Extracranial Malignant Rhabdoid Tumors in Childhood

The Childrens Hospital Los Angeles Experience

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BACKGROUND. Extracranial malignant rhabdoid tumor (MRT) is a rare, aggressive, pediatric malignancy with a historically poor outcome. Recent efforts to intensify treatment for MRT have resulted in isolated reports of long-term survival.

METHODS. The authors conducted a retrospective review of consecutive patients with MRT at Childrens Hospital Los Angeles over the 20 years from 1983 to 2003.

RESULTS. Fourteen children were diagnosed with MRT over the 20-year study period. The median age at presentation was 22.5 months (range, 0.5–108 months). Five patients had renal primary tumors, and 9 patients had extrarenal tumors. Eleven of 14 patients had stage III or IV disease at diagnosis. Five patients (35.7%) were long-term survivors. The time to disease progression was rapid (mean, 3.6 months). There were no recurrences or deaths beyond 10 months after diagnosis. All survivors received multimodal therapy, including both chemotherapy and surgery with or without radiation. In addition, 2 patients received high-dose chemotherapy with hematopoietic stem cell rescue (HSCT) after neoadjuvant chemotherapy and local tumor control. Both of those patients were long-term survivors. There were no survivors after disease recurrence or progression.

CONCLUSIONS. Patients with localized disease and complete surgical resection were most likely to survive long-term. Consolidation with HSCT may benefit selected patients with advanced disease stage. International collaboration and further understanding of the biology of this disease is necessary to improve the survival of children with MRT. ***Cancer*** **2007;110:2061–6.** © *2007 American Cancer Society.*

KEYWORDS: rhabdoid, renal, extrarenal, extracranial, malignant, tumor, kidney, children.

Extracranial malignant rhabdoid tumor (MRT) is a rare, highly aggressive malignancy that presents in young children, often at an advanced stage.[1–3] It arises most commonly in the kidney and comprises from 1.5% to 4% of malignant renal tumors.[4,5] It has been reported that second primary tumors in the central nervous system (CNS), which are classified as atypical teratoid rhabdoid tumors, occur in from 10% to 20% of these individuals.[6,7] A variety of extracranial, extrarenal sites, such as the liver, abdomen, retroperitoneum, or other soft tissues, have been reported.[3,8–10] The recent finding that most MRTs have deletions or mutations of the hSNF5/INI1 gene on chromosome 22q has provided evidence of a common origin for cranial and extracranial MRT and has enabled the distinction of this neoplasm from other soft tissue neoplasms.[11,12]

Initially described as a "rhabdomyosarcomatoid" variant of Wilms tumor, MRT was treated in accordance with Wilms tumor protocols for many years.[4] Regimens containing vincristine, dactinomycin,

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doxorubicin, and cyclophosphamide produced little improvement in mortality rates of approximately 70% to 80%.[4,5,8] Poorer outcomes have been reported in younger patients, in patients with higher stage or metastases at presentation, and in patients with concurrent CNS disease.[4] Recent attempts to intensify therapy and incorporate alternative agents have resulted in clinical responses and even anecdotal reports of long-term survival in patients with advanced-stage disease.[13–15] The rarity of MRT and its universally poor prognosis pose a unique challenge to clinicians who treat this disease.

To gain further insight into this disease, we reviewed all patients who had extracranial MRT diagnosed at our institution over 20 years. In this report, we describe their clinical features, management, and outcomes.

MATERIALS AND METHODS

Fourteen consecutive patients with primary extracranial MRT presented to Childrens Hospital Los Angeles (CHLA) between 1983 and 2003. Information on their clinical features, laboratory findings, pathology (including cytogenetic studies), treatment, and survival were recorded by retrospective medical record review. Patients were staged according to the National Wilms Tumor Study Group surgical-pathologic staging system for renal tumors.[16]

The Committee on Clinical Investigation at CHLA approved the conduct of this study and waived individual informed consent to review the medical records of the patients who were included. The Kaplan-Meier method was used to estimate disease progression-free survival (PFS) and overall survival (OS).

