Osteonecrosis in Pediatric, Adolescent, and Young Adult Acute Lymphoblastic Leukemia (ALL)  
Meeting Summary

**Background and Goals**

On January 25-26, 2010, the National Cancer Institute (NCI) and Children’s Oncology Group (COG) sponsored a workshop to focus on the development of osteonecrosis in pediatric, adolescent, and young adult acute lymphoblastic leukemia (ALL) patients attended by over 40 participants. The perspective is that researchers are attempting to cure childhood ALL and are currently making great strides, however, the scope of patients developing a high degree of osteonecrosis during the course of treatment needs to be explored. Strategies for risk reduction will be investigated and therapies may need to be modified to have an immediate impact on reducing the risk of toxicity; however, it must be examined if the cure for ALL is being jeopardized by modifying key therapeutic agents that are also key toxic agents.

**Overview of Osteonecrosis and ALL**

In 2008, SEER data was published that examined the overall patient survival outcome from 1960-2004 for ALL patients from 14 years of age and younger. The current survival rate stands at 88%, but success has been directly proportional with increased intensity in therapy.

The Berlin Childhood ALL Therapy Study (precursor to BFM), performed from 1970-1976, used reinforced reinduction, an aggressive two stage induction (now referred to as reduction consolidation) as a treatment strategy of 28 days of prednisone (with l-asparaginase) was administered with vincristine and daunorubicin, followed by consolidated therapy. The observed overall efