Ewing's Sarcoma

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In 1921, James Ewing described a non-osteogenic bone cancer characterized by islands of apparently anaplastic, small round cells.1 Though still controversial, most investigators believe that the primary tumor originates in immature reticulum cells,2 an impression recently confirmed by electron microscopy.3

Ewing’s sarcoma is a disease of children and young adults, with 95 percent of patients between four and 25 years old. Peak incidence occurs in the second decade of life. Males outnumber females almost two to one. The predominant symptom is pain, often intermittent, but usually persistent for at least one month prior to diagnosis. Pain, fever and a mass associated with leukocytosis, anemia and an elevated sedimentation rate is a common symptom-complex of Ewing’s sarcoma, and must be differentiated from osteomyelitis or eosinophilic granuloma of bone. An initially rapid growth rate often followed by spontaneous improvement with periods of quiescence lasting for a few weeks or many months, adds to the difficulty of diagnosing or even suspecting a bone tumor. Ewing’s sarcoma may develop in any bone, but predominantly in the shafts of the humerus, femur and tibia. The fibula is also a surprisingly common presenting site.

Asymptomatic and often clinically undetectable metastases are common. It is estimated that 15 to 30 percent of patients with Ewing’s sarcoma have asymptomatic metastases at diagnosis, usually to the lung or bone. (Table 1.) A similar anatomic distribution of metastases was found in an analysis of 27 patients at the Mayo Clinic who developed metastases after treatment: 21 patients (80 percent) had metastases to the lung; two (seven percent), to multiple bones; two (seven percent), to the skull; one (three percent) to nodes;4 and one (three percent), to the central nervous system. The incidence of CNS metastases is controversial.

An extensive work-up is essential to establish the diagnosis and properly stage the disease. A thorough history and physical examination must pay special attention to possible lymph node involvement, frequently missed initially. Laboratory studies include hemoglobin or hematocrit, leukocyte count, differential and platelet count, sedimentation rate, and a urinalysis with VMA spot test or total urinary catecholamine determinations.

An adequate radiologic examination involves high quality anterio-posterior and lateral projections of the entire sus-
On the other hand, isotopic scans, which are of little value in studying a primary lesion, can detect even minimal metastases in bone and, sometimes, in lung. Bone scanning using isotopes with long physical half-lives, such as $^{47}$Ca and $^{85}$Sr, carry a risk of radiation damage when deposited in the bone. For this reason, they are seldom used in children. Total body scanning devices that produce a "minified" image and employ isotopes with short half-lives ($^{99m}$Tc polyphosphate, $^{18}$F, $^{87}$Sr, $^{75}$Se methionine and $^{67}$Ga) provide excellent resolution and can identify metastases when conventional methods fail. Since scanning time is short and radiation dosage low, these methods are used in children with little danger and minimum discomfort.

A representative open biopsy of the tumor under general anesthesia is mandatory. Deep biopsies and definitive treatment based solely on examination of frozen sections are not recommended, since many lesions are necrotic or surrounded by uninvolved reactive inflammatory tissue. Frozen sections are valu-

| Table 1. Site of Metastases in Ewing’s Sarcoma |
|-----------------------------------------------|
| Site and No. of Patients | Series |
|-------------------------|--------|
|                         | Freman $^8$ | Bhansali $^9$ | Rosen $^8$ | Total |
|-------------------------|------------|-------------|-----------|-------|
| Number of Patients      | 20         | 107         | 12        | 139   |
| Number with Metastases  | 3          | 15          | 2         | 20    |
| Pulmonary               | 3          | 4           | 2         | 9     |
| Bone                    | 0          | 3           | 0         | 3     |
| Lymph Nodes             | 0          | 3           | 0         | 3     |
| Multiple                | 0          | 5           | 0         | 5     |

A representative open biopsy of the tumor under general anesthesia is mandatory. Deep biopsies and definitive treatment based solely on examination of frozen sections are not recommended, since many lesions are necrotic or surrounded by uninvolved reactive inflammatory tissue. Frozen sections are valu-
able, however, in determining whether an adequate sample has been taken.

