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ORIGINAL ARTICLE

The impact on outcomes by using thiotepa in tandem transplant for pediatric high-risk embryonal brain tumors

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Abstract

Background: Despite aggressive treatment including surgery, radiotherapy, and adjuvant chemotherapy, the outcome of pediatric high-risk embryonal brain tumors remains poor; especially in young children, in whom early radiotherapy inevitably brings significant long-term morbidities. Single or tandem autologous stem cell transplant has been reported to improve outcomes; but optimal use is not well defined.

Methods: Pediatric patients with high-risk embryonal brain tumors who underwent tandem transplant as consolidation from August 2011 to December 2017 were included. We performed a retrospective chart review and analyzed the outcomes to identify possible prognostic factors.

Results: Eleven pediatric patients with high-risk embryonal brain tumors were enrolled. They received double or triple autologous transplant at complete response in 5 patients and at partial response in 6 for a total of 24 transplants. There were five atypical teratoid rhabdoid tumors, four medulloblastoma, one primitive neuroectodermal tumors, and one pineoblastoma. Median age at diagnosis was 1.8 years (range, 0.6-11.2 years) and at transplant was 2.2 years (range, 1.2-11.9 years). Thiotepa-based regimens were used in 13 cycles of conditioning. All patients achieved successful engraftment. No transplant-related mortality was identified. With a median follow-up of 21.2 months (range, 6.9-51.8 months), seven patients had disease progression. Disease entity and the use of one or more cycles of thiotepa-based regimen during tandem transplant had statistically significant impact on both progression-free survival and overall survival.

Conclusion: With successful engraftment and manageable toxicity, tandem transplant in pediatric patients with high-risk embryonal brain tumor is feasible and safe. Patients receiving tandem transplant with one or more cycles of thiotepa-based regimen might have better outcome than those without. In combination with salvage radiotherapy, a favorable 2-year overall survival could be achieved in the majority of patients.

Keywords: Pediatric embryonal tumors; Tandem transplant; Thiotepa-based conditioning regimen

1. INTRODUCTION

Brain tumors are the second most common cancer in childhood. Embryonal brain tumors including medulloblastomas (MB), atypical teratoid rhabdoid tumors (ATRT), primitive neuroectodermal tumors (PNET), and pineoblastomas are the most frequent malignant brain tumors in children.[1] Even with contemporary treatment such as surgery, radiotherapy (RT), and chemotherapy, those patients with high-risk features, including recurrent or metastatic disease, residual tumors, and children <3 years of age, still have worse prognosis.[1,2] Radiotherapy has been shown to be important in the treatment for those patients with embryonal tumors, however, at the price of endocrine disorders, cognitive impairment, intellectual disability, and second malignancy; especially in young children, in whom the developing brain is at risk.[1-5]

During past few decades, a series of prospective studies with the aims of effective and optimal treatment in children with embryonal tumors had been performed, taking into consideration of age range, clinical risk stratification, and molecular classification. For MB, the clinical factors for high-risk group include age <3 years old, the size of residual tumor >1.5 cm^2, initial leptomeningeal seeding according to Chang's classification,[6] and the histological phenotype of large cell/anaplastic features.[7] The most updated MB classifications identified four distinct molecular subgroups: WNT, SHH, group 3, and group 4 by their genetic expression profile.[8] Patients with WNT subtypes had significant better survival than those with SHH or non-SHH/WNT tumors. However, clinical high-risk factors still significantly influenced survival in both SHH and non-SHH/WNT subgroups.[9] The clinical trial of treatment stratification by combining molecular

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and clinical factors in newly diagnosed MBs was still ongoing (NCT01878617).

