Pediatr Blood Cancer 2014;61:1357–1361

High Dose Alkylator Therapy for Extracranial Malignant Rhabdoid Tumors in Children

Rajkumar Venkatramani, MD, MS,[1,2]* Poone Shoureshi, BA,[1] Jemily Malvar, MS,[1] Shengmei Zhou, MD,[3] and Leo Mascarenhas, MD, MS[1,2]

Background. Extracranial malignant rhabdoid tumor (MRT) is a rare pediatric cancer with a poor prognosis. The kidney is the most common site. Isolated reports have shown improvements in patient survival, but no specific treatment regimen has shown efficacy over others. ***Procedure.*** Retrospective review of patients diagnosed with extracranial MRT at Children's Hospital Los Angeles between 1983 and 2012. ***Results.*** The median age at presentation for the 21 patients was 13 months (range, 0–108 months). Ten patients had renal primary tumors. The median time to progression was 4 months (range, 0.4–7 months). The 5-year event free survival (EFS) and overall survival (OS) of the entire cohort was $38 \pm 10.6\%$. After 2002, patients diagnosed with extracranial MRT were administered a chemotherapy regimen of vincristine, doxorubicin and high dose cyclophosphamide (VDC). The OS for the patients diagnosed before and after 2002 were $20 \pm 12\%$ and $54 \pm 15\%$, respectively. Of the 13 patients who received VDC containing regimen, eight patients achieved a complete radiological remission; five of these patients are long-term survivors. Four patients who received autologous bone marrow transplantation were alive at last follow-up. All patients with unresectable primary tumors died. Patients who had disease progression or relapse did not survive. ***Conclusions.*** Patients with extracranial MRT have a poor prognosis. Treatment with high dose alkylator therapy followed by consolidation with high dose chemotherapy and autologous bone marrow transplant for those patients in radiographic complete remission appears to have a beneficial effect on survival. Pediatr Blood Cancer 2014;61:1357–1361. © 2014 Wiley Periodicals, Inc.

Key words: autologous bone marrow transplant; chemotherapy; cyclophosphamide; extrarenal; radiation; rhabdoid tumor; surgery

INTRODUCTION

Malignant rhabdoid tumors (MRT) are rare and aggressive childhood neoplasms that arise in the kidney, non-renal soft tissue, and central nervous system (CNS). The primary CNS tumors are referred to as atypical teratoid/rhabdoid tumors [1]. Studies have shown that the majority of MRT cases have a bi-allelic deletion of the SMARCB1/INI1 gene on chromosome 22q, suggesting a common biology underlying MRT [2]. The incidence of MRT is estimated at 0.6 per million [3]. The median age at diagnosis for patients with extracranial MRT ranges from 11 to 18 months and 5-year survival rates have been reported to range from 17% to 36% [3–6]. The time to progression is usually short and the patients who relapse generally do not survive [1].

The current treatment for MRT employs a multimodal approach that includes surgical resection of the primary tumor, chemotherapy, and radiation therapy. We have previously published our institutional experience with extracranial rhabdoid tumors in patients diagnosed between 1983 and 2003 [7]. In this report, we have updated those results with additional patients and longer follow-up. We discuss the outcomes following treatment with vincristine, doxorubicin, and high dose cyclophosphamide (VDC).

METHODS

Patients diagnosed with extracranial MRT at Children's Hospital Los Angeles (CHLA) between 1983 and 2012 were identified from the pathology database. A retrospective review was conducted to examine the clinical presentation, treatment, and patient outcomes. Each patient was staged using the surgical-pathologic staging system for renal tumors used by the National Wilms Tumor Study Group. Archived tumor tissues were examined by a pathologist, and were stained for INI1 expression if not previously performed. The CHLA Committee on Clinical Investigation approved the conduct of this study and waived the need for individual informed consent to review the medical records. Event free survival (EFS) was defined as the time from the date of diagnosis to progression, relapse, or death from any cause. Overall survival (OS) was defined as time from the date of diagnosis to death. The EFS and OS of these patients were calculated using the Kaplan–Meier method.

