Updates in the Treatment of Bone Cancer

Presented by J. Sybil Biermann, MD

Abstract
Although extremely rare, primary bone cancers are often curable with proper treatment. Effective management of primary bone tumors hinges on the involvement of a multidisciplinary team of physicians with expertise in this area, both in the realms of diagnosis and treatment. In her presentation at the NCCN 18th Annual Conference, Dr. J. Sybil Biermann reviewed the changes to the 2013 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for bone cancer, featuring the introduction of new sections on giant cell tumor of bone (GCTB) and chordoma. The benefits of denosumab for the benign GCTB and the unique challenges associated with the malignant chordoma are also explored. (JNCCN 2013;11:681–683)

New treatment pathways for giant cell tumor of bone (GCTB) and chordoma make their debut in the updated version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for bone cancer, joining those for osteosarcoma, nonmetastatic Ewing’s sarcoma, and chondrosarcoma. Guidelines for managing these bone cancers are especially important, given the rarity of these neoplasms and most clinicians’ lack of familiarity with them, said J. Sybil Biermann, MD, Professor and Medical Director of the Sarcoma Program at the University of Michigan Comprehensive Cancer Center in Ann Arbor, and Chair of the NCCN Guidelines Panel on Bone Cancer. Although metastatic osteosarcoma was also newly added to the guidelines, it was not included in Dr. Biermann’s presentation, as it generally follows the previous recommendations for osteosarcoma.

Giant Cell Tumor of Bone: Sparing Joints with Denosumab
Although considered a benign disease, “GCTB has a 2% incidence of metastasis, and that together with the significant local morbidity is why it deserves special treatment,” noted Dr. Biermann. “In the past, this aggressive, destructive lesion has largely been the domain of the orthopedic surgeon.” Intralesional excision with the use of a high-speed burr is preferred in this relatively younger age group over more extensive surgery requiring skeletal reconstruction (Figure 1). The challenge with surgery is to remove as much tumor as possible while leaving the joint intact, she added. However, although surgery has been “the tried and true for GCTB,” it has been linked to a relatively high tumor recurrence rate.

“Historically, surgeons scraped out the entire lesion and filled it with bone graft or cement,” reviewed Dr. Biermann. The use of adjuvant treatments after surgery, whether thermal or chemical, has markedly improved the local tumor recurrence rate. In the past, the local tumor recurrence rate had approached 50%, she noted. With the use of adjuvant treatments such as polymethyl-methacrylate, an overall recurrence rate of 22% has been reported.

When these bone tumors do recur, however, they are highly problematic, admitted Dr. Biermann. “It often involves replacing and restoring the joint in an otherwise young person with a reconstruction that will not be durable for the life of the individual. If we can perform the surgery with minimal morbidity and spare
The joints, we think that is the best option," stated Dr. Biermann.

With this in mind, studies have shown that denosumab may be an emerging treatment for GCTB. Significant activity with denosumab has been seen in patients with unresectable or recurrent GCTB, with one phase II study reporting a tumor response rate of 86%. "Denosumab is one of the things that has changed my craft as a musculoskeletal oncologist the most in the past 2 to 5 years," she declared.

In the NCCN Guidelines discussing GCTB, workup begins with a history, physical examination, cross-sectional imaging of the primary site, chest imaging, and biopsy to confirm the diagnosis. Bone scan is considered optional.

Regarding treatment, the algorithm splits depending on whether the disease is localized or metastatic. For localized disease, the choice of surgery is next. If the tumor is resectable, excision is the primary treatment. If the tumor is resectable with unacceptable morbidity or unresectable, the options include serial embolization (primarily for tumors of the pelvis, added Dr. Biermann), denosumab, interferon, pegylated interferon, and/or radiotherapy. "Unacceptable morbidity is a floating term," acknowledged Dr. Biermann, "but most of us would consider the removal of a joint in a young person unacceptable morbidity if we had an alternative." Although radiotherapy is effective, it is typically a last resort, she added.

For metastatic disease, the feasibility of surgery guides the decision-making. If the tumor is resectable, the primary treatment pathway for localized disease should be followed and excision of metastatic sites considered. If the tumor is unresectable, treatment options include denosumab, interferon, pegylated interferon, radiotherapy, or observation.

