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Clinical Investigation

Outcomes and Acute Toxicities of Proton Therapy for Pediatric Atypical Teratoid/Rhabdoid Tumor of the Central Nervous System

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Summary

Proton therapy is increasingly used to treat pediatric patients with atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system, but the outcomes are poorly defined. Records of 31 patients with AT/RT treated with protons were retrospectively reviewed. Median overall survival was 34.3 months. Five patients (16%) developed brainstem changes consistent with radiation reaction. Aggressive

Purpose: Atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system is a rare cancer primarily affecting children younger than 5 years old. Because patients are young and receive intensive chemotherapy, there is concern regarding late radiation toxicity, particularly as survival rates improve. Therefore, there is interest in using proton therapy to treat these tumors. This study was undertaken to investigate outcomes and acute toxicities associated with proton therapy for AT/RT.

Methods and Materials: The records of 31 patients with AT/RT treated with proton radiation from October 2008 to August 2013 were reviewed. Demographics, treatment characteristics, and outcomes were recorded and analyzed.

Results: Median age at diagnosis was 19 months (range, 4-55 months), with a median age at radiation start of 24 months (range, 6-62 months). Seventeen patients received local radiation with a median dose of 50.4 GyRBE (range, 9-54 GyRBE). Fourteen patients received craniospinal radiation; half received 24 GyRBE or less, and half received 30.6 GyRBE or more. For patients receiving craniospinal radiation, the median tumor dose was 54 GyRBE (range, 43.2-55.8 GyRBE). Twenty-seven patients (87%) completed the planned radiation. With median follow-up of 24 months for all

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multimodality therapy including protons may improve outcomes, but there is potential for radiation reaction, even when routine dose constraints are satisfied.

patients (range, 3-53 months), median progression-free survival was 20.8 months and median overall survival was 34.3 months. Five patients (16%) developed clinical findings and imaging changes in the brainstem 1 to 4 months after radiation, consistent with radiation reaction; all cases resolved with steroids or bevacizumab.

Conclusions: This is the largest report of children with AT/RT treated with proton therapy. Preliminary survival outcomes in this young pediatric population are encouraging compared to historic results, but further study is warranted.

Introduction

Atypical teratoid/rhabdoid tumor (AT/RT) is a highly lethal tumor of the central nervous system (CNS) that primarily affects children less than 5 years of age. Despite aggressive multi-modality intervention, median survival is historically 6 to 11 months (1, 2).

Because AT/RT is an uncommon malignancy, the optimal approach to treatment has not been identified. Surgery and chemotherapy are mainstays of therapy; the role of radiation remains ill defined, because many patients are younger than 3 years of age and highly susceptible to radiation toxicities. Initial approaches in this disease have emphasized delayed radiation to minimize neurotoxicity (3). Emerging evidence supports early radiation, even in very young patients, to increase the likelihood of disease control and long-term survival (4-7).

Given the increasing awareness of the role of radiation in AT/RT and the young age of patients, there is considerable interest in using proton radiation. Proton therapy decreases low-dose radiation exposure to uninvolved brain as well as to structures anterior to the craniospinal axis compared with standard photon-based radiation therapy (8-10). Therefore, the use of proton therapy may allow therapeutic doses of radiation to the target volumes with greater sparing of adjacent normal tissue compared to photon therapy (11-15). In the short term, these features of proton therapy may increase tolerance of concurrent and adjuvant chemotherapy by decreasing hematologic and gastrointestinal side effects (16). In the long term, protons may decrease the neurocognitive, endocrine, vascular, and developmental sequelae of treatment, as well as the risk of radiation-induced second malignancies (17, 18). This is particularly important because AT/RT typically affects very young children who are more likely to have devastating late effects from therapy (19-21).

The aim of this study was to evaluate a single-institutional experience in the use of proton radiation for the treatment of pediatric AT/RT of the CNS.

Methods and Materials

Almost all patients treated with protons at MD Anderson Cancer Center are enrolled on a prospective in-house registry protocol to follow the normal tissue toxicity and outcomes of patients. The registry protocol was approved by the institutional review board, and informed consent was obtained at the time of enrollment. Thirty-one patients with AT/RT of the CNS with at least 6 months of potential follow-up treated at MD Anderson Cancer Center from October 2008 to August 2013 were identified from the registry of 700 patients. Their medical records were retrospectively reviewed for clinical data, treatment details, and outcomes.

Patients had undergone initial diagnosis and treatment at 23 different institutions. Surgical pathology for 26 of 31 patients (84%) was reviewed at MD Anderson Cancer Center or Texas Children's Hospital before radiation therapy. Patients underwent lumbar puncture, magnetic resonance imaging (MRI) of the brain, and MRI of the spine at diagnosis and prior to the initiation of radiation therapy. The extent of resection was defined as a gross total resection (GTR) or subtotal resection (STR) based on analysis of postoperative imaging and the intraoperative determination of the neurosurgeon (4). Metastatic disease was staged according to the modified criteria of Chang et al (22). Briefly, M0 indicates no evidence of microscopic or gross metastatic disease; M1 indicates microscopic tumor cells present in cerebrospinal fluid; M2, gross disease in the subarachnoid space of the cerebellum or cerebrum or in the lateral or third ventricles; M3, gross disease in the subarachnoid space of the spine; and M4, metastatic disease present outside the neuroaxis.

Chemotherapy was delivered according to a variety of protocols (see Supplementary Material E1; available online at www.redjournal.com). All protocols but St. Jude's Medulloblastoma SJMB03 in cluded patients less than 3 years of age and had a period of induction chemotherapy after surgery and before radiation therapy.

All patients were treated with passive scatter proton therapy. For craniospinal irradiation (CSI), the brain was treated with opposed oblique fields and the spine was treated with 2 posterior−anterior spinal fields (23). Junctions between fields were 1 cm apart and were shifted every 4 to 5 fractions. Because of the young age of the patients in this study, the entire vertebral body was covered for all patients. Figure 1 shows a representative CSI plan.

The CSI was followed by a focal boost to the tumor bed. Boost plans and focal radiation alone were delivered with passive scatter proton therapy using 2 or 3 beams. Gross tumor volume (GTV) included the surgical cavity and any gross residual disease identified from imaging or the neurosurgeon's assessment. Clinical tumor volume (CTV) was a 1-cm anatomically constrained volumetric expansion