Pediatr Pract Res 2023; 11(3): 78-85
DOI: 10.21765/pprjournal.1351608

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Clinical Characteristics and Outcomes of Rhabdoid Tumors in Childhood

Çocukluk Çağındaki Rabdoid Tümörlerin Klinik Özellikleri ve Sonuçları

Zeliha Güzelküçük[1], Derya Özyörük[2], Arzu Yazal Erdem[2], Ayça Koca Yozgat[2], Can Barış Aker[3], İnci Yaman Bajin[3], Suna Emir[3], Namık Yaşar Özbek[2]

[1]Ankara City Hospital, Pediatric Hematology and Oncology, Ankara, Turkey
[2]Health Sciences University Ankara City Hospital, Pediatric Hematology and Oncology, Ankara, Turkey
[3]Ankara Child Health and Diseases Pediatric Hematology Oncology Training and Research Hospital, Ankara, Turkey

Abstract

Aims: Pediatric Rhabdoid tumors are highly aggressive tumors with poor prognosis. There is no consensus on standart treatment currently. It was aimed to evaluate the clinical characteristics and outcomes of pediatric rhabdoid tumors.

Material and Method: Eight patients with malignant rhabdoid tumor were evaluated retrospectively from the data set between 2013 to 2020.

Results: Out of 8, 5 patients were male (Male/female: 5/3). Median age was 24 months, (range; 4 months-10 years) 6 patients (75%) were younger than 3 years (4 months-10 years). Localizations of the tumors were heterogeneous: (5 central nervous system, 1 multifocal, 1 kidney, and 1 bladder). Genetic analysis revealed germline heterozygous SMARCB1 mutation in one (12%) patient. Patients experienced various toxicities including Wernicke's-like encephalopathy, vincristine neuropathy, veno-occlusive disease mainly hematologic toxicity/mucositis and febrile neutropenia. Five patients died due to progressive disease (62%). The median follow-up time of all patients was 24.5 months (range 6-41 months). The 2-year-event-free and overall survival rates were 37.5% and 50%, respectively.

Conclusion: It should kept in mind that pediatric rhabdoid tumors may present with various ages and localizations, but mainly under 3 years old and central nervous system. The experience is limited due to rarity, but addition of high-dose chemotherapy with autologous hematopoietic stem cell transplantation could be effective in subset of patients who achieved complete remission before transplantation. The toxicities resulting from intensive treatments could be managable, butnew targeted therapies areneeded to improve survival rates.

Keywords: Children, rhabdoid tumor, atypical teratoid rhabdoid tumor

Öz

Amaç: Pediatrik Rabdoid tümörler oldukça agresif, kötü prognozlu tümörlerdir. Şu anda standart tedaviler hakkında fikir birliği yoktur. Bu çalışmada pediatrik rabdoid tümörlerin klinik özelliklerinin ve tedavi sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2013-2020 yılları arasındaki veri setinden sekiz malign rabdoid tümör retrospektif olarak değerlendirildi.

Bulgular: 8 hastanın 5'i erkekti (erkek/kadın: 5/3). Ortanca yaş 24 aydı (aralık; 4 ay-10 yaş), 6 hasta (%75) 3 yaşın (4 ay-10 yaş) altındaydı. Tümör lokalizasyonları heterojendi (5 merkezi sinir sistemi, 1 multifokal, 1 böbrek ve 1 mesane). Bir hastada germ line heterozigot SMARCB1 mutasyonunu saptandı (%12). Hastalarda Wernicke benzeri ensefalopati, vinkristin nöropatisi, veno-tıkayıcı hastalık başta olmak üzere hematolojik toksisite/mukozit ve febril nötropeni görülmüştür. Beş hasta progresif hastalık nedeniyle öldü (%62). Tüm hastaların ortanca takip süresi 24,5 aydı (minimum-maximum: 6-41 ay). 2 yıllık olaysız ve genel sağkalım oranları sırasıyla %37,5 ve %50 olarak hesaplanmıştır.

Sonuç: Pediatrik rabdoid tümörlerin çeşitli yaş ve lokalizasyonlarda ortaya çıkabileceği, ancak çoğunlukla 3 yaş altı ve santral sinir sistemi tutulumu olabileceği akılda tutulmalıdır. Nadir görülmesi nedeniyle deneyim sınırlıdır, ancak otolog hematopoietik kök hücre transplantasyonu ile yüksek doz kemoterapinin eklenmesi, transplantasyondan önce tam remisyona ulaşan hasta alt grubunda etkili olabilir. Yoğun tedavilerden kaynaklanan toksisiteler yönetilebilir, ancak hayatta kalma oranlarını iyileştirmek için yeni hedefli tedaviler gereklidir.

