties in five (83.3%). Three survivors (50%) developed moderate to severe sensorineural hearing loss. One patient who received a total of 59.4 Gy of intensity modulated RT to primary tumor plus an additional 12 Gy

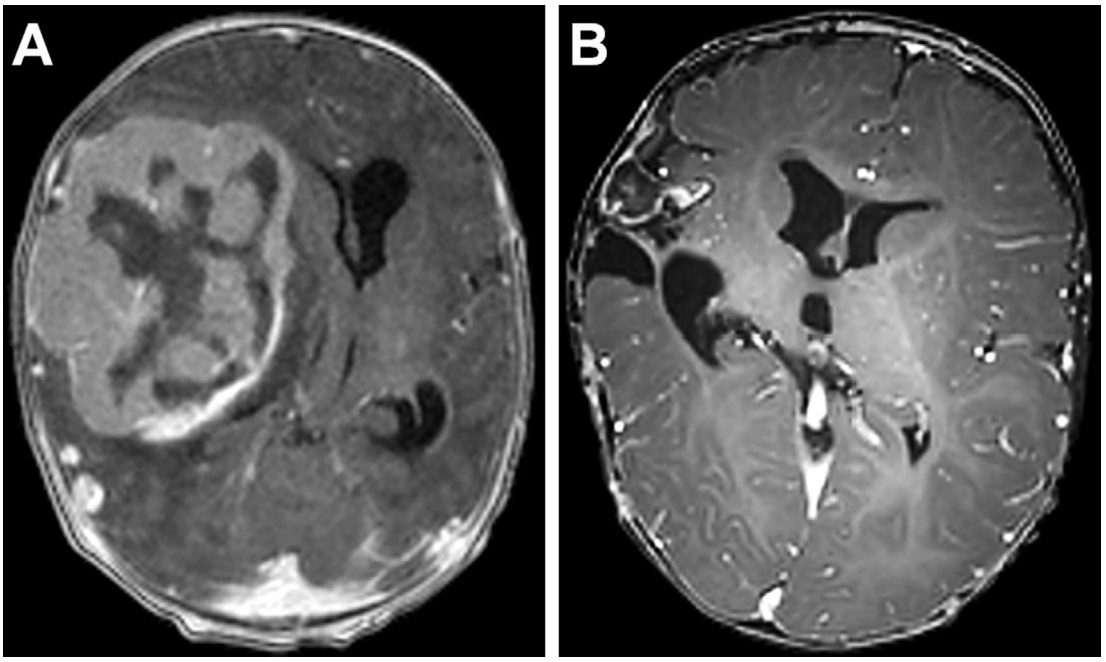

FIGURE 2 Axial post-gadolinium images of a patient with gliosarcoma (patient 7 in Table 1). (A) At diagnosis. Subsequently underwent biopsy with minimal debulking of tumor followed by regrowth to original size prior to initiation of chemotherapy. (B) After five cycles of chemotherapy and prior to second surgery