High-dose chemotherapy with autologous hematopoietic stem cell transplant (HSCT) has been used as consolidation to overcome chemotherapy resistance of tumor and the blood-brain barrier (BBB),[2,10,11] and typically it has been given after operation, with or without definite RT, and conventional chemotherapy. This therapy has been shown to improve results, not only as salvage therapy,[12-15] but also as up-front treatment in pediatric patients with embryonal brain tumors.[16-18] Some study groups also found that RT could be safely delayed or avoided in selected young children by using HSCT.[17-19] Different combinations in the conditioning regimen have been used, and thiotepa often has been included[12-15,18] for its lipophilic nature and better BBB penetration.[10] Less commonly, nonthiotepa-based condition regimen also has been applied.[10,13] The impact of different combinations in the conditioning regimen on outcome in pediatric patients with embryonal brain tumors receiving autologous stem cell transplant is still not known.

With increasing evidence of clinical benefit in pediatric patients with high-risk features receiving a single transplant, further dose intensification by using tandem transplant to safely deliver several courses of high-dose chemotherapy was revealed to improve outcomes[3,20-27] and avoid or reduce RT dose without compromising survival.[22,24] In this study, we retrospectively evaluated the feasibility and efficacy of tandem transplant in children with high-risk embryonal brain tumors, while deferring RT in young children until disease has progressed.

2. METHODS

2.1. Patients

Between February 2011 and December 2017, 11 children with embryonal brain tumors receiving tandem transplant as consolidation treatment at Division of Pediatric Hematology/Oncology of Taipei Veterans General Hospital were enrolled, according to the consensus of pediatric neuro-oncology multidisciplinary team, which consists of hemato-oncologists, neuro-oncologists, neurosurgeons, radiation oncologists, and neuroradiologists. All patients and parents or legal guardians provided informed consent before chemotherapy treatment. The cutoff point for data analyses was April 2018.

2.2. Treatment before tandem transplant

All patients underwent an evaluation of extent of disease, including whole brain and spine magnetic resonance imaging at initial diagnosis and every 3 months during treatment. Maximal surgical resection of the primary lesion was performed with attention to preservation of neurological function. For children with MB with high-risk features, eg residual tumor >1.5 cm^2, <3 years of age, leptomeningeal seeding, or recurrence, and for children of any age with embryonal brain tumors other than MB, conventional chemotherapy with ifosphamide (2400 mg/m^2/day, days 1-3), cisplatin (90 mg/m^2/day, day 2), and etoposide (150 mg/m^2/day, days 1-3) for five cycles was given, followed by tandem transplant for 2 to 3 cycles, depending on the sufficiency of peripheral blood stem cells and also the reimbursement of insurance coverage from the national health insurance system in our country. Focal or craniospinal RT was deferred in those <3 years of age unless progression or leptomeningeal seeding occurred during conventional chemotherapy. The average dose for salvage RT was 45 to 50 Gy/1.8 Gy per fraction to the primary tumor bed and 36 Gy/1.8 Gy per fraction to craniospinal axis. For patients >3 years without seeding, the total dose to the primary tumor bed and craniospinal axis was 50 to 56 Gy and 30 Gy, respectively.

2.3. Tandem transplant

The conditioning regimens in tandem transplant included either thiotepa-based regimen (carboplatin 500 mg/m^2/day, day −8 to −6; thiotepa 300 mg/m^2/day, day −5 to −3; etoposide 250 mg/m^2/day, day −5 to −3) or melphalan-based regimen (cyclophosphamide 1500 mg/m^2/day, day −8 to −5; melphalan 60 mg/m^2/day, day −4 to −2) at about an 8-week interval to prevent toxicity from tandem transplant. Hematopoietic stem cells containing $\geq 2 \times 10^6$ CD34+ cells/kg were infused on day 0. During transplant, patients were isolated in a single room and received antibiotic prophylaxis including levofloxacin, micafungin, and metronidazole from day −10 until engraftment. Neutrophil engraftment is defined as the first day of absolute neutrophil count exceeding 500/uL for 3 successive days and platelet engraftment as the date of platelet count exceeding 20 000/uL without transfusion for 7 days.

2.4. Data collection

Patient characteristics, disease status before transplant, stem cell dose, times of transplant, use of a thiotepa-based regimen, engraftment, posttransplant complications, and outcome were evaluated by retrospective chart review.