Anahtar Kelimeler: Çocuk, rabdoid tümör, atipik teratoid rabdoid tümör

Corresponding Author: Zeliha GUZELKUCUK
Address: Ankara City Hospital, Pediatric Hematology and Oncology, Ankara, Turkey
E-mail: drguzelkucuk@hotmail.com

Başvuru Tarihi/Received: 28.08.2023
Kabul Tarihi/Accepted: 26.09.2023

INTRODUCTION

Rhabdoid tumors are rare and highly aggressive tumors with poor prognosis. They were first described in 1981 by Haas et al. (1). Since their initial description, rhabdoid tumors have been described in multiple localisations including brain, kidney and soft tissue. The common feature of rhabdoid tumors in all localisations is a genetic mutation of SMARCB1. SMARCB1 is a member of the SWI/SNF chromatin-remodeling complex and functions as a tumor suppressor in rhabdoid tumors (2). Despite the heterogeneous morphology and/or immunoprofile, the diagnosis of rhabdoid tumors currently depends on the loss of expression of SMARCB1/INI1 or SMARCA4/BRG1 in the tumor cell. Deletion or mutation of the SMARCB1 locus on 22q11.2 results in loss of the integrase interactor 1 (INI1) protein (3,4). INI1 is expressed in the nuclei of normal cells as well as in most tumors and can be detected by immunohistochemical methods (5). Although there are many ongoing trials related to pediatric rhabdoid tumors, there is no consensus on the standard treatment. In addition, despite multimodal treatments including resection of the tumor mass and chemotherapy and radiotherapy, the prognosis has not improved so far. Although autologous stem cell transplantation has been reported for atypical teratoid/rhabdoid tumor (ATRT), rhabdoid tumor of kidney (RTK) and extrarenal malignant rhabdoid tumor (MRT), experience is limited in developing countries (6,7). The aim of the present study is to evaluate the characteristics, treatments and outcomes of rhabdoid tumors in our pediatric oncology center.

MATERIAL AND METHOD

This study was approved by the Ankara Child Health and Diseases Pediatric Hematology Oncology Training and Research Hospital Ethics Committee (Date: 30.07.2019, Decision No: 2019-229). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The present report was conducted with patients diagnosed with rhabdoid tumors in the Pediatric Oncology Department of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital. A total of 8 patients with rhabdoid tumors followed up between 2013 and 2020 years were retrospectively evaluated using oncology database files. Among them, 5 patients were diagnosed with the AT/RT, 1 with synchronous AT/RT and RTK with metastatic lung nodules, 1 with RTK, and 1 with MRT of the bladder. All patients received multimodal treatments including surgical resection, radiotherapy and chemotherapy. A subset of patients treated with high-dose chemotherapy and autologous stem cell rescue. Carboplatinum and thiotepa were used as the conditioning regimen. All patients were analyzed for clinical characteristics, histopathologic findings, treatment details, genetic testing and prognosis. All patients were diagnosed with malignant rhabdoid tumor by pathology based on the morphological and immunohistochemical evaluation. Staging was performed according to the Chang staging system for AT/RT, SIOP renal tumor staging for malignant rhabdoid tumor of kidney, and TNM staging for malignant rhabdoid tumor of soft tissue.

Statistical Analysis

Statistical Analysis SPSS 22.0 was used as a package program in the analysis. Descriptive statistics were used. Categorical measurements were summarized as numbers and percentages, and numerical measurements were summarized as median and ranges, minimum-maximum. Overall survival (OS) and event-free survival (EFS) were estimated by Kaplan-Meier survival analysis. For OS analysis, survival time was calculated from the date of initial diagnosis to the date of death or last follow-up. For EFS analysis, an event was either relapse (or progression) or death in the absence of relapse (or progression). EFS time was calculated from the date of initial diagnosis to the date of relapse, death in the absence of relapse or progression or last follow-up visit.

RESULTS

Clinical characteristics 8 patients were diagnosed with rhabdoid tumor between 2013-2020 years in a single pediatric oncology clinic. Of the 8 patients, 5 were male and 3 were female. The median age was 24 months (range, 4 months-10 years). Six patients (75%) were below 3 years of age. The most common presenting signs in patients with AT/RT were weakness of extremities (n=3), seizures (n=2) and gait disturbance (n=2). A 10 year-old patient presented with headache, nausea, vomiting ,and gait disturbance. Another patient presented with fever, cough, abdominal distention, ptosis and upward gaze restriction. The others were gross hematuria (n=1) and abdominal pain (n=1). Primary localization of rhabdoid tumors was different inpatients with AT/RT, RTK and MRT. Six tumors were located in the CNS (1 temporal lobe, 1 frontal lobe, 1 intraventricular, 1 posterior fossa, 1 cervical spinal cord and 1 synchronous in frontal lobe, pineal region, lung and kidney), 1 only in kidney (n=1) and 1 in bladder (**Figure 1**-**3**). Three patients had metasthases at initial diagnosis, 1 spinal cord, 1 multifocal involvement and lung nodules and 1 lymph node. The others were localized stages (n=5). All patients were diagnosed as a rhabdoid tumors based on histopathologic and immunohistochemical analysis showing loss of nuclear expression of INI1. Genetic analysis was performed in all patients except the spinal AT/RT. The germline heterozygous SMARCB1 mutation was detected in only one (12%) patient with spinal metasthasis at diagnosis.

