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Intra-arterial *Cis*-platinum in Osteosarcoma

C.H. Carrasco, C. Charnsangavej, W.J. Richli, and S. Wallace

Conventional radiography continues to be the most important imaging modality in the initial diagnosis and assessment of skeletal neoplasms. However, this technique is usually inadequate to determine the local extent of the tumor, particularly in malignancies. Angiography also fails to define accurately the local extent of most skeletal neoplasms. Computed tomography, however, demonstrates the intramedullary and extraosseous extent of skeletal neoplasms much more accurately and is currently the modality most frequently used for this purpose.

The use of angiography in skeletal neoplasms is now almost completely limited to those that are managed with intra-arterial therapy, either infusion chemotherapy or embolization, including osteosarcomas, nonresectable giant cell tumors, and metastases. Angiography is employed to define the vascular anatomy for optimal catheter placement and also to assess the therapeutic response, including detection of residual or recurrent tumor. In addition, demonstration of abnormal vascularity is employed in the planning of the biopsy with some neoplasms.

A. Osteosarcoma

Osteosarcoma comprises a variety of neoplasms capable of osteoid matrix production in at least a small focus. These tumors vary in their biological behavior from the relative indolence of the parosteal osteosarcoma to the extreme aggressiveness of the telangiectatic type. The etiology of osteosarcoma is unknown; however, Paget's disease, radiation, and osteogenesis imperfecta are known precursors in some instances. Osteosarcoma is the most frequent primary malignant neoplasm of bone after myeloma, and its peak incidence is in the second decade of life. Males are more frequently affected than females.

The site of predilection for osteosarcoma is the metaphyseal portion of the long bones, with the distal femur, the proximal tibia, and the proximal humerus accounting for the majority of the cases. Conventional radiographs usually suggest the diagnosis, but the relative nonspecificity of the radiographic signs makes a tissue diagnosis mandatory prior to the initiation of therapy. Osteosarcoma may be completely lytic or predominantly sclerotic, but it usually exhibits a combination of these features. The hallmark of the roentgenologic diagnosis of osteosarcoma is given by mineralized tumor osteoid matrix, which characteristically presents as nests of cloud-like to ivory-like density.

B. Therapy

For many years, radical surgery was the principal mode of therapy for primary osteosarcoma and yielded an overall survival rate of approximately 20% [1]. Radiologic evidence of pulmonary metastases was seen at a median of 8.5 months following po-

1515 Holcombe BLVD., Department of Diagnostic Radiology, The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas 77030 USA. Phone (713) 792-8295

tentially curative surgery [2, 3], and patients usually died within 6 months after detection of pulmonary metastases.

The fatal outcome of most osteosarcoma patients following surgery led to the use of radiation therapy for local control [4–6] in an effort to spare patients likely to develop pulmonary metastases from unnecessary mutilation. Preoperative radiation therapy was also employed with the hope of changing tumor cell viability and to prevent implantation of cells dislodged during surgery. However, this approach yielded survival rates comparable to those achieved by surgery alone [1], so radiation therapy was discarded as a primary treatment modality.

Subsequently, various chemotherapeutic agents were shown to be active against established metastases and the primary tumor, resulting in prolongation of survival. The fact that osteosarcoma is microscopically disseminated at the time of diagnosis in the vast majority of patients, as evidenced by the rapid onset of clinically evident pulmonary metastases soon after amputation, has led to the administration of adjuvant chemotherapy following surgery [7, 8].

Advances achieved with chemotherapy led to the search for alternative methods to treat the primary tumor short of amputation, the most significant of which has been limb salvage [9–11]. Preoperative chemotherapy was initially used to control the primary tumor while awaiting the production of a customized endoprosthesis for limb salvage surgery [12]. Subsequently, preoperative chemotherapy was employed with the intent to treat the primary tumor and identify an effective chemotherapeutic agent for adjuvant therapy based on the degree of tumor necrosis [10, 13]. Using a combination of various chemotherapeutic agents, Rosen et al. [14] reported a 92% continuous disease-free survival for a median of 2 years in a group of 79 patients.

