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LOCAL CONTROL AND SURVIVAL OF EWING'S SARCOMA IN CHILDREN WITH RADIOTHERAPY AND CHEMOTHERAPY WITHOUT RADICAL SURGERY

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Abstract

The present study was undertaken in 27 children with localized Ewing's sarcoma treated at our hospital. In 9 cases the lesion was central and in 18 peripheral. Treatment consisted of: 1) Chemotherapy with 6 drugs (vincristine, cyclophosphamide, methotrexate, bleomycin, dactinomycin and doxorubicin) for one year in all patients; 2) Radiotherapy in 24 patients at a dose of 30–40 Gy in the entire bone with a booster dose of 10–15 Gy in the lesion. In 7 patients debulking surgery was performed followed by irradiation. Two cases with tumor in expendable bones and one with extensive destructive lesion in the tibia underwent radical surgery. One patient suffered local recurrence (femur) and 6 developed distant metastases. The remaining 20 (74%) patients were alive and tumor-free after follow-up periods of 17–80 months. Among the 12 patients with extremity lesions who were alive, 7 (58%) had minimal or mild treatment sequelae, 2 moderate, and 3 severe sequelae but no amputation has been required. Our study shows that local control can be achieved in almost all patients without radical surgery and with acceptable extremity function in the majority.

Key words: Ewing's sarcoma, children, chemotherapy, radiotherapy.

Ewing's sarcoma accounts for about 1% of all malignant childhood tumors and about 30% of all bone tumors in children (1). Over the last 2 decades the therapeutic possibilities for this tumor have considerably increased due to systemic polychemotherapy (2–5). Thus the risk of distant metastases, which was previously about 80% (6, 7), has been dramatically reduced.

The present study was undertaken to assess the results of an intensive chemotherapy protocol and the use of local radiotherapy in order to obtain tumor control without radical surgery.

Material and Methods

From January 1980 to December 1985, 30 patients with Ewing's sarcoma under 18 years of age were diagnosed in our hospital. Two patients presented with metastases at diagnosis and one patient abandoned the treatment regimen. The remaning 27 patients entered the study and all had localized disease. No patient had received previous treatment.

Pre-treatment investigations included clinical history and physical examination, with measurements of the size of the primary tumor. Laboratory studies consisted of routine hemogram and urine tests, urinary catecholamine determination, and bone marrow aspiration; blood chemistry included creatinine clearance and serum lactic acid dehydrogenase (LDH).

A diagnostic surgical biopsy was performed in all cases. Histologic slides were reviewed by the same pathologist. In addition to standard staining with hemotoxylin and eosin, PAS diastase for glycogen and silver stain for reticular fibers were used. Only cases undoubtful diagnosis of Ewing's sarcoma were included.

Radiological examinations included radiography of the entire tumor bearing bone and the chest and a $^{99}Tc^{m}$ disphosphorate bone scan.

Follow-up studies included radiographs of the primary lesion and the chest every 3 months for 2 years, then every 6 months. A bone scan was obtained every 6 months for 2 years.

Surgery. Conservative surgery was performed in 7 patients. The primary lesions were situated in the ribs (n=2),

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fibula (n=3), sacrum (n=1) and scapula (n=1). In these cases the margins of resection were free of disease. In 2 patients with tumor in spendable bones, the affected bone was completely removed: metacarpus (n=1) and clavicle (n=1). Amputation was performed in only one patient with primary lesion in the tibia and extensive bone destruction.

Chemotherapy. All patients received a combination of 6 cytostatic agents, vincristine (VCR), cyclophosphamide (CYC), actinomycin-D (DACT), doxorubicin (ADR), bleomycin (BLEO) and methotrexate (MTX) following the protocol recommended by Rosen et al. (8). The treatment protocol is detailed in Fig. 1. ADR was withdrawn when a total accumulated dose of 450 mg/m^2 was reached. Chemotherapy was started immediatly after biopsy or surgery. Most patients received a complete course of chemotherapy prior to radiotherapy. Treatment was delayed if myelosuppression became evident (leukocyte count less than 2500 or platelet count less than 100000/mm^3). The duration of the treatment was approximately 1 year.