RESULTS

Clinical Features

Twenty-one patients were diagnosed with extracranial MRT during the study period. The median age at diagnosis was 13 months (range, 0–108 months). Fourteen were less than 2 years of age and seven were female (Table I). The median follow-up for the entire group was 7 months and the median follow-up of survivors was 71 months. The presenting symptoms included a visible or palpable mass in nine patients, fever in six, decreased appetite in five, abdominal discomfort in three, and signs of spinal cord compression in three. One patient exhibited severe respiratory distress and tachycardia. Another patient presented with polydipsia, polyuria, and urinary retention.

[1]Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Hospital Los Angeles, Los Angeles, California; [2]Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, California; [3]Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, Los Angeles, California

Conflict of Interest: Nothing to report.

*Correspondence to: Rajkumar Venkatramani, Division of Hematology/Oncology, Children's Hospital Los Angeles, 4650, Sunset Boulevard, Mailstop 54, Los Angeles, CA 90027.
E-mail: rvenkatramani@chla.usc.edu

Received 7 December 2013; Accepted 23 January 2014

© 2014 Wiley Periodicals, Inc.
DOI 10.1002/pbc.25093
Published online 30 April 2014 in Wiley Online Library (wileyonlinelibrary.com).

Pediatr Blood Cancer DOI 10.1002/pbc

TABLE I. Patient Characteristics and Outcome

Patient	Age at Dx, Mo/ sex	Primary site	Metastases	Stage	INI1 expression	Surgery for primary	Chemotherapy regimen	HSCT (conditioning regimen)	Radiation, cGy	Time to progression, Mo	Vital status
1	0.07/M	Kidney	No	I	Negative	Upfront CR	VDC + Carbo/E/C	No	None	6 (local and lung)	DOD (6)
2	3/F	Kidney	No	II	Negative	Upfront CR	Carbo/E + ID	No	None	7 (brain)	DOD (7)
3	108/F	Kidney	No	II	Negative	Upfront CR	Carbo/E + C	No	1,080	No progression	NED (130)
4	75/M	Retroperitoneum	No	II	Negative	Upfront CR	ID + Carbo/E	No	4,500	No progression	NED (66)
5	0/F	Face	No	III	Negative	Unresectable	VDC	No	None	0.5 (local)	DOD (0.5)
6	1/M	Retroperitoneum	No	III	NA	Unresectable	VDC	No	Palliative	1 (meningeal)	DOD (2)
7	4/M	Neck	No	III	Negative	Unresectable	VDC + IE	No	1,950	3 (local)	DOD (5)
8	7/M	Liver	No	III	Negative	Delayed CR	VDC + Carbo/E	No	None	4.5 (abdomen)	DOD (6)
9	21/M	Kidney	Lymph nodes	III	NA	Upfront; MRD	VDC + CDDP/E	No	2,400	7 (local and lung)	DOD (9)
10	6/M	Kidney	No	III	Negative	Delayed CR	VDC + CDDP/E	Yes (CEM)	None	No progression	NED (103)
11	0.5/M	Back	No	III	NA	Delayed CR	VDC + VAC + CDDP/IE	No	None	No progression	NED (77)
12	30/F	Neck	No	III	Negative	Delayed; MRD	VAC + ID	Yes (CEM)	4,500	No progression	NED (78)
13	6/F	Liver	Lung	IV	NA	Unresectable	None (declined)	No	None (declined)	0.4 (local and lung)	DOD (0.4)
14	12/M	Retroperitoneum	Lung, lymph nodes	IV	NA	Unresectable	Carbo/E + ID	No	None	1 (local and lung)	DOD (2)
15	36/M	Pelvis	Lung, mediastinum, liver	IV	Negative	Unresectable	VDC	No	None	2 (local, lung and mediastinum)	DOD (2)
16	12/M	Kidney	Lungs, liver, T6, hilar, retroperitoneal and mediastinal lymph nodes	IV	Negative	Delayed CR	VDC	No	None	4 (lung)	DOD (4.5)
17	96/M	Kidney	Lung	IV	NA	Delayed resection; MRD	CDDP/D + IE+VAC	No	1,400 (lung)	6 (lung)	DOD (6)
18	24/F	Kidney	Lung	IV	Negative	Delayed resection; MRD	Carbo/E + ID	No	None	6 (local and lung)	DOD (8)
19	22/M	Kidney	Lung	IV	Negative	Upfront CR	VDC + CDDP/E/C	No	1,950, 1,200 (lung)	No progression	NED (12)
20	4/F	Kidney	Lung	IV	Negative	Upfront resection; MND	VDC + VAC	Yes (CEM)	None	No progression	NED (40)
21	34/M	Liver	Lung, mediastinal lymph nodes	IV	Negative	Delayed CR	VDC + Carbo/E	Yes (CEM)	1,200 (lung)	No progression	NED (55)