All patients with ATRT underwent maximal possible surgical resection of the primary lesion consistent with preservation of neurologic function except for one patient with synchronous rhabdoid tumors in the brain and kidney. One patient who diagnosed with spinal AT/RT underwent C1-3 laminectomy and gross total excision. Unilateral radical nephrectomy was performed in 2 patients with renal tumor; one upfront surgery, the other after neoadjuvant chemotherapy for multifocal tumors in brain and kidney together with lung metastasis. The patient with bladder tumor underwent delayed total surgical resection together with partial cystectomy after 6 cycles of chemotherapy.

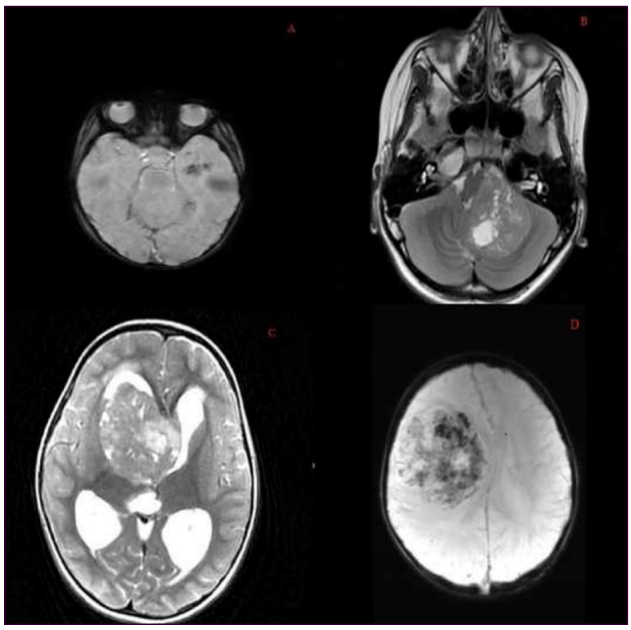

Figure 1: **A:** Magnetic resonance imaging (MRI) of the brain revealed a calcific and partially cystic heterogeneous mass in the left temporal area (2×3 cm) **B:** Magnetic resonance imaging of the brain revealed a mass (3.5 × 2.5cm) in the posterior fossa **C:** Magnetic resonance imaging of the brain revealed a mass in the right lateral ventricle (5×6×6.4) **D:** Cranial MRI showed a mass in the frontal region (7.5×6.2×6.1 cm)

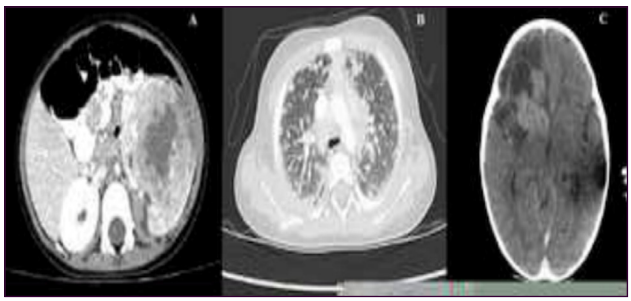

Figure 2 A: Computed tomography showed a heterogeneous mass (6×7×8 cm), centrally hypodense, cystic and necrotic areas in the lower middle pole of the left kidney **B:** Computed tomography showed multiple nodular metastatic lesions and infiltration in the bilateral lung **C:** Computed tomography of brain showed a mass (2×3 cm) in the pineal region and a solid mass (2×2 cm) in the left frontal lobe

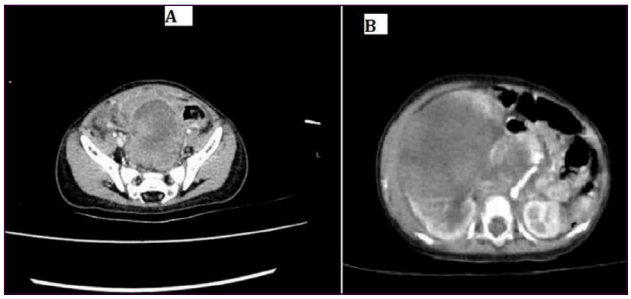

Figure 3 A: Imaging study showed a heterogeneous mass (9x8.7 cm) on the right kidney B: Imaging study showed e pelvic mass (7.9x4.8x4.6 cm) adjacent to posterior wall of bladder

Seven patients were treated according to EU-RHAB protocol consisting of doxorubicin, ifosfamide, carboplatinum, etoposide vincristine, cyclophosphamide and actinomycin-D. One of them (ATRT and RTK) was treated with EU-RHAB protocol after neoadjuvant treatment consisting of doxorubucin, actinomycin-D and vincristine followed by radical unilateral nephrectomy. One patient with spinal AT/RT received vincristine, cyclophosphamide, cisplatin, etoposide. Another patient with intraventricular localization received intraventricular methotrexate therapy via Ommaya reservoir.

