COMMON MUSCULOSKELETAL TUMORS OF CHILDHOOD AND ADOLESCENCE

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COMMON malignant tumors of the musculoskeletal system in children, adolescents, and young adults (<30 years old) include rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma. Together they constitute about 10 percent of newly diagnosed cancers in children, adolescents, and young adults (about 1000 cases annually in the United States). Although relatively common in young persons, these tumors are rare in older people.

Rhabdomyosarcomas constitute more than half of all soft-tissue sarcomas in children. Other soft-tissue sarcomas are highly heterogeneous and individually rare (e.g., synovial sarcoma and sarcomas of soft parts); thus, they are not discussed further. Osteosarcoma comprises several high-grade histologic variants and two rare clinical subtypes, periosteal and parosteal osteosarcoma. The Ewing family of tumors (Ewing’s sarcoma and primitive neuroectodermal tumor) may arise in either bone or soft tissues.

There has been substantial progress in our understanding of both the biology and the treatment of these tumors during the past 30 years. The identification of specific, recurring genetic alterations in rhabdomyosarcoma and Ewing’s sarcoma has clarified pathogenesis and led to improved diagnosis and classification. Better supportive care and systematic application of increasingly effective multimodal treatment have improved survival dramatically over this period, with five-year survival rates rising from approximately 10 to 20 percent in 1970 (Fig. 1) to about 60 to 70 percent currently. In this review, we discuss clinical and laboratory advances that have improved our understanding of the pathogenesis and treatment of these cancers.

EPIDEMIOLOGY

The incidence of rhabdomyosarcoma is about 4 to 7 per million children under 15 years of age in the United States (about 250 cases annually in the United States). It is the fourth most common solid tumor in children, and two thirds of patients are less than 10 years of age. Slightly more boys than girls are affected, and black and Asian children are affected less commonly than white children.

Most rhabdomyosarcomas occur sporadically and are of unknown cause. However, rhabdomyosarcoma and osteosarcoma can occur as part of a pattern of familial cancer, including the Li–Fraumeni syndrome (familial clustering of rhabdomyosarcoma or osteosarcoma and certain other tumors in children whose first-degree relatives have adrenocortical carcinoma, breast cancer, or other tumors before the age of 45 years). This syndrome is associated with germ-line mutations in the tumor-suppressor gene p53.

Osteosarcoma is the most frequent malignant condition of bone, with an incidence of approximately 5.6 per million children under 15 years of age. The peak frequency is during the adolescent growth spurt, and there is no sex- or race-based predilection. Ionizing radiation contributes to the development of some osteosarcomas. Certain genetic or acquired conditions increase the risk of osteosarcoma. Patients with hereditary retinoblastoma have a high risk of second cancers, 50 percent of which are osteosarcomas. Osteosarcoma can arise in patients with Paget’s disease of bone, enchondromatosis, hereditary multiple exostoses, and fibrous dysplasia.

Ewing’s sarcoma is the second most common cancer of bone in children and adolescents, with an incidence of 2.1 per million children in the United States. It occurs most often in the second decade of life and is extremely uncommon in children of African or Asian descent. Its cause is unknown. In contrast to osteosarcoma, Ewing’s sarcoma does not appear to be caused by exposure to radiation, nor has it been associated with familial cancer syndromes.

CLINICAL FEATURES

Rhabdomyosarcoma may occur at any site. Signs, symptoms, and prognosis are site-dependent. Tumors arising in the orbit often produce proptosis; tumors of the limbs are generally manifested as a painless mass; bladder or prostate tumors may produce urinary tract obstruction, hematuria, or an abdominal mass. Tumors arising from the mediastinum or retroperitoneum may become large before producing signs and symptoms. Most tumors arising in the orbit are embryonal, are localized at pres-
entation, and have a high rate of cure. In contrast, almost half of tumors of the limbs are alveolar on histologic analysis, in about half of cases there is regional lymphatic spread at diagnosis, and the prognosis is much less favorable.

About one third of patients with rhabdomyosarcoma have readily resectable tumors, half do not, and about 15 percent have metastatic disease at presentation. Common sites of metastases include regional lymph nodes, the lungs, bone, and bone marrow. The primary sites of the tumor in 2747 patients are shown in Figure 2.

