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E06-03 Management of Bone Metastasis, Mon, Sept 3, 16:00 – 17:30

Management of bone metastasis - role of bisphosphonates

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Bisphosphonates are used in patients with metastatic bone disease to prevent skeletal-related events (SREs) such as bone pain, fractures and spinal cord or nerve compression and hypercalcemia of malignancy. (1) Bisphosphonates are synthetic analogs of pyrophosphate. The four bisphosphonates used are Clodronate, Pamidronate, Zoledronic acid and Ibandronate. (2) The latter drug is the newest and it is used outside of the U.S. since it has not been approved yet by the U.S. Food and Drug Administration.

Bisphosphonates work mainly by inhibiting normal and pathologic osteoclast-mediated bone resorption thereby preventing bone loss. They do this by accumulating in sites of active bone formation making the sites more resistant to dissolution by osteoclasts.

In lung cancer patients who die from their disease, 30%-40% will be diagnosed with bone metastases. The majority of these patients will have symptomatic bone involvement.

In the U.S., Zoledronic acid, 4 mg infused for 15 minutes every 3-4 weeks is used to treat lung cancer patients with metastatic bone disease. In a randomized phase III double-blind, placebo controlled trial, in patients with non-small cell lung cancer (NSCLC) and other solid tumors, in a 21-month follow-up of the patients, the patients receiving Zoledronic acid, 4 mg experienced less SRE's (38%) compared to the patients receiving the placebo (47%). (3) Median times to first SRE were 230 days and 163 days respectively.

Bisphosphonates are generally well tolerated. The most common side effects include flu-like symptoms (e.g. fever, myalgia, arthralgia) occurring in 10%-20% of patients which usually occurs 12 to 48 hours after the infusion and lasting 6 to 24 hours. Other side effects include bone pain, weakness, anemia, nausea, dyspnea and peripheral edema. These are usually mild to moderate. Ocular effects include uveitis which is rare. Oral bisphosphonates are generally associated with gastrointestinal intolerance, esophagitis and diarrhea.

Two more serious complications include renal dysfunction and osteonecrosis of the jaw (ONJ). Since all bisphosphonates undergo renal clearance, their administration may result in elevated serum creatinine

levels. Therapy should be withheld with increase in serum creatinine levels > 0.5 mg/dL above upper limits of normal. ONJ is a rare disorder characterized by temporary or permanent loss of blood supply to the jaw resulting in the development of necrotic bone in the mandible or maxilla. Symptoms include pain, swelling or infection of gums, loosening of teeth and poor healing of the gums. To minimize the risk of ONJ, patients must maintain excellent oral hygiene, limit alcohol and tobacco use, obtain dental assessments prior to starting bisphosphonates and avoid dental procedures while being treated with bisphosphonates. Bisphosphonates should be discontinued for 3 months prior to undergoing a dental procedure.

Future development of the use of bisphosphonates include (1) trials investigating whether high-dose bisphosphonates can reduce metastatic bone pain, (2) studies of adjuvant therapy with bisphosphonates in order to prevent bone metastases and (3) Use of bisphosphonates to prevent cancer-therapy induced bone loss.

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E06-04 Management of Bone Metastasis, Mon, Sept 3, 16:00 – 17:30

Surgical treatment of bone metastases

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Approximately 30-40% of all lung cancer patients will develop bone metastases during the course of their disease and the care for these patients has drawn increased attention during the last decade. In orthopedic practice there is increased demand for reconstructive surgery for pathological fracture and for paraplegia due to spinal cord compression. By applying surgical techniques developed in joint arthroplasty, trauma surgery, degenerative spinal disease and limb sparing surgery, the orthopedic surgeon is well armed for restoring function to cancer patients with skeletal complications.

Survival

Bone metastases often dramatically affect quality of life by causing pain, pathologic fracture, hypercalcemia, anemia and paraparesis. These complications often occur during the last months of life; however, some patients will live for years. It would be of clinical importance if this subgroup of patients could be identified since the reconstructive procedure for a patient who will survive 2 months should not necessarily be the same as for one who will live 2 years. We have recently performed a study of a consecutive series of 100 lung cancer patients treated surgically for metastatic lesions from 1986 through 2006. Sixty-eight patients were surgically treated for a long bone fracture and thirty-two patients due to paraparesis. We found that only 19% of the patients were living one year after surgery and 7% after two years. The median survival was 319 days for patients with adenocarcinoma, 253 days for patients with SCLC and 244 days for squamous cell carcinoma. One of three patients had skeletal metastasis as the first sign of