All patients received local radiotherapy according to tumor localization. Post-operative radiotherapy to the flank for RTK was given 19.8 Gy for a child >12 months, and 10.8 Gy for another patient.

High-dose chemotherapy followed by autologous stem cell transplantation was performed in 3 patients. Two of them were diagnosed with AT/RT and one patient with malignant rhabdoid tumor of the bladder in the present study. Before transplantation, one patient with AT/RT achieved complete remission, and another partial remission. The patient with bladder rhabdoid tumor also attained complete remission before transplantation. The conditioning regimen consisting of carboplatinum (500mg/m2/day) and thiotepa (300mg/m2/day) was administered from day -6 to -4. The median number of stem cells infused was 4.6x106 /kg (range, 4.25x106 / kg - 5.31x106 /kg) on day 0. The median neutrophil and platelet engraftment days were day +12 (day +11-13) and +15 day +13-17), respectively. Neither toxicity nor delayed engraftment was observed. One of the patients with AT/RT remained in remission for 30 months after transplantation and the other, who was not in complete remission relapsed and died with progressive disease. In addition, a patient with malignant rhabdoid tumor of the bladder achieved remission without any sequelae after high-dose chemotherapy with autologous hematopoietic stem cell transplantation. He is still alive and disease free for 41 months.

Patients have experienced several treatment-related toxicities. The most common toxicities were grade III/IV hematologic toxicity/ mucositis and febrile neutropenia episodes. One patient had infective endocarditis and

Wernicke's-like encephalopathy due to ifosfamide. Magnetic resonance imaging of the brain showed symmetrical T2 hyperintensities in the thalamus, mammillary bodies and tectal plate. He responded to methylene blue and thiamine replacement therapy. Infective endocarditis also responded to antibiotic therapy. Another patient had veno-occlusive disease. She also responded to supportive therapy. Another patient had vincristine neuropathy.

The median follow-up duration of all patients was 24.5 months (range 6-41 months). Three patients are still alive without disease at 28, 30 and 41 months following diagnosis, respectively. Five patients died with progressive disease at 3, 6, 11, 24 and 25 months after initial diagnosis. The median time to death was less than 12 months. The 2-year event-free and overall survival rates fort he entire study population were determined 37.5% and 50%, respectively (**Figure 4**, **5**). The median follow-up duration of patients who underwent autologous hematopoietic stem cell transplantation was 30 months (range, 25-41 months). Of the 3 patients, 1 patient died 25 months after diagnosis, and the other 2 patients are currently disease-free for 30 and 41 months following initial diagnosis, respectively. All patients with metastases at diagnosis (n=3/3) died with progressive disease. Among patients without metastases at diagnosis (n=5), 2 patients died, 3 patients (60%) are currently alive and disease free for median 30 months follow-up duration. Among patients younger than 3 years (n=6), 2 patients (33%) (No# 1 and #8) are still alive and disease-free, others have died. The only one of the 2 patients older than 3 years is still alive with neurological sequale (No#2). The other 5 years old female patient who was diagnosed with spinal AT/RT died with progressive disease (No#5). The clinical characteristics and outcomes of the patients are summarized in the **Table 1**.

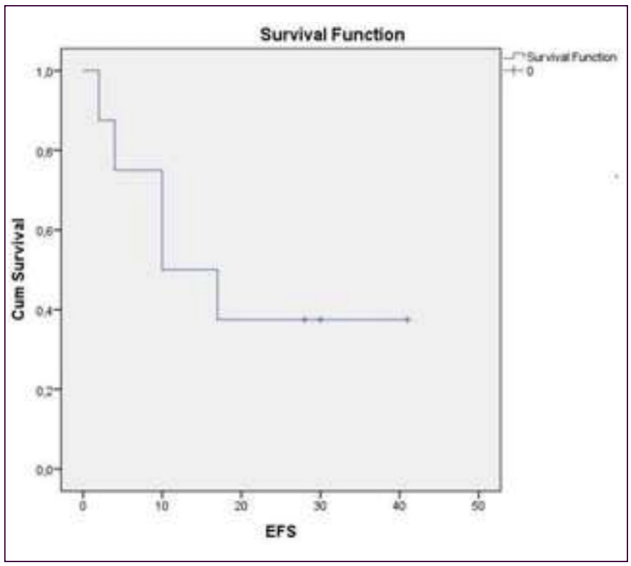

Figure 4: The 2-year event-free survival (EFS) of patients with malignant rhabdoid tumor

