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CLINICAL INVESTIGATION **Sarcoma**

PREOPERATIVE INTENSITY-MODULATED RADIOTHERAPY COMBINED WITH TEMOZOLOMIDE FOR LOCALLY ADVANCED SOFT-TISSUE SARCOMA

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Purpose: To evaluate the toxicity and efficacy of preoperative intensity-modulated radiotherapy (IMRT) combined with temozolomide to improve local tumor control in soft-tissue sarcoma (STS).

Patients and Methods: A cohort of 15 consecutive patients with nonmetastasized, primary high-grade or locally recurrent Stage III (n = 14) or IIb (n = 1) STS not amenable to surgical resection without significant organ or extremity function loss was prospectively investigated. Median tumor size was 9.8 cm, and most tumors were non-extremity sarcomas. Patients preoperatively received 50 mg/m^2 of temozolomide during IMRT (50.4 Gy). Resection was intended 6 weeks thereafter. Toxicity was assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, and response was assessed by Response Evaluation Criteria in Solid Tumors.

Results: Of 15 patients, 14 completed preoperative treatment. No Grade 4 toxicities occurred. Nausea and vomiting were the most frequent Grade 3 toxicities. The most frequent toxicities of any grade were dermatologic, gastrointestinal, and hematologic. Response was partial response in 5, stable disease in 7, and progressive disease in 2 patients. Ten patients underwent surgery: 7 were resected with clear margins (R0), and 2 patients had an R1 resection; in 1 patient the tumor was not resectable. Postoperative complications occurred in 4 patients. Five patients did not undergo surgery because of intercurrent metastatic disease, unresectable disease, or refusal.

Conclusions: Preoperative chemoradiation with temozolomide and IMRT can be administered safely and with promising efficacy in patients with locally advanced STS. © 2009 Elsevier Inc.

Soft-tissue sarcoma, Radiotherapy, Temozolomide, Preoperative therapy, IMRT.

INTRODUCTION

Soft-tissue sarcomas (STS) form a heterogeneous group of malignant neoplasms arising in the mesenchymal connective tissues. They can develop at any anatomic site, but 60% occur in the extremities (1). A considerable proportion of sarcoma patients presents with locally advanced primary or recurrent tumors. Despite improvements in surgical technique, such as compartment-oriented resection and microvascular muscle flaps, these patients face the risk of amputation or mutilating surgery for complete tumor removal (2). Sarcomas of the retroperitoneum, trunk, and proximal extremities form a subgroup in which treatment difficulties occur because of the localization of the tumor. Multimodal treatment has been introduced to STS therapy to enable tumor resection where critical anatomic structures are involved and can be administered pre- or postoperatively (3). The aim of preoperative multimodal treatment is to devitalize and downsize the tumor (4). In the past, radiotherapy and isolated limb perfusion proved effective in the preoperative setting (5, 6). More recently, combined neoadjuvant and adjuvant systemic chemotherapy combined with deep-wave hyperthermia were shown to improve disease-free survival in a large, randomized, Phase III study (7).

The advantage of intensity-modulated radiotherapy (IMRT) over conventional radiation techniques is the optimal coverage of the tumor volume. Dosimetric reports demonstrate that IMRT significantly reduces the dose to adjacent structures, whereas coverage of the tumor volume is at least equal to that obtained with three-dimensional conformal radiotherapy (3D-CRT) (8, 9). The rationale behind a combination of chemotherapy and radiation is to exploit the radiosensitizing effect of the added drug. Temozolomide is an oral

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prodrug of 3-methyl-(triazen-1yl)imidazole-4-carboximide, the active metabolite of dacarbazine (10). Combined with radiotherapy, it has substantially changed therapy options for patients with malignant glioblastoma. The drug has only modest activity against recurrent glioma as a single agent, but survival is significantly prolonged if the drug is administered in combination with radiotherapy (11). In STS, temozolomide alone was not active in patients with advanced STS as a second-line treatment if administered in a 28-day cycle (12). However, activity was reported using an oral 6-week continuous schedule, which is suitable for combination therapy with irradiation (13). Here we report on the toxicity and efficacy of combined temozolomide chemotherapy and IMRT.