On gross inspection, Ewing's sarcoma appears firm, white and has usually widely infiltrated surrounding tissue. Hemorrhage and necrosis can be extensive. Microscopically, the tumor reveals large fields of closely packed cells with reticulum confined to perivascular regions. Ewing's sarcoma is often confused with other small, round cell tumors, such as neuroblastoma, lymphoma and rhabdomyosarcoma.

The primary tumor can be controlled in more than 60 percent of patients with radiotherapy alone. Fernandez reported that five of 15 patients (33 percent) had local recurrence after high-dose radiotherapy, but only one of 19 (5.2 percent) occurred after high-dose radiotherapy plus systemic chemotherapy. A dose of 4,500 to 6,500 rads delivered by super-voltage sources to the entire affected bone and surrounding tissue is recommended. Additional radiation therapy of 1,000 to 1,500 rads to the primary lesion is also advised. Except for a primary localization in the ribs, surgical resection is rarely the treatment of choice. If, on the other hand, results indicate that in

| Series                        | No. of Patients | Primary Therapy          | Mean Survival After Diagnosis (Months) | Five-year Survival No. | Percent |
|-------------------------------|----------------|--------------------------|----------------------------------------|------------------------|---------|
| Geschickter and Copeland 20   | 22             | Surgery and radiotherapy | 17                                     | 3                      | 14      |
| Geschickter and Copeland 20   | 37             | Surgery                  | 11                                     | 7                      | 19      |
| Geschickter and Copeland 20   | 44             | Radiotherapy             | 15                                     | 3                      | 7       |
| McCormack, Dockerty and Ghormley 21 | 26 | Surgery                  | —                                      | 4                      | 15      |
| McCormack, Dockerty and Ghormley 21 | 37 | Radiotherapy             | —                                      | 4                      | 11      |
| Scanlon 22                    | 71             | Radiotherapy             | —                                      | 7                      | 10      |
| Borges, Paymaster and Bhansai 23 | 86 | Radiotherapy             | —                                      | 2                      | 2       |
| Falk and Alpert 24            | 30             | Radiotherapy             | 18                                     | 2                      | 7       |
| Dahlin, Coventry and Scanlon 25 | 21 | Surgery and radiotherapy | —                                      | 4                      | 19      |
| Total                         | 374            |                          | 36                                     | 10                     |         |
certain sites there are a significant number of local recurrences with the combined treatment, the merit of radical surgical removal must be reconsidered.

However, despite the high frequency of local control, cure is seldom effected because of dissemination to lungs, bones and lymph nodes. Indeed, early and often clinically undetectable metastases are probably the most important factor in the tumor’s poor prognosis. A summary of the survival results of several reported series of patients with Ewing’s sarcoma initially treated with surgery, radiotherapy or both, reveals that only 36 of 374 children (10 percent) survived five years. (Table 2.) The method of treatment for the primary tumor did not appear to alter the results.

The additional use of chemotherapy seems logical, and various agents have already been employed with some success in patients with metastases. Cyclophosphamide is probably the most effective single agent for metastatic disease, although results have only been palliative, probably because of excessive tumor load. Freeman reported three of nine long-term survivals when patients were treated with courses of cyclophosphamide given at six-week intervals. Vincristine sulfate, 5-fluorouracil and dactinomycin have also been reported useful.

Based on the partial effectiveness of chemotherapy in patients with metastases, several recent attempts have been made to treat patients with localized Ewing’s sarcoma with combination chemotherapy, plus radiotherapy to the primary lesion. Using cyclophosphamide and vincristine, Hustu has reported four of six patients with long-term survival, free of metastases. Pomeroy and Johnson recently followed 28 patients with localized Ewing’s sarcoma who were treated from 1964 to 1971 with cyclophosphamide alone (six patients) or cyclophosphamide and vincristine (six patients) or the two drugs plus dactinomycin, as well as cranial and intrathecal methotrexate (16 patients). Forty percent of the patients are continuously free of disease at 24 months. Rosen reported that 10 patients with localized Ewing’s sarcoma who were treated with adriamycin, dactinomycin, vincristine and cyclophosphamide were free of disease 10 to 37 months after treatment.