2.5. Statistics

Overall survival (OS) rate was defined from the first stem cell infusion date to death or the date of the last follow-up for living patients. Progression-free survival (PFS) rate was assessed from the first stem cell infusion date to the date of progression, relapse, or death. OS and PFS were estimated by using the Kaplan-Meier analysis, and the impact of the patient-, disease-, or treatment-related variables on survival was compared using log-rank test, in which $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Patient characteristics

Patient demographics, disease status, and treatment for 11 patients are listed in Table 1. Gross total or near total removal of the primary tumor was achieved in seven patients, and leptomeningeal seeding was present at initial diagnosis in three patients. Among seven patients <3 years of age at diagnosis, one received focal RT before transplant due to progression, and the other patient (with pineoblastoma) received craniospinal RT with boosting on primary tumor bed due to his age, approaching 3 years. Of the four patients with MB receiving tandem transplant, two had leptomeningeal seeding at diagnosis, one had recurrent disease, and one was <3 years old. Complete response (CR) was achieved by the end of induction chemotherapy in five patients and partial response (PR) in six.

3.2. HSCT details and complications

Nine patients received autologous HSCT twice and the others received three times. Thirteen (54%) cycles of thiotepa-based conditioning were used among a total of 24 transplants. Table 2 shows the treatment details and patient outcomes of tandem transplant. The median infused CD34+ cell dose was 4.709×10^6/kg (range, $1.808\text{-}28.962 \times 10^6$/kg). Ten patients had 22 infusions of autologous peripheral blood stem cells (PBSC), while the other one had coinfusions of PBSC and bone marrow for each HSCT due to poor PBSC mobilization, probably related to heavy treatment before PBSC harvest. All patients achieved successful engraftment. The median days for neutrophil and platelet engraftment were 10 days (range, 8-15 days) and 18 days (range, 7-56 days), respectively.

Posttransplant complications included 22 episodes of neutropenic fever (92%), 14 cases of gastroenteritis or mucositis (58%), three instances of sepsis or bacteremia (13%), six fungal infections (25%), four instances of upper or lower gastrointestinal bleeding (17%), two cases of hemorrhagic cystitis (8%), one cytomegaloviral viruria (4%), and one instance of skin exfoliation over skin folds (4%). No transplant-related mortality was identified.

3.3. Use of irradiation

Of the seven children <3 years of age, pretransplant craniospinal RT was avoided in six patients. One patient (no 3) with intradural and extramedullary spinal ATRT over T11-L4 with extraspinal extension received scheduled posttransplant focal and craniospinal RT at the age of 2.8 years due to persistence of residual tumor after a triple transplant, but he remains progression free for 46.3+ months to date. Among the other five young children without craniospinal RT, four had progression or relapse requiring salvage RT after tandem transplant and were <24 months of age at diagnosis (three ATRT, one PNET). Only one young patient with MB who received no focal and craniospinal RT had no subsequent relapse.

3.4. Outcome

With a median follow-up of 21.2 months (range, 6.9-51.8 months) after the first HSCT, the 2-year Kaplan-Meier estimate for PFS and OS were 36 ± 15% and 80 ± 13%, respectively (Figure 1A). Seven patients had tumor progression or relapse at a median interval of 8.7 months (range, 2.9-16.1 months) and received salvage treatment, including intrathecal chemotherapy and RT. Four patients died of disease progression.

The disease entity had a statistically significant impact on 2-year PFS (Figure 1B) but not on OS. Patients with MB had 2-year PFS of 50 ± 25%, while patients with ATRT or other diseases had that of 40 ± 22% and 0%, respectively (p = 0.02). The 2-year OS were 100% for MB, 80 ± 18% for ATRT, and 0% for other diseases (p = 0.10). In addition, patients who received ≧1 cycle of thiotepa-based regimen during tandem transplant had significantly better outcome on both 2-year PFS (44 ± 17% vs 0%) (Figure 1C) and OS (100% vs 0%) than those who did not (p < 0.001 for PFS; P = 0.001 for OS). The 2-year PFS and OS rates were also higher in patients with CR before the first HSCT than in those with PR (PFS 60 ± 22% vs 17 ± 15%, OS 100% vs 63 ± 21%) (Figure 1D), which were statistically insignificant (P = 0.16 for PFS, p = 0.11 for OS). Neither age at diagnosis or at first HSCT, interval between diagnosis to first HSCT, operative resectability, initial seeding, use of RT before the first HSCT, nor times of HSCT had statistically significant impact on outcome.