RESULTS

Clinical Features

The median age at presentation was 22.5 months (range, from 0.5 months to 13 years). There were 5 girls and 9 boys (Table 1). The most common presenting symptoms were a palpable or visible mass in 5 patients, followed by fever in 4 patients, back pain or signs of spinal cord compression in 4 patients, loss of appetite in 3 patients, and gross hematuria and vomiting in 2 patients each. One patient presented with polyuria, polydypsia, and urinary retention (Patient 7), whereas another patient presented in significant respiratory distress (Patient 11). Laboratory abnormalities at presentation included anemia (hemoglobin <11g/dL) and elevated serum lactate dehydrogenase (LDH) (>1000 U/L) in 7 patients, thrombocytosis (>450,000/mm^3) in 6 patients, leuko-

TABLE 1
Patient Characteristics, Treatment, and Outcome

Patient	Age at DX, mo	Sex	Primary site	Metastases	Stage	Surgery for primary	Chemotherapy	Local radiation, cGy	Time to progression	Vital status (Mo after DX)
1	3	Girl	Kidney	No	II	Upfront CR	Carbo/VP+Ifos/Adria	None	7 (Brain)	DOD (7)
2	75	Boy	Paraspinal	No	II	Upfront CR	Ifos/Adria+Carabo/VP	4500	No progression	NED (26)
3	108	Girl	Kidney	No	II	Upfront CR	Carbo/VP+C	1080	No progression	NED (78)
4	0.5	Boy	Back	No	III	Delayed CR	VAC+VAdriaC+CDDP/VP/Ifos	None	No progression	NED (33)
5	1	Boy	Retroperitoneum	No	III	Unresectable	VAdriaC	Palliative	1 (Meningeal)	DOD (2)
6	6	Boy	Kidney	No	III	Delayed CR	VAdriaC+CDDP/VP→CEM with HSCT	None	No progression	NED (34)
7	21	Boy	Kidney	Yes (lymph nodes)	III	Upfront resection; MRD	VAdriaA+CDDP/VP	2400	7 (Local and lung)	DOD (9)
8	30	Girl	Neck	No	III	Delayed resection; MRD	VAC+Ifos/Adria→CEM with HSCT	4500	No progression	NED (104)
9	54	Boy	Neck	No	III	Unresectable	VAdriaC+Ifos/VP	1950	2 (Local)	DOD (5)
10	6	Girl	Liver	Yes (lung)	IV	Unresectable	None (declined)	None (declined)	0.4 (Local and lung)	DOD (0.4)
11	12	Boy	Retroperitoneum	Yes (lung, lymph nodes)	IV	Unresectable	Carbo/VP+Ifos/Adria	None	1 (Local and lung)	DOD (2)
12	24	Girl	Retroperitoneum	Yes (lung)	IV	Delayed resection; MRD	Carbo/VP+Ifos/Adria	None	6 (Local and lung)	DOD, 8
13	36	Boy	Pelvis	Yes (lung, liver)	IV	Unresectable	VAdriaC	None	2 (Local and distant)	DOD (2)
14	96	Boy	Kidney	Yes (lung)	IV	Delayed resection; MRD	CDDP/Adria+Ifos/VP+VAC	1400	6 (Lung)	DOD (6)

DX indicates diagnosis; cGy, centigrays; CR, complete resection; Carbo, carboplatin; VP, etoposide; Ifos, ifosphamide; Adria, doxorubicin; DOD, died of disease; NED, no evidence of disease; C, cyclophosphamide; V, vincristine; CDDP, cisplatin; CEM, carboplatin, etoposide, and melphalan, HSCT: hematopoietic stem cell transplantation.

cytosis (>15,000/mm^3) in 4 patients, and hypercalcemia (>12 mg/dL) in 3 patients. The serum LDH level did not correlate with tumor burden, and hypercalcemia was not related to the presence of bone metastases.

