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Perspectives and Commentaries

Adjuvant Chemotherapy for Osteogenic Sarcoma

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(A COMMENT ON: Gasparini M, Tondini C, Azzarelli A, Fossati-Bellani F. Long-term evaluation of surgery followed by adjuvant adriamycin in osteogenic sarcoma. *Eur J Cancer Clin Oncol* 1987, **23**, 433–436.)

PRIOR to the use of adjuvant chemotherapy, the prognosis for patients with osteogenic sarcoma was poor and their quality of life was compromised. Even though control of the primary tumor was achieved in most patients by amputation, only 20% of patients survived 5 years after diagnosis. It was presumed that for the vast majority of patients, undetectable micrometastatic disease was present at the time of surgery of the primary tumor, since these patients developed clinically apparent metastatic disease, often within 6 months of diagnosis [1]. The concept of adjuvant chemotherapy of cancer is based on experimental models in which chemotherapy given to animals with a microscopic tumor burden is more effective in curing the animals than chemotherapy given to animals with macroscopic amounts of tumor [2]. Additionally, in patients with other childhood tumors including leukemia and Wilms' tumor, chemotherapy that produces regression of bulky measurable disease is capable of destroying micrometastatic disease and increasing the cure rate [3]. As effective chemotherapeutic agents were identified in patients with measurable metastatic osteogenic sarcoma, post-surgical adjuvant chemotherapy was employed in an attempt to reduce the relapse rate. These adjuvant chemotherapy trials were instituted in the early 1970s in many centers. The two original and most important single agent adjuvant chemotherapy trials were the initial adjuvant trial of high dose methotrexate (HDMTX) done at the Dana Farber Cancer Institute that resulted in a 5 year disease-free survival (DFS) plateau of 44% [4], and the trial by Cortez *et al.* using doxorubicin as adjuvant therapy for 21 patients that produced an estimated DFS at 5 years of 39% [5].

Both of these studies, as well as multiple other non-randomized chemotherapy trials using single and multiple agents, all produced 45–60% DFS plateaus which were increased when compared to an abundant non-concurrent historical experience. The validity of the historical experience, however, began to be questioned when three non-randomized studies reported in the 1970s indicated improvement in DFS of 30–40% in patients not receiving adjuvant chemotherapy. Additionally, studies using methods believed to be ineffective in osteosarcoma such as transfer factor and tumor-cell vaccine reported DFS plateaus of nearly 40% [1]. Finally, improved radiodiagnostic technology developed in the 1970s could be expected to identify patients with pulmonary metastases that would not have been appreciated previously.

In 1976, to clarify the issues surrounding the value of adjuvant chemotherapy in osteosarcoma, the Mayo Clinic conducted a prospective study in which patients were randomly assigned to a group that was treated with HDMTX after surgical control of the primary tumor or to one that received no adjuvant chemotherapy after such surgery. At 5 years of follow-up, the DFS rate in both groups was 42% [6]. Although the prognosis for patients with osteosarcoma appeared to be dramatically improved since these initial adjuvant chemotherapy trials were undertaken in the 1970s, the explanations for this improved prognosis was very controversial [7], until a recent randomized multi-institutional trial unequivocally confirmed the benefit of adjuvant chemotherapy in decreasing the chance of relapse in patients with osteosarcoma of the extremity [8]. Thirty-six patients with non-meta-

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static extremity osteosarcoma were randomly assigned to a group that received six agent adjuvant chemotherapy after surgical control of the primary or to one that received no adjuvant chemotherapy following their surgery. The DFS for the randomized patients treated with adjuvant chemotherapy was 66% compared to 17% for those patients randomized to surgery only ($P < 0.001$). An additional 77 patients were eligible for this study but refused randomization. Eighteen of the 77 chose no chemotherapy and 59 chose six agent adjuvant chemotherapy. The DFS for the 59 patients who received adjuvant therapy in 67% compared to 9% for the 18 patients who not receive adjuvant therapy.

