Advances in the management of musculoskeletal tumors in adolescents

Paul G. Dyment, M.D.

Department of Pediatrics and Adolescent Medicine

The three common malignancies of the musculoskeletal system in the adolescent patient, osteogenic sarcoma, Ewing's sarcoma, and rhabdomyosarcoma have been known as usually fatal diseases. Despite heroic therapeutic maneuvers such as hip disarticulations and other mutilating surgical techniques, the prognosis has remained bleak with surgery or radiotherapy alone. The concept of treating the patient with chemotherapy along with the primary mode of therapy, either radiation or surgical removal of the tumor, has radically altered our methods of treating these patients and given rise to a significant change in their prognoses. Chemotherapy has been considered to be "adjuvant" to the primary therapy, acting by destroying occult metastases while they are still small and susceptible to eradication by drugs, and possibly by acting synergistically with irradiation when this mode of therapy is primary. Results have been so good that chemotherapy should no longer be considered "adjuvant," but rather as part of a combined primary therapeutic approach. However, the term "adjuvant therapy" has become part of the medical literature and will probably persist in this context. This paper reviews the recent advances in adjuvant therapy of these three malignancies.

Ewing's sarcoma

Since 1921 when James Ewing[1] described this highly anaplastic bone tumor, it has been among the most fatal of all malignancies. A composite series of 987 cases accumulated from the published literature in 1967 revealed a 5-year survival rate of only 8%.[2] Although there is no clinical evidence of metastatic disease in most cases by the time of diagnosis, rapid and extensive hematogenous spread of the tumor generally develops within a year, despite treatment of the primary tumor by amputation or intensive radiation therapy. Radiation therapy to the involved bone has been considered the treatment of choice, even though not only do metastases soon appear but local regrowth of the tumor has appeared despite high dose levels of over 6,000 rads.[3]

The tumor is probably a sarcoma of nonosseous origin involving bone, and like most sarcomata it is a disease of the young. The majority of patients are adolescents, and as with osteogenic sarcoma, the male adolescent is the most frequently affected.

In 1969 Johnson and Humphreys[4] of the National Cancer Institute reported that when high dose cyclophosphamide was given for a 3-day period in addition to local radiation therapy, two of three patients with no evidence of metastases at the time of diagnosis survived the disease. Several years later Hustu et al[5] from St. Jude's Hospital reported on 10 of 15 similar patients in whom the adjuvant chemotherapy regimen consisted of vincristine and cyclophosphamide. There was no evidence of disease from 4 to 91 months. The same year, similar data were reported by Freeman et al[6] of Roswell Park Memorial Institute; these investigators gave just the cyclophosphamide as adjuvant chemotherapy and three of nine patients showed no metastases for 3 or more years.

Rosen et al[7] from the Memorial Sloan-Kettering Cancer Center in 1974 reported the most encouraging series to date; 12 children for 2 years received four-drug adjuvant chemotherapy of dactinomycin, adriamycin, vincristine, and cyclophosphamide. All these children remained free of disease from 10 to 37 months. More recently, Pomeroy and Johnson[8] summarized the results of treating 66 patients with local radiation along with progressively more intensive systemic chemotherapy regimens; the same four drugs in different schedules were used as well as intrathecal methotrexate and whole brain irradiation. Although their median survival for patients treated with adjuvant chemotherapy is more than 5 years, in their most recent series of 15 patients, 14 have been free of disease from 3 to 24 months.

Because factors such as age and site of tumor affect the prognosis (older patients and those with primary tumors of the extremities have better survival rates),[8] small series of patients treated by the different methods reported above cannot be compared when choosing optimal therapy. For instance, one institution might have a referral pattern which excludes a certain age group, and their patient samples would then be biased. Therefore, large scale randomized studies must be undertaken to answer such questions as whether four-drug adjuvant chemotherapy is better than three drugs, and whether radiation therapy to the lungs will eradicate subclinical disease. However, even a cooperative

cancer study group will not have access to sufficient numbers of patients to make a statistically significant randomized trial because of the relative infrequency of this form of cancer. Therefore, the three childhood cooperative cancer groups in the United States (Acute Leukemia Group B, Childrens Cancer Group, and the Pediatric Division of the Southwest Oncology Group) are combining their patients in a protocol now in progress designed to answer these questions.

