Efficacy of high-dose chemotherapy or standard salvage therapy in patients with recurrent medulloblastoma

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The efficacy of high-dose chemotherapy (HDC) or standard salvage therapy was evaluated in patients with recurrent medulloblastoma (MBL) using retrospective chart review of all patients with recurrent MBL treated at Duke University Medical Center between 1995 and 2005 and who had undergone HDC with or without radiotherapy (RT) or standard salvage therapy after relapse. A total of 30 patients were diagnosed with recurrent MBL after standard RT alone or chemotherapy with RT. Nineteen patients (7 who received no RT before recurrence [group A] and 12 who received definitive RT before recurrence [group B]) underwent surgery and/or induction chemotherapy followed by HDC plus autologous stem-cell rescue. Eleven patients (group C) underwent standard salvage therapy. Six of seven group A patients also received standard RT just before or after recovery from HDC, and 5 of 12 group B patients received adjuvant palliative focal RT post-HDC. At a median follow-up of 28 months, three of seven patients in group A are alive and disease-free at ⩾34, ⩾110, and ⩾116 months, respectively, post-HDC. All patients in groups B and C have died of tumor, at a median of 35 months and 26 months from HDC and standard salvage therapy, respectively. HDC or standard salvage therapy was ineffective in our patients with recurrent MBL who had received standard RT before recurrence. The favorable impact of HDC on disease control in the two long-term survivors cannot be clearly established due to the cofounding effect of definitive RT postrecurrence. *Neuro-Oncology 10, 745–751, 2008 (Posted to Neuro-Oncology [serial online], Doc. D08-00011, August 28, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-044)*

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Medulloblastoma (MBL) is the most common malignant embryonal brain tumor in children, with an incidence of approximately 0.5 per million children and an average of 400 cases per year in the United States.[1] Although significant advances have been made in the treatment of children with this aggressive malignancy, especially for older children with localized disease (average risk),[2,3] the prognosis remains dismal for infants (children <3 years of age) and those with extensive or recurrent tumors.[4] Alkylator-based high-dose chemotherapy (HDC) with stem-cell rescue has been used in children with recurrent MBL for the last several years with modest success.[5–10] However, the true impact of this strategy on long-term disease con-

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trol is hard to interpret in these studies because most survivors had also received adjuvant focal or focal plus craniospinal radiotherapy (RT) around HDC. We therefore did a retrospective study to (1) evaluate the efficacy of HDC in children with recurrent MBL treated at our institution based on having received definitive RT before recurrence and (2) measure outcomes of those who had only standard salvage therapy at relapse.

Patients and Methods

Between 1995 and 2005, a total of 30 patients were treated for recurrent MBL at Duke University Medical Center. Nineteen patients underwent HDC with autologous hematopoietic stem-cell rescue (ASCR) after recurrence. Seven of the 19 patients who underwent HDC had not received standard RT (focal and/or craniospinal RT) before recurrence due to their young age (group A). The other 12 older patients had received standard RT with or without chemotherapy at initial diagnosis and before recurrence (group B). Eleven of 30 patients received only standard salvage therapy after tumor recurrence (group C). Informed consent as approved by the local institutional review board (IRB) was obtained for all patients before commencement of HDC. This retrospective study received formal IRB review and approval before database query and chart review.

Diagnosis and Initial Workup

All patients were subjected to biopsy and/or surgical resection of the primary tumor at diagnosis and relapse. Pathologic diagnosis of MBL was made by one of us (R.E.M.) using standard criteria.[11] All patients underwent a metastatic workup either before or 3 weeks postsurgery that included MRI of brain and spine with and without gadolinium, cerebrospinal fluid (CSF) cytology obtained via lumbar puncture, Tc99m bone scan, and bone marrow aspirate and biopsy. Metastatic spread of tumor was classified as CSF spread only (M1 disease), nodular disease in the brain or spine only (M2 disease), nodular disease in brain and spine (M3 disease), and extraneural spread (M4 disease).