The most common initial symptom of Ewing’s sarcoma or osteosarcoma is pain or swelling in a bone or joint, frequently after a sports-related injury, a factor that sometimes delays the diagnosis. The presence of systemic symptoms such as weight loss and fever may initially lead to an erroneous diagnosis (e.g., osteomyelitis). Osteosarcoma generally involves the metaphyses of long tubular bones, especially the distal femur or proximal tibia (in 45 percent of cases), whereas Ewing’s sarcoma occurs with almost equal frequency in flat bones and diaphyses of tubular bones and may occasionally arise in soft tissues.

The skeletal distributions of 1649 cases of osteosarcoma and 512 cases of Ewing’s sarcoma are shown in Figure 2. Approximately 20 to 25 percent of patients with Ewing’s sarcoma and osteosarcoma have metastatic disease at presentation. Of patients who present with metastatic disease, the sites of metastases are the lungs in 50 percent of cases, bone in 25 percent of cases, and bone marrow in 25 percent of cases of Ewing’s sarcoma and the lungs in 90 percent of cases and bone in 10 percent of cases of osteosarcoma.

**DIAGNOSIS AND STAGING**

Rhabdomyosarcoma should be suspected in a patient with a painless soft-tissue mass at any site. The typical histologic and radiographic appearances of rhabdomyosarcoma of the limbs and bladder are shown in Figures 3A, 3B, 3C, and 3D. Precise determination of the primary site and the extent of disease at presentation is crucial, because these features are strongly associated with prognosis and the optimal approach to treatment varies according to these features. Bone pain alone or accompanied by swelling in association with an abnormal radiograph suggests the presence of a bone tumor.

Patients who are thought to have sarcoma of bone or soft tissue should be referred to a cancer center. Such centers have facilities to assess the immunohistochemical and genetic features of the tumor in order to establish the diagnosis and can provide the expert multidisciplinary team required to deliver therapy. Appropriate tumor samples, including fresh tissue, should be obtained for routine pathological evaluation, as well as cyogenetic and molecular studies. Because Ewing’s sarcoma and rhabdomyosarcoma often metastasize to bone marrow, patients in whom these tumors are suspected must undergo bone marrow aspiration and biopsy at two or more sites. The initial biopsy incision for bone tumors should be positioned so that it can be incorporated into future incisions at the time of definitive surgery.

The evaluation of patients with bone tumors should include plain radiographs and magnetic resonance imaging of the entire affected bone. The typical radiographic features of osteosarcoma and Ewing’s sarcoma are shown in Figures 3F and 3H, respectively. For patients with rhabdomyosarcoma, evaluation of the primary tumor site and draining local and regional lymph nodes with the use of magnetic resonance imaging or computed tomography is ideal. Bone scanning and computed tomography of the chest are also necessary, regardless of the type of tumor. Surgical sampling of ipsilateral inguinal or axillary lymph nodes in patients with rhabdomyosarcoma of the limbs and thin-cut computed tomography of retroperitoneal lymph nodes in patients with paratesticular rhabdomyosarcoma are recommended because of the high risk of lymphatic spread and the need to alter treatment in patients with positive nodes.
Figure 2. Primary Sites of Rhabdomyosarcoma, Osteosarcoma, and Ewing's Sarcoma.
The numbers of patients with primary tumors at specific sites are shown. Data on 2747 patients with rhabdomyosarcoma are from Pappo et al. Data on 1649 patients with osteosarcoma and 512 patients with Ewing's sarcoma are from the Mayo Clinic files. (Two patients with Ewing's sarcoma had two sites each.) The illustrations of the sites of osteosarcoma and Ewing's sarcoma are adapted from Unni with the permission of the publisher.