Table 1

Patient characteristics

Characteristics	Patients (n = 11)
Gender (Male:Female)	5:6
Median age at diagnosis, y (range)	1.8 (0.6-11.2)
Median age at first HSCT, y (range)	2.2 (1.2-11.9)
Interval between diagnosis to first HSCT, m (range)	7.3 (4.8-20.5)
Diagnosis	
Medulloblastoma	4
ATRT	5
PNET	1
Pineoblastoma	1
Disease status before first HSCT	
Complete response	5
Partial response	6
Radiotherapy before first HSCT	
Focal alone	1
Focal + Craniospinal axis	5
No	5
Times of HSCT	
2	9
3	2
Conditioning regimen (n = 24)	
Thiotepa based	13
Nonthiotepa based	11

ATRT = atypical teratoid rhabdoid tumor; HSCT = hematopoietic stem cell transplant; PNET = primitive neuroectodermal tumor.

4. DISCUSSION

Our retrospective study demonstrated the feasibility of tandem transplant in pediatric patients with high-risk embryonal brain tumor with successful engraftment and manageable toxicity profile. In our study, the 2-year Kaplan-Meier estimate for PFS was 36 ± 15%, which is comparable with other contemporary studies.[3,22,24,27] The relatively high 2-year OS (80 ± 13%) might be related to use of salvage RT and chemotherapy, which nevertheless did not prevent further recurrence.

For our four patients with MB, the efficacy of tandem transplant is not satisfactory with the 2-year PFS 50 ± 25%. In a study by Dufour et al,[23] patients with high-risk embryonal tumors, mostly MB, were enrolled and received tandem transplant as frontline therapy. Their 3-year EFS and OS were greater, 79% and 82%, respectively, which reflected enrollment of older patients and the use of tandem transplant as frontline treatment. Sung et al [20] and Gilman et al[25] both investigated the feasibility of tandem transplant in MB patients with relapse and reported a 3-year EFS 29% and 25%, respectively. With the introduction of subgrouping by genetic signatures in MBs according to WHO classification in 2016,[8] the outcome differences among MB subgroups may be revealed, which may also guide in optimal use of tandem transplant in patients with MB in the future.

The treatment results in five children with ATRT seem promising with 2-year PFS and OS of 40.0 ± 22% and 80 ± 18%, respectively. In the past, patients with ATRT receiving conventional therapy had a dismal prognosis with a 3-year EFS of 13% in a German HIT database during 1988-2004.[28] In Head Start III using single transplant in patients with ATRT at frontline

Table 2

Summary of treatment details and patient outcomes

Patient	Age at diagnosis and first HSCT, y	Disease and status before first HSCT	Radiotherapy before first HSCT	Times of HSCT	Times of thiotepa-based regimen usage	PFS, mo	OS, mo	Disease status
1	1.3/1.8	ATRT, PR	Focal	2	0	5.7	13.9	DOD
2	1.3/1.9	MB, CR	…	2	2	51.8+	51.8+	NED
3	1.8/2.2	Spinal ATRT, PR	…	3	3	46.3+	46.3+	NED
4	1.5/2.0	Spinal PNET, PR	…	2	0	2.9	6.9	DOD
5	0.6/1.2	ATRT, PR	…	2	2	8.7	28.0	DOD
6	11.2/11.9	MB with seeding, PR	Focal + CSI	2	1	16.1	27.3	DOD
7	0.9/1.5	ATRT, CR	…	3	1	12.0	21.8+	AWD
8	8.1/9.0	MB with seeding, CR	Focal + CSI	2	1	21.2+	21.2+	NED
9	7.1/7.8	ATRT, CR	Focal + CSI	2	1	18.2+	18.2+	NED
10	3.9/5.6	MB, 2nd PR	Focal + CSI	2	1	9.1	9.2+	AWD
11	2.9/3.6	Pineoblastoma, CR	Focal + CSI	2	1	7.2	8.3+	AWD

ATRT = atypical teratoid/rhabdoid tumor; AWD = alive with disease; CR = complete response; CSI = craniospinal irradiation; DOD = died of disease; HSCT = hematopoietic stem cell transplant; MB = medulloblastoma; NED = no evidence of disease; OS = overall survival; PFS = progression-free survival; PNET = primitive neuroectodermal tumor; PR = partial response.