Diagnosis

The diagnosis of MRT was established histologically by the presence of sheets of cells with eccentric oval nuclei, prominent nucleoli, and eosinophilic cytoplasm that often contained hyaline inclusions.[1,3] Cytogenetic analyses in 2 patients confirmed the presence of the *hSNF5/INI1* mutation (Patients 2 and 4). The tumors in these 2 patients did not stain for *INI1* on immunohistochemistry, thus supporting the cytogenetic finding. Cytogenetic analysis and immunohistochemistry for *INI1* were not performed on the other 12 patients.

Tumor Location and Stage

Table 1 summarizes the details of the location of the primary tumor and extent of disease for all 14 patients, their treatment, and their outcomes. Five patients had renal primary tumors, and 9 tumors were extrarenal. No patient had CNS involvement at diagnosis. Sites of extrarenal disease included the retroperitoneum in 3 patients, paraspinal or back locations in 2 patients, the neck in 2 patients, the pelvis in 1 patient, and the liver in 1 patient.

Eleven of 14 patients (79%) had stage III or IV disease at diagnosis. Metastases were present in 6 of 14 patients (43%), including 3 patients with metastases to the lung, 2 patients with metastases to the lung and liver, and 1 patient with lymph node metastases.

Treatment

One patient declined therapy (Patient 10). Various combinations of multimodal therapy, including chemotherapy, surgery, and radiation, were used to treat all other patients except for 2 (Patients 11 and 13) who received chemotherapy alone because of unresectable and disseminated disease.

Surgery

Nine of 14 patients (64%) underwent surgical resection of their primary tumors. Four patients underwent upfront resection (3 patients underwent complete resection, and 1 patient underwent resection with microscopic residual disease), and the other 5 patients underwent delayed surgery after chemotherapy (2 patients underwent complete resection, and 3 patients underwent resection with microscopic residual disease).

Chemotherapy

The median duration of chemotherapy was 5.5 months (range, 1–9 months). Table 1 lists the various drug combinations that were used. Most patients received regimens that contained vincristine, dactinomycin, doxorubicin, and cyclophosphamide. Ten patients received additional platinum-based chemotherapy (carboplatin, cisplatin), and 7 patients received ifosfamide. Two patients with stage III disease received high-dose chemotherapy with carboplatin, etoposide, and melphalan and underwent hematopoietic stem cell transplantation (HSCT) after receiving neoadjuvant chemotherapy and achieving local tumor control.

Radiation

Seven of 13 treated patients received radiation, including 1 patient who received palliative radiation. The amount and extent of radiation to the primary site varied. Radiation primarily was limited to older patients (median age, 64 months; range, 21–108 months), and the median dose was 2640 centigrays (cGy) (range, 1080–4500 cGy). The 6 patients who did not receive radiation for adjuvant local tumor control were younger (median age, 9 months; range, 0.5–36 months). Three patients had stage IV disease, 1 patient underwent an upfront complete surgical resection, and 2 patients underwent delayed complete surgical resections.

Outcome

The estimated PFS was $36 \pm 13\%$ for the entire cohort after a median follow-up of 36 months. The median time to progression—which was measured as the time from diagnosis to recurrence or disease progression—was 2 months (range 0.4–7 months). Disease progression was both local and distant in 4 patients, distant only in 3 patients, and local only in 1 patient. Radiation to the primary tumor site did not appear to influence the pattern of disease progression. All patients died within the first 10 months after diagnosis and within 3 months of disease progression. The cause of death in all patients was progressive disease or recurrence. The estimated overall survival for the entire cohort of after a median follow-up of 36 months was $35.7 \pm 13\%$ (Fig. 1).