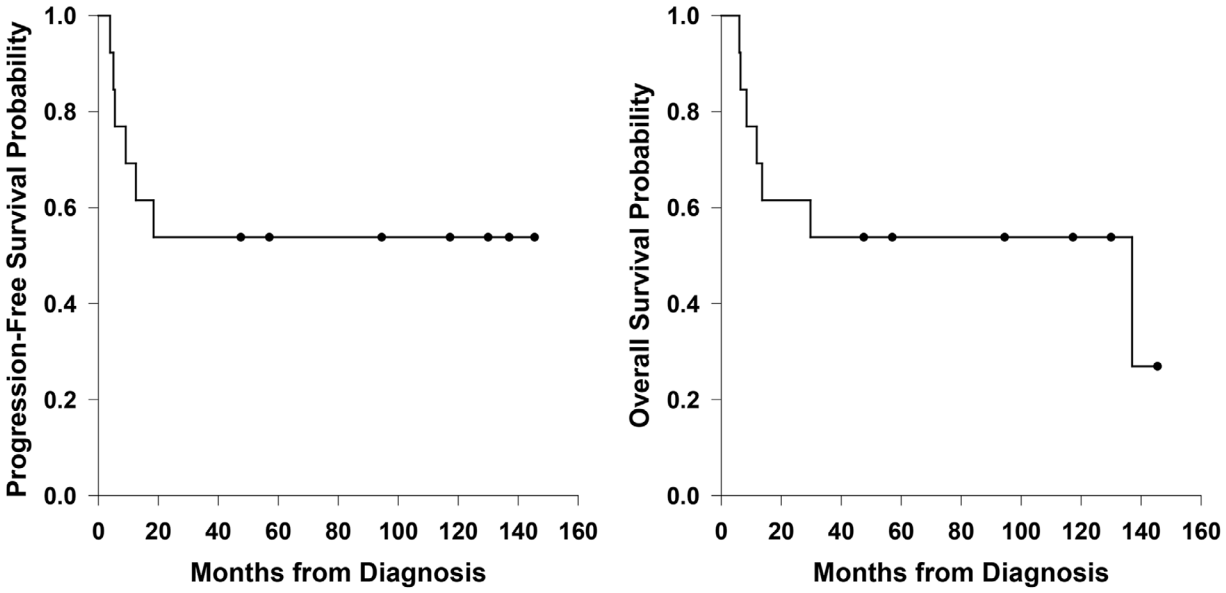

FIGURE 3 Kaplan-Meier OS and PFS curves for patients treated with high-dose methotrexate combined with multiagent chemotherapy without autologous stem cell rescue. Median PFS was 9.1 months (95% CI, 2.4-15.8 months). Six of 13 patients remain alive and free of disease. One patient that was free of disease for 137 months died from an unrelated infection

with radiosurgery, developed brain necrosis that was treated with steroids, bevacizumab, and hyperbaric oxygen therapy.

4 | DISCUSSION

Based on this pediatric cohort, we conclude that HDMTX combined with dose-intensified multiagent chemotherapy for five to six cycles may be an effective treatment for CNS embryonal tumors. By completion of therapy, 11 patients (84.6%) achieved a response (6 complete, 5 partial). The response was durable in many; with a median follow-up of 48 months, seven patients (53.8%) had no evidence of disease. Although RT was incorporated as part of the first-line therapy for seven patients, the benefit of chemotherapy is evidenced by two patients who initially underwent subtotal resection and achieved long-term responses (117 months and 137 months) from the chemotherapy

alone. In addition, one patient with an initially unresectable tumor was able to undergo gross total resection after chemotherapy alone and is alive without disease 57 months from diagnosis. The major treatment-related toxicities were fever with neutropenia and bacteremia. The high prevalence of cytopenias caused a 35-day average length between cycles as opposed to the planned 22 days.

After disappointing results using conventional dose chemotherapy while trying to avoid or postpone RT for infants and young children with malignant brain tumors, Children's Cancer Group (CCG) conducted a phase 1/2 study of high-dose chemotherapy with etoposide and thiotepa for infants and young children with malignant brain tumors (CCG 9883), which was open from 1986 to 1991.[15] Data were encouraging with a CR + PR rate of 23% and five long-term survivors, all with high-grade glioma. However, the toxic mortality rate was 16%. Following this trial, a combination of thiotepa, etoposide, and BCNU was studied in CCG 9922.[16] Despite a two-year PFS of 46%, significant (pulmonary) toxicities were observed with this combination, and there was a toxic mortality rate of 18%. A follow-up study was conducted substituting carboplatin for BCNU (CCG 9883) for children with recurrent malignant brain tumors from 1989 to 2000.[17] The three-year event-free survival (EFS) rate was 47% for 20 patients enrolled on the trial, and the toxic mortality rate dropped to < 10%. Dunkel et al. reported on an expanded cohort of 20 medulloblastoma patients treated with the same regimen with three-year EFS and OS rates of 34% and 46%, respectively.[18] This regimen was subsequently adopted for treatment of newly diagnosed children with malignant brain tumors on "Head Start" I, II, and III studies. Children's Oncology Group (COG), on the other hand, used three tandem HDCSCR cycles using thiotepa and carboplatin at slightly reduced doses (but higher cumulative doses of each drug) for all consortium HDCSCR trials in pediatric brain tumors (CCG99703, ACNS0333, and ACNS0334). These regimens (single HDCSCR cycle used in "Head Start" studies and three tandem HDCSCR cycles used in COG studies) are currently being compared in a randomized fashion for efficacy and toxicity on the currently active "Head Start" IV clinical trial.