Figure 3. Histologic and Clinical Features of Rhabdomyosarcoma, Osteosarcoma, and Ewing's Sarcoma.
Panel A shows the histologic appearance of embryonal rhabdomyosarcoma. This spindle-cell tumor is composed of small, elongated cells with plump pink cytoplasm in a loose stromal background. On radiography, embryonal rhabdomyosarcoma of the bladder is seen as a large mass compressing the rectum posteriorly (Panel B). Panel C shows classic alveolar rhabdomyosarcoma, with neoplastic cells lining and lying freely within the alveolar spaces. There are multinucleated malignant giant cells. On radiography, alveolar rhabdomyosarcoma is seen as a mass in the vastus lateralis muscle of the thigh (Panel D). Panel E shows a malignant spindle-cell neoplasm with osteoid formation by the malignant cells. Panel F shows a radiograph of osteosarcoma of the distal femur, with calcification, new bone formation, and a typical "sunburst" appearance. Histologically, Ewing's sarcoma appears as an undifferentiated round-cell neoplasm, with uniform cells that have vesicular nuclei, inconspicuous nucleoli, and indistinct vacuolated cytoplasm (Panel G). Panel H shows the radiographic appearance of Ewing's sarcoma of the humerus; periosteal elevation and onionskin changes are present. (Panels A, C, E, and G: hematoxylin and eosin; Panels A and G, ×160; Panel C, ×50; and Panel E, ×20.)
Embryonal Rhabdomyosarcoma

Alveolar Rhabdomyosarcoma

Osteosarcoma

Ewing’s Sarcoma
A widely used system of classification groups patients according to the extent of disease remaining after initial surgery for rhabdomyosarcoma. Group I includes patients with completely resected tumors; group II, patients with microscopical residual tumor; group III, patients with gross residual tumor; and group IV, patients with metastatic disease. The classification group is strongly correlated with survival.1,4,7

A modified, preoperative staging system has now been devised that includes prognostic factors such as the location of the primary tumor, the invasiveness and size of the tumor, the presence or absence of lymph-node involvement, and the presence or absence of metastasis.30 The surgical staging system of Enneking et al. is used for soft-tissue and bone tumors and includes prognostic variables such as the histologic grade of the tumor, the location of the tumor, and the presence or absence of metastases.31 Clinical studies of patients with Ewing’s sarcoma and osteosarcoma stratify patients according to the presence or absence of metastatic disease.

MORPHOLOGIC AND IMMUNOHISTOCHEMICAL FEATURES

Typical appearances of Ewing’s sarcoma, osteosarcoma, and rhabdomyosarcoma on light microscopy and radiography are shown in Figure 3. The diagnosis of rhabdomyosarcoma rests on the identification of skeletal-muscle differentiation with evidence of myogenin (plump pink cytoplasm) on light microscopy, with or without cross-striations. The detection of actin and myosin filaments or Z bands on electron microscopy can facilitate the diagnosis. There are two common variants of rhabdomyosarcoma, embryonal (80 percent of cases) and alveolar (20 percent of cases), with relatively distinct histologic appearances, as shown in Figure 3. Immunohistochemical stains generally reveal the expression of muscle-specific actin, desmin, and vimentin without the expression of the neural adhesion antigen MIC2 (also referred to as HBA71, 013, and CD99) in tumor cells.1,7,32 Immunohistochemical detection of myogenin, myoD1, or myf5 expression or on the basis of electron-microscopical evidence of neurosecretory granules. Cell-surface staining for MIC2 is observed more frequently in Ewing’s sarcoma than in other types of sarcomas, making it helpful in the differential diagnosis.8

GENETIC FEATURES

Rhabdomyosarcoma

Somatically acquired mutations underlie all forms of human cancer, but until recently little was known about those associated with rhabdomyosarcoma. Cytogenetic and molecular genetic studies have identified both numerical and structural abnormalities of tumor-cell chromosomes. Numerical abnormalities have not been consistently related to clinical features or outcome. However, recurring chromosomal translocations, including t(2;13)(q35;q14) (Fig. 4) and less commonly t(1;13)(p36;q14), have been identified in most cases of alveolar rhabdomyosarcoma.1,31,34 The t(2;13) translocation results in fusion of part of the PAX3 gene, which encodes a transcription factor involved in development, to part of the FKHR gene, which encodes a more widely expressed transcription factor (Fig. 4), leading to the formation of a chimeric protein, PAX3–FKHR. In the case of the t(1;13) translocation, the PAX7–FKHR chimeric protein is formed, which contributes to transformation.4,31,35,36