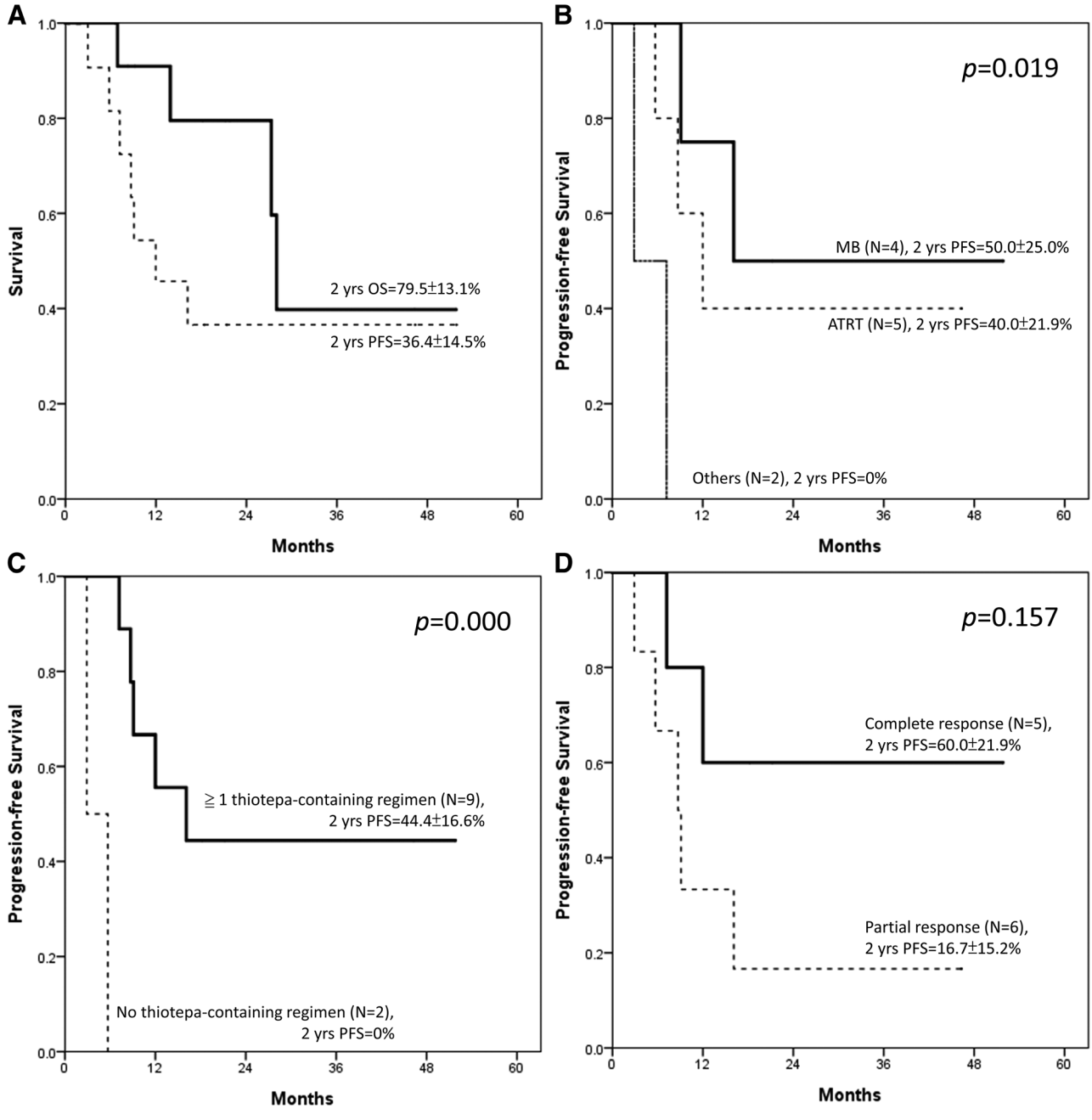

Fig. 1 Survival of 11 patients with embryonal brain tumors receiving tandem transplant. A, 2-year PFS and OS. B, 2-year PFS among different disease groups. C, 2-year PFS in patients receiving no cycles or ≧1 cycle of thiotepa-based regimen. D, 2-year PFS in patients achieving CR or PR before first HSCT. ATRT, atypical teratoid rhabdoid tumor; CR, complete response; HSCT, hematopoietic stem cell transplant; MB, medulloblastoma; OS, overall survival; PFS, progression-free survival; PR, partial response.

during 2003-2009, 21% EFS was achieved at 3 years.[29] With the advancement of tandem transplant later, induction chemotherapy, followed by tandem transplant using three cycles of thiotepa and carboplatin conditioning, was applied in children with ATRT in the study of Sick Kids with promising results.[26] In a COG study (ACNS0333),[27] 65 patients with ATRT of any age were treated with tandem transplant frontline and involved field RT, and the 2-year EFS was 42%.

A retrospective study by Guerra et al. of 44 pediatric patients receiving tandem transplant showed that 7 of 12 children with embryonal brain tumors receiving tandem transplant and who were <3 years of age did not relapse despite avoiding any RT, including five patients with MB and two with PNET.[24] However, three children with ATRT who were <3 years of age relapsed at posttransplant 0.1-0.56 years and ultimately received RT. Sung et al[20] reported a series of 25 children <3 years of age withholding RT till 3 years of age or avoiding until relapse, in which a total of 16 patients had embryonal brain tumors. Use of any RT was abandoned until relapse/progression in five children with embryonal tumors completing double transplant, among whom only one child with MB did not have subsequent relapse. The other four children (two with ATRT, one with MB, and one with PNET) experienced progression of disease after double transplant, and three of them received salvage RT. Our data, consistent