Implant-related carcinogenesis has been a concern for orthopaedic surgeons for many years. Extensive work has been done with metals and metal alloys commonly used in orthopaedics, but no convincing evidence of a causal relationship has been found. Although isolated case reports of carcinogenesis have been reported, most surgeons feel confident using modern metallic and plastic implants.

Recently, bone morphogenetic proteins (BMPs)—potent biomolecules that have been shown to aid bone repair—have been produced using recombinant technology. BMP-2 and BMP-7 have been approved by the U.S. Food and Drug Administration (FDA) for very specific indications. In granting approval, the FDA requested the manufacturers to include contraindications, including a history of cancer. The question arises, what evidence exists that these recombinant proteins may cause or promote cancer?

The literature has only a few references pertaining to carcinogenicity of clinically available BMPs, even though these cytokines and their receptors are routinely found in tumors. Because each commercially available product has unique properties, each must be considered separately. In addition, because orthopaedic problems requiring grafting occur in all ages and at various anatomic sites, discussion of additional effects will be presented.

**rhBMP-2: Bone grafts**

rhBMP-2 (Infuse® Bone Graft, Medtronic, Minneapolis) has been approved by the FDA and indicated for treatment of acute, open tibial shaft fractures that have been stabilized with intramedullary nail fixation after appropriate wound management, according to the product insert. This product must be applied within 14 days after the initial fracture and should be used only in patients who are skeletally mature. The product insert also specifies that it has been approved for spinal fusions using the LP-CAGE lumbar fusion device.

rhBMP-2 has been shown to inhibit tumorous cell lines from prostate, ovarian, and breast cancer. Unpublished data from the manufacturer would indicate an inhibitory effect on human sarcomas, prostate, breast, and lung carcinoma. Despite any direct evidence of carcinogenesis, the manufacturers, in their product insert, have supplied contraindications regarding tumor situations (Table 1).

**rhBMP-7: Autograft alternative**

rhBMP-7 (OP-1, Stryker Biotech, Hopkinton, Mass.) “is authorized by Federal law as a humanitarian device for use as an autograft alternative for recalcitrant long bone nonunions where autograft is unfeasible and other treatments have failed,” according to the package insert. rhBMP-7 has shown increased carcinogenicity in a rat study. Pleomorphic sarcomas were found around heterotopic bone nodules in some of the animals; a dose-response phenomenon was observed. These tumors may have resulted from the presence of foreign materials implanted subsequently in these rats rather than as a direct tumorogenetic effect.

Cancer developed in five of 370 humans who received OP-1; four were nonosseous cancers in elderly patients, and the fifth was a recurrence of chondrosarcoma. No published, nonmanufacturer-related information pertaining to the carcinogenicity involved with the use of this material exists. The product insert, as dictated by the FDA, contains warnings and precautions that are common to those listed in Table 1 for rhBMP-2.

Even though little evidence exists that either of these powerful materials is carcinogenic, the product inserts list specific warnings and contraindications regarding their use in tumorous areas, skeletally immature patients, and women who are pregnant or may become pregnant. The use of these products in those instances is essentially “off-label.” Materials used in an off-label situation must be considered quite carefully in light of increased government oversight and the current legal atmosphere.

**Current investigations**

The effect of exogenous BMP-2 on cancer cells is a focus of investigation. Conflicting data exist about its proliferative effect on cancer cells. Although BMP-2 and BMP-2 receptors in humans are expressed in both normal and malignant cells, a BMP-induced proliferative effect on cancer cells in vitro is not supported by the preponderance of evidence to date. In fact, in several studies, an antiproliferative effect on primary human cancer cell isolates and human cancer cell lines has been observed.

Recently, Golden et al responded electronically to a letter to the editor (Journal of Bone and Joint Surgery, Jan. 22, 2008) regarding the clinical safety of rhBMP-2. The questions asked concerned the following areas:

- Any report of the development of primary and secondary tumors in patients treated with rhBMP
- The surveillance of patients for the development of tumors
- The need for comparative studies of tumor prevalence of rhBMP-2 in treated and untreated patients
- The authors responded that surveillance of the estimated 500,000 patients worldwide to whom rhBMP-2 has been administered to date has yielded no reported osseous malignancies related to its clinical use and that ongoing monitoring is being done.

They further commented on an analysis of the frequency of malignancies diagnosed in rhBMP-2-treated patients in clinical studies compared to the general population stratified for gender, age, and race using a standardized incidence ratio and SEER (Surveillance, Epidemiology and End Results) cancer registry data. No increased frequency of malignancies has been observed to date in the treated population as compared to the general population.

Because the data on safety remain incomplete, guidance on the use of BMPs in cancer patients remains incomplete. With limited FDA-approved indications for rhBMP-2 and rhBMP-7 and the current label guidance supporting the contraindication of their use in cancer patients, orthopaedic surgeons must exercise caution.

The potential advantages of these recombinant proteins with respect to reducing reconstruction-related morbidity must be considered and weighed carefully in the risk-benefit equation. The absence of clinical data to support a claim of an increased risk should stimulate continued dialogue and investigation to answer the question of the appropriateness of any recommendation to apply rhBMP-2 and rhBMP-7 clinically in these patients.

References to the studies cited in this article may be found in the online version, available at www.aaosnow.org.

Disclosure information on the authors may be accessed online at www.aaos.org/disclosure

**Table 1 Contraindications for use of rhBMP-2 (Infuse®) and rhBMP-7 (OP-1)**

<table>
<thead>
<tr>
<th>Contraindication</th>
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<tbody>
<tr>
<td><strong>Pregnant women or women who are about to become pregnant</strong></td>
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<tr>
<td><strong>Skeletally immature patients</strong></td>
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<tr>
<td><strong>A site of a resected tumor</strong></td>
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<tr>
<td><strong>Patients with a history of malignancy (OP-1)</strong></td>
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<tr>
<td><strong>Patients with an active malignancy or patients undergoing treatment for malignancy (Infuse®)</strong></td>
</tr>
<tr>
<td><strong>Warnings: Women of childbearing potential should be advised to take measures to prevent pregnancy for 1 year following treatment with OP-1 or rhBMP-2.</strong></td>
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