Studies have suggested that the clinical features, the natural history of disease, and the response to therapy differ in subgroups of patients defined according to the presence of the t(2;13) or the t(1;13) translocation or the absence of both translocations.34,37 A major clinical advance resulting from these studies has been the development of fluorescence in situ hybridization and reverse-transcriptase–polymerase-chain-reaction molecular assays that are more sensitive than cytogenetic analyses and can identify cryptic translocations at the molecular level.1

Embryonal tumors generally have a loss of heterozygosity for multiple closely linked loci at chromosome 11p15.5, suggesting the inactivation of a tumor-suppressor gene. This gene has not yet been identified. Other mutations or amplifications of tumor-suppressor genes, oncogenes, or tumor-specific fusion genes (e.g., p53, N-ras, K-ras, and N-myc) are frequently observed and may be involved in the pathogenesis of rhabdomyosarcoma or may represent secondary events related to progression of the tumor.1,38-40

Osteosarcoma

The increased risk of osteosarcoma among patients with hereditary retinoblastoma and those with the Li–Fraumeni syndrome points to important pathogenetic roles of two tumor-suppressor genes, p53 and RB. Available data suggest that osteosarcoma arises from the inactivation of a series of tumor-sup-
pressor genes. Alterations in p53, RB, and the MDM2 oncogene are found in about 50 percent of cases of osteosarcoma; however, germ-line mutations are rare. Loss of heterozygosity for chromosomes 3q, 13q, and 18q suggests that additional inactivation events are responsible for tumorigenesis.

Ewing’s Sarcoma

About 95 percent of patients with Ewing’s sarcoma have a t(11;22) or t(21;22) translocation, which results in fusion of the EWS gene on chromosome 22 with the FLI1 gene on chromosome 11, the ERG gene on chromosome 21, or rarely, other genomic loci on chromosomes 7, 17, and 2. FLI1 and ERG are two closely related members of the ETS family of genes. The portion of the FLI1 or ERG gene that fuses with EWS to create the chimeric transcription factor contains a DNA-binding domain. Ewing’s sarcoma and primitive neuroectodermal tumor are thought to be the same tumor because they have the same molecular features.

TREATMENT

The dramatic improvement in the rates of cure among children with musculoskeletal tumors (Fig. 1) is attributable to the development of effective multimodal therapy and improved diagnosis, classification, and supportive care. In recent trials of effective chemotherapy, amputation has been avoided in most patients with osteosarcoma with the use of limb-salvage procedures such as tumor resection followed by the implantation of cadaveric allografts, vascularized grafts, or prostheses. Also, more patients with Ewing’s sarcoma are being treated with surgery because of the high risk of second tumors after radiation therapy. Because of the rarity of these tumors, studies that enroll patients over a broad geographic region, such as the Intergroup Rhabdomyosarcoma studies, which include most patients in North America, have been necessary to address important research questions.

Principles of Therapy

Because hematogenous spread occurs early in these musculoskeletal tumors, chemotherapy is a corner-
stone of treatment (Table 1). Surgery and radiation therapy are important local treatments for most patients. Because osteosarcoma is relatively resistant to radiation therapy, complete surgical extirpation of the primary tumor and any metastases is essential to cure. Surgical removal of the primary tumor is also desirable in patients with rhabdomyosarcoma or Ewing’s sarcoma if complete surgical removal is feasible and will not cause unacceptable loss of function. If possible, irradiation should be avoided in young children because of its adverse effects on growth and in patients with Ewing’s sarcoma, in whom its use is associated with an incidence of secondary cancers of approximately 10 percent 20 years after treatment.5,18 However, radiation therapy is highly effective for local control of tumors in patients with rhabdomyosarcoma and Ewing’s sarcoma and is thus considered a standard part of care in many cases.

In children with rhabdomyosarcoma, the intensity of treatment depends on the risk of failure predicted by analysis of prognostic factors (referred to as risk-adapted therapy).1,4,7,29 Important prognostic factors in rhabdomyosarcoma include the extent of disease at presentation, the location of the tumor (non-parenchymal sites within the head and neck and genitourinary sites except for the bladder or prostate have a favorable prognosis), and histologic findings (the alveolar type has a worse prognosis than the embryonal type). The presence of metastatic disease at diagnosis confers a worse prognosis in these musculoskeletal tumors.1,29,58,59 Tumors in truncal bones and large tumors are associated with a poorer prognosis in patients with Ewing’s sarcoma, but only the presence of metastatic disease warrants a change in the therapeutic approach.5 Patients with localized osteosarcoma of a limb fare better than patients with axial and pelvic tumors or metastatic disease.2 The aim of risk-adapted therapy is to increase the cure rate while decreasing the incidence of late effects.