with the reports in the literatures, showed four (3 ATRT and 1 PNET) of five young children <2 years of age without craniospinal RT had progression or relapse requiring salvage RT after tandem transplant. These findings demonstrate that tandem transplant may safely delay and even avoid the use of RT in some selected cases with embryonal brain tumors, but may not prevent tumor progression/relapse, especially in children with ATRT under 3 years of age.

Table 3

Outcome of tandem transplant in pediatric patients with embryonal brain tumors

Study	Period	Patient inclusion (n)	Disease (n)	HSCT times	Conditioning regimen	Interval	PFS or EFS	OS
This study	2011-2017	Fresh (10) Relapse (1)	ATRT (5) MB (4) Others (2)	2-3	Thio + carbo + VP16 or Mel + endoxan	8 wks	2-y PFS: 36%	2-y OS: 40%
ACNS0333 (COG)[27]	2008-2014	Fresh (65)	ATRT (65)	3	Thio + carbo → Thio + carbo → Thio + carbo	4 wks	2-y EFS: 42%	2-y OS: 53%.
Korea[22]	2004-2012	Fresh (13)	ATRT (13)	2	Thio + carbo + VP16 → Mel + endoxan	12 wks	5-y EFS: 39%	5-y OS: 35%
Children Hospital of Los Angeles[24]	1999-2012	Fresh (27) Relapse (17)	MB (11) PNET (10) ATRT (8) Others (14)	2-3	Thio ± others	3-4 wks	5-y EFS: 46%	5-y OS: 52%
Sick Kids[26]	2003-2008	Fresh and <4 y/o (8)	ATRT (8)	3	Thio + carbo → Thio + carbo → Thio + carbo	3 wks	4 patients are alive without evidence of tumor at a median follow-up of 52 mo	
France[23]	2001-2010	Newly diagnosed high risk (24) (mostly <5 y/o)	MB (21) PNET (3)	2	Thio → Thio	3 wks	3-y EFS: 79%	3-y OS: 82%
Korea[20]	1999-2005	Relapse (11) Newly diagnosed high risk (14)	MB (18) PNET (7)	1-2	Mel + endoxan → Thio + carbo + VP16	12 wks	3-y EFS: (>3 y/o and fresh) 83% (relapse) 29%	3-y OS: (>3 y/o and fresh) 83% (relapse) 26%
CCG99703[3]	1998-2004	Fresh and <3 y/o (92)	MB (36) PNET (17) ATRT (8) Others (31)	3	Thio + carbo → Thio + carbo → Thio + carbo	3 wks	5-y EFS: 44%	5-y OS: 64%
CCG[25]	1995-2002	Relapse (32)	MB (18) PNET (1) Others (13)	2	Thio + BCNU → Thio + carbo	4-6 wks	3-y EFS: 25%	3-y OS: 38%