Autologous stem cell transplantation aims to reestablish hematopoietic function following myelosuppression caused by high-dose chemotherapy regimens. Because autologous stem cell transplantation uses a patient's own stem cells, it is not associated with graft-versus-host disease, as in allogenic stem cell transplantation. However, HDCSCR is not a benign intervention and carries significant short- and long-term risks. Most reported toxicities are acute in nature and related to myelosuppression and related infections. A study of pediatric patients with high-risk neuroblastoma who received HDCSCR found that 30% of patients developed transplant-associated thrombotic microangiopathy. Further, a dramatic reduction in renal function was observed in the patients who developed transplant-associated thrombotic microangiopathy.[10] Long-term survivors of pediatric hematopoietic stem cell transplantation are two to three times more likely to develop hypertension,[13] and a five-year follow-up on pediatric survivors of hematopoietic stem cell transplantation found that 40% had either restrictive, obstructive, or mixed restrictive/obstructive lung disease. Of those with lung disease, 45% had moderate-severe impairment in pulmonary function.[12] Long-term neuropsychological outcome has been shown to be preserved with both single HDCSCR cycles and the tandem HDCSCR approach.[19–21] No significant immune dysregulation or infectious complications have been reported long term.[22] In a study involving 30 children with newly diagnosed malignant CNS tumors treated with HDCSCR approaches, most patients had normal hormone levels, including growth hormone; however, 10 patients (33%) were found to have proportional short stature.[23] Finally, the psychological impact of the stem cell transplantation, not only on the patients but on their families should not be overlooked. Multiple studies have demonstrated that children undergoing stem cell transplantation suffer from anxiety, depression, peer isolation, and behavioral problems.[24,25] Additionally parents of children undergoing HDCSCR experience significant distress and disturbances in their social and professional relations.[26]

Although HDCSCR is being increasingly used in a variety of pediatric cancers,[27–30] including high-risk CNS tumors, there are some patients where HDCSCR may not be a safe/feasible option or some families may not want to pursue HDCSCR. HDCSCR is often utilized in the youngest patients (< 36 months of age) with high-risk CNS tumors to delay and/or eliminate the use of RT. In our cohort of very young patients (median age of 22 months at diagnosis, range 2-155 months), the treating physicians had varying reasons for not utilizing HDCSCR. These included poor functional status of the child, very young age at diagnosis (8 weeks), inadequate stem cell collection, and parental refusal. Although these types of barriers may be rare, the results of our cohort suggest HDMTX without HDCSCR is a reasonable alternative approach.

In this cohort, seven patients were treated with RT in addition to the HDMTX containing chemotherapy regimen. Methotrexate and RT are both known to be toxic to the CNS, and the timing of these agents may play a critical role in toxicity. In adult randomized trials of HDMTX in the treatment of patients with primary CNS lymphoma, RT has been feasible during consolidation (after methotrexate). In contrast, CNS lymphoma treated with primary RT and salvage HDMTX (after RT) has been associated with very high rates of leukoencephalopathy. One hypothesis is that RT may change the brain penetrance of methotrexate.[31] In this series, HDMTX was utilized prior to RT and was associated with a low rate of severe encephalopathy or necrosis mirroring adult clinical trials of CNS lymphoma.[32–34] Long-term follow-up of survivors will be critical to understand the developmental and cognitive changes in pediatric patients.[35,36]