DX, diagnosis; cGy, centigray; CR, complete resection; Carbo, carboplatin; A, actinomycin D; E, etoposide; I, ifosfamide; D, doxorubicin; DOD, died of disease; NED, no evidence of disease; C, cyclophosphamide; V, vincristine; CDDP, cisplatin; CEM, carboplatin, etoposide, and melphan; HSCT, hematopoietic stem cell transplantation; MRD, microscopic residual disease; MND, margins not determined; NA, not available.

Diagnosis

MRTs were diagnosed pathologically by round to oval-shaped cells arranged in nests and sheets, with an abundant acidophilic cytoplasm, distinct cell borders, large eccentric nuclei, and a large nucleolus. INI1 protein expression was absent in all 15 tumor samples tested. Archived tumor samples were not available in the other six patients. One patient was initially diagnosed as malignant peripheral nerve sheath tumor. The diagnosis was later revised to MRT based on cytogenetic results.

Tumor Location and Stage

Ten patients had renal primary tumors. The primary location of the extrarenal tumors included the liver in three patients, neck in two patients, pelvis in one patient, face in one patient, back in one patient, and retroperitoneum in three patients. Twelve patients had localized disease at diagnosis (stage I–III). Nine patients (39%) had distant metastases at diagnosis. Metastatic sites included the lungs in nine patients, lymph nodes in five patients, and liver in two patients.

Treatment

Patients were treated with chemotherapy, surgery, radiation therapy, or a combination of these modalities. Three patients received chemotherapy alone either due to disseminated disease or due to disease progression (patients 5, 14, and 15). One patient declined treatment (patient 13).

Surgery

Fifteen patients (71%) underwent surgical resection of their primary tumors. Seven patients had upfront resections (five patients underwent complete resection, one had a microscopic residual disease, and the margins could not be determined for another patient as surgery was performed at another hospital). Eight patients underwent delayed resection following neo-adjuvant chemotherapy (five patients had a complete resection, and three underwent resection with microscopic residual disease). In the six patients who had unresectable primary tumors, the neoplasms were located in the retroperitoneum (two patients), the face, neck, pelvis, and liver (this patient declined treatment).

Chemotherapy

Patients were initially administered chemotherapy regimens which included combinations of the following drugs: carboplatin, etoposide, ifosfamide, doxorubicin, cyclophosphamide, actinomycin D, cisplatin, and vincristine. After 2002, we used vincristine, doxorubicin, and cyclophosphamide (VDC) containing regimens for most patients with extracranial MRT. VDC regimen was administered as follows in 7 patients: vincristine 1.5 mg/m^2/day on Days 1, 8, and 15; doxorubicin 37.5 mg/m^2/day; and cyclophosphamide 2.1 g/m^2/day on Days 1 and 2. One patient diagnosed after 2002 did not receive VDC containing regimen (initial diagnosis of malignant peripheral nerve sheath tumor). Four patients received a lower dose of cyclophosphamide than described above (patients 1, 5, 10, 11); three of them were neonates. Two patients (patients 7, 9) diagnosed before 2002 received a VDC containing regimen but received lower doses of doxorubicin and cyclophosphamide. In total, thirteen patients were administered a chemotherapy regimen containing VDC.

Autologous Bone Marrow Transplantation

High dose chemotherapy followed by autologous bone marrow transplantation (ABMT) was planned in 10 patients. Carboplatin, etoposide and melphalan (CEM) was used as the conditioning regimen. Only four received ABMT. Five of the remaining six patients did not receive ABMT due to early disease progression and ABMT was deferred in the sixth patient due to post-chemotherapy microangiopathic hemolytic anemia and renal failure. Of the four patients who received ABMT, two had stage III disease (initially unresectable with lymph node involvement) and two had stage IV disease (pulmonary metastases).