C. Intra-arterial Chemotherapy

Since the therapeutic activity of most antineoplastic agents is related to their concentration at the site of the tumor, several authors administered them intra-arterially in an attempt to improve on the results achieved with intravenous administration. *Cis*-platinum has been demonstrated to be an active agent against osteosarcoma [15], yielding a response rate of 67% in 17 patients in whom it was administered via the intra-arterial route [16]. There were nine complete and two partial responses as determined by clinical, angiographic, and pathological parameters. The local concentrations of *cis*-platinum in the vein draining the region of the neoplasm were higher than those of a peripheral vein, reflecting the systemic concentration of the drug. It was also noted that increased tumor destruction was a function of the number of infusions, high *cis*-platinum concentration within the tumor, and the tumor subtype. In another report, Benjamin et al. [17] noted ten responses in 18 adult patients treated with intra-arterial *cis*-platinum and systemic adriamycin.

Preoperative intra-arterial *cis*-platinum 120–200 mg/m^2 is currently being administered to patients with localized osteosarcomas at UT M.D. Anderson Hospital and Tumor Institute in order to treat the primary tumor and determine the efficacy of this agent for adjuvant therapy. Patients who are 16 years of age or older also receive systemic adriamycin 90 mg/m^2.

D. Technical Considerations

In pediatric patients, the procedure is performed under general anesthesia. In older patients, mild sedation and local anesthesia suffice. The usual access route for the arterial catheterization is the contralateral femoral artery for patients with lower extremity and pelvic neoplasms, while either femoral artery can be used for tumors located elsewhere. Catheterization is performed employing the Seldinger technique. The patients are anticoagulated with 50 U/kg heparin as soon as the catheter is in the arterial system, and an equal dose is administered during the course of the infusion of *cis*-platinum.

Since thrombotic complications are related in part to the caliber of the catheters employed, these should be of the smallest caliber that will allow for a safe and atraumatic catheterization. We prefer to use 3.5-F catheters in the pediatric age-group and 5-F catheters for older patients. Straight guide wires will decrease the likelihood of producing vascular spasm in younger patients.

Although curved catheters facilitate catheterization, their tip will often rest on the vessel wall, thus exposing a localized area of endothelium to a greater concentration of the chemotherapeutic agent; this can be avoided with the use of straight catheters. A deflector wire is employed to advance the straight catheter over the aortic bifurcation to the contralateral extremity. For upper-extremity neoplasms, the catheter tip is preshaped to facilitate engagement of the brachiocephalic vessels, and it should conform to the anatomy of the catheterized vessel to provide greater stability and decrease endothelial trauma.

Since the majority of osteosarcomas are located about the knee, the vessels most frequently catheterized for their infusion are the superficial femoral and popliteal arteries. Neoplasms in this region are frequently supplied by multiple vessels consisting of the geniculate arteries and hypertrophied periosteal-cortical arteries. The catheter tip should be placed proximally to the branches supplying the tumor, bypassing as many musculocutaneous branches as possible. Laminar flow within the infused vessel may prevent adequate mixing of the chemotherapeutic agent and result in streaming of the infusion for variable distances from the catheter tip. This phenomenon may cause large amounts of the chemotherapeutic agent to bypass some of the branches supplying the tumor, to flow into a branch supplying only part of the tumor, or to flow into a musculocutaneous branch that does not supply the tumor at all. In the latter instance, necrosis of normal tissues and subsequent scarring may occur. Streaming of the infusion can be disrupted by the use of a pulsatile pump (Gianturco; Cook, Inc.) which delivers the infusion in one to three short pulses per second, creating turbulence, better mixing, and a more homogeneous distribution of the infusion chemotherapy.

Rarely, a tumor will have a single branch providing most of its blood flow, and at least one of the chemotherapy infusions is then delivered selectively into this vessel. In this manner, a greater cytotoxic effect related to the greater drug concentration is achieved.

The main blood supply to proximal femoral osteosarcomas is provided by the femoral circumflex artery, which arises from the deep femoral artery, frequently just beyond its origin, providing an extremely short segment in which to place the tip of the infusion catheter. A catheter in this position is unstable and may dislodge into the superficial femoral artery, whose contribution to proximal femoral neoplasms is negligible. When this situation is encountered, the catheter tip is placed within the common femoral artery.