The article in this journal by Gasparini *et al.* [9] presents results of a trial of surgery followed by adjuvant doxorubicin for osteosarcoma having a minimum follow-up of 7 years. Although not randomized, 29 patients received either 75 mg/m^2 or 90 mg/m^2 of doxorubicin. Overall DFS is 45% for all patients. Nine of 15 (60%) patients who received 90 mg/m^2 of doxorubicin remain long-term disease free survivors compared to four of 14 (29%) who received 75 mg/m^2 (no statistically significant difference). The authors suggest that their study supports a positive dose effect associated with doxorubicin and that doxorubicin alone as post-operative adjuvant chemotherapy achieved results comparable to those obtained by more complex and potentially more toxic multi-agent combination chemotherapy regimens. Since this, is a non-randomized trial with only 29 patients, it is difficult to draw firm conclusions. The trend toward a positive dose effect of adjuvant doxorubicin reported by Gasparini *et al.* is in agreement with Cortez *et al.*'s [5] initial trial of doxorubicin in osteosarcoma.

The authors' conclusion that the results with doxorubicin are similar to those obtained with the best multi-agent chemotherapy regimens is open to debate. Gasparini *et al.* report a 45% DFS for all patients which is similar to other single agent reports of HDMTX [4] and doxorubicin [5]. In order to address the problems of tumor-cell heterogeneity and drug resistance and to increase tumor cytoreduction almost all effective chemotherapeutic regimens involve combinations of active agents with differing mechanisms of action and toxicity. Combination chemotherapy is only effective to the extent that the dose of individual agents and rate of administration of those agents is not compromised. As an example, HDMTX and doxorubicin have different dose-limiting toxicities and different mechanisms of action. They are good agents to employ in combination since both can be given at full dose. If independent and at least additive effects of these agents are assumed (45% DFS for each), one would predict that the combination of doxorubicin and HDMTX at full dose would yield a 60% DFS plateau. Two studies done at the Dana Farber Cancer Institute using HDMTX at 7.5 g/m^2 and doxorubicin at 75 mg/m^2, confirm this prediction. Adjuvant treatment with these two agents given to a total of 68 patients with a minimum follow-up of 5 years yielded a DFS rate of 59% [4]. Additionally, two recent randomized multi-institutional trials with large numbers of patients treated with multiple agent chemotherapy regimens both had DFS of nearly 70% [8, 10].

As patients with osteosarcoma treated with adjuvant chemotherapy survived longer orthopedic surgeons attempted less mutilative surgery (limb-sparing segmental resection surgery) compared to cross bone amputations in order to try to improve patients' quality of life. In addition to the use of multiple agents for the treatment of osteosarcoma, the original order of surgery followed by chemotherapy was altered by some investigators to permit time for custom-made prosthesis to be available for these limb resection operations. Induction (neo-adjuvant) chemotherapy was demonstrated by some of these investigators to improve DFS to approx. 70% [10, 11]. There are several theoretical arguments favoring neo-adjuvant chemotherapy. First, patients receive early systemic chemotherapy to treat micrometastic disease. Second, if induction chemotherapy produces primary tumor regression, then less aggressive surgical treatment might be possible. Finally, in some hands, the effect of neo-adjuvant chemotherapy produces risk groups based on primary tumor response to the induction chemotherapy. It is uncertain whether the early administration of chemotherapy is crucial or whether the use of additional active agents improves overall DFS by decreasing the emergence of drug resistant tumor. A recently opened (December 1986) randomized Pediatric Oncology Group osteosarcoma study that compares induction chemotherapy to the identical chemotherapy regimen given post-surgically will attempt to gain insight into the role of neo-adjuvant chemotherapy.

The outlook for patients diagnosed with osteosarcoma has dramatically improved with the use of adjuvant chemotherapy. Long-term relapse-free 'cure' is now a reality for well over half the patients afflicted with this disease. Recent advances in osteosarcoma research include the identification of a human DNA segment located on the q14 band of human chromosome 13 with properties of the gene that predispose to both retinoblastoma and osteosarcoma [12]. Monoclonal antibodies to human osteosarcoma are available and are being studied for both diagnostic and therapeutic use [13, 14]. Recent identification of prognostic factors

including serum levels of LDH [8], response to induction chemotherapy [10, 11], tumor ploidy [15] and naturally occurring tumor infiltrating lymphocytes [16] are permitting separation of patients into risk groups. Future directions of research will continue to be aimed at improving therapeutic and diagnostic techniques in order to try to increase the proportion of patients who remain relapse-free. Active new drugs such as isosfamide need to be properly integrated into chemotherapy regimens without compromising the dose rate of the other active agents. Separation of patients into standard and high risks groups offers the potential of directing new therapeutic approaches to those patients in greatest need. Novel therapeutic modalities including adoptive immunotherapy merit a trial under carefully controlled circumstances in patients at greatest risk.

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