Complications Associated With Treatment of Malignancies: A Focus on Avascular Necrosis of the Bone

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Corticosteroids, the second most common cause of avascular necrosis, are a primary treatment for nearly all hematologic malignancies and are used in essentially all solid tumor patients to prevent or treat toxicities (eg, nausea and vomiting).

Cancer patients have a better prognosis now than in the past. An estimated 66% of patients diagnosed with cancer between 1996 and 2004 were alive at 5 years.1 As patients are living longer after treatment, long-term complications associated with treatment are becoming a greater issue. Avascular necrosis, also referred to as osteonecrosis, ischemic necrosis, subchondral avascular necrosis, aseptic necrosis of bone, and osteochondritis dissecans, is one such complication.2

Avascular necrosis is a disorder involving breakdown of the bone and has been reported as a complication associated with a number of different disease states and drug therapies. Joint replacement surgery may be required in cases of severe bone destruction, and avascular necrosis has been reported to be the cause for >10% of joint replacement procedures in the United States.2

Chemotherapy agents and other medications used in the treatment of malignancy have been associated with the development of avascular necrosis, including corticosteroids, bisphosphonates, asparaginase, and others (Sidebar). It is important to be aware of these potential drug causes of avascular necrosis, as early recognition and management of the disease process, including early cessation of causative therapy, is necessary to improve patient outcomes, reduce morbidity, and improve quality of life.2

**Pathophysiology of Avascular Necrosis**

Avascular necrosis is a pathological process involving death of bone and bone marrow cells secondary to compromise of the bone vasculature and blood flow. With interrupted blood flow, osteocytes and fat cells die, leading to marrow edema and changes in bone structure.3 This leads to infarction and death of bone, causing the collapse of the architectural structure of the bone and mechanical failure.2 Avascular necrosis most commonly occurs in weight-bearing joints such as the hips, knees, humeral head, and jaw.3,4 Although the exact mechanism for development of avascular necrosis is unknown, several mechanisms have been proposed, including vascular occlusion, altered lipid metabolism and fat emboli, intravascular coagulation, healing processes, and primary cell death.2

Symptoms associated with avascular necrosis include pain at the injury site, swelling, and limited range of motion. Pain may start as mild but can progress rapidly to severe pain in situations involving avascular necrosis secondary to trauma. Range of motion is generally not an issue initially, but as the disease progresses, it can lead to functional limitations.

**Etiology of Avascular Necrosis**

A number of causes of avascular necrosis, including local trauma, hematologic disorders, metabolic abnormalities, chronic renal failure, pancreatitis, and infectious processes...
necrosis are at an increased risk of developing avascular necrosis compared to patients without preexisting risk. Cancer patients commonly fit into this multiple avascular necrosis risk factor category with associations documented in acute myeloid leukemia, acute lymphoblastic leukemia, lymphomas, testicular cancer, ovarian cancer, breast cancer, and multiple myeloma.5

**INCIDENCE OF AVASCULAR NECROSIS IN CANCER PATIENTS DURING AND AFTER THERAPY**

The incidence of avascular necrosis in cancer patients is not well studied, particularly when investigating specific agents. One of the main factors limiting the research is the retrospective nature of most studies, which presumably misses patients with no or mild symptoms. Despite the limited data, the prevalence of avascular necrosis with corticosteroids has been reported anywhere between 3% and 52%.6 Avascular necrosis has been reported to occur in 1% to 10% of patients receiving chemotherapy or radiation therapy. The incidence in pediatric patients treated for high-risk acute lymphoblastic leukemia has been reported to be similar; however, disease risk category appears to influence the risk of avascular necrosis.7 Although the incidence data are variable, it appears clear that given the hundreds of thousands of cancer patients treated each year, this treatment complication is relatively common.

**MEDICATIONS USED IN THE TREATMENT OF CANCER ASSOCIATED WITH AVASCULAR NECROSIS**

Corticosteroids

Steroids are the second most common cause of avascular necrosis next to trauma and are commonly used in the treatment of acute lymphoblastic leukemia, lymphomas, testicular cancer, and ovarian cancer, and as an adjunctive therapy following hematopoietic stem cell transplant.2 The mechanism of action associated with corticosteroids and development of avascular necrosis is unclear, but several effects could describe the pathogenesis.

Corticosteroids can increase osteoblast apoptosis, leading to a decrease in bone formation and bone density. Increased osteoclast apoptosis in metaphyseal cortical bone has also been demonstrated, which leads to a decrease in bone turnover.2 It is postulated that the accumulation of apoptotic osteocytes may contribute to osteonecrosis.2 Corticosteroids have also been shown to increase coagulation protein concentrations.5 The attribution to each of these pathways is unknown, but collectively the increased risk with corticosteroids is well documented.

The onset of steroid-associated symptomatic avascular necrosis varies. Retrospective studies report that the onset of avascular necrosis symptoms typically occurs >6 months after steroid administration and has been reported to occur >3 years after steroid administration.3 Prospective studies have demonstrated a shorter interval between steroid administration and development of avascular necrosis.3 Prospective studies that involve regular screening reveal that imaging changes of the bone typically occur before the onset of pain, which can explain why avascular necrosis is identified earlier in prospective studies.3

The length of treatment with steroids is also an important factor to consider, as it appears the risk of avascular necrosis with steroids is cumulative, and risk decreases after cessation of steroid treatment.2 It is more common for patients receiving long-term courses of steroids to develop avascular necrosis, although there are reports of avascular necrosis in patients who received a short treatment course. A review showed an increase in risk of avascular necrosis with increasing total daily doses of steroids, with a 4.6% increase in risk of avascular necrosis for every 10 mg/day increase in prednisone.8 This review also demonstrated an increased risk with oral steroids compared to parenteral steroids.5 Long-acting steroids may also increase the risk of avascular necrosis as opposed to shorter acting steroids. Non-systemic steroid treatments including intra-articular steroid injections and steroid enemas have been reported to cause avascular necrosis, although this is less common.2

**Asparaginase in Combination With Corticosteroids**

Patients with acute lymphoblastic leukemia common-
Patients with cancer are living longer, and the early identification and proper management of complications is important to improve outcomes and quality of life.

The cause of avascular necrosis is likely multifactorial in patients receiving chemotherapy, and the true incidence of this complication remains unknown.

Chemotherapy and medications used as an adjunct to chemotherapy have been associated with the development of avascular necrosis, with the most significant cause being the use of high-dose corticosteroids.

If possible, the causative agent should be discontinued.

Treatment options for avascular necrosis include surgical or pharmacological treatments, with palliation as the primary goal of management.

A retrospective review of adult patients with acute lymphoblastic leukemia reported avascular necrosis in 32% of patients who received intensification therapy, which included dexamethasone and asparaginase.11 The authors speculated that the high doses of corticosteroids could have led to increased rates of avascular necrosis, which may have been further exacerbated by the use of asparaginase.

Bisphosphonates

Bisphosphonates are a class of medications commonly used as an adjunct therapy in patients with certain solid malignancies and multiple myeloma. Bisphosphonates primarily work by inhibition of osteoclastic bone resorption. It has also been shown that bisphosphonates have anti-angiogenic potential and cause a decrease in vascular endothelial growth factor. The anti-angiogenesis effects may be an additional contributing mechanism to the development of avascular necrosis. Clinical pediatric studies evaluating dexamethasone and asparaginase have reported avascular necrosis rates >6%.5

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