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ORIGINAL REPORT

Intensive Multimodality Treatment for Children With Newly Diagnosed CNS Atypical Teratoid Rhabdoid Tumor

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Atypical teratoid rhabdoid tumor (ATRT) of the CNS is a highly malignant neoplasm primarily affecting young children, with a historic median survival ranging from 6 to 11 months. Based on a previous pilot series, a prospective multi-institutional trial was conducted for patients with newly diagnosed CNS ATRT.

Patients and Methods
Treatment was divided into five phases: preirradiation, chemoradiation, consolidation, maintenance, and continuation therapy. Intrathecal chemotherapy was administered, alternating intralumbar and intraventricular routes. Radiation therapy (RT) was prescribed, either focal (54 Gy) or craniospinal (36 Gy, plus primary boost), depending on age and extent of disease at diagnosis.

Results
Between 2004 and 2006, 25 patients were enrolled; 20 were eligible for evaluation. Median age at diagnosis was 26 months (range, 2.4 months to 19.5 years). Gross total resection of the primary tumor was achieved in 11 patients. Fourteen patients had M0 disease at diagnosis, one patient had M2 disease, and five patients had M3 disease. Fifteen patients received radiation therapy: 11 focal and four craniospinal. Significant toxicities, in addition to the expected, included radiation recall (n = 2) and transverse myelitis (n = 1). There was one toxic death. Of the 12 patients who were assessable for chemotherapeutic response (pre-RT), the objective response rate was 58%. The objective response rate observed after RT was 38%. The 2-year progression-free and overall survival rates are 53% ± 13% and 70% ± 10%, respectively. Median overall survival has not yet been reached.

Conclusion
This intensive multimodality regimen has resulted in a significant improvement in time to progression and overall survival for patients with this previously poor-prognosis tumor.

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INTRODUCTION

First described in the 1980s,[1] atypical teratoid rhabdoid tumor (ATRT) of the CNS is a highly malignant neoplasm primarily affecting young children. It is thought that the actual number of cases of ATRT has been significantly underestimated because of historical grouping with other malignant high-grade embryonal CNS tumors, such as medulloblastoma and primitive neuroectodermal tumor.[2,3] Though treatment regimens designed for these other CNS neoplasms have been used in patients with ATRT, most patients with ATRT have suffered rapid disease recurrence and death owing to progression.[3,4] Consequently, the generally accepted outcome for patients with ATRT is dismal, with median survival time reported between 6 and 11 months.[3,5] Information presented at a National Cancer Institute Workshop in 2001,[5] including data from a national rhabdoid tumor registry, demonstrated a median survival of approximately 8.5 months. This workshop also reported on more favorable outcomes when aggressive surgery and early radiotherapy were incorporated. In a review of 32 infants and children treated for CNS ATRT,[6] treatment was highly variable but typically included multimodality treatment that included surgery, radiation, and chemotherapy. Median survival in this analysis was 6.5 months.

In a case series reported by Olson et al,[7] three patients with newly diagnosed ATRT achieved prolonged remission after surgery, radiation therapy (RT), and chemotherapy (systemic and intrathecal) based on a protocol for children with rhabdomyosarcoma with parameningeal extension (Intergroup

Rhabdomyosarcoma Study-III [IRS-III], Regimen 36). Two of those three patients were long-term survivors. Similarly, Weinblatt and Kochen[8] published a single case report of sustained remission of ATRT after surgery, RT, and the same IRS III–based therapy. Our institution has previously reported on four patients using the IRS III-based therapy, including two patients with newly diagnosed and two with recurrent ATRT.[9] Three of the four patients remain alive and well without evidence of disease a median of 6.5 years since the completion of treatment. Based on the four patients previously described in the literature and the four treated at the Dana-Farber Cancer Institute (Boston, MA), a multi-institutional phase II clinical trial was conducted to test the efficacy of aggressive multimodality approach for children with newly diagnosed ATRT.

PATIENTS AND METHODS

Patients

Between February 2004 and September 2006, 25 children with newly diagnosed primary ATRT were enrolled. Three patients were deemed ineligible after central pathology review; one patient was deemed ineligible by the Dana-Farber Cancer Institute institutional review board, and a fifth patient withdrew before receiving any therapy. The 20 remaining eligible patients were treated at the Dana-Farber Cancer Institute or one of the participating institutions. The cutoff point for data analyses was May 2008.