Radiation

Eight of the 21 patients received therapeutic irradiation to either the primary or metastatic site. One patient received palliative radiation. The median age of patients who received radiation was 32 months (range, 4–108 months). Six patients received radiation to the primary site of disease with doses ranging from 1,080 to 4,500 cGy. Patient 7 received radiation after local disease progression at 4 months of age. Three patients received whole lung irradiation.

Outcome

The 5-year PFS and OS of the entire cohort were both $38 \pm 10.6\%$ (Fig. 1). Eight of the 21 patients were alive at last follow-up. The OS for the ten patients diagnosed before 2002 was $20 \pm 12\%$ (95% CI 3, 48) compared to $54 \pm 15\%$ (95% CI 23, 78) for the 11 patients after 2002 (Fig. 2). The time to progression after diagnosis was rapid, with a median time of 4 months (range, 0.4–7 months). Eight patients progressed on therapy and five relapsed after achieving complete remission. All patients who progressed or relapsed did not survive. Two patients progressed locally, five patients progressed at a distant site, and six patients progressed both locally and distantly. The median follow-up of survivors was 72 months (range, 12–130 months). The survival of patients $\geq$24 months of age at diagnosis was $57 \pm 18\%$ compared to $29 \pm 12\%$ for those less than 24 months. The median age of survivors at the time of diagnosis was 26 months (range, 0.5–108 months), compared to 7 months (range, 0–96 months) for those that did

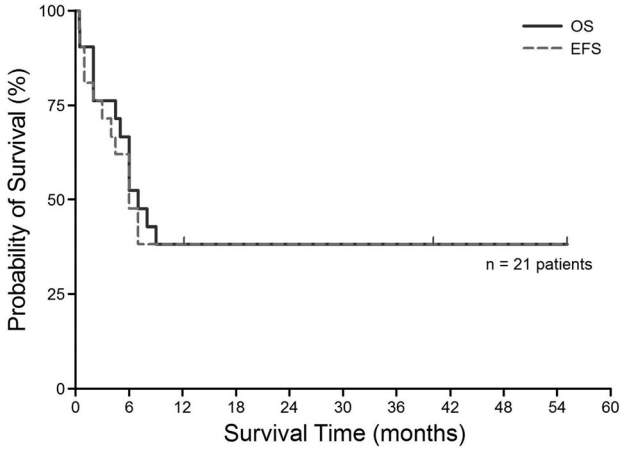

Fig. 1. EFS and OS of the entire cohort.

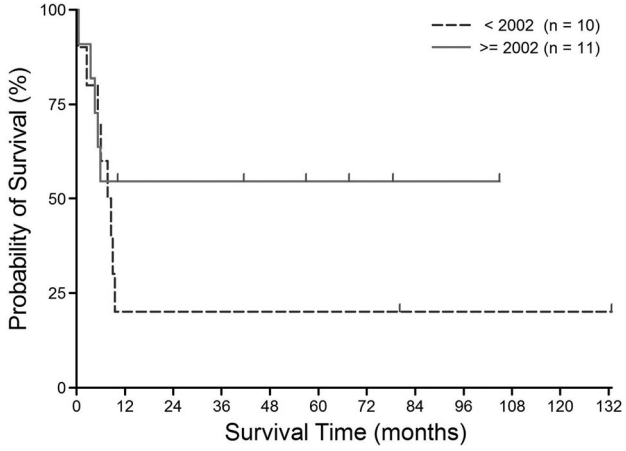

Fig. 2. OS comparison: before and after 2002.

not survive. Four of 10 patients with a renal primary survived. Four of eleven patients with extra-renal tumors survived.

All six patients who had unresectable primaries did not survive. Four of eight survivors underwent an upfront complete surgical resection. The other four survivors underwent a delayed resection. Only one of four patients that had minimal residual disease after surgery survived. This patient received local irradiation and underwent ABMT. Five of the eight patients who received radiation were long-term survivors (63%). Three of the five patients who received radiation to the primary tumor site did not progress at the primary site. Three patients received radiation to the lungs, and two of them did not have a pulmonary relapse. Three survivors did not receive radiation therapy to the primary or metastatic site; two of them had an ABMT. All four patients who received ABMT were disease free at last follow-up.