To illustrate the changing treatment paradigm for GCTB, Dr. Biermann shared a case study of a patient with pelvic GCTB. In the past, extensive surgery with joint reconstruction would have been indicated. "Joint reconstruction is not functional for a young patient or of significant longevity," she noted. Instead, this patient received 1 year of denosumab, with relief of pain reported within 3 months. As a result, the patient had enough restoration of the skeletal architecture to undergo a joint-conserving procedure. "In some patients, denosumab allows us not to operate at all," remarked Dr. Biermann.

The NCCN Guidelines also contain recommendations for surveillance, which Dr. Biermann noted were largely based on Panel consensus due to the paucity of data. Recommendations include physical examination, imaging of the surgical site as clinically indicated, and chest imaging every 6 months for 2 years and then annually thereafter. For a resectable local tumor recurrence, chest imaging and denosumab may be considered before surgery.

**Chordoma: Getting It Right the First Time**

“There are more misunderstandings about chordoma than any other bone malignancy,” said Dr. Biermann. “As with many pelvic malignancies, there can be a delay of up to 11 months or so in diagnosis, as this disease rarely shows up on plain films until very late.”

“The majority of chordomas have an initial surgical misadventure, which leads to considerable downstream morbidity,” she revealed. The challenge with chordoma is that if it is inadequately diagnosed and treated with a transrectal biopsy, disease can spread. “There is a lower likelihood of cure with subsequent surgeries, so the best chance we have for curing chordoma is the first operation,” she explained. This clinical scenario underscores the need for any patient with suspected chordoma to be referred to a multidisciplinary team for treatment, which is clearly stated in the NCCN Guidelines.

The NCCN Guidelines for the workup of chordoma include a history, physical examination, adequate imaging of the primary site, and screening MRI of the spinal axis. “Sagittal MRI is the best way to visualize chordoma,” according to Dr. Biermann. PET scan can be considered, and bone scan is an option if the PET scan is negative.
Biopsy can confirm the histologic subtype. The pathway for histologic subtype centers on conventional or chondroid versus dedifferentiated. If the tumor presents in the sacrococcygeal and mobile spine (about two-thirds of cases) and is resectable, wide resection with or without radiotherapy is recommended. (The benefits of surgery for chordoma can be found in supporting data.) “Chordomas will recur almost invariably if not completely extirpated,” cautioned Dr. Biermann. If the tumor is not resectable, radiotherapy is indicated. “We would consider adjuvant radiotherapy for positive surgical margins or for large extracompartmental tumors,” she added. For resectable chordomas that present in the skull base or clivus, intracranial excision with or without radiotherapy is suggested. (A follow-up MRI may assess the adequacy of resection.) For nonresectable chordomas in this location, radiotherapy is an option.

Surveillance guidelines for chordoma include physical examination, imaging of the surgical site as clinically indicated, chest imaging every 6 months for 5 years and then annually thereafter, and cross-sectional abdominal imaging annually. “Chordoma is associated with very late local recurrence and late metastases,” warned Dr. Biermann.

The Multidisciplinary Team for Bone Cancer

The importance of the multidisciplinary team in the management of primary bone cancers is noted in the NCCN Guidelines, both for diagnosis and for treatment. Primary bone tumors and selected metastatic tumors should be evaluated and treated by a multidisciplinary team with expertise in these tumors. The team, which should meet regularly, consists of a core group of professionals: a musculoskeletal oncologist, bone pathologist, medical or pediatric oncologist, radiation oncologist, and musculoskeletal radiologist. In certain cases, other specialists may be needed, such as a thoracic surgeon, plastic surgeon, interventional radiologist, physiatrist, vascular or general surgeon, or neurosurgeon.

The NCCN Guidelines for bone cancer also include general principles of management, focusing primarily on the topics of biopsy and surgery. Biopsy diagnosis is necessary before any surgical procedure. The placement of the biopsy is critical, and optimally it should be performed at a center that will do definitive management. “The problem with bone sarcomas is they are mesenchymally derived tissues,” explained Dr. Biermann. “So unlike carcinomas, they seed the tissues on the way out, and everywhere you have biopsied has to be taken out.” Furthermore, “how a biopsy is performed will have tremendous ramifications down the line for the treating physicians and surgeons,” noted Dr. Biermann. According to a recent study, 18% of those with bone sarcomas needed additional surgery because of a poorly placed or performed biopsy or suboptimal initial surgical intervention.

During surgery, wide excision should achieve histologically negative surgical margins. Limb-sparing resection for local tumor control is preferred to optimize function if reasonable function is possible. In addition, the NCCN Guidelines include recommendations on laboratory studies, fertility issues, and long-term follow-up.

References