Induction Chemotherapy, RT, and HDC with ASCR

Details of type and dosage schedules of induction chemotherapy, RT, and HDC used in these patients after recurrence are summarized in Table 1. Standard salvage chemotherapy included agents known to be effective in MBL, such as cyclophosphamide (CTX), oral or intravenous etoposide (VP-16), platinum compounds, high-dose methotrexate, CPT-11 (Camptosar, Pfizer Corporation, New York, NY, USA), and temozolomide (Temodar, Schering Plough Corporation, Kenilworth, NJ, USA); in two patients, investigational agents included intrathecal Spartaject busulfan (BU; SuperGen, Inc., San Ramon, CA, USA) or VNP40101M (Cloretazine, Vion Pharmaceuticals, New Haven, CT, USA). Response assessment was made by assessing tumor size (derived from the product of the maximal tumor diameters) on a gadolinium-enhanced MRI of brain and/or spine obtained regularly during treatment. Response criteria were as follows: complete response, disappearance of all tumor and no new lesions; partial response, ⩾50% reduction in tumor size; minimal response, 25%–50% reduction in tumor size; stable disease, <25% increase or decrease in tumor size; progressive disease, ⩾25% increase in tumor size and/or appearance of new lesions.

Evaluation before transplant in those undergoing

Table 1. Details of type and dosage schedules of induction chemotherapy, radiotherapy, and high-dose chemotherapy used in patients with recurrent medulloblastoma

Induction chemotherapy (agents used either alone or in combination as indicated in Tables 2 and 3)

- High-dose cyclophosphamide 2 gm/m^2/day i.v. for 2 days with mesna rescue and hydration, given every 4 weeks for four cycles
- Vincristine 1.5 mg/m^2 (0.05 mg/kg in children <10 kg) i.v. on day 1 and then weekly for 2 weeks, cisplatin 75 mg/m^2 (2.5 mg/kg in children <3 years) i.v. on day 1, cyclophosphamide 2 gm/m^2 (65 mg/kg in children <3 years) i.v. on day 2, and etoposide 100 mg/m^2 (4 mg/kg for children <3 years) i.v. on days 2 and 3 every 3 weeks
- Carboplatin (dose based on Calvert's formula using glomerular filtration rate and an area under the curve concentration of 5 mg/ml per minute) i.v. on day 1 and etoposide 100 mg/m^2 i.v. on days 2 and 3 every 4 weeks
- Oral etoposide 50 mg/m^2 per day for 21 days every 4 weeks

Radiotherapy

- Craniospinal: Treatment administered in the prone position using a thermoplast stabilization device with a 6 MV photon beam and customized blocking (general anesthesia or sedation used as necessary), given at 1.5–1.8 Gy per fraction
- Posterior fossa or three-dimensional conformal: Treatment to the posterior fossa or tumor bed given in the supine position at 1.8–2 Gy per fraction

High-dose chemotherapy with autologous hematopoietic stem-cell rescue

- Bone marrow stem cell harvest: Bone marrow harvest performed under general anesthesia after the first or second cycle of induction chemotherapy after granulocyte-colony-stimulating factor, frozen and stored using dimethyl sulfoxide as a cryopreservative; peripheral blood stem cells collected through a double-lumen catheter on alternate days for 3 days, with CD34$^+$ cells separated, frozen, and stored
- High-dose chemotherapy: All patients received one of the following high-dose chemotherapy regimens:
  - (a) Cyclophosphamide 50 mg/kg daily for 4 days followed by melphalan 60 mg/m^2 per day for 3 days
  - (b) Busulfan 1 mg/kg every 6 h for 16 total doses over 4 days (plasma concentrations measured and doses adjusted to yield a steady-state concentration of 600–900 ng/ml) followed by melphalan 60 mg/m^2 per day for 3 days
  - (c) Carboplatin (either 500 mg/m^2 or a dose based on Calvert's formula to achieve an area under the curve concentration of 7 mg/ml per minute, whichever was less) on days –8, –7, and –6, followed by thiotepa 300 mg/m^2 and etoposide 250 mg/m^2 daily on days –5, –4, and –3
- Stem-cell rescue: Three days after the last dose of chemotherapy, frozen bone marrow and peripheral blood stem cells, thawed at room temperature, infused through a double-lumen broviac catheter