Although this study was a relatively small retrospective cohort with a variety of different tumor types, three patients with ATRT were included. Two of the three patients had a CR, and one patient is still alive 146 months later. Several case reports and series indicated that intrathecal methotrexate may be potentially efficacious in the treatment of ATRT.[37,38] In the Head Start I and II trials, 13 children with ATRT were treated with surgery followed by five cycles of cisplatin, vincristine, cyclophosphamide, and etoposide. Consolidation included carboplatin, thiotepa, and etoposide with autologous hematopoietic progenitor cell rescue. Seven of these patients received HDMTX

(400 mg/kg) during each induction trial. Three of the seven patients achieved EFS up to 67 months, whereas none of the six patients who did not receive methotrexate survived.[6] These results helped form the basis for the recently completed COG trial for ATRT investigating the efficacy of HDMTX, vincristine, cyclophosphamide, etoposide, and cisplatin for induction therapy, followed by three cycles of high-dose thiotepa and carboplatin with autologous stem cell rescue and involved field RT (ACNS0333). Preliminary data for this trial show significant improvements in EFS and OS compared with historical controls, with 24-month EFS and OS of 42% and 53%.[9]

HDCSCR has also been investigated for the treatment of high-risk medulloblastoma and supratentorial PNETs (SPNETs), although results have varied. In a trial of patients with high-risk medulloblastoma, five-year OS and EFS were 70%.[39] In a study of high-risk medulloblastoma and SPNETs, three-year EFS for patients diagnosed over three years of age was 83.3% ± 15.2% but only 62.5% ± 20.5% for patients diagnosed under three years of age.[40] Another study of newly diagnosed high-risk medulloblastoma and SPNETs treated with HDCSCR found a two-year EFS of 57% ± 15%.[41] Risk-adapted chemotherapy that includes HDMTX without HDCSCR for young medulloblastoma patients was recently explored.[42] Although the risk-adapted approach did not improve outcomes for all patients, the study did find excellent progression-free survival in a specific group of Sonic Hedgehog (SHH) patients. In our study, four of the five medulloblastoma and embryonal tumor NOS patients responded to treatment (PR for both medulloblastoma, two CR and one PD for embryonal tumor NOS). Three of the five (60%) patients were without evidence of disease at the end of follow-up. One medulloblastoma patient, whose tumor is now known to be SHH molecular subgroup, achieved a PR at the end of the chemotherapy, survived for 11 years, and then died without disease from sepsis. Of note, all five of these patients were diagnosed before three years of age. However, one patient with spinal-embryonal tumor NOS displayed a CR, but ultimately died of their disease.

Although interpretation of results from the present retrospective study is limited by the small sample size, it includes several very rare tumors including three with ATRT, two sarcoma, and one pineoblastoma. Based on this pediatric primary CNS tumor patient cohort, we conclude that HDMTX combined with dose-intensified multiagent chemotherapy for five to six cycles with or without age-adapted RT may be an effective treatment for a variety of embryonal CNS tumors. Given the rarity and poor outcomes of CNS embryonal tumors, enrollment of patients on a clinical trial when available is encouraged.

5 | CONCLUSIONS

High-grade CNS tumors in children are difficult to treat and a leading cause of cancer-related mortality. In this retrospective cohort study, we show that treatment with HDMTX and dose-intensified chemotherapy may be a relatively safe and efficacious treatment approach alone or combined with RT for select patients with embryonal CNS tumors. However, both short-term and long-term toxicities resulted from this therapy. Based on our data, a randomized perspective trial is warranted.

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AUTHOR CONTRIBUTIONS

G.K.F. and A.R. conceived and supervised the study. J.D.B. and E.A. collected and managed data, and wrote the majority of the manuscript. J.L.C., M.L., G.C., and G.A.E. prepared figures, wrote sections of the manuscript, and provided edits and revisions. C.R., B.R., J.B., and J.M.J. performed the operations, provided expert consultation, and provided expert revisions to the manuscript. B.A.O. performed and analyzed molecular analyses. R.L., J.F., and G.D. provided expert consultation in their respective fields and contributed expert revisions to the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

J.D.B. has positions and equity in CITC Ltd and Avidea Technologies and is a member of the POCKiT Diagnostics Scientific Advisory Board.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon request.

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