Radiotherapy. Of the 27 patients, 24 received radiotherapy. One patient with primary lesion in the tibia and 2 patients with rib primaries did not receive radiotherapy.

Radiotherapy started after completion of the first chemotherapy course (on the 7th week after biopsy or surgery) and continued simultaneously with chemotherapy.

A ^{60}Co unit was used. The total tumor dose ranged from 40 Gy (TDF 66) to 55 Gy (TDF 92). The dose was adjusted to the patient's age and the tumor extension and location. Patients with primary tumor in the lower limbs received 40 Gy in the entire bone followed by a booster dose of 10–15 Gy delivered to the primary lesion. The treatment was given from 2 opposing anterior–posterior ports with 1.8 Gy fractions 5 times a week. If the tumor was close to the end of a bone, the opposite epiphysis was excluded from irradiation in order to minimize the effects on growth. A margin of skin and subcutaneous tissues was also spared from radiation exposure considering the lymphatic drainage.

Evaluation of functional sequelae. Functional impairment from treatment was assessed according to criteria proposed by Jentzsch et al. (9).

Statistical analysis. Actuarial tumor-free survival was calculated using the Kaplan-Meier method.

Results

Patients' ages ranged from 4–16 years (median 10 years); there were 19 boys and 8 girls.

Presenting symptoms and findings: 23 patients (85%) had pain, and a mass was noted in 11 patients (40%); 8 cases (28%) showed high levels of LDH. The sites of the primary lesion are shown in Table 1. In 9 cases the lesion was centro-axial and in the remaining patients it was localized to the limbs (9 proximal and 9 distal). The maximum linear diameter of the primary tumor was 80 mm or larger in 8 patients and shorter in the remaining ones.

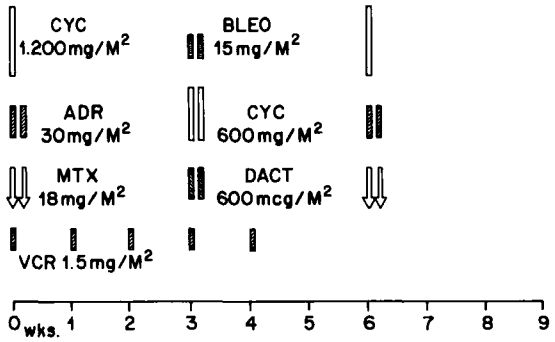

Fig. 1. Combination chemotherapy used for the treatment of localized Ewing's sarcoma.

Table 1

Distribution of primary Ewing's sarcoma in 27 patients

Centro-axial		Extremities	
Pelvis	2		
Rib	2	Femur	7
Mandible	1	Tibia	4
Scapula	1	Fibula	3
Spine	1	Humerus	2
Sacrum	1	Metacarpus	1
Clavicle	1	Foot	1
Total	9	Total	18

Toxicity: all patients had moderate to severe myelosuppression and variable degree of skin reactions. Transfusions with packed red cells were required in 6 patients (21%). There was one case of doxorubicin cardiomyopathy and 3 patients showed transient hematuria following cyclophosphamide. No fatal toxicity was recorded.

Twenty (74%) children remained tumor-free after a follow-up of 17–80 months (median 38 months). Actuarial tumor-free survival rate was 64% at 58 months (Fig. 2). Seven patients have died. In one of these patients with primary lesion in the femur, local recurrence and distant metastases occurred simultaneously. Six patients developed distant metastases in lung and/or bone; no clinical or radiologic evidence of local recurrence was observed until their deaths, 6–12 months after the appearance of distant metastases. Local recurrence and/or distant metastases were observed between 9 and 25 months after diagnosis (median 19 months). The characteristics of patients with treatment failure are described in Table 2. All children with primary tumor in the femur or in the pelvis with treatment failure, had primary tumors larger than 80 mm. Autopsy could not be performed in any patient.