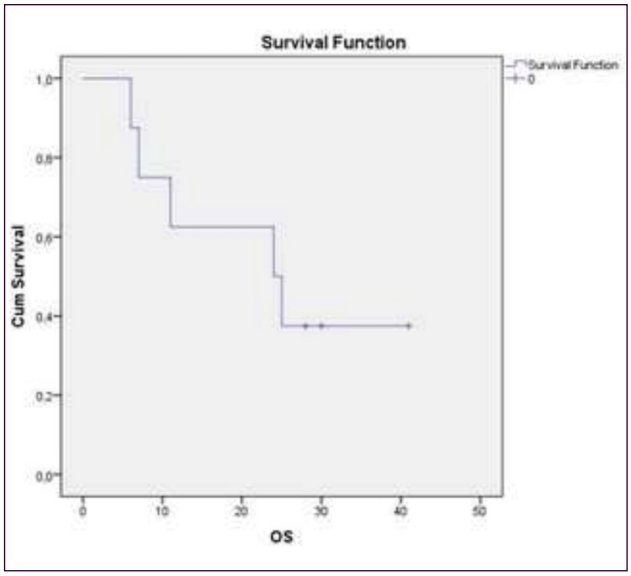

Figure 5: The 2-year overall survival (OS) rates of patients with malignant rhabdoid tumor.

DISCUSSION

In the present study, we described 8 cases diagnosed with rhabdoid tumors. Among 8 cases, the most common type was AT/RT (n=6). Atypical Teratoid Rhabdoid Tumor is an aggressive tumor that was first described in 1996 and included in the World Health Organization classification of the brain tumors in 2000 (8,9). Clinical findings vary with the age of the patients. Signs such as vomiting, lethargy, irritability, weight loss, macrocephaly and seizures are observed in children younger than three years of age. On the other hand, findings of increased intracranial pressure are common in older children similar to our patient (No#2) in the present study (10). Weakness in extremities, walking difficulties and seizures were main complaints at initial presentation of patients with AT/RT in our study. Most ATRTs occur in the posterior cerebral fossa, but can be found anywhere in the central nervous system. Although, it is rare, it may present with multifocal locations (9). In the present study tumors were located differently; 1 patient had spinal mass, 1 patient had intraventricular mass, 1 patient had posterior cerebral fossa mass, 1 patient had frontal mass, 1 patient had temporal mass, and 1 patient had frontal lobe/pineal together with kidney/ lung tumors. Intraventicular and spinal cervical spine locations are very rarely reported and poor prognostic localizations(12-14). Differential diagnosis of AT/RT must be kept in mind in cases of lateral ventricle tumor as well as spinal tumors in pediatric population. In the present study, the number of malignant rhabdoid tumor of kidney(n=2) was less than AT/RT. Malignant rhabdoid tumor of kidney is the most aggressive renal tumor in childhood. They represent 2% of all renal tumors in children and the OS rates ranged from 22% to 42%.

Table 1 The clinical characteristics and outcomes of patients

Patient	Gender	Age	Symptom	Localization	Size (cm)	Metastasis	Immunopathology	SMARC B1	Surgery	RT/ dose	Chemotherapy	Toxicity(Grade III/IV)	Follow up time (month)	Time to relapse (month)	Outcome
1	M	14 months	Seizure	Left temporal lobe	2 x3	No	Beta catenin cytoplasmic +, synaptophysin -, chromogranin -, GFAP +, EMA +, IDH -, CD 56-, loss of INI 1 expression, Ki 67 proliferation index 90%	Negative	Microscopic total excision	54 Gy/ local RT	EU-RHAB regimen and ASCT	Hematological toxicity, mucositis, febril neutropenia	30		Alive
2	M	10 years	Nausea, vomiting	Posterior fossa	3.5 x 2.5	No	Beta catenin cytoplasmic +, synaptophysin -, chromogranin -, GFAP patched +, EMA patched +, IDH -, CD 56-, loss of INI 1 expression	Negative	Microscopic total excision	54 Gy/ local RT	EU-RHAB regimen	Hematological toxicity, mucositis, febril neutropenia, infective endocarditis, Wernicke's- like encephalopathy	28		Alive
3	M	30 months	Impaired walking, convulsion	Right lateral ventricle	5x6x6.4	Spinal	Vimentin +, myogenin -, p 53 +, CD56 -, synaptophysin -, PANCK-, EMA patched +, GFAP- Loss of INI 1 expression Ki 67 index > 50%	c.592C>T(p.gln198*) (p0198*) heterozigot mutant	Microscopic total excision	36 Gy CSI/ 18 Gy posterior fossa	EU-RHAB regimen	Hematological toxicity, mucositis, febril neutropenia	24	17	DOD
4	F	5 years	Weakness	Cervical vertebra	2x 1.8x1	Yes	Loss of INI 1 expression	Unavailable	C1-C2-C3 total laminectomy and gross total mass excision	36 Gy / local RT	Vincristine, cyclophosphamide, cisplatin, doxorubicin	Hematological toxicity, mucositis, febril neutropenia	11	10	DOD
5	M	36 months	Weakness	Right frontal lobe	7.5x6.2x6.1	No	GFAP +, Ki 67 70%, vimentin +, chromogranin -, synaptophysin- p 53 -loss of INI 1 expression	Negative	Microscopic total excision	54 Gy/ local RT	EU-RHAB regimen and ASCT	Hematological toxicity, mucositis, febril neutropenia, vincristine neuropathy	25	10	DOD
6	F	18 months	Fever, cough, abdominal distantion, ptosis and upward gaze restriction	Pineal, frontal lobe, kidney, lung nodules	2x3, 2x2, 8x7, multiple > 1x1	Lung	Vimentin +, PANCK +, EMA +, Loss of INI 1 expression	Negative	Microscopic total excision of brain mass, radical nephrectomy after neoadjuvan treatment	8.4 Gy/ whole abdomen and lung / 9 Gy left flank/ total 17.4 Gy / local RT	EU-RHAB regimen after neoadjuvan (V, A,D)	Hematological toxicity, mucositis, febril neutropenia, VOD	3	2	DOD
7	F	4 months	Hematuria	Right renal mass	9x 8.7	Lymphadenopathy	Vimentin +, p 53 +, EMA +, Loss of INI 1 expression	Negative	Upfront right radical nephrectomy	10.8 Gy / right flank	EU-RHAB regimen	Hematological toxicity, mucositis, febril neutropenia	6	4	DOD
8	M	20 months	Pelvic mass	Pelvic mass adjacent to bladder	7.9X 4.8X 4.6	No	Vimentin -, EMA -,CD34 -, Loss of INI 1 expression	Negative	Total mass resection and partial cystectomy	50.4 Gy / local RT	EU-RHAB regimen and ASCT	Hematological toxicity, mucositis, febril neutropenia	41		Alive

DOD; dead of disease, CT;chemotherapy, RT; radiation therapy, ASCT; autologous stem cell transplantation, VOD; veno occlusive disease, NA; not available, (V,A,D); vincristine, actinomycin D, doxorubicine, CSI;cranio-spinal irradiation, EMA; epithelial membrane antigen, GFAP; glial fibrillary acidic protein.

A retrospective analysis of 58 patients with RTK from Austria, Switzerland, and Germany reported comparable outcomes for patients with and without autologous hematopoietic stem cell transplantation. Thirty-seven (64%) patients achieved a complete remission, 17 (29%) relapsed, 34 (59%) died of disease progression, and two (3%) died of a treatment-related complication. The mean time to the first event was 3.5 months in their study. They reported that methastatic/multifocal disease, younger age, and local stage III were associated with significantly worse survival (15). According to the SIOP study, RTK has a poor outcome especially in young patients and those with advanced disease. Neither tumur volume at diagnosis, nor pre-operative chemosensitivity are prognostic factors for survival (16). In the present study, both patients with malignant rhabdoid tumor of the kidney died. One patient who was 4 months old age relapsed at 4 months and died at6 months after initial diagnosis despite unilateral radical nephrectomy, radiotherapy and chemotherapy. Another patient with synchronous AT/RT and RTK with metastatic lung nodules relapsed after 2 months and died 3 months after diagnosis. It is difficult to exclude the possibility of metastasis from kidney to frontal lobe, pineal region and lung and/or simultaneous occurance of multiple tumors such as malignant rhabdoid kidney tumor and atypical teratoid rhabdoid tumor in this case., An infant case with synchronous malignant rhabdoid tumor in the kidney and the brain similar to our case has been reported in the literature (17). Malignant rhabdoid tumors of soft tissues can present in any part of the body. The bladder localization is rarely seen. So far, 9 patients with bladder malignant rhabdoid tumors have been reported. Malignant rhabdoid tumors of the bladder seem to be less aggressive compared to other rhabdoid tumors. Therefore, the partial cystectomy together with high-dose chemotherapy and radiotherapy could be appropriate treatment when feasible (18). In the present study, only one patient was diagnosed with malignant rhabdoid tumor of the bladder. He achieved remission with high-dose chemotherapy with autologous hematopoietic stem cell transplantation.

Although several chemotherapy-related toxicities were developed during the treatment, no toxicities were observed during or after transplantation except for grade III/IV haematologic toxicity/mucositis and febrile neutropenia. One patient experienced ifosfamide associated Wernicke-like encephalopathy. It is associated with a classic triad of symptoms consisting of ataxia, ocular motor cranial neuropathies, and altered consciousness, but not may be seen in the majority of patients. The diagnosis could be more difficult in brain tumors, because of the overlapping symptoms and the risk of encephalopathy related to both the disease and treatment. When the diagnosis is clinically suspected, treatment should be initiated immediately without waiting for laboratory confirmation. The most common magnetic resonance findings are symmetrical T2 hyperintensities in the dorsal medial thalamus, mammillary bodies, periaqueductal gray matter, and tectal plate (19,20). Therefore it is rare and under-recognized in childhood, it could be fatal without proper management. Therefore, Wernicke's encephalopathy should be considered in all children with cancer who present with acute neurologic deterioration during ifosfamide treatment, especially in brain tumors.