Surgery

All patients underwent maximal possible surgical resection of the primary lesion consistent with preservation of neurologic function. The extent of surgical resection, defined as gross total resection (GTR), subtotal resection, or biopsy, was based on review of postoperative magnetic resonance imaging (MRI) and the surgeon's intraoperative assessment. Patients without obstruction of CSF flow, based on CSF flow study, underwent placement of an intraventricular catheter and reservoir to enable administration of intraventricular chemotherapy. Patients with a ventriculoperitoneal shunt were permitted to enter onto the study.

Pathologic Analysis

Pathologic diagnosis of ATRT was confirmed by immunohistochemistry demonstrating loss of nuclear expression of INI1 (BAF47). Tumor specimens were also reviewed by one of two neuropathologists (P.B., L.R.A.). In addition, for any available specimens, molecular genetic studies were also performed, confirming the diagnosis of ATRT (J.A.B.).

Staging

All children underwent an extent of disease evaluation, including MRI of the brain and spine, evaluation of CSF cytology, computed tomography of the chest and abdomen, and bone marrow aspirate and biopsy. Metastatic disease was assessed using the Chang staging system.[10] Patients with evidence of neuraxis dissemination were eligible for enrollment, but children with metastatic or synchronous tumor outside the brain and spine were excluded.

Chemotherapy

Induction chemotherapy was required to be initiated within 50 days of the most recent definitive surgery. Postsurgical treatment was divided into five phases, using a modified IRS-III regimen, consisting of preirradiation induction therapy (weeks 1 through 6), chemoradiation induction therapy (weeks 7 through 12), postradiation induction therapy (weeks 13 through 18); maintenance therapy (weeks 19 through 44), and continuation therapy with or without doxorubicin (weeks 45 through 51; see Appendix, online only). The chemotherapy backbone of the IRS-III regimen included the agents vincristine, dactinomycin, cyclophosphamide (specifically, in combination), cisplatin, doxorubicin, and imidazole carboximide (DTIC). This regimen was modified to include temozolomide, an oral analog of DTIC with the ability to penetrate the CNS, in lieu of DTIC. Intrathecal (IT) chemotherapy was also included. Patients with M0 disease received IT chemotherapy with methotrexate, cytarabine, and hydrocortisone, coinciding with a cycle of chemotherapy. Patients with initially positive CSF cytology received IT chemotherapy weekly until two consecutive CSF samples were negative for malignant cells. Once two consecutive CSF samples were negative for malignant cells, patients then received IT therapy as scheduled for patients with M0 disease. Intrathecal chemotherapy administration alternated between the intralumbar and intraventricular routes. For patients ineligible for placement of an intraventricular device, intrathecal chemotherapy was administered via the intralumbar route only.

RT

Patients with M0 stage at presentation received focal RT. Treatment technique involved three-dimensional conformal or intensity-modulated delivery. Fraction sizes were 1.8 Gy for all target volumes, with total dose of 54 Gy. For infratentorial tumors, a 1.5-cm margin was respected and for supratentorial tumors, a 1.0-cm margin. For patients older than 3 years with M+ disease at diagnosis, craniospinal irradiation was prescribed. The total dose to the craniospinal axis was 36 Gy in 1.8 Gy fractions, and primary sites of disease received a total dose of 54 Gy. Spinal or brain metastases could be boosted, each with an additional 5.4 Gy in three fractions of 1.8 Gy. Patients with evidence of residual disease $\leq$ 2.5 cm on post-RT imaging studies could receive stereotactic radiosurgery.

Supportive Care

Platelet counts and hemoglobin were maintained with irradiated blood products, as necessary. Filgrastim was administered after chemotherapy cycles. Febrile neutropenic patients were treated with broad-spectrum intravenous antibiotics and antifungal agents when appropriate. Patients received trimethoprim-sulfamethoxazole or an equivalent *Pneumocystis carinii* pneumonia prophylactic regimen during therapy. Nonenzyme-inducing anticonvulsants were allowable.

Toxicity and Disease Evaluation

The Common Terminology Criteria for Adverse Events (version 2.0) was used to grade toxicity. The site and measure for all grade 3 and 4 toxicities were collected.

At prescribed times throughout treatment, disease status was assessed with appropriate neurologic examinations, CSF cytologic examinations, and neuroimaging studies. Criteria for response/relapse were defined as follows: continued complete response, complete surgical resection of all initially demonstrable tumor on MRI without the appearance of any new areas of disease and M0 staging at diagnosis; complete response (CR), complete resolution of all initially demonstrable and/or residual tumor on MRI without the appearance of any new areas of disease and negative CSF cytology; partial response, $\geq$ 50% decrease in the sum of the products of the maximum perpendicular diameters of the residual tumor relative to the baseline postsurgical evaluation, without the appearance of any new areas of disease, CSF cytology unchanged from that at diagnosis or clearing after being initially positive; stable disease, less than 50% decrease in the radiologic imaging, as calculated above, and CSF cytology unchanged from that at diagnosis or clearing after being initially positive; and progressive disease, $\geq$ 25% increase in the radiologic imaging, calculated as above, or the appearance of any new areas of disease or appearance of positive cytology after two consecutive negative samples.