Of the 13 patients who were administered a VDC regimen, eight achieved a radiological complete remission. Three of these eight patients later relapsed. Of the five patients who are alive after VDC treatment, two were diagnosed with stage III MRT and three had stage IV disease. Eight of 13 patients who were administered VDC containing regimen did not survive. Of the five patients with lung metastases that received VDC regimen, four patients had an objective radiographic response including three with complete resolution of lung nodules.

DISCUSSION

We have described the clinical characteristics, treatment and outcome of 21 consecutively diagnosed extracranial rhabdoid tumor patients at CHLA. The OS for the entire cohort was poor and comparable to other published studies [4–6]. MRT is an aggressive tumor with a short time to disease progression. The majority of events occur within 2 years of diagnosis [4]. In our series, there was no progression/relapse 7 months after diagnosis. None of our patients who progressed survived even though there have been isolated reports of survival after relapse [4,8]. Age is an important prognostic factor in MRT with younger age associated with worse prognosis [5]. Infants typically receive less aggressive treatment as a result of reduced dose chemotherapy and avoidance of radiation therapy. This may have contributed to the poor prognosis of younger patients in our series and in other reports [4,5]. Similar to previous studies, there was no difference in outcome based on sex of the patient or primary site of disease [3,5]. The majority (80%) of our patients had advanced disease (stage III and IV). This is higher than previously published series, where approximately two-thirds of patients had advance disease [4–6]. Though previously reported, we did not find a difference in outcome based on disease stage [3,5]. This may be due to our smaller sample size.

Our study reinforces the importance of surgical resection of the primary tumor as none of the patients with an unresectable primary tumor survived. There is one previous report of a patient with an incompletely resected primary cured after irradiation and chemotherapy [9]. There was no difference in survival between patients who received an upfront surgical resection versus a delayed resection in our study. This is in contrast to the results from the SIOP Renal Tumor Study Group study that reported worse survival for patients with delayed surgery [4]. Although radiation therapy seems to improve prognosis in atypical teratoid/rhabdoid tumor, its role in extracranial MRT is unclear [10]. The apparent benefit of radiation therapy may be confounded by age, as radiation therapy is generally avoided in the youngest of patients [11]. We did not administer radiation therapy to patients less than 2 years of age as part of initial treatment. Three of these patients are long-term survivors. Only one patient less than 2 years of age received radiation in our series. This was administered after disease progression. Tomlinson et al. [5] investigated the role of radiation therapy, in MRT of the kidney, after correcting for age. They did not find a difference in outcome between those who received radiation and those who did not. In contrast, analysis of children with extra-renal, non-cranial MRT from SEER database revealed tumor stage, and radiation therapy as significant predictors of outcome [3].

Unlike the cohorts from the SEER database [3], our patients that were diagnosed more recently (after 2002) had a better OS than those diagnosed before 2002. The reason for improved survival after 2002 is unclear. We treated patients diagnosed after 2002 uniformly with VDC regimen that had higher doses of doxorubicin and cyclophosphamide. The SIOP group found that pre-operative chemotherapy with vincristine, actinomycin D, and doxorubicin resulted in decreased tumor size, but did not correlate with improved survival [4]. Two previous studies examined the role of doxorubicin in MRT and concluded that it did not make a difference in outcome [4,5]. Gururangan et al. [12] were the first to report responses to ifosfamide, carboplatin, and etoposide (ICE) regimen in patients with extracranial rhabdoid tumors. Subsequently, two patients with stage IV MRT of the kidney treated with alternating cycles of VDC and ICE were reported to be disease free at 1- and 2-years following diagnosis [13]. In a more recent publication, none of the nine patients with MRT treated with ICE regimen survived [9]. Therefore, there is no definitive evidence of cure using ICE regimen in the absence of VDC. The current Children's Oncology Group clinical trial uses alternating VDC, and cyclophosphamide, carboplatin, and etoposide (CCE) regimens along with radiation therapy for MRT. This clinical trial and the studies described previously used approximately half of the dose of cyclophosphamide we used in our patients who received VDC. Higher dose of cyclophosphamide may have contributed to the better outcome in our patients diagnosed after 2002. In fact, all our stage IV patients who survived received VDC regimen with high dose cyclophosphamide.