Microscopically, the rhabdoid tumors are characterized by diffuse proliferation of rounded or polygonal cells with eccentric nuclei, prominent nucleoli and eosinophilic cytoplasm containing hyaline-like inclusion bodies, arranged in sheets and nests together with cellular atypia and high mitotic activity. Immunohistochemically, the tumor cells are characterized by the expression of vimentin and epithelial markers such as epithelial membrane antigen, and cytokeratin, less commonly smooth muscle actin. The absence of INI1 protein expression is a distinctive feature of these tumors (21). Similarly, the common feature of patients with rhabdoid tumors of any location was loss of INI1 expression in the present study. A germline mutation of SMARCB1/B4 is observed in 25–30% of the patients with rhabdoid tumors. Under 2 years of age, tumor is usually multifocal, and affects more than one relative in patients with germline mutation (2). In the present study, genetic analysis of demonstrated a denovo germline heterozygous SMARC B1 gene mutation in one patient with AT/RT who has a localized intraventricular mass with spinal metastasis (his parents have no mutations) (No#3 patient). He died of progressive disease 24 months after diagnosis. Despite multimodal treatment approaches, the median OS of the patients is approximately 1 year or less (22). Moreover, there are studies reporting median overall survival as low as 2.5 months (23). The overall survival and event-free survival of childhood extracranial malignant rhabdoid tumors were reported 53.0%, 54.5%, respectively with a median follow-up duration of 17.8 months (range, 2.3 to 112.3 months). In addition, they reported that the OS of patients who underwent autologous hematopoietic stem cell transplantation was 66.7% and EFS was 75.0% with a median follow-up duration of 23.8 months (range, 8.1 to 42.6 months) (24). Overall survival of the rhabdoid tumors was found to be 27% at 5 years and there was no significant difference in prognosis regarding the different tumor locations (kidney 24%, soft tissue 30%, CNS 29%) in a study from Germany (25). A recent study reported that the ACNS0333 regimen dramatically improved survival rate (OS: 43%) compared to historical therapies in patients with AT/RT (26). The analysis of 130 patients with AT/RT revealed a 3-year OS of 25% in recent meta-analysis (27). In the present study, 2- year event-free and overall survival rates of all patients were

37.5% and 50%, respectively. Although the number of cases underwent autologous hematopoietic stem cell transplantation was limited, two of 3 patients are still alive. The addition of the high-dose chemotherapy with autologous hematopoietic stem cell transplantation might be have a role for prolonged survival rates in these patients. It has been suggested that aggressive therapy including early adjuvant radiotherapy and HDCT could be considered to improve the outcome of ATRT in children younger than 3 years (28). The mortality rate of rhabdoid tumors is high especially in children with germline SMARC B1 mutation, with younger age and metastasis at the time of diagnosis. Although, the present study has some limitations including retrospective nature, limited number of patients and heterogeneous group of rhabdoid tumor, it might have a role to increase the awareness of this rare disease especially in developing countries.

