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CLINICAL INVESTIGATION **Sarcoma**

THE CHALLENGING ROLE OF RADIATION THERAPY FOR VERY YOUNG CHILDREN WITH RHABDOMYOSARCOMA

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Purpose: To evaluate local control and toxicity for very young children treated with multimodality therapy for rhabdomyosarcoma (RMS).

Methods and Materials: From 1990 to 2004, 20 patients ≤36 months at diagnosis were treated at our institution. Nineteen underwent chemotherapy (CMT), surgery and/or intraoperative high-dose-rate brachytherapy (IOHDR), and external-beam radiation (EBRT). Median age was 17 months. Sites included extremity (7), trunk (5), parameningeal (4), orbit (1), head/neck (1), bladder/prostate (1). Histologies consisted of 10 embryonal (53%) and 9 alveolar/undifferentiated (47%). Ten had delayed gross total resection (GTR) at median time of 17 weeks after the start of CMT, and 8 of these underwent IOHDR. Median interval between start of CMT and EBRT was 18 weeks. Median EBRT dose was 36 Gy. EBRT technique was either intensity-modulated (11), three-dimensional (3), or two-dimensional (5). Functional outcome was assessed for patients alive ≥1 year after diagnosis (15) in terms of mild, moderate, or severe deficits.

Results: Median follow-up was 33 months for survivors and 23 months for all patients. Two-year actuarial local control, event-free survival, disease-specific survival, and overall survival were 84%, 52%, 74%, and 62%, respectively. All patients who began EBRT ≤18 weeks after the start of CMT had their disease controlled locally. Five have mild deficits and 10 have no deficits.

Conclusions: A reduced dose of 36-Gy EBRT after delayed GTR may maximize local control while minimizing long-term sequelae for very young children with RMS, but unresectable tumors (e.g., parameningeal) require higher doses. Normal-tissue-sparing techniques such as intensity-modulated radiation therapy and IOHDR are encouraged. Local control may be maximized when EBRT begins ≤18 weeks after initiation of CMT, but further study is warranted. Longer follow-up is required to determine the full extent of late effects.

Rhabdomyosarcoma, Radiation therapy, Very young children, Infants, Multimodality therapy.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood. Currently, children with nonmetastatic RMS can be cured in >70% of cases with appropriate multimodality therapy (1, 2). Although RMS can occur at any age, approximately two-thirds of cases are diagnosed in children younger than 6 years of age. Within this younger age group, infants and toddlers (i.e., ≤36 months of age) pose a special therapeutic challenge. Concerns especially relevant to this youngest age group include the life-altering consequences of amputations, the morbidity of full-dose chemotherapy (CMT), and the late effects and technical difficulties associated with external-beam radiotherapy (EBRT).

The use of upfront EBRT for the youngest children has become an especially controversial topic (3–5). Underdeveloped organs, including the brain, lung, liver, kidney, and bone, are thought to be more radiosensitive, and resultant late effects can be significant (6). In addition, technical difficulties exist in ensuring immobility for infants and toddlers during treatment planning and delivery. General anesthesia is usually required on a daily basis for children ≤3 years and is not without potential complications (7). Finally, the carcinogenic effect of irradiation must be considered, given the long anticipated life span of the youngest children (8). Considerations such as these prompted the Malignant Mesenchymal Tumor (MMT) committee of the International Society of Pediatric Oncology (SIOP) in MMT-89 to specify that children with parameningeal RMS <3 years of age not undergo routine local irradiation (3). In addition, this study, in which almost one-third of patients were <3 years of age at diagnosis, was designed to avoid

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EBRT if at all possible in patients with nonparameningeal tumors. Irradiation was reserved only for incomplete surgical resection, documented nodal involvement, and poor clinical response to CMT. Other international RMS cooperative groups have also limited the use of EBRT for children <3 years of age to decrease treatment-related morbidity (9).

Although avoiding EBRT in the youngest patients with RMS may be desirable from a "total burden of therapy" perspective, doing so risks compromising local control and, potentially, survival. The resultant challenge is to find the appropriate treatment combination that will provide adequate local control while minimizing long-term toxicity. For eligible cases, we routinely use a combination of surgery with the goal of organ/limb preservation and/or intraoperative high-dose-rate brachytherapy (IOHDR), CMT, and EBRT with selective use of intensity-modulated radiation therapy (IMRT) for normal tissue sparing. We performed a retrospective study to evaluate the outcomes and toxicity in children ≤36 months at diagnosis treated at our institution.