Five of 14 patients are long-term survivors (range, 26–104 months). No patient with stage IV disease at diagnosis survived. The median age of survivors at diagnosis was 30 months (range, 0.5–108 months) compared with 21 months (range, 1–96 months) for patients who did not survive. Two of the survivors had stage II disease, and 3 had stage III disease. All 5 survivors underwent surgery for local

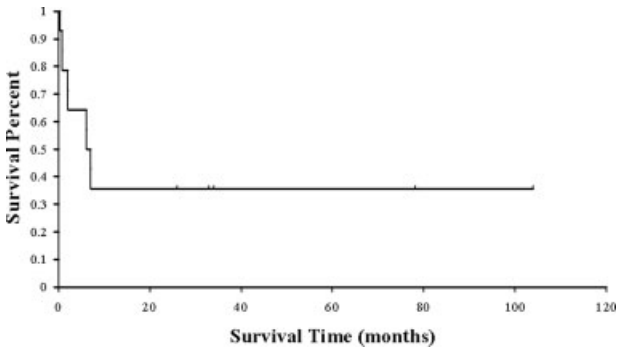

FIGURE 1. This Kaplan-Meier curve illustrates survival for 14 patients who had extracranial malignant rhabdoid tumors.

tumor control (3 patients underwent upfront resection, and 2 patients underwent delayed resection), and a complete surgical resection was achieved in all but 1 survivor. Three of the survivors received radiation to the primary site in addition to chemotherapy and surgery. Of the treated patients who did not survive, 1 patient received palliative radiation, and 3 of 7 patients received therapeutic radiation (2 for microscopic residual disease after surgical resection).

There did not appear to be improved survival among the patients who received regimens that contained ifosfamide. Ifosfamide was used in 3 of 5 survivors and in 5 of 8 patients who did not survive. The addition of platinum agents (carboplatin, cisplatin) also did not change outcome. All 5 survivors received a platinum agent (including 2 patients who received high-dose carboplatin in the conditioning regimen before HSCT) compared with 5 of 9 patients who did not survive. Both HSCT recipients are long-term survivors—1 patient who underwent a delayed complete surgical resection and received no radiation (Patient 6) and 1 patient who underwent a delayed surgical resection followed by adjuvant radiation for microscopic residual disease (Patient 8).

DISCUSSION

The treatment of patients with MRT remains a challenge. The management of MRT is complex; and, in most patients, various combinations of therapeutic approaches are needed to achieve a satisfactory result. To our knowledge, the current case series of patients with MRT is the largest reported to date from a single institution. The results reaffirm that 1) MRT is highly aggressive, and disease progression or recurrence occur early; 2) gross total surgical resection of the primary tumor is necessary for successful treatment; 3) salvage is not successful after disease progression or recurrence; and 4) patients who have metastatic disease at diagnosis have a dismal prognosis. Our series also suggests that there may be a role for high-dose chemotherapy and HSCT in achieving long-term survival after surgical resection of the primary tumor and neoadjuvant or adjuvant chemotherapy. Furthermore, the results from our series suggest that the role of radiation is unclear in the treatment of select patients.

Age at diagnosis was a highly significant prognostic factor in a recent review of 142 patients who had MRT of the kidney from National Wilms Tumor Studies (NWTS) 1 through 5.[4] In those studies, the 4-year survival rate for the youngest group of patients (0–5 months) was 8.8% compared with 41% for patients who were diagnosed at age $\geq$24 months. The median age in our patient population was 22.5 months and was higher than in the NWTS review (median age, 11 months). This difference remained even for patients who had renal primaries only (21 months). It is noteworthy that, in the current study, 2 survivors (Patients 4 and 6) were very young at diagnosis (0.5 months and 6 months, respectively). Both presented with stage III disease, received aggressive chemotherapy regimens, and required repeated surgeries to achieve complete resection.

Presenting symptoms varied in our patients, depending on tumor location. Hypercalcemia, which is an uncommon finding in childhood tumors but has been reported in infants with MRT,[8,17] was observed in 3 patients (all aged $<$12 months). Consistent with past series,[4,5,8] our patients tended to present with advanced disease—all but 3 patients had stage III or IV disease at diagnosis. Like what was reported in the NWTS series,[4] advanced stage was a poor prognostic factor, because all patients who presented with metastases died from progressive disease.

