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## *Perspectives and Commentaries*

# Review: Therapy of Osteogenic Sarcoma: Local, Systemic or Both?

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(A COMMENT ON: Kim EE, Legaspi JR, Haynie TP, Wallace S. Transcatheter infusion of $^{99m}$Tc MAA for predicting response of intra-arterial chemotherapy in osteogenic sarcoma. *Eur J Cancer Clin Oncol* 1985, **21**, 35-42.)

UNTIL the early 1970s, the most common approach to the management of localized osteosarcoma was surgical extirpation of the tumor when possible, followed by careful observation. Radiation therapy was utilized for control of primary lesions not amenable to surgical removal. Unfortunately, in most large series of patients treated in this manner the long-term survival was no better than 20% [1]. Because of the poor prognosis when therapy was directed at the primary alone, randomized trials to evaluate adjuvant chemotherapy were not initially felt to be necessary, it being assumed that any measurable benefit of chemotherapy would be readily appreciated. Subsequently, the results of a number of trials suggested that the survival for localized disease could be improved to at least 40% at 5 yr with the addition of chemotherapy.

However, in evaluating these initially encouraging results, investigators at the Mayo Clinic suggested that perhaps they did not represent an improvement in survival due to chemotherapy, but rather reflected a change in the natural history of the disease [2]. To support this hypothesis, the Mayo Clinic group conducted and recently reported the results of a randomized trial that indeed showed that there was no difference between those patients treated with adjuvant chemotherapy and those treated with surgery alone [2]. Since the overall 5-yr survival of the entire group was 52%, this study raised significant questions about the role of adjuvant chemotherapy and raised doubts about the results of adjuvant chemotherapy trials conducted without a control group not receiving chemotherapy [2].

Faced with this dilemma, a multi-institutional bone study group (including the National Cancer Institute and Pediatric Oncology Group) began in 1982 a trial for patients with localized, surgically ablated, high-grade extremity osteosarcoma to evaluate the role of adjuvant chemotherapy (high-dose methotrexate, adriamycin, *cis*-platinum, bleomycin, dactinomycin and cyclophosphamide) by comparing the disease-free survival and survival of those receiving adjuvant therapy to those initially treated with surgery alone who were to receive 'delayed' chemotherapy only if there was recurrence of disease [M. Link, personal communication]. This trial, recently closed, has demonstrated a significant difference in disease-free survival favoring the 'initial' adjuvant chemotherapy arm; however, the long-term survival of the two groups remains to be determined. Consequently, adjuvant chemotherapy does appear to have a role in the treatment of patients with high-grade localized osteosarcoma.

With this background, two major issues that currently face those evaluating the treatment for osteosarcoma are: (1) the role of other strategies for local tumor control that avoid amputation; and (2) the improvement in long-term and disease-free survival. Addressing these two issues, Rosen *et al.* [3, 4] evaluated a strategy using the pathologic response of the primary tumor to preoperative chemotherapy to help determine the

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adjuvant therapy used postoperatively. For example, this approach allowed the elimination of an agent (methotrexate) and the substitution of *cis*-platinum in those patients who did not show an 'adequate' (grade III or IV) pathologic response and avoided the use of *cis*-platinum in those 'responsive' to a regimen containing methotrexate without *cis*-platinum [3, 4]. The excellent results of this trial using preoperative chemotherapy (greater than 90% survival) were confirmed in a German-Austrian study group trial that reported a 30-month disease-free survival of greater than 65% [5]. These studies also allowed many patients to be treated with surgical resection rather than amputation without a clear deleterious effect on survival. However, the non-statistically significant but slightly higher systemic failure rate of patients treated with limb-salvage rather than amputation in the German-Austrian study is worrisome.

These initial studies of preoperative intravenous chemotherapy provide the basis for its use in determining postoperative adjuvant systemic therapy by assessing the pathologic response of the local tumor. However, they also provide the basis for the use of systemic preoperative chemotherapy as a means to achieve local control while maintaining maximal function. Not only might the preoperative chemotherapy result in a reduction in tumor size that would allow some patients to benefit from limb-salvage procedures, but this approach might actually permit the complete elimination of surgical extirpation from the therapeutic strategy in selected patients. The intra-arterial chemotherapy reported by Kim *et al.* [6], while primarily aimed at improving local control without ablative surgery [7, 8], may also provide an indication of the optimal systemic therapy for the individual patient. In summary, preoperative systemic *intravenous* therapy may actually have an important impact on not only subsequent adjuvant systemic therapy but also local control. Conversely, *intra-arterial* chemotherapy may not only result in excellent local control but may also identify important agent(s) to be used systemically.

This shift in strategy from the more conventional approach of using local therapy (i.e. surgery) to treat local disease and systemic therapy (i.e. chemotherapy) to treat systemic disease, to an approach that is based on the interaction of local and systemic therapy, represents an exciting development in the treatment of osteosarcoma. That the interaction between chemotherapy and surgery can be optimally designed to result in both an excellent cure rate and a reduction in morbidity has already been demonstrated in other solid tumors of childhood, most notably very large stage III Wilms' tumors and genito-urinary rhabdomyosarcomas (the so-called 'special pelvic tumors'). In the therapy described by Rosen the postoperative adjuvant chemotherapy regimen was determined by the degree of necrosis on pathologic evaluation of the tumor specimen [3]. Less invasive techniques yielding comparable response information would be most valuable [9]; an example of such an imaging study has been discussed by Kim *et al.* [6]. This article, which suggests that tumor vascularity and the shunting of radioactivity to the lungs following intra-arterial infusion of $^{99m}$Tc macro-aggregated albumin are valuable in assessing changes in tumor viability in osteosarcoma following intra-arterial chemotherapy, describes a method which deserves further study. The rapidly advancing field of diagnostic imaging will almost certainly provide even more sophisticated techniques for assessing the response of a given tumor to various anti-cancer agents and will perhaps play a crucial role in individualizing therapy.

It will be critically important, however, to confirm in appropriately designed clinical trials the value of chemotherapy modification based on this form of gross *in vivo* tumor destruction. The realization that tumors are composed of cells with heterogeneous properties and presumably different metastatic potentials [10] demands extreme caution before the widespread approval of a concept that restricts the use of front-line agents. In spite of the potential positive interaction of local and systemic therapies, the modification of effective chemotherapy in order to enhance gross local tumor shrinkage and hence improve the possibility of limb salvage may permit the growth of metastases resistant to limited-agent chemotherapy. This result must be guarded against.

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