Cytologic response was defined as follows: CR, the absence of tumor cells on two consecutive samples taken at least 1 week apart in a patient with previously documented positive cytology; progressive disease, the occurrence of positive cytology after two consecutive negative reports at least 1 week apart in a patient who was initially negative or had a prior response.

Informed Consent

Signed, informed consent was obtained for each child from at least one parent or legal guardian. Protocols were approved by each local institutional review board.

Statistical Analysis

Overall survival (OS) and progression-free survival (PFS) were estimated by the method of Kaplan and Meier. For OS analysis, survival time was calculated from the date of diagnosis to the date of death or last follow-up. For

PFS analysis, an event was either relapse (or progression) or death in the absence of relapse (or progression). PFS time was calculated from the date of diagnosis to the date of relapse, death in the absence of relapse or progression, or last follow-up visit. Log-rank tests and Cox regression models were also performed to investigate the impact of the variables—extent of resection, M stage, primary tumor location, and age—on survival.

RESULTS

Patient Demographics

Patient demographics, responses, and outcomes are listed in Table 1. Of the 20 eligible patients, there were nine male and 11 female patients. The median age at diagnosis for patients was 26 months (range, 2.4 months to 19.5 years). Twelve patients were younger than 3 years of age at diagnosis. Primary tumors were located in the supratentorial compartment in 12 patients and in the posterior fossa in eight patients. Among the 12 patients whose tumors were located in the supratentorial compartment, only two patients were younger than 2 years (17%); for patients whose tumors were located in the posterior fossa, six (75%) of eight were younger than 2 years. GTR of the primary tumor was achieved in 11 patients, seven of whose tumors were located in the posterior fossa. Subtotal resections were achieved in six patients, and three patients had biopsy only. There were 14 patients with M0 disease at diagnosis, one patient with M2 disease, and five patients with M3 disease.

Responses and Outcomes

Twelve patients completed the prescribed treatment. Eight patients came off study for the following reasons: toxic death (n = 1), progressive disease on treatment during weeks 2 through 13 (n = 4), radiation recall at week 50 (n = 1), transverse myelitis at week 21 (n = 1), and noncompliance with the protocol treatment at week 7 (n = 1). All patients received some IT therapy, either via lumbar only or via both lumbar and intraventricular routes.

Fifteen patients received RT on study, 11 of whom received conformal focal RT, and four of whom received craniospinal irradiation. Four patients did not receive any RT either because of early progression (three patients) or toxic death (one patient). One patient received RT after the patient was taken off study for noncompliance; this patient ultimately experienced disease recurrence and died. Of the 11 patients who received conformal RT, two patients have experienced relapse. Among the four patients who received craniospinal irradiation, three have experienced relapse, at 1.8 to 2.2 years postdiagnosis.

Disease evaluations were performed at prescribed times, including pre-RT at week 7, post-RT at week 19, and at the end of therapy. Of the 12 patients assessable for chemotherapeutic response (pre-RT), the objective response rate (CR plus partial response) was 58% (seven of 12 patients). Of the eight patients assessable for response post-RT, the objective response rate was 38% (three of eight patients).

The 1-year PFS and OS rates (± standard error) are 70% ± 10% and 75% ± 10%, respectively, and the 2-year PFS and OS rates (± standard error) are 53% ± 13% and 70% ± 10%, respectively (Fig 1). Median OS has not yet been reached.

Feasibility of Chemotherapy Delivery and Toxicities

For the 12 patients who completed all protocol treatment, the 51-week treatment plan required 52 to 78 weeks to complete. In addition, there were frequent dose adjustments for grade 3 to 4 toxicities. The most frequently reported significant toxicities included bone marrow suppression; febrile neutropenia; infection; GI (anorexia, mucositis, nausea, vomiting, abdominal pain); electrolyte and hepatic