CONCLUSION

The most common tumor site of rhabdoid tumors is the central nervous system in children. Because of its rarity and poor prognosis, management and treatment of rhabdoid tumors is challenging and requires a multidisciplinary team. Despite intensive treatment modalities, the mortality rate is still being high. Also, the high level of awareness for rhabdoid tumor is required both definitive diagnosis at initially and chemotherapy related various toxicities during treatment. The addition of high-dose chemotherapy with autologous hematopoietic stem cell transplantation seems efficious in subset of patients who achieved complete remission. In addition, the toxicities resulting from intensive treatments could be manageable but new targeted therapies are also needed to improve survival rates of rhabdoid tumors.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ankara Child Health and Diseases Pediatric Hematology Oncology Training and Research Hospital Ethics Committee (Date: 30.07.2019, Decision No: 2019-229).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Haas JE, Palmer NF, Weinberg AG, Beckwith JB. Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children. Hum Pathol1981;12(7):646-57.
2. Gellera JI, J. Rothb JJ, Biegelb JA. Biology and Treatment of Rhabdoid Tumor. Crit Rev Oncog 2015; 20(3-4): 199– 216.
3. Fossey M, Li H, Afzal S, et al. Atypical teratoid rhabdoid tumor in the first year of life: the Canadian ATRT registry experience and review of the literature. J Neurooncol. 2017;132(1):155-62.
4. Fischer-Valuck BW, Chen I, Srivastava AJ, et al. Assessment of the treatment approach and survival outcomes in a modern cohort of patients with atypical teratoid rhabdoid tumors using the National Cancer Database. Cancer. 2017;123(4):682-7.
5. Al-Hussaini M, Dissi N, Souki C, Amayiri N. Atypical teratoid/rhabdoid tumor, an immunohistochemical study of potential diagnostic and prognostic markers. Neuropathology. 2016;36(1):17-26.
6. 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(7):888–90.
7. Morgenstern DA, Gibson S, Brown T, Sebire NJ, Anderson J. Clinical and Pathological Features of Paediatric Malignant Rhabdoid Tumors. Pediatr Blood Cancer. 2010;54:29–34.
8. Buscariollo DL, Park HS, Roberts KB, Yu JB. Survival outcomes in atypical teratoid rhabdoid tumor for patients undergoing radiotherapy in a Surveillance, Epidemiology, and End Results analysis. Cancer. 2012;118(17): 4212-9.
9. Samaras V, Stamatelli A, Samaras E, et al. Atypical teratoid/rhabdoid tumor of the central nervous system in an 18- year-old patient. Clin Neuropathol. 2009;28(1):1-10.
10. Appaji L, Aruna Kumari BS, Babu KG, et al. Atypical teratoid rhabdoid tumor of the central nervous system: Case series from a regional Tertiary Care Cancer Centre in South India. J Cancer Res Ther. 2017;13(6):1015-22.
11. Masoudi MS, Derakhshan N, Ghaffarpasand F, Geramizadeh B, Heydari M. Multifocal atypical teratoid/rhabdoid tumor: a rare entity. Childs Nerv Syst. 2016;32(12):2287-8.
12. Li F, Gui Q, Piao Y. Primary supratentorial atypical teratoid/rhabdoid tumor in children: a report of two cases. J Child Neurol. 2013;28(3):399-403.
13. Li D, Heiferman DM, Syed HR, et al. Pediatric primary spinal atypical teratoid rhabdoid tumor: a case series and review of the literature . J Neurosurg Pediatr. 2019;1-17.
14. Sharma A, Sable MN, Singla R, Dash C, Sahu RN. Lateral Ventricle Atypical Teratoid/Rhabdoid Tumor (AT/RT): Case Report and Review of Literature Neurol India Nov-Dec 2020;68(6):1465-68.
15. Furtwangler R, Kager L, Melchior P et al. High- dose treatment for malignant rhabdoid tumor of the kidney: No evidence for improved survival—The Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) experience. Pediatr Blood Cancer 2018;65(1):1-7.
16. Heuvel-Eibrink MM, Rehorst H, Coulom A 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(5):733-7.
17. Morizane A, Nakahara I, Takahashi JA, et al. A malignant rhabdoid tumor appearing simultanously in the kidney and the brain of an ainfant: case report. No Shinkei Geka.1997;25(7):665-9.
18. Assadi A, Alzubaidi A, Lesmana H et al. Pure Bladder Malignant Rhabdoid Tumor Successfully Treated With Partial Cystectomy, Radiation, and Chemotherapy: A Case Report and Review of the Literature. J Pediatr Hematol Oncol 2020. doi: 10.1097/MPH.0000000000001963.
19. Cefalo MG, De Ioris MA, Cacchione A, et al. Wernicke encephalopathy in pediatric neuro-oncology: presentation of 2 cases and review of literature. J Child Neurol. 2014;29(12):181-5.
20. White ML, Zhang Y, Andrew LG, et al. MR imaging with diffusion-weighted imaging in acute and chronic Wernicke encephalopathy. Am J Neuroradiol. 2005;26(9):2306-10.

21. Oda Y, Tsuneyoshi M. Extrarenal rhabdoid tumors of soft tissue: clinicopathological and molecular genetic review and distinction from other soft tissue sarcomas with rhabdoid features. Pathol Int2006;56(6):287-95.
22. Babgi M, Samkari A, Al-Mehdar A, Abdullah S. Atypical Teratoid/Rhabdoid Tumor of the Spinal Cord in a Child: Case Report and Comprehensive Review of the Literature. Pediatr Neurosurg. 2018;53(4):254-62.
23. Appaji L, Aruna Kumari BS, Babu KG, et al. Atypical teratoid rhabdoid tumor of the central nervous system: Case series from a regional Tertiary Care Cancer Centre in South India. J Cancer Res Ther. 2017;13(6):1015-22.
24. Hong CR, Kang HJ, Ju HY, et al. Extra-cranial Malignant Rhabdoid Tumor in Children: A Single Institute Experience. Cancer Res Treat. 2015;47(4):889-96.
25. Reinhard E, Reinert R, Beier R, et al. Rhabdoid tumors in children: prognostic factors in 70 patients diagnosed in Germany. Oncol Rep 2008;19(3):819-23.
26. Reddy AT, Strother RD, Alexander R. Judkins AR, et al. Efficacy of High-Dose Chemotherapy and ThreeDimensional Conformal Radiation for Atypical Teratoid/Rhabdoid Tumor: A Report From the Children's Oncology Group Trial ACNS0333. J Clin Oncol 2020;38(11):1175-85.
27. Underiner RM, Eltobgy M, Stanek JR, Finlay JL, AbdelBaki MS. Meta-Analysis of Treatment Modalities in Metastatic Atypical Teratoid/Rhabdoid Tumors in Children. Pediatr Neurol 2020;108:106-12.
28. Park M, Han JW, Hahn SM, et al. Atypical Teratoid/Rhabdoid Tumor of the Central Nervous System in Children Under the Age of 3 Years. Cancer Res Treat. 2021; 53(2): 378-88.