It is apparent that the treatment of choice for a patient with Ewing's sarcoma without clinical evidence of metastases consists of radical dose radiation to the entire involved bone (6,000 to 7,000 rads) and intensive adjuvant chemotherapy. With this treatment approach it is believed that the majority of these unfortunate young people will now be "long-term survivors."

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common form of soft tissue sarcoma in children. It occurs in any anatomic location where there is skeletal muscle tissue, presumably arising from undifferentiated mesenchymal cells found in muscle.

RMS has been grouped into three cell types, alveolar, embryonal, and pleomorphic; these were originally thought to have prognostic significance. However, it now appears that with adjuvant therapy the survival rate is the same regardless of the cell type.[9] The alveolar form is most frequently found in the extremities, and it is the type most commonly seen in adolescents.

RMS is highly malignant with a tendency for early local recurrence and generalized metastases, despite radical surgical excision of what appears to be localized disease. With surgical management alone, metastatic disease develops in 83% within 1 year of diagnosis.[10] Another complicating fact was that only 20% to 25% of primary tumors could be completely removed surgically. This dismal outlook has changed dramatically during the past few years and we can now expect a cure, or at least prolonged survival for most of these patients.

Wilbur et al[11] at the M. D. Anderson Hospital treated 21 children with inoperable or metastatic RMS with a combination of irradiation, vincristine, cyclophosphamide, and dactinomycin, and 16 patients were without evidence of disease for 1 to 4 years. Holton et al[12] from the University of Colorado treated 19 children with nonmetastatic RMS with the same three drugs with a different schedule as well as radiation therapy and surgery. Eleven of the 19 were reported as being free of disease for 4 to 49 months. Although the follow-up is not long enough to predict the eventual cure rate, their experience is encouraging.

A similar approach with the same three drugs and irradiation was reported by Donaldson et al[13] in patients with inoperable head and neck RMS. Of 19 patients treated, the minimum 2-year survival was 74%, and at least local control was achieved in 89%.

Ghavini et al[14] at Memorial Sloan-Kettering Cancer Center treated 29 children with embryonal RMS with surgical removal of the tumor if possible, followed by chemotherapy with vincristine, dactinomycin, and adriamycin as well as radiation therapy in patients with gross or microscopic resi-

dual disease. The chemotherapy was given in repeated cycles of sequential administration followed by rest periods for 2 years. Eighty-two percent are alive with no evidence of disease for 4 to 42 months.

It is apparent that the combination of surgery, irradiation, and chemotherapy has virtually eliminated the need for mutilating surgery in this disease. The surgical procedure should remove as much tumor as possible without damaging vital structures, and amputations for tumors of the extremity are, therefore, only rarely indicated now. Radiation therapy to the entire muscle involved should then be administered along with some form of either three- or four-drug combination chemotherapy for at least 2 years.

Many questions remain unanswered, such as whether postoperative radiotherapy is indicated if the primary tumor has been completely excised, whether a three- or four-drug combination chemotherapy is optimal, and what is the optimal duration of chemotherapy. As with Ewing's sarcoma, the three childhood cancer cooperative groups have combined their resources in a single randomized protocol which is attempting to answer these questions.

Osteogenic sarcoma

Osteogenic sarcoma arises from bone-forming mesenchyme, and the histologic picture shows sarcomatous stroma apparently producing osteoid. Almost half the patients with this disease are between 10 and 19 years of age.[15] There is a definite male preponderance (M:F ratio of 1.6), and bones of the lower extremity are the most common site. Amputation alone has resulted in cure rates only slightly better than Ewing's sarcoma and RMS. The Mayo experience of 600 patients was a 20%, 5-year survival rate with amputation alone.[15] The tumor metastasizes principally to the lungs, usually within 9 months from the time of amputation. Death usually follows rapidly since the tumor is both chemoresistant and radioresistant.

When amputation is indicated, usually the entire bone is removed, the amputation site being usually above the adjoining joint. This unfortunately means a hip disarticulation for lesions of the femur, above-the-knee amputation for tibial lesions, and a forequarter amputation for tumors of the head of the humerus. Despite this kind of mutilating surgery, most of these youngsters eventually die. If the tumor is in an area which cannot be excised, the outlook is generally hopeless.