HDC included physical examination; pulmonary function tests including diffusing capacity of the lung for carbon monoxide; electrocardiogram, echocardiogram, and resting multiple uptake gated acquisition scan; and antiviral antibody titers (cytomegalovirus, hepatitis C virus, varicella zoster virus, and hepatitis B and C). Supportive care after transplant included granulocyte colony-stimulating factor; intravenous antibiotics; blood products as needed; pain control; intravenous hyperalimentation; antibiotic prophylaxis for *Pneumocystis* pneumonia, herpes simplex, and varicella zoster virus for up to 6 months after transplant; and prophylaxis for veno-occlusive disease with low-dose heparin. Patients were followed by the bone marrow transplant (BMT) service for at least 6 months after discharge. MRI scan of brain and spine was obtained 6 weeks after BMT and periodically thereafter.

Statistical Analysis

Overall survival (OS) and progression-free survival (PFS) were determined using the Kaplan-Meier product limit method.[12] OS was calculated from the date of diagnosis until death from any cause or last follow-up. PFS was calculated from the date of diagnosis until death from disease progression, death from any cause, or last follow-up.

Results

Patients Who Received No RT before Relapse and HDC, Group A (n = 7)

The median ages at diagnosis and relapse were 2 years (range, 2–7 years) and 4 years (range, 3–7 years), respectively. All patients had received standard chemotherapy only before relapse due to their young age. The median time to progression from initial diagnosis was 6 months (range, 3–16 months), with five of seven patients (71%) suffering a local relapse (Table 2). All seven patients achieved minimal residual disease (MRD) before HDC with surgery, chemotherapy, and RT ($n = 4$), RT only ($n = 2$), or surgery + chemotherapy ($n = 1$) (Table 2). The myeloablative regimens included BU + melphalan (MEL) in five patients, CTX + MEL in one, and carboplatin (CARBO) + VP-16 + thiotepa (TT) in one. At a median follow-up of 28 months (range, 4 to ⩾116 months), only patients 1, 2, and 3 (Table 2) are alive and disease-free after HDC. Patients 1 and 2 also received adjuvant craniospinal RT (30–36 Gy) and focal boost (54 Gy) to the primary site after relapse. Patient 3 (Table 2) was diagnosed with Gorlin's syndrome after diagnosis of MBL, and RT was withheld despite relapse in view of the risk of inducing secondary malignancies due to radiation exposure. The remaining four patients died of progressive disease despite receiving adequate doses of RT before HDC at a median of 7 months post-HDC (range, 4–37 months; Table 2). The 3-year OS for this group is 14% (95% confidence interval, 0%–30%) (Fig. 1).

Patients Who Received Definitive RT before Relapse and HDC, Group B (n = 12)

The median ages at diagnosis and relapse were 7.5 years (range, 5–12 years) and 12 years (range, 8–19 years), respectively. All patients had received surgery and definitive RT with or without chemotherapy before relapse. The median time to progression from initial diagnosis was 44 months (range, 15–140 months), with 5 of 12 patients (42%) suffering a local relapse (Table 3). Eleven

Table 2. Clinical characteristics, treatment, and outcome in seven patients with recurrent medulloblastoma treated with high-dose chemotherapy (group A)

Patient No.	Age at Diagnosis (Years)	M Stage at Diagnosis	Rx prior to Relapse	Interval from Diagnosis to Relapse (Months)	Site(s) of Relapse	Chemo Post-relapse	RT Post-replapse	HDC Regimen	Relapse Post-HDC	Interval from HDC to Relapse (Months)	Final Outcome
1	2	M0	Chemo	16	Local	CARBO + VP-16	CSI + focal	BU + MEL	None	116+	Alive NED
2	2 Gorlin's Syndrome	M0	Chemo	15	Local	HD CTX	None	BU + MEL	None	34+	Alive NED
3	2	M0	Chemo	6	Local	Oral VP-16	CSI + focal	BU + MEL	None	110+	Alive NED
4	3	M0	Chemo	15	Local	Oral VP-16	Focal	CTX + MEL	LMD	4	Dead
5	2	M0	Chemo	6	Local	HD CTX	CSI + focal	BU + MEL	Spine	7	Dead
6	4	M1	Chemo	6	Brain, CSF	None	CSI+ focal	BU + MEL	LMD	37	Dead
7	7	M3	Chemo	3	Local, CSF	None	CSI+ focal	CARBO, TT, VP-16	LMD, BM	7	Dead

Abbreviations: Rx, treatment; Chemo, chemotherapy; RT, radiotherapy; HDC, high-dose chemotherapy; CARBO, carboplatin; VP-16, etoposide; CSI, cerebrospinal irradiation; BU, busulfan; MEL, melphalan; NED, no evidence of disease; HD, high dose; CTX, cyclophosphamide; LMD, leptomeningeal disease; TT, thiotepa; BM, bone marrow.

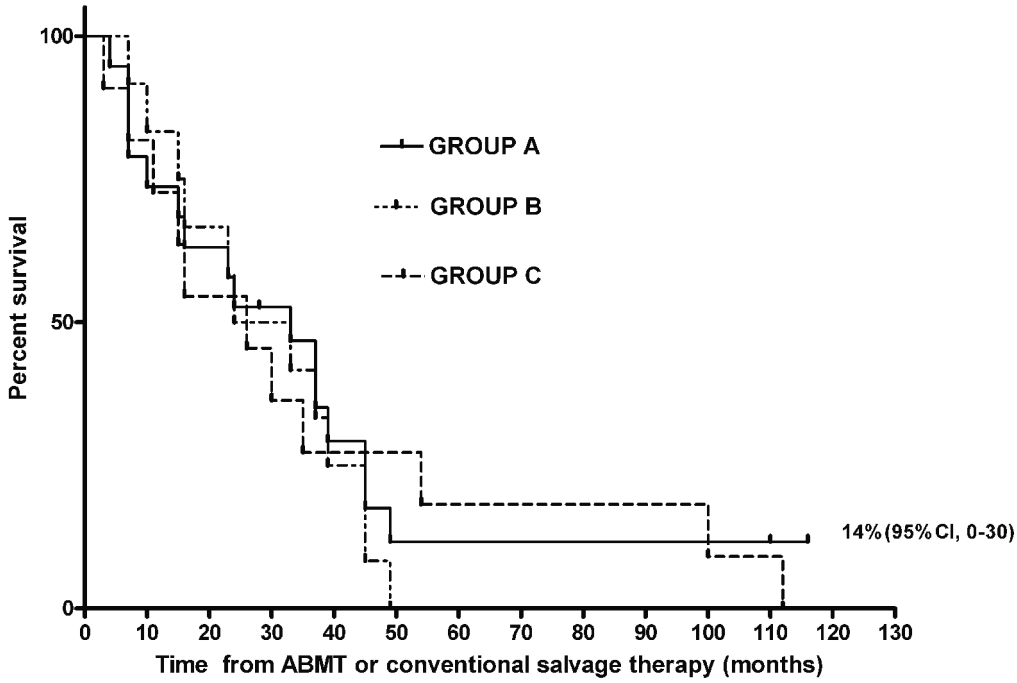

Fig. 1. Overall survival for patients in groups A, B, and C.

of 12 patients achieved MRD before HDC with chemotherapy alone (n = 9), surgery + chemotherapy + RT (n = 5), and surgery + chemotherapy alone (n = 4; Table 3). The myeloablative regimens included CTX + MEL in nine patients and BU + MEL in three patients. At a median follow-up of 35 months (range, 7–49 months), all patients have died of progressive disease (Table 3, Fig. 1).

Patients with Recurrent MBL Who Received Standard Salvage Therapy, Group C (n = 11)

The median ages at diagnosis and relapse for this group were 6 years (range, 2–24 years) and 11 years (range, 3–26 years), respectively. Eight patients had received standard therapy, including surgery, RT, and/or chemotherapy, at diagnosis (Table 4). The remaining three patients received surgery and chemotherapy only due to their young age (Table 4). Relapse after initial diagnosis occurred at a median of 18 months (range, 1–85 months) (Table 4). All patients have died at a median period of 26 months (range, 3–112 months) from relapse despite treatment with a variety of standard chemotherapeutic or investigational agents with or without standard RT (Table 4, Fig. 1).

Discussion

MBL is curable in a significant proportion of patients with average-risk disease at initial diagnosis.[2,13] However, outcome for patients with recurrent disease continues to be suboptimal. Tumor progression on or off therapy is possibly due to emergence of drug-resistant clones, and alkylator-based HDC is one strategy that could potentially overcome this therapeutic obstacle. Alkylators, including CTX, MEL, BU, CARBO, and TT, demonstrate steep log-dose response that is maintained with increasing doses of drug, resulting in progressive depletion of putative tumor stem cells and potential cure.[14] Specific properties of alkylators, including high lipid solubility, lack of cross resistance with other alkylators, and synergistic activity with topoisomerase inhibitors such as VP-16 or CPT-11 (Camptosar), are particularly suitable for treatment of patients with CNS malignancies either as single agents or in combination.[4] With myelosupression the predominant toxicity from these drugs, it is possible to use myeloablative drug doses followed by ASCR, although nonhematologic toxicities, including liver or lung damage, begin to emerge with increasing doses. Alkylator-based HDC with ASCR has gained wide prevalence in the treatment of patients with recurrent brain tumors, especially MBL.[4] Patients with tumors that are localized, chemosensitive, and in MRD before HDC are those who have responded well to this procedure.[4] While a subset of patients with recurrent MBL have been shown to have durable disease control, most of them have also received adjuvant RT either before or after HDC, making it difficult if not impossible to assess the true value of this approach. In addition, this treatment has rarely been effective in patients who suffered recurrence after definitive RT or in those with bulky metastatic disease.[4,6,10,15]

Only 3 of 19 patients with recurrent MBL who received

Table 3. Clinical characteristics, treatment, and outcome in 12 patients with recurrent medulloblastoma treated with high-dose chemotherapy (group B)

Age at Diagnosis (Years)	M Stage at Diagnosis	Rx prior to Relapse	Interval from Diagnosis to Relapse (Months)	Site(s) of Relapse	Chemo Post-relapse	RT Post-replapse	HDC Regimen	Relapse Post-HDC	Interval from HDC to Relapse (Months)	Final Outcome
6	M0	S, C, RT	27	Local	HD CTX	None	CTX + MEL	LMD	4	Dead
5	M0	S, C, RT	65	Brain	HD CTX + oral VP-16	Focal	CTX + MEL	LMD	16	Dead
7	M3	S, C, RT	25	Brain	Oral VP-16	None	CTX + MEL	LMD	5	Dead
7	M0	S, RT	102	Brain	HD CTX, CDDP, + VP-16	Focal	BU + MEL	Local	12	Dead
12	M0	S, RT	50	Local	HD CTX	None	CTX + MEL	LMD	14	Dead
8	M0	S, C, RT	45	Brain + spine	HD CTX + oralVP-16	None	BU + MEL	LMD	7	Dead
6	M0	S, C, RT	52	Brain	HD CTX + oral VP-16	Focal	CTX + MEL	Local + METS	5	Dead
8	M0	S, RT	43	Brain	CDDP, CTX, VCR, + VP-16	Focal	CTX + MEL	LMD	5	Dead
12	M3	S, C, RT	31	Local	None	None	CTX + MEL	Local	12	Dead
8	M0	S, C, RT	15	Local	None	None	BU + MEL	Local	9	Dead
7	M0	S, RT	140	Local + LMD	CTX + VCR	CSI	CTX + MEL	METS	24	Dead
8	M0	S, RT	36	Local	HD CTX, CDDP, + VP-16	None	CTX + MEL	Local + METS	13	Dead

Abbreviations: Rx, treatment; Chemo, chemotherapy; RT, radiotherapy; HDC, high-dose chemotherapy; S, surgery; C, chemotherapy; HD, high dose; CTX, cyclophosphamide; MEL, Melphalan; LMD, leptomeningeal disease; VP-16, etoposide; CDDP, cisplatin; BU, busulfan; METS, metastasis; VCR, vincristine; CSI, cerebrospinal irradiation.

Table 4. Clinical characteristics, treatment, and outcome in 11 patients with recurrent medulloblastoma treated with standard salvage therapy (group C)

Age at Diagnosis (Years)	M Stage at Diagnosis	Rx prior to Relapse	Interval from Diagnosis to Relapse (Months)	Site(s) of Relapse	Chemo Postrelapse	RT Postrelapse	Final Outcome
14	M0	S, C, RT	26	Local + LMD	CARBO, VP-16, + CPT-11	None	Dead
5	M0	S, C, RT	85	Brain	HD CTX + oral VP-16	None	Dead
3	M0	S, C, RT	1	Local + METS	HD CTX	None	Dead
10	M0	S, C, RT	14	Local	CTX, CDDP, + VP-16	Focal	Dead
20	M2	S, RT	23	LMD	IT BU + HD TEMO	None	Dead
4	M2	S, C	1	LMD	IT BU	CSI + focal	Dead
3	M2	S, C	1	LMD	None	CSI + focal	Dead
20	M0	S, C, RT	22	BM	CTX + HD MTX	None	Dead
6	M0	S, C, RT	20	LMD	Oral VP-16 + Cloretazine	None	Dead
2	M3	S, C	13	LMD	None	None	Dead
24	M4	S, C, RT	18	BM	HD CTX + oral VP-16	Focal	Dead

Abbreviations: Rx, treatment; Chemo, chemotherapy; RT, radiotherapy; S, surgery; C, chemotherapy; LMD, leptomeningeal disease; CARBO, carboplatin; VP-16, etoposide; CPT-11, irinotecan; HD, high-dose; CTX, cyclophosphamide; METS, metastasis; CDDP, cisplatin; IT, intrathecal; BU, busulfan; TEMO, temozolimide; BM, bone marrow; MTX, methotrexate.

HDC in our study had durable disease control, with two of them being long-term survivors after adjuvant definitive RT. These results seem to support the notion that HDC with regimens used in our study cures only a small number of young children with locally recurrent MBL who also received definitive RT after recurrence. One patient with Gorlin's syndrome and recurrent localized MBL is also alive and disease-free for ⩾34 months after HDC only (RT was withheld out of concern for increased risk of secondary malignancies), but her follow-up is relatively short. Similar outcomes have been reported previously in the literature in children with recurrent

Table 5. Results of prior studies of high-dose chemotherapy in patients with recurrent medulloblastoma

No. of Patients	Age (Years)	Prerelapse Definitive RT	HDC Conditioning Regimen	Post-HDC RT	Progression-Free Survivors	Reference
20	0.75–6	No	BU + TT	Focal (10)	10/20	Dupuis-Girod et al.[6]
8	2.5–15	Yes (8)	CTX + MEL	None	0/8	Mahoney et al.[20]
18	0.8–27	Yes (18)	CTX + MEL BU + MEL CARBO + VP-16	Yes (18)	4/18	Graham et al.[8]
23	2–44	Yes (16)	CARBO, TT, + VP-16	Focal or CSI (7)	7/23	Dunkel et al.[5]
5	1.5–5.4	No	CARBO, TT, + VP-16	Focal + CSI (5)	3/5	Gururangan et al.[9]
17	0–21	Yes	TT × 2	Yes (11)	1/17	Massimino et al.[10]
13	0–21	Yes (11) No (2)	CARBO + VP-16 BU + TT CTX + TT CTX + MEL CTX + TOPO BU + MEL	Yes (4)	3/13	Shih et al.[16]
26	0–21	NA	CARBO, TT, + VP-16	Yes (4)	2/26	Bode et al.[15]

