"To B(MP-2) or Not To B(MP-2)" or "Much Ado About Nothing": Are Orthobiologics in Tumor Surgery Worth the Risks? "

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Geller and colleagues report that adjuvant chemotherapy affected the adequacy of osteosarcoma local surgical control. Exogenous bone morphogenetic protein-2 (BMP-2) did not increase local recurrence, but the limited theoretical benefits of BMP-2 for a subset of patients with osteosarcoma may not justify the systemic and long-term risks. Clin Cancer Res, 21(13): 2889–91. ©2015 AACR.

See related article by Geller et al., p. 3003

In this issue of Clinical Cancer Research, Geller and colleagues (1) report that in a xenograft model of osteosarcoma, systemic chemotherapy affects the adequacy of surgical margins. They demonstrate that, with adjuvant chemotherapy, smaller margins are necessary to avoid local recurrence. Multiagent chemotherapy was superior to single-agent therapy vis-à-vis protection from local recurrence. Finally, they report that the application of exogenous bone morphogenetic protein-2 (BMP-2) did not increase the local recurrence rate, and suggest that BMP-2 may be utilized to diminish structural bone allograft nonunion in osteosarcoma surgery.

This article addresses two controversial areas of musculoskeletal oncology: the concept of adequate margins and the use of growth factors in the setting of malignancy.

Osteosarcoma is the most common primary malignancy of bone. An essential component of osteosarcoma treatment is surgery with negative margins. The modern concept of margins in musculoskeletal oncology was popularized by the late Dr. William F. Enneking (2), who described margins as intraleisional (dissection passes through the tumor and is grossly contaminated), marginal (dissection passes through the tumor pseudocapsule and may contain malignant cells), wide (dissection passes through a plane of normal tissue beyond the pseudocapsule), and radical (the entire anatomical compartment involved by the tumor is removed; refs. 2, 3). Herein lies our first controversy: While it is accepted that osteosarcoma must be resected with at least wide margins, "how wide is wide enough" is a persistent question among musculoskeletal oncologists.

Surgeons carefully tread the line between performing oncologically adequate surgery and inflicting unnecessary collateral damage during tumor resection. Geller and colleagues’ contribution to this debate is their finding that the treatment of experimental animals with systemic chemotherapy (doxorubicin and/or cisplatin) subsequent to tumor removal resulted in decreased volumes of tissue removal that were required to avoid local recurrence. In other words, adjuvant chemotherapy effectively extended the surgical margin such that local recurrence was only observed with margins smaller than in animals who did not receive chemotherapy. This protection was additive: animals who received multiagent chemotherapy required even less of a margin to avoid local recurrence. The important translational implications of these data suggest that while adjuvant chemotherapy cannot provide unlimited protection against local recurrence, it certainly assists the surgeon in this regard. Perhaps all "close" or "microscopically positive" osteosarcoma margins are not created equally, and must be evaluated through the lens of a patient's chemotherapy regimen and his or her histologic response. The data endorse experimentally what Gherlinzoni and colleagues (4) observed clinically: Good histologic response to chemotherapy leads to more effective local control.

The next area of controversy involves the use of exogenous growth factors in musculoskeletal oncology.

After the musculoskeletal oncologist resects a bone tumor, he or she must replace it with a device that fills the void of the resected bone and imparts stability and function to the skeleton. These goals are typically achieved through one of two broad strategies: structural bone allografts or megaprostheses. Structural allografts are large segments of cadaveric bone that are typically freeze-dried, irradiated, or both to reduce their antigenicity and the possibility of disease transmission while approximating the mechanical properties of living bone. Megaprostheses are modular "off the shelf" systems that allow the surgeon to create artificial replacements for bone and joint defects of virtually any size and location. The relative advantages and disadvantages of these strategies are beyond the scope of this discussion, but the enthusiasm for structural allograft has declined as megaprostheses have become more popular. Geller and colleagues focus on a complication unique to allografts known as nonunion (1).