Table 1. Patient Demographics, Responses, and Outcomes

Patient	Age at Diagnosis (years)	Primary Tumor Location	INI-1/Baf 47 Status	Chang Stage	Extent of Resection	Response to Induction	RT Field	Response Post-RT	Time to Relapse (years)	Duration of Survival (years)	Disease Status
1	0.3	PF	Negative	M0	GTR	CCR	Conformal	CCR		1.6	NED
2	0.4	Supratentorial	Negative	M0	STR	PR	N/A	PD	0.3	0.3	DOD
3	0.8	PF	Negative	M0	GTR	CCR	Conformal	CCR		1.5	NED
4	0.9	PF	Negative	M2	GTR	SD	Conformal	SD		1.5	AWD
5	1.3	PF	Negative	M0	GTR	CCR	Conformal	CCR		2.9	NED
6	1.4	Supratentorial	Negative	M0	GTR	CCR	Conformal	CCR		1.7	NED
7	1.6	PF	Negative	M0	STR	CR	Conformal	CCR		2.6	NED
8	1.6	PF	Negative	M3	STR	PR	Off-study	N/A	0.3	1.5	DOD
9	2.2	Supratentorial	Negative	M0	STR	SD	Conformal	PD	0.6	0.9	DOD
10	2.2	Supratentorial	Negative	M0	Bx	PD	N/A	N/A	0.1	0.2	DOD
11	2.4	Supratentorial	Negative	M0	STR	PR	Conformal	SD		1.4	AWD
12	2.7	Supratentorial	Negative	M0	GTR	TD	N/A	N/A	N/A	0.1	TD
13	3.1	Supratentorial	Negative	M0	GTR	CCR	Conformal	CCR		1.9	NED
14	3.2	Supratentorial	Negative	M0	STR	SD	Conformal	CR		3.3	NED
15	4.6	Supratentorial	Negative	M3	Bx	PR	N/A	PD	0.2	0.7	DOD
16	5.2	Supratentorial	Negative	M3	GTR	CR	CSI	CCR		2.6	NED
17	5.3	PF	Negative	M0	GTR	CCR	Conformal	CCR		2.6	NED
18	7.0	PF	Negative	M3	STR	PR	CSI	PR	1.8	2	DOD
19	8.4	PF	Negative	M0	GTR	CCR	CSI	CCR	2.2	2.8	AWD
20	19.5	Supratentorial	Negative	M3	Bx	Mixed	CSI	PR	2.0	2.1	DOD

Abbreviations: RT, radiation therapy; PF, posterior fossa; GTR, gross total resection; CCR, continued complete response; NED, no evidence of disease; STR, subtotal resection; N/A, not applicable; PD, progressive disease; DOD, dead of disease; AWD, alive with disease; CR, complete response; PR, partial response; SD, stable disease; Bx, biopsy; TD, toxic death; CSI, craniospinal irradiation.

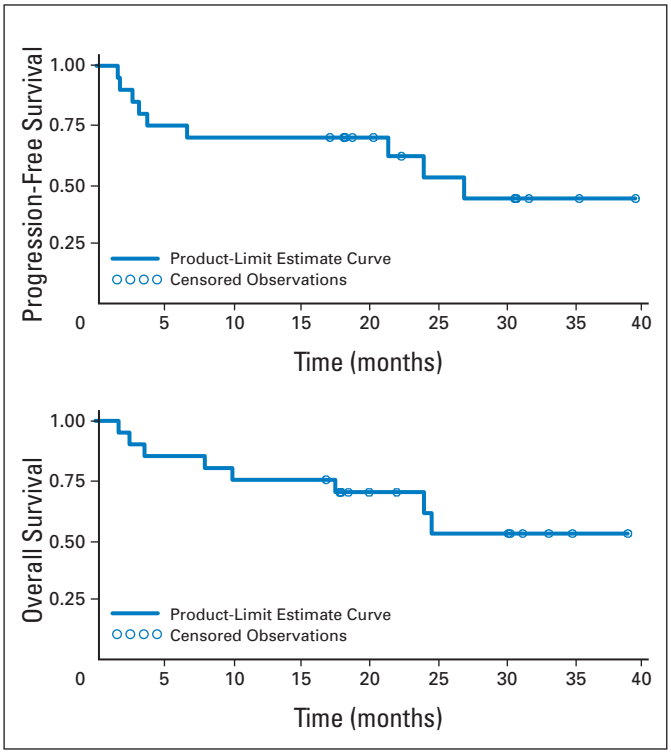

Fig 1. Progression-free and overall survival by Kaplan-Meier method among children with CNS atypical teratoid rhabdoid tumor.

disturbances (hypokalemia, hyponatremia, hypomagnesemia, hypophosphatemia, hyperglycemia, ALT elevation); cranial, motor, and sensory neuropathies; and high-frequency hearing loss.