Of the 12 patients with tumors localized to extremities who received radio- and chemotherapy and were alive

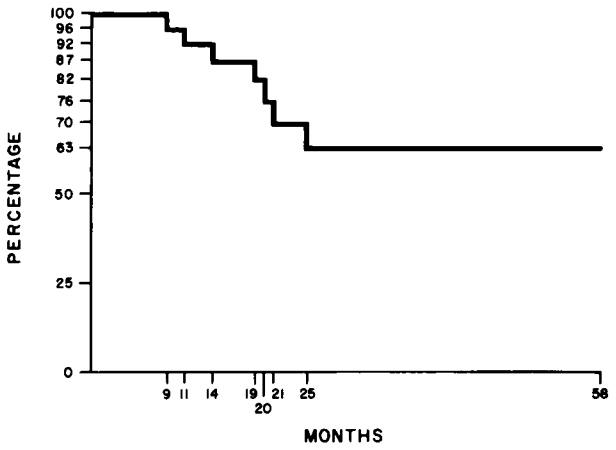

Fig. 2. Actuarial disease-free survival in 27 children with localized Ewing's sarcoma.

Table 2

Local recurrence and metastases in patients with treatment failure

Case No.	Site of primary	Local recurrence	Metastases	
			Bone	Lung
1	Femur	Yes	×	–
2	Femur	–	×	–
3	Femur	–	–	×
4	Femur	–	–	×
5	Pelvis	–	×	–
6	Pelvis	–	–	×
7	Foot	–	×	×

All patients had received combined chemo- and radiotherapy. Time to relapse 9–25 months (median 19 months).

Table 3

Treatment sequelae in surviving patients. Extremity tumors (14 cases)

Minimal or mild		9
Fibula	3	
Humerus	2	
Tibia	2	
Metacarpus	1	
Moderate		2
Tibia	1	
Femur	1	
Severe		3
Femur	2	
Tibia	1	

(minimum follow-up 2 years), 7 had minimal or mild functional impairment. Two patients showed moderately severe growth disturbance with leg length discrepancy up to 25 mm while 3 got severe sequelae (pathologic fracture in 2 cases, leg shortening of 40 mm in 1 case). The results are summarized in Table 3.

Discussion

The need to give all patients with Ewing's sarcoma intensive polychemotherapy for prevention of tumor spread and control of the primary tumor is today widely accepted (8, 10–14). Our own results support this policy.

The treatment method for the primary lesion is still a matter of discussion. Complete surgical excision of the tumor is not possible in most patients with centro-axially located tumors. Lesions in the limbs require, for radical removal, severely mutilating procedures in most patients. It seems reasonable, however, to completely remove affected expendable bones, which does not cause important anatomic defects or functional impairement (3, 15). However, this approach does not ensure control of the lesion when there is soft tissue involvement (1, 16, 17). Debulking surgery has not been shown to be more effective than radiotherapy in the treatment of the primary tumor (16). Radiotherapy has been reported to achieve local control of the disease in more than 80% of the patients (18, 19). In our series only one radiation treated patient suffered local recurrence. Although true local control rate can only be established by histological assessment, the National Cancer Institute series showed no significant difference in local recurrence rate between patients whose recurrence was detected by clinical assessment and those who were reassessed pathologically by biopsy or autopsy (19).

The sequelae of radiotherapy which may be specially severe in children, can be reduced by adequate irradiation technique (16, 18). In our experience, only 20% of the children with lesions in the limbs developed severe sequelae but none of them belonged to the most severely affected group according to the criteria of Jentzsch et al. (9) and none of them required amputation. We believe that treatment of the primary lesions should be carefully individualized according to the criteria mentioned earlier.

Finally, it should be remembered that the main cause of therapeutic failure is the appearance of distant metastases. Despite the good results obtained with chemotherapy in combination with radiotherapy, newer therapeutic procedures should be sought, particularly for the high risk patients: i.e. patients with large primary tumors (2) and with certain tumors localized centro-axially as in the pelvic bone.

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