**Rhabdomyosarcoma**

The Intergroup Rhabdomyosarcoma Study Group, which was formed in 1972, conducted four sequential studies between 1972 and 1998 that included more than 3000 children (about three fourths of all patients in North America). These and several European studies reported markedly improved rates of cure (25 to 75 percent) and refined therapy while advancing our state of knowledge of the biology of this tumor.1,4,25,27,49,50 Tumors that are initially unresectable should first be treated with chemotherapy. After the tumor has shrunk sufficiently, complete resection may be possible, thus allowing a reduction in the dose of radiation needed to achieve local control and decreasing

### Table 1. Outcome of Therapy for Musculoskeletal Tumors of Childhood and Adolescence.

<table>
<thead>
<tr>
<th>Type of Tumor</th>
<th>Commonly Used Agents</th>
<th>Duration of Therapy</th>
<th>Long-Term Survival*</th>
<th>Additional Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhabdomyosarcoma</strong></td>
<td></td>
<td></td>
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<tr>
<td>Low-risk group (those with group I or II embryonal tumors at sites with a favorable outcome or group III orbital tumors)</td>
<td>Vincristine, actinomycin</td>
<td>8–12</td>
<td>90–95</td>
<td>Resection of primary tumor for all but orbital tumors; irradiation of group II or III tumors</td>
</tr>
<tr>
<td>Intermediate-risk group</td>
<td>Vincristine, actinomycin, cyclophosphamide</td>
<td>8–12</td>
<td>70–80</td>
<td>Irradiation of primary tumor and metastases, if present</td>
</tr>
<tr>
<td>High-risk group (all those with metastases [group IV] except patients under 10 years old who have embryonal tumors)</td>
<td>Vincristine, actinomycin, cyclophosphamide; new agents; high-dose therapy with hematopoietic stem-cell transplantation</td>
<td>8–12</td>
<td>20</td>
<td>Irradiation of primary tumor and all metastatic lesions</td>
</tr>
<tr>
<td><strong>Osteosarcoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized to limb</td>
<td>Doxorubicin, high-dose methotrexate, ifosfamide, cisplatin</td>
<td>8–12</td>
<td>58–76</td>
<td>Surgery for control of tumor</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Doxorubicin, methotrexate, ifosfamide, cisplatin</td>
<td>8–12</td>
<td>14–50</td>
<td>Resection of primary tumor and metastases needed for cure</td>
</tr>
<tr>
<td><strong>Ewing’s sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>Vincristine, doxorubicin, cyclophosphamide, actinomycin, etoposide–ifosfamide</td>
<td>8–12</td>
<td>50–70</td>
<td>Surgery, radiation therapy, or both for local control of tumor</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Vincristine, doxorubicin, cyclophosphamide, actinomycin, etoposide–ifosfamide; high-dose therapy with hematopoietic stem-cell transplantation</td>
<td>8–12</td>
<td>19–30</td>
<td>Surgery, radiation therapy, or both for local control of tumor</td>
</tr>
</tbody>
</table>

*The estimated rates of survival at three to five years without the need for retreatment (progression-free or relapse-free survival) are shown.*
the incidence of late effects. For unresectable local or regional tumors in less favorable sites, radiation therapy is recommended early in the course of treatment. Patients with metastatic tumors should receive radiation therapy at all sites whenever feasible.1

In patients with embryonal rhabdomyosarcoma in a site associated with a favorable outcome (i.e., the head and neck but not the parameningeal area and the entire genitourinary tract except for the bladder and prostate) who have undergone complete or nearly complete resection (with only microscopic residual tumor), treatment with vincristine and actinomycin for 8 to 12 months and radiation therapy if any tumor remains is usually adequate (Table 1).25 This approach is also appropriate for patients with embryonal tumors of the orbit or eyelid, even when gross residual tumor remains postoperatively. However, patients with alveolar tumors but otherwise similar characteristics require the addition of cyclophosphamide to the regimen. The cure rate among such low-risk patients is 90 to 95 percent, and about one third of patients with newly diagnosed rhabdomyosarcoma are in this low-risk group.14,60