Bone allograft provides a scaffold that theoretically encourages the ingrowth of the host bone with which it is brought into contact. It is hoped that the patient's native bone cells will populate the allograft, which manifests as bridging of the bony
anastomosis between host and allograft bones. Nonunion occurs when this process does not take place: the host never unites with the allograft. Nonunion can occur in more than 25% of patients with osteosarcoma (5). Geller and colleagues suggest that enhancing the union rate of structural allografts would be beneficial to patients with osteosarcoma, and the addition of BMP-2 might offer a solution to this problem. In their recent work, they added various concentrations of BMP-2 to the surgical bed at the time of amputation in their mouse model of osteosarcoma. They did not report an increase in local recurrence in the BMP-2-treated animals.

BMP-2 is a member of the transforming growth factor β (TGFβ) superfamily of cytokines. It is a powerful growth factor with multiple cellular targets and effects (6). Recombinant human BMP-2 (rhBMP-2) is a commercially available product (INIFUSE; Medtronic) and has been approved for the treatment of tibia fracture nonunion, anterior lumbar interbody fusion spine surgery, and limited maxillofacial procedures. There is a strict "Black Box" contraindication to the use of this product in patients with cancer. Even in approved settings, its use remains highly controversial. Two systematic reviews recently reported on the safety and efficacy of rhBMP-2 in orthopedic surgery (7, 8). The Spine Journal review (7) reported that, "This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications." The other review from the Annals of Internal Medicine (8) concluded that, "At 24 months, the cancer risk was increased with rhBMP-2 (risk ratio, 3.45 [95% CI, 1.98 to 6.00]), but event rates were low and cancer was heterogeneous." To muddy these waters even more, there is a paucity of evidence to suggest that BMP-2 treatment is beneficial to structural allograft incorporation.

The role of BMP-2 in osteosarcoma biology is also controversial. Many authors report that the expression of BMPs and their receptors correlate with tumor progression and metastasis (9). BMP-2 has been reported to increase osteosarcoma cell proliferation, migration, and invasion (10). Conversely, some authors suggest that BMP-2 increases osteosarcoma cell differentiation (11) and is therapeutic rather than harmful.

Like all provocative science, the work by Geller and colleagues leaves us with more questions to ponder. Virtually all osteosarcoma deaths are due to pulmonary metastases, but Geller and colleagues neither used osteosarcoma cell lines with known metastatic rates, nor did they report any observations beyond 8 weeks. What are the long-term systemic consequences of BMP-2 treatment vis-à-vis metastatic potential? Intellectually, is it simply a "bridge too far" to place a supraphysiologic concentration of a potentially harmful growth factor where a sarcoma was just removed? Is BMP-2 even helpful to structural allograft union, or does its use pose unacceptable risks for unknown benefit in a limited subset of patients with osteosarcoma (Fig. 1)? Unless the efficacy of BMP-2 is clearly demonstrated and poses no harm, this discussion may indeed be "much ado about nothing."

The controversies regarding the use of BMP-2 in orthopedic surgery and its functional role (friend or foe?) in osteosarcoma make these challenging questions to answer. However, as Geller and colleagues correctly suggest, they must be answered unequivocally before BMP-2 can be used in children and adults with osteosarcoma. Even then, it would be irresponsible to use BMP-2 without full disclosure of the aforementioned controversies to patients and their families.

Speaking of full disclosure, I am an osteosarcoma surgeon/scientist and have published that BMP-2 drives the metastatic potential of osteosarcoma cells. I am also an osteosarcoma survivor and have ironically experienced both structural allograft nonunion and pulmonary metastatic disease. Allograft nonunion necessitated the amputation of my right leg, but did not claim my life. Pulmonary metastases, on the other hand, very nearly did. As treating oncologists, we must not lose sight of which complications are difficult, and which are deadly.
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