Osteosarcomas of the femoral diaphysis may receive their blood supply from branches of both the superficial and deep femoral arteries. When the contribution by the superficial femoral artery is provided by only a few vessels, redistribution of the blood supply may be performed by occluding these branches with segments of Gelfoam. The blood supply to the tumor will then be provided solely by the deep femoral artery, the infusion of which will cover the entire neoplasm. When flow redistribution is impractical, the infusions should be alternated between the deep and the superficial femoral arteries or should be performed in the common femoral artery.

Osteosarcomas located in the proximal humerus usually receive a major portion of their blood supply from the circumflex humeral artery, which should be selectively infused for at least one of the courses of preoperative chemotherapy.

Angiography in the frontal and lateral planes is performed at the time of each catheterization. Photographic subtraction of the arteriograms allows assessment of the degree of vascularity of the neoplasm.

E. Determination of Response

A cytotoxic effect may be apparent on the plain radiographs of the tumor by the appearance of reactive calcification and a decrease in the size of the soft tissue mass. The margins of the neoplasm may become better defined, and varying degrees of cortical remodeling occur. Computed tomography will demonstrate similar findings in cross section. An increase in the size of the soft tissue mass or in the area of osteolysis usually indicates progression of the disease. However, the conventional determination of response, where a complete response is indicated by total disappearance of the tumor and a partial response represents at least a 50% decrease in the size of the tumor, cannot be employed in skeletal neoplasms since they frequently do not decrease in size as they respond to therapy.

In a group of 37 patients treated prior to 1983, we observed that those with 90% or more histologic tumor necrosis had a 95% disease-free survival at 2 years, compared with 21% for those with lesser degrees of necrosis. Therefore, a clinical test that correlates with the degree of histologic tumor necrosis would be useful in devising the therapeutic strategy prior to resection. The features of healing noted by conventional radiography and computed tomography are variable and not predictive of the degree of tumor necrosis. However, the tumor vascularity as noted on subtraction arteriograms correlates reasonably well with the histologic tumor necrosis. In a group of 79 patients with osteosarcoma, we observed that a complete or near-complete disappearance of the tumor vascularity had a sensitivity of 95% and a specificity of 58% in predicting 90% or more histologic tumor necrosis in the resected specimen. The presence of residual tumor vascularity almost always indicates the presence of significant viable tumor.

Following several courses of preoperative chemotherapy, the neoplasm is resected as part of a limb salvage procedure or an amputation, depending on the response. The neoplasm is sectioned longitudinally, and a slice through the center of the tumor or through the region where residual vascularity was noted in the last arteriogram is mapped out in multiple sections. The percentages of viable and necrotic tumor within each section are estimated, averaged for all sections, and expressed as an overall percentage of tumor necrosis.

F. Results

A group of 65 patients 16 years of age or older with extremity osteosarcomas were evaluated. These patients were treated preoperatively with systemic adriamycin and intra-arterial *cis*-platinum for a total of three to six courses. Adjuvant chemotherapy of adriamycin and *cis*-platinum was continued until cumulative *cis*-platinum toxicity and then changed to adriamycin and dacarbazine. Since 1983, patients with less than 90% tumor necrosis have been treated with an alternating program adding high-dose methotrexate and bleomycin, cyclophosphamide, and dactinomycin. The overall 3-year disease-free survival is 65%, which is superior to our historical control of 20%. The 28 patients treated since 1983 have a 75% disease-free survival at 2 years, compared with 62% for those treated from 1979–1982 [18].

Downstaging the tumor with preoperative chemotherapy increased the number of patients who were considered for limb salvage procedures. Only 8% of the patients fulfilled the criteria for limb salvage procedures prior to chemotherapy, but 60% underwent limb salvage following chemotherapy [19].

Two groups of patients with favorable prognosis were identified, those with osteosarcomas in the humerus and those with the telangiectatic type. All six patients with humeral osteosarcomas underwent limb salvage and are alive and free of disease. Six of the seven patients with telangiectatic osteosarcomas are alive and free of disease; the seventh died of treatment-related complications.

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