PATIENTS AND METHODS

Study design

A cohort of 15 consecutive patients with locally advanced or recurrent, nonmetastasized STS of the retroperitoneum, trunk, or proximal limbs was preoperatively treated with concurrent temozolomide and IMRT (Fig. 1). Data were documented prospectively and are presented descriptively. The primary endpoint was the safety of the applied chemoradiation regimen. Response and short-term outcome were secondary endpoints. In brief, patients received temozolomide p.o. 7 days per week during radiation and for 2 weeks thereafter. Tumor resection was scheduled 6–8 weeks after completion of radiotherapy. No adjuvant therapy was applied. All procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Study population

The treatment of 15 consecutive patients at the Interdisciplinary Tumor Center Mannheim between 2004 and 2007 was evaluated. We included patients with primary or recurrent high-grade STS not amenable to surgical resection with clear margins without amputation, significant organ sacrifice, or extremity function loss. Eligibility criteria were histology of STS, age >18 years, Karnofsky Index ≥80, adequate liver and kidney function (creatinine and transaminases levels not elevated more than twofold above normal range), absence of myelodepression (platelet count >100,000/mL, absolute granulocyte count >1,500/mL), and ability to give informed consent. Patients who had undergone prior radiotherapy were excluded, as were patients with extremity sarcoma amenable to isolated limb perfusion.

Treatment plan

The dose of IMRT was 50.4 Gy given in 28 fractions. In case of positive margins an additional boost of 16 Gy was given after surgery. All patients were immobilized during radiation. A planning CT was performed, and all patients had CT simulation (Philips Brilliance Big Bore, Cleveland, OH). The gross tumor volume (GTV) was defined as identifiable from a calculated 3D computer model derived from the planning CT. The clinical target volume was defined as the GTV with a 2-cm margin axially. In the superior–inferior direction, the margin placed around the GTV was 5 cm. The planning target volume was defined as the clinical target volume with a 5-mm margin. The dose constraint for the small intestine was 45 Gy at the maximum, and the mean dose for the kidneys was <10 Gy. Optimized intensity profiles were obtained from an inverse planning algorithm (Corvus; Nomos, Cranberry Township, PA).

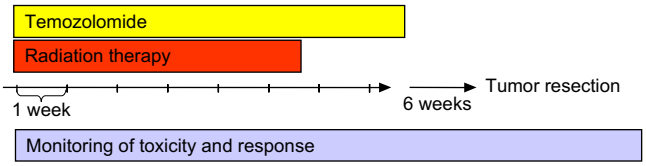

Fig. 1. Study design.

Treatment was performed using step-and-shoot IMRT (Elekta Synergy, Cranley, UK). Intensity-modulated radiotherapy was applied using five to nine fields, depending on the tumor localization. A strip of 2 to 3 cm was spared in case of extremity STS. No analysis of the correlation between inhomogeneity or dosimetry and toxicity was performed.

Temozolomide was given orally at a dose of 50 mg/m^2 once daily, 7 days per week (the recommended dose for concurrent radiotherapy and temozolomide in glioblastoma is 50–75 mg/m^2). Dose selection for sarcomas took into account the larger radiation volume and the presence of intestine in the radiation field in retroperitoneal sarcomas.

Assessment of toxicity

Treatment toxicity and postoperative complications were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (14). Clinical examination and blood counts were documented weekly during temozolomide therapy. In case of Grade 3 and 4 toxicity, medical therapy and radiotherapy were suspended until recovery to Grade 1 toxicity.

Response assessment

Local response was assessed using standardized MRI or CT. Imaging studies were performed before study treatment started and 4–6 weeks after completion of radiotherapy. Radiographic response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) (15). To determine pathologic response, the proportion of necrosis and scar tissue in the resection specimen was assessed and documented with cut-off points at 50% and 90% of scar tissue or necrosis.

Follow-up

For follow-up, chest CT scan and local MRI/CT at 3-month intervals were performed. Progression-free and overall survival time was calculated from the start of treatment.

RESULTS

Patient characteristics

Fifteen patients with a median age of 63 years were enrolled (Table 1). Soft-tissue sarcoma not otherwise specified was the most frequent histologic subtype treated. Median tumor size was 9.8 cm (range, 6.5–22 cm). The most frequent tumor sites were the retroperitoneum and the thigh. Two patients had received anthracycline-based chemotherapy before protocol entry.

Treatment summary and toxicity

Fourteen patients completed the protocol. One patient with a retroperitoneal sarcoma suspended study treatment because of abdominal discomfort, anorexia, and nausea, which impaired further medication and radiotherapy despite supportive measures.