There was one toxic death from pneumococcal sepsis at week 2. Also notable were two patients who experienced radiation recall; one patient was removed from therapy at week 50 and the other completed all prescribed therapy. Both of these patients are currently alive, 2.8 and 1.4 years from diagnosis, respectively. There was also one patient who experienced transverse myelitis at week 21 and was taken off therapy; this patient is currently alive with no evidence of disease 2.6 years from diagnosis.

Relapses

To date, eight patients have experienced relapse, seven of whom have died of progressive disease. The sites of relapse include local (three patients), distant metastases (two patients), and disseminated (three patients). The time to progression for all patients who experienced relapse ranged from 2 weeks to 2.2 years postdiagnosis. Overall, eight patients have died, seven of progressive disease and one of toxic death.

Prognostic Factors

On univariate analyses, the extent of resection significantly influenced both PFS and OS ($P = .008$ and $P = .004$, respectively). For patients who achieved a GTR, the 2-year OS was 91% $\pm$ 9%. The median OS time for those who achieved less than GTR was 18 months (95% CI, 8.1 to 24.8). Tumor location was also statistically significant in OS ($P = .04$). The median OS for patients with supratentorial tumors was 24 months (lower 95% CI, 24.3 months), whereas the median OS has not yet been reached for patients with posterior fossa tumors. M stage and age at diagnosis were not statistically significant ($P = .30$ and $P = .40$, respectively).

DISCUSSION

To our knowledge, this is the first documented prospective clinical trial for children with primary CNS ATRT. The relatively new classification of CNS rhabdoid tumors, heterogeneous treatment regimens historically used for this disease, and the reporting bias associated with this group of patients make a true understanding of the prognosis of this disease difficult to estimate, but the overall common experience has been bleak.

The role of resection and age at diagnosis have been previously reported as important factors in predicting prognosis.[11,12] What is evident among our cohort is that achieving a complete response is an important factor in survival. The nine patients who currently have no evidence of disease had a CR. However, independent of upfront prognostic factors, ultimately, it is the consequences of treatment that influence the overall future direction of therapy.

The importance of RT has been highlighted previously by several investigators.[11-14] In our cohort, 15 patients received RT and, of the 11 patients who received conformal RT, eight received RT before the age of 3 years. IT therapy was incorporated as a method of providing prophylaxis and/or treatment to the CNS axis. Whether IT therapy can substitute for craniospinal irradiation for CNS treatment and/or prophylaxis remains unclear, because both modalities were used in our protocol. Certainly, the use of IT methotrexate is a concern, given its known short- and long-term effects. Prior experiences with both leukemia and medulloblastoma populations that have received IT therapy, including methotrexate, have shown that these children have significant deficits in neurocognitive functioning.[15-18] Comprehensive neuropsychologic assessments are planned for our surviving cohort.

The role of anthracyclines has been well documented in a variety of pediatric malignancies, although doxorubicin has not been commonly used in the treatment of pediatric CNS malignancies. We[9] and other investigators[7,8] have previously shown that multiagent chemotherapy containing an anthracycline can be efficacious, and our current regimen and another recent report[19] support the rationale for anthracycline-based regimens.

Metastatic disease is present relatively frequently among patients with ATRT and occurs predominantly among the youngest children.[11,12] The frequency of metastases at diagnosis in our cohort is consistent with the previously published retrospective experiences at 27%; however, four of six of our patients were older than 3 years of age. What is notable among our cohort is that two patients with metastases are alive: a patient with M3 disease with no evidence of disease 2.5 years from diagnosis and a patient with M2 disease with stable disease 1.5 years from diagnosis.

As our treatment regimen was multimodal and highly intensive, further improvements in outcome may require improved understanding of the biology of this tumor. Extensive effort and laboratory investigation has been carried out to better understand the development of ATRT as well as to identify potential therapeutic targets. The Pediatric Preclinical Testing Program, among other groups, has within its panel rhabdoid cell lines and xenografts and has shown data that are provocative with regard to the chemotherapy-responsiveness of ATRT.[20] What remains a limitation, however, is the lack of genetically engineered or orthotopic CNS ATRT animal models that reflect the human condition. We hope future clinical studies will incorporate

targeted approaches based on an improved biologic understanding of these tumors.

It has been shown that aggressive therapy can prolong survival in a subset of children with CNS ATRT,[11,12,21] although most succumb to their disease. This protocol is the first prospective report with surgery, multiagent systemic and IT chemotherapy, and radiotherapy for this tumor with previously dismal prognosis, demonstrating significant progress in both PFS and OS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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