All patients that received ABMT in our series are long-term survivors. Koga et al. [14] reported two patients with MRT who

achieved long term remission following ABMT with the same conditioning regimen used in our series. At the same time, two patients who underwent ABMT in another series did not survive [9]. It is difficult to draw conclusions about the efficacy of ABMT, as only four of the initially intended 10 patients received ABMT in our study. This may represent a selection bias. On the other hand, high dose chemotherapy conditioning regimen (CEM) used prior to ABMT in our series expands on the theme of high dose alkylator therapy used during induction either in the neoadjuvant or adjuvant setting.

Extracranial MRT is an aggressive disease with poor prognosis. The outcome of patients diagnosed in the first year of life continues to be dismal. Our approach of treating with a VDC regimen containing high dose cyclophosphamide is feasible and appears to produce superior response rates when compared to other published regimens. We propose a strategy to treat all extracranial MRT patients in a phase 2 multi-institutional clinical trial using VDC with high dose cyclophosphamide followed by consolidation with CEM and ABMT for responding patients in complete radiographic remission and compare their outcomes to historical controls in order to further evaluate the efficacy of this regimen.

REFERENCES

1. Palmer NF, Sutow W. Clinical aspects of the rhabdoid tumor of the kidney: A report of the national wilms' tumor study group. Med Pediatr Oncol 1983;11:242–245.
2. Roberts CWM, Biegel JA. The role of SMARCB1/INI1 in development of rhabdoid tumor. Cancer Biol Ther 2009;8:412–416.
3. Sultan I, Qaddoumi I, Rodríguez-Galindo C, et al. Age, stage, and radiotherapy, but not primary tumor site, affects the outcome of patients with malignant rhabdoid tumors. Pediatr Blood Cancer 2010;54:35–40.
4. Van den Heuvel-Eibrink MM, van Tinteren H, Rehorst H, et al. Malignant rhabdoid tumours of the kidney (MRTKs), registered on recent SIOP protocols from 1993 to 2005: A report of the SIOP renal tumour study group. Pediatr Blood Cancer 2011;56:733–737.
5. Tomlinson GE, Breslow NE, Dome J, et al. Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: Age at diagnosis as a prognostic factor. J Clin Oncol Off J Am Soc Clin Oncol 2005;23:7641–7645.
6. Reinhard H, Reinert J, Beier R, et al. Rhabdoid tumors in children: Prognostic factors in 70 patients diagnosed in Germany. Oncol Rep 2008;19:819–823.
7. Madigan CE, Armenian SH, Malogolowkin MH, et al. Extracranial malignant rhabdoid tumors in childhood: The Childrens Hospital Los Angeles experience. Cancer 2007;110:2061–2066.
8. Kato M, Koh K, Oshima K, et al. Long-term survivor of relapsed stage IV malignant rhabdoid tumor of the kidney. Pediatr Int Off J Jpn Pediatr Soc 2013;55:245–248.
9. Bourdeaut F, Fréneaux P, Thuille B, et al. Extra-renal non-cerebral rhabdoid tumours. Pediatr Blood Cancer 2008;51:363–368.
10. Squire SE, Chan MD, Marcus KJ. Atypical teratoid/rhabdoid tumor: The controversy behind radiation therapy. J Neurooncol 2007;81:97–111.
11. Morgenstern DA, Gibson S, Brown T, et al. Clinical and pathological features of paediatric malignant rhabdoid tumours. Pediatr Blood Cancer 2010;54:29–34.
12. Gururangan S, Bowman LC, Parham DM, et al. Primary extracranial rhabdoid tumors. Clinicopathologic features and response to ifosfamide. Cancer 1993;71:2653–2659.
13. Wagner L, Hill DA, Fuller C, et al. Treatment of metastatic rhabdoid tumor of the kidney. J Pediatr Hematol Oncol 2002;24:385–388.
14. Koga Y, Matsuzaki A, Suminoe A, et al. Long-term survival after autologous peripheral blood stem cell transplantation in two patients with malignant rhabdoid tumor of the kidney. Pediatr Blood Cancer 2009;52:888–890.