METHODS AND MATERIALS

Patient and disease characteristics

From 1990 through 2004, 20 consecutive patients ≤36 months at the time of RMS diagnosis were treated at our institution. All but 1 were treated with a combination of CMT, surgery, and EBRT (Table 1). This 1 patient was a 2-year-old girl with a Stage 3, Group III embryonal rhabdomyosarcoma (ERMS) of the left gluteal region who received neoadjuvant CMT followed by wide local excision with negative surgical margins. EBRT was recommended but declined. The analyzed group thus consisted of the remaining 19 patients. Median age at diagnosis was 17.2 months (range: 0.1 to 36 months). Five patients were <12 months at the time of diagnosis. Ten were boys, and 9 were girls. The tumor stage, clinical group, and histologic type are summarized in Table 2. Table 3 indicates the tumor breakdown by site.

Chemotherapy

All 19 patients received multiagent CMT. Six patients were treated with four to five cycles of high-dose cyclophosphamide and doxorubicin with weekly vincristine (VAdriaC), and six to seven cycles of ifosfamide plus etoposide (IE) on an institutional protocol (10). Seven patients were treated on or according to Regimen A ($n = 7$) of the Intermediate-Risk Intergroup Rhabdomyosarcoma Study V (IRS-V) Study (Children's Oncology Group Study D9803) with 14 cycles of vincristine, actinomycin-D, and cyclophosphamide (VAC). One of these 7 patients developed local progression of his primary tumor after seven cycles of VAC, following which treatment was changed to IE. After progressing through one cycle of IE, he underwent surgery. Three patients received ifosfamide, etoposide, doxorubicin, dactinomycin, cyclophosphamide, and vincristine followed by consolidation with high-dose melphalan and etoposide and autologous bone marrow transplant (institutional regimen for high-risk patients with RMS, extraosseous Ewing's sarcoma, or undifferentiated sarcoma) (11). A fourth patient was treated according to this protocol but did not receive consolidation with melphalan/etoposide and autologous bone marrow transplant. One patient was treated on a pilot institutional study with three cycles of carboplatin plus irinotecan and three cycles of VAdriaC before surgery. Postoperatively, he received one additional cycle of carboplatin plus irinotecan, one additional cycle of doxorubicin plus cyclophosphamide, four cycles of IE, and six "maintenance" cycles of single-agent irinotecan. One infant received two cycles of VAC (with progression), followed by seven cycles of full-dose IE, and one cycle of VAdriaC before undergoing surgical resection of his primary tumor. Dose-reduced CMT was administered to all patients <1 year of age in accordance with standard guidelines.

Surgery

Ten patients had a delayed gross total resection (GTR) at a median time of 17.4 weeks (range: 14.1–33.1 weeks) after the start of CMT. Two patients had a GTR before the start of CMT. The other 7 did not have tumors amenable to resection. Nine patients (6 extremity, 3 trunk) underwent a limb-sparing surgery. No amputations were performed.

Intraoperative high-dose-rate brachytherapy

Eight patients underwent IOHDR at the time of delayed surgical resection. The details of the IOHDR technique at our institution have been published elsewhere, and the use of this technique for pediatric solid tumors has also been reported (12, 13). Indications for IOHDR treatment included gross residual disease and suspected microscopic disease or if the site was otherwise deemed to be at high risk for recurrence. Radiation was delivered using an iridium-192 (^{192}Ir) source via a high-dose-rate remote afterloader.

External-beam radiation therapy

All 19 patients received EBRT using either photons, electrons, or a combination of the two. Median interval between the start of CMT and the beginning of EBRT was 18.3 weeks (range, 2.4–52.9 weeks). Median EBRT dose to the primary site was 36.0 Gy (range, 24.0–54.0 Gy). For the 10 patients who underwent delayed GTR of the primary tumor (with or without IOHDR), median time from surgery to the start of EBRT was 34 days (range, 21 to 271 days). Ten patients who underwent GTR received ≤36 Gy. Eleven patients received IMRT, 3 had three-dimensional, and 5 had two-dimensional EBRT. Of the 11 patients who underwent IMRT, 5 had extremity tumors, 2 had parameningeal tumors, 2 had truncal tumors, 1 had a prostate RMS, and 1 had a perianal RMS. Three patients received hyperfractionated EBRT administered in two courses separated by a 4-week interval according to institutional protocol (11). The average treatment time was 37 days (range: 21–60 days). All patients completed their treatment without unplanned interruption of more than 2 days. Two patients also received additional EBRT to bony metastatic sites (1 contiguous with the primary tumor, 1 distant) and 2 patients received whole-lung EBRT for pathologically confirmed lung metastases.

EBRT target volumes and dose

All children underwent simulation and treatment under general anesthesia. Our approach to delineating the target volumes in pediatric patients with RMS has been described previously and will be briefly outlined here (14, 15). The gross tumor volume (GTV) was defined as the extent of disease at diagnosis (pre-CMT volume). However, if an anatomic structure had been displaced by tumor and then fell back into position by the time of simulation, the GTV was modified accordingly. The goal was to include any tissue with which the tumor had been in contact, without unnec-