It was not until 1972 that chemotherapy had any effect on a significant number of cases of metastatic disease. Jaffe[16] from the Children's Cancer Research Foundation in Boston used high-dose methotrexate with citrovorum factor rescue, and demonstrated regression of roentgenographically evident pulmonary metastases. Cortes et al[17] from Roswell Park Memorial Institute reported the same result with adriamycin.

Applying the concept of adjuvant chemotherapy, Sutow et al[18] from the University of Texas Cancer Center and the Southwest Oncology Group gave a 72-week course of the four drugs known at that time to have some effect on metastatic osteogenic sarcoma (adriamycin, phenylalanine mustard, vincristine, and cyclophosphamide); these drugs were given as "pulses," allowing intervals of time between

heavy doses for the bone marrow to recover. Their initial, good results were reported in 1974, and 10 of 18 of their original patients are still free of disease 9 to 23 months since completing the chemotherapy course and after the original operation. There have been no "late" recurrences of disease in this series once the chemotherapy course has been completed, so it appears that 55% of these patients are probably "cured." A larger and more recent series of patients from the same group has shown a similar early survival curve.[19] They have added three "pulses" of high-dose methotrexate with citrovorum factor rescue to their current series of patients being treated with this same four-drug adjuvant program. Their preliminary data reveal that only 25% have metastases during the first 12 months, a considerable improvement over the historic 80% that have had evidence of metastases by this time.

Two other groups have also reported early encouraging results with adjuvant chemotherapy. According to Burchenal,[20] Cortes used adriamycin alone for 6 to 8 months after amputation; 10 of 13 patients were free of disease 9 to 40 months after operation. Jaffe used the combination of vincristine and high-dose methotrexate, with citrovorum factor rescue every 3 weeks for 2 years, and 11 of 12 patients were free of disease 6 to 27 months after the operation.

This high-dose methotrexate regimen is hazardous because its toxicity is erratic and unpredictable. There have been 12 drug-related deaths reported to the Investigational Drug Branch of the National Cancer Institute by experienced investigators from several major cancer centers, and it should only be undertaken in a medical center well equipped with experienced personnel, blood products, and pharmacologic testing procedures available. The doses of methotrexate administered are up to 500 mg/kg, which is almost 500 times more than the usual weekly dose given a child with leukemia.

Because of the infrequency of this tumor, none of these studies were randomized, but the results are so much better than historic controls that randomized controls are now not only unnecessary but at present even unethical.

Discussion

It is obvious that if metastases appear following the removal of any primary tumor by amputation or after adequate treatment of the primary tumor by radical radiation therapy, the metastases were present but not clinically detectable at the time of the primary treatment. These "micrometastases" are the target of adjuvant chemotherapy, since they appear to be sensitive to drugs and drug combinations not generally effective against grossly visible disease. All of these chemotherapeutic regimens are associated with considerable morbidity and even some mortality. They should still be considered experimental, but results are so striking that all young people with any of these three tumors in which metastases are not detectable should be given the opportunity of receiving this kind of treatment.

It is apparent that survival rates in nonmetastatic Ewing's sarcoma, osteogenic sarcoma, and RMS have improved dramatically with the use of adjuvant chemotherapy along with irradiation and surgery. Probably

more than half of all such patients will now be cured of the disease.

Summary

Three tumors of the musculoskeletal system have a proclivity for the adolescent patient. Osteogenic sarcoma, Ewing's sarcoma, and RMS are generally fatal, despite heroic surgical and radical radiation therapeutic techniques. Adjuvant therapy is a new concept, and it consists of giving chemotherapeutic drugs for 1 or 2 years after the primary surgical or irradiation treatment to patients who do not have clinically apparent metastases at the time of diagnosis. This is based on the assumption that in most such cases "micrometastases" have already occurred, but they are sensitive to drugs which are not effective against bulk tumor. The results have been dramatic in these patients, and it is now probable that most of these youngsters without demonstrable metastases at the time of diagnosis can be cured of cancer.

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