Patients with all types of gross residual tumor except orbital tumors are considered to be at intermediate risk, with a cure rate of 70 to 80 percent, and require more intensive therapy than low-risk patients. Chemotherapy includes at least three drugs (vincristine, actinomycin, and cyclophosphamide).14,61 The recently completed fourth Intergroup Rhabdomyosarcoma Study demonstrated no advantage in substituting ifosfamide for cyclophosphamide or etoposide for dactinomycin for 8 to 12 months and radiation therapy if any tumor remains is usually adequate (Table 1).25

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About one fifth of patients with newly diagnosed rhabdomyosarcoma have metastatic disease, and the five-year survival rate among these patients is low — 20 percent — despite the use of intensive therapy. Affected patients are likely to be adolescents with prognostically unfavorable alveolar tumors. One fifth of the patients in this high-risk group are children under the age of 10 years who have embryonal tumors, and the outcome in this subgroup is much better, with a cure rate of 50 percent.62

Osteosarcoma

About 15 percent of patients with osteosarcoma are cured with surgery alone.63 Randomized clinical trials have demonstrated that the use of multiagent chemotherapy in combination with surgery markedly improves the cure rate, which ranges from 58 to 76 percent.2,55,56,64 Chemotherapeutic agents used in the treatment of osteosarcoma include doxorubicin, cisplatin, high-dose methotrexate, ifosfamide, and cyclophosphamide and are generally given in combination.

Seventy percent of patients have nonmetastatic osteosarcoma of the limbs, and these patients have the best outcome (five-year relapse-free survival rate, about 60 to 70 percent) (Table 1).26,55,57 Since a greater degree of tumor necrosis after multiagent chemotherapy is associated with better survival,65 several studies have used salvage chemotherapy regimens for patients in whom the degree of tumor necrosis is deemed insufficient. Thus far, no study has conclusively shown that this strategy improves the outcome,66-69 although a study that used salvage therapy with ifosfamide and etoposide in patients with a poor response to the initial chemotherapeutic regimen reported that the outcome was better in this group than in historical controls.70

Most investigators advocate treatment with cisplatin and doxorubicin for patients with newly diagnosed osteosarcoma, and many studies include high-dose methotrexate, although this approach is more controversial.71,72 A national, randomized trial is examining the potential efficacy of ifosfamide, which is active against osteosarcoma,73,74 as a component of multiagent therapy. The trial is also evaluating an immunomodulatory agent, muramyl tripeptide phosphatidylethanolamine, that improved survival in a dog model of osteosarcoma.75

Studies of intraarterial chemotherapy (usually cisplatin or doxorubicin) delivered directly into the feeding arteries of tumors have shown that this approach produces marked tumor necrosis but no clearcut survival advantage.76,78 Intraarterial therapy is also more difficult to deliver than conventional chemotherapy.76,78

Patients who have metastatic disease continue to pose challenges to successful treatment. Those with numerous lung nodules or bone metastases fare the worst.58,79-82 In addition to chemotherapy, surgery is essential to remove metastatic disease.79,83 Patients with axial or pelvic lesions also have a poor prognosis.

Ewing's Sarcoma

Multiagent chemotherapy is essential for Ewing's sarcoma because of the high risk of micrometastatic disease. In the first Intergroup Study of Ewing's sarcoma in patients with nonmetastatic disease, which was conducted between 1973 and 1978, the patients received vincristine, actinomycin, and cyclophosphamide alone or in combination with either pulmonary radiation or doxorubicin.81 The primary lesion was treated with radiation therapy. The rate of relapse-free survival at five years was 60 percent for the doxorubicin-containing regimen, 44 percent for the regimen that included pulmonary irradiation, and 24 percent for the three-drug regimen alone. Patients with pelvic tumors did not benefit from the addition of pulmonary radiation or doxorubicin to triple-drug therapy.