The time to progression was rapid, but no patients progressed or developed recurrent disease beyond 10 months after diagnosis. This is consistent with previous series, which demonstrated that tumor recurrence is rare after 2 years.[4,5,18] The estimated overall survival of 35.7 $\pm$ 13% in our series is equivalent to and, in most instances, better than previously reported. In 1992, Gurangan et al.[8] were among the first to report responses to ifosfamide-containing regimens; however, all 13 reported patients in that series eventually died of progressive disease. Wagner et al.[13] and Waldron et al.[14] subsequently reported anecdotal cases of long-term survival in individuals with metastatic MRT. Their patients underwent aggressive surgery and received chemotherapy regimens that included combined ifosfamide, carboplatin, and etoposide and combined vincristine,

doxorubicin, and cyclophosphamide. The largest reported experience with MRT of the kidney is through the NWTS group: The 4-year survival rate was 23.2% for patients who were enrolled on NWTS 1 through 5.[4]

All treated patients in our series received multiagent chemotherapy. The chemotherapy agents included vincristine, dactinomycin, doxorubicin, and cyclophosphamide, all of which have been used traditionally in the treatment of Wilms tumor. Other agents that were used included varying combinations of cisplatin, etoposide, ifosfamide, and carboplatin. Of those agents, it has been suggested that patients who receive ifosfamide-containing regimens have prolonged disease-free progression.[8,19] However, our data did not appear to demonstrate this survival advantage.

Complete surgical resection, whether at diagnosis or after neoadjuvant chemotherapy, appeared to be correlated positively with survival. Four of 5 survivors underwent complete surgical resection, and there were no survivors among the patients who had unresectable disease. The role of radiation was less clear, because radiation to the primary tumor site did not correlate with better local control or prevent disease progression.

It has been demonstrated that the use of high-dose chemotherapy with HSCT is beneficial in patients with high-risk neuroblastoma[20] and is efficacious in patients with high-risk Wilms tumor.[21] There has been only a single previous report of successful treatment of MRT with HSCT in 1 patient.[15] Our case series, with 2 successfully treated patients who had advanced-stage disease and received high-dose chemotherapy followed by HSCT, adds to this experience. Both of those patients survived, despite their young age at presentation, delayed surgical excision of the primary tumor (Patient 6), and residual disease after delayed resection (Patient 8). Only 1 patient received radiation to the primary tumor site (Patient 8). Although this group was too small to draw conclusions about the role of HSCT in MRT, our findings suggest a possible role for HSCT in select patients who present with advanced-stage MRT. However, this advantage may have been caused by selection bias, because the median time to disease progression in our series was 2 months.

Although the long-term survival rate of $35.7 \pm 13\%$ in our series still is relatively poor, survival at all with this malignancy has been reported only recently. The limitations of our study include the small sample size, its retrospective nature, and the relative heterogeneity of treatment provided. However, the results from our series suggest that long-term survival can be achieved in the setting of localized disease, complete resection (upfront or delayed), and aggressive chemotherapy, including the successful use of HSCT for patients with advanced disease.

Because MRT is such a rare childhood malignancy, single-institution experiences like ours can provide some insight for potential trials that can be conducted in the cooperative group setting. Larger cooperative group experiences have failed to demonstrate an improvement in the outcome of children with MRT to date.[4,5] Based on our results, a Phase II clinical trial of high-dose chemotherapy followed by HSCT could be conducted in children with advanced-stage disease comparing their outcomes with those of historic controls. Furthermore, it is possible to consider omitting local radiation for patients who have complete surgical resection of their tumors at diagnosis or after neoadjuvant chemotherapy. Because the majority of patients with MRT are very young, eliminating the late effects of radiation is desirable, especially when the benefit is unclear. International collaboration and further study of the biology of this disease will be necessary to improve long-term survival in children with MRT.

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