These initially successful reports have resulted in the formation of a large cooperative study of a four-drug combination chemotherapy program for all patients with Ewing’s sarcoma. Under the direction of the Intergroup Ewing’s Sarcoma Study, a multi-institutional program has been undertaken to answer some of the following questions: (1) What combination of chemotherapeutic agents is most effective for the treatment of localized Ewing’s sarcoma? (2) Does the use of bilateral pulmonary irradiation plus chemotherapy increase the disease-free status and survival of patients with Ewing’s sarcoma? (3) What prognostic factors are important in survival? An outline of this on-going, randomized study is shown in Figure 1.

While it has been fairly well established that chemotherapy will most likely improve the survival of patients with localized Ewing’s sarcoma, a coordinated attack has not yet been undertaken on disseminated Ewing’s sarcoma. In the last decade, an aggressive approach has resulted in the cure of some patients with disseminated Wilms’ tumor, leukemia, Hodgkin’s lymphoma, and rhabdomyosarcoma. Rosen recently reported two patients with metastases who are free of disease following irradiation and a four-drug therapeutic regimen of vincristine, cyclophosphamide, dactinomycin and adriamycin. In January, 1975, the Intergroup Ewing’s Sarcoma Committee initiated a clinical trial using this four-drug regimen for patients with metastatic Ewing’s sarcoma to determine response rate and duration of response.
Regimen I

Chemotherapy

| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
|--------|--------|--------|--------|--------|--------|
|        |        |        |        |        |        |

Regimen II

Chemotherapy

| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
|--------|--------|--------|--------|--------|--------|
|        |        |        |        |        |        |

Regimen III

Chemotherapy

| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
|--------|--------|--------|--------|--------|--------|
|        |        |        |        |        |        |

Surgical Biopsy

Randomization

Rest Period

Recurrent Phase

Seven Week Course Starting at Three Months

Repeated Every Three Months

Key:

- X=Local primary radiation: 4,500-6,000 rads total midplane.
- ▲=Bilateral pulmonary radiation: 100-200 rads daily, 1,500-1,800 total midplane.
- V=Vincristine: 1.5 mg./m.2 IV weekly (single dose ≤ 2 mg.)
- C=Cyclophosphamide: 500 mg./m.2 IV weekly
- D=Dactinomycin: 15 μg./kg. IV daily x 5 (total = 75 μg./kg.) Maximum 500 μg./day.
- A=Adriamycin: 60 mg./m.2 IV.
Figure 2.
Ewing's Sarcoma Protocol
(Intergroup Study)

**Initial Phase**

| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
|--------|--------|--------|--------|--------|--------|
| V C    | V C    | V C    | V C    | V C    | A V C  |

Surgical Biopsy

Rest Period (six weeks)

**Continuation Phase**

Seven Week Course Starts at 12 Weeks
Repeated Every 12 Weeks

| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 |
|--------|--------|--------|--------|--------|--------|--------|
| D D D D| V C    | V C    | V C    | V C    | A V C  | Rest Period |

**Check**
Every Three Months

**Key:**

- X = Radiation therapy. Local primary radiotherapy: 3,500-4,500 rads total midplane plus radiotherapy to all overt metastases. (Doses vary according to location of metastatic lesions).
- Radiation therapy should not be given to more than 60 percent of the active myeloproliferative tissue.
- V = Vincristine: 1.5 mg./m.²/week IV (Single dose ≤ 2 mg.)
- C = Cyclophosphamide: 500 mg./m.²/week IV
- A = Adriamycin: 60 mg./m.²/course at end of V and C
- D = Dactinomycin: 0.015 mg./kg./day IV × 5. Total dose: 0.075 mg./kg.
- Maximum dose: ≤ 0.5 mg./day or 2.5 mg. total dose.
toxicity and ultimate survival. (Fig. 2.) It is hoped that the efforts of a large, centralized clinical trial will increase the survival of patients with Ewing’s sarcoma. Because of the need for expertise in dealing with newer techniques and treatment plans, it is vital that patients be managed by physicians who have had experience with this rare tumor.

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