The second Intergroup Study of Ewing's sarcoma, which was conducted between 1978 and 1982, dem-
onstrated that intermittent high-dose therapy with vincristine, doxorubicin, cyclophosphamide, and dactinomycin was superior to continuous moderate-dose therapy with these agents for the treatment of localized extrapelvic tumors (five-year relapse-free survival rate, 73 percent vs. 56 percent; P = 0.03).52 All patients with localized pelvic tumors were treated with high-dose intermittent therapy (five-year relapse-free survival rate, 55 percent).53

The third Intergroup Study of Ewing's sarcoma evaluated the addition of etoposide–ifosfamide to the four-drug regimen in a randomized trial and reported a significant improvement in survival among patients with localized disease.54 The survival rate at three years was 80 percent for patients who received the six-drug regimen, as compared with 56 percent for the patients who received the four-drug regimen. Neither regimen improved survival among the 25 percent of patients who had metastatic disease at diagnosis.59 Two non-randomized European studies have failed to confirm the advantage of the six-drug regimen.84-86 The use of lower doses and different drug schedules in the European studies may account for this difference. A fourth Intergroup Study is now evaluating dose intensity among patients with localized disease in a randomized trial of a five-drug regimen (vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide) that is given for either 30 weeks or 48 weeks.

Patients with Ewing's sarcoma who have metastatic disease at diagnosis remain a therapeutic challenge. Only about one fifth have not relapsed at five years. Attempts to improve the outcome in this group by intensifying treatment through the use of myeloblastic therapy and stem-cell transplantation have met with limited success.87-91

Treatment of Relapse

Patients with recurrent disease generally have a poor prognosis. They should undergo a complete reevaluation of the extent of disease. The prognosis depends on the type of therapy given previously, the duration of remission, and the extent of metastases. Patients with osteosarcoma in whom relapse is confined to one or a limited number of pulmonary nodules more than one year after initial chemotherapy have a 25 percent chance of cure after complete surgical resection of all nodules.92-94 High-dose chemotherapy, followed by hematopoietic stem-cell transplantation, given as salvage therapy for patients with heavily pretreated rhabdomyosarcoma, has not improved the outcome.95 However, this approach may be effective for some patients with relapsed Ewing's sarcoma that is responsive to chemotherapy.87,95,96

About half of children who initially have group I or II embryonal rhabdomyosarcoma who relapse can be cured. This group constitutes about one fifth of patients who relapse. The cure rate is less than 15 percent among other patients who relapse.97,98 Multimodal therapy, including agents that were not used initially, is recommended. The disease is generally incurable in patients whose tumors recur or progress during initial therapy.

FUTURE DIRECTIONS

Despite dramatic improvements in treatment over the past 30 years, 30 to 40 percent of patients with rhabdomyosarcoma, osteosarcoma, or Ewing's sarcoma have relapses or do not have a first remission, and most such patients subsequently die of tumor progression. Also, a disturbing number of successfully treated patients have severe late effects, including second cancers (such as radiation-induced sarcomas or treatment-related leukemia, particularly after high-dose therapy with an alkylating agent) and anthracycline-induced cardiomyopathy. The development of more effective, less toxic therapies remains an important challenge. Special effort must be focused on patients who have metastatic disease at diagnosis and those who relapse, since their outcomes have not improved greatly. More intensive therapy is being evaluated, and the search for new agents is ongoing.

Further delineation of the clinical and biologic features that are predictive of treatment failure will help identify patients who require either more intensive or novel treatments. For high-risk patients, the use of more intensive therapy combined with hematopoietic colony-stimulating factors is being evaluated, as is the use of hematopoietic stem-cell transplantation to aid in hematologic recovery. Novel strategies include the use of biologic-response modifiers, antibody targeting of immunotoxins to tumor cells, and evaluation of vaccines against Ewing's sarcoma and rhabdomyosarcoma that are designed to elicit T-cell immunity with specificity for tumor-specific fusion peptides.75,99,100

The molecular characterization of chromosomal translocations associated with rhabdomyosarcoma and Ewing's sarcoma has provided markers that are useful in diagnosing and classifying some of these tumors, as well as in monitoring the response to therapy (through the identification of minimal residual disease in patients who are in clinical remission). Finally, a better understanding of the molecular pathogenesis of these tumors has already permitted the development of therapeutic strategies that target tumor-specific molecular lesions. The expectation is that the use of such tumor-specific treatment together with conventional therapy will improve the outcome for patients with these diseases.

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