Abbreviations: RT, radiotherapy; HDC, high-dose chemotherapy; BU, busulfan; TT, thiotepa; CTX, cyclophosphamide; MEL, melphalan; CARBO, carboplatin; VP-16, etoposide; CSI, craniospinal irradiation; TOPO, topotecan; NA, not available.

MBL after HDC (Table 5). In a recent publication from St. Jude Children's Research Hospital, Shih et al.[16] had only 3 survivors among 13 patients with recurrent MBL treated with a wide variety of myeloablative regimens (Table 5). All three of these patients also received adjuvant definitive RT along with HDC.[16] Similarly, Dunkel et al.[5] reported seven disease-free survivors after HDC for recurrent MBL. Five of these seven patients also received definitive RT around HDC, and the remaining two had received RT only before recurrence and were hence chemonaive at the time of HDC. In a report from the Children's Cancer Group, three of five infants with recurrent MBL, who also received definitive RT along with HDC, were long-term survivors.[9] Thus, these studies and ours validate the usefulness of RT in achieving cure in patients with recurrent MBL who had received chemotherapy only before relapse.[17,18] In this context, it should be mentioned that RT alone can cure 20%–50% of young children with MBL who suffer recurrence after standard chemotherapy.[17,19]

However, HDC was distinctively unsuccessful in improving survival in our 12 patients in group C who suffered relapse after definitive RT with or without chemotherapy, similar to what has been observed in other HDC studies. In a Pediatric Oncology Group study, Mahoney et al.[20] treated eight patients with recurrent MBL who had received definitive RT previously with HDC using CTX + MEL and reported no disease-free survivors after the procedure (Table 5). Massimino et al.[10] reported in abstract form no disease-free survivors in 17 previously irradiated patients with recurrent MBL who were treated with two sequential doses of high-dose TT and adjuvant reirradiation. The reasons for failure of HDC in these patients are unclear and may be related to lack of eradication of residual tumor stem cells in the local site or neuraxis with relatively large doubling times that might have escaped the cytotoxic effects of the HDC regimen given over a short duration.[21] While it is possible that choice of myeloablative alkylator regimens for HDC may have influenced outcomes in our patients, no published studies have clearly shown the superiority of one HDC regimen over another.[7,15,16]

The outcomes of the 11 patients in our study who were treated with conventional salvage therapy were similarly dismal, which is not surprising since most of these patients had extensive metastatic disease at recurrence after initial RT and/or chemotherapy and were unlikely to have durable disease control with any available therapy.[22,23] These patients were intentionally not given HDC due to reported poor survival after this procedure in those with metastatic disease.[6] However, the results of our study should be interpreted with caution due to the relatively small number of patients from a single institution, the limited variety of myeloablative regimens used in patients receiving HDC, and variability in the type of salvage chemotherapy used in patients in group C.

The relentless disease progression and ultimate death of 27 patients in our study irrespective of treatment received serves to underscore the fact that recurrent MBL is an invariably fatal disease. There is a desperate need for alternatives to HDC to treat these patients. Future therapies should look beyond dose escalation and focus on treatment options that minimize toxicity, maximize benefit, and maintain quality of life. In this context, metronomic therapies that provide continuous drug exposure to both tumor cells and vasculature over extended periods might provide benefit.[21,24,25] Such therapy could be combined with small-molecule kinase inhibitors against rational molecular targets, appropriate for inhibition, that signal tumor angiogenesis, proliferation, and invasion.[26]

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