ATRT = atypical teratoid rhabdoid tumor; CCG = Children Cancer Group; COG = Children Oncology Group; EFS = event-free survival; HSCT = hematopoietic stem cell transplant; MB = medulloblastoma; OS = overall survival; PFS = progression-free survival; PNET = primitive neuroectodermal tumor; VP16 = etoposide.

The lipophilic nature of thiotepa and better BBB penetration led to the investigation of its use combined with stem cell rescue to increase dose intensity of chemotherapy for better tumor control in central nervous system.[2,10,13] In the literature, many investigators describe the use of thiotepa-based conditioning regimen in the setting of single transplant,[12-15,18] and others chose a non-thiotepa-based regimen,[13,16,17] mostly melphalan-based chemotherapy,[10,13,17] which also has been used as a conditioning regimen in other childhood solid cancers.[10,17] While using tandem transplant as part of consolidation in those patients, most transplants relied on two or three successive courses of a thiotepa-based regimen during tandem transplant at an interval of 3-8 weeks (Table 3).[3,23-27] Investigators in Korea used a different approach by alternating a thiotepa-based or melphalan-based conditioning regimen in double transplant at an interval of 12 weeks[20-22]; however, no studies have yet established the optimal use of a conditioning regimen for patients with embryonal tumors in the setting of either single or tandem transplant.

Because thiotepa is not readily available in our country, and because of its high price without insurance reimbursement in our healthcare system, we did not routinely administer a thiotepa-based regimen during tandem transplant. Comparisons of possible benefits, risks, and costs of a thiotepa-based versus a melphalan-based regimen were discussed with parents, which created an opportunity to observe a difference in outcome between patients receiving a thiotepa-based regimen or those not receiving it. Our study, although a retrospective analysis with a small number of patients, identified a difference in outcome in pediatric patients with high-risk embryonal brain tumors receiving tandem thiotepa-based regimens for one or more cycles in both PFS (Figure 1D) and OS (not shown) ($p < 0.001$ for PFS, $p = 0.001$ for OS). Two patients who chose to use nonthiotepa-based conditioning regimens in double transplant eventually relapsed within 6 months, while four patients were disease free after tandem transplant using at least one cycle of thiotepa-based regimen with a median PFS of 16.1 months (range, 7.2-51.8 months), for a total of nine patients.

The limitations of our study include its retrospective nature, small number of cases, and different disease entities, which might prevent us from formulating a universal recommendation. With enrollment of more cases of a uniform disease entity in a prospective setting, the differences in outcome between use of thiotepa and lack thereof, and the effect of withholding RT among different embryonal brain tumors in patients receiving tandem transplant might be revealed.

In conclusion, the data in our series shows that tandem transplant is feasible and safe for the treatment of high-risk embryonal brain tumors in young children, with a manageable toxicity profile. Combined with salvage RT, a favorable 2-year OS could be achieved in the majority of patients in the study. Patients receiving tandem transplant for one or more cycles of thiotepa-based regimen might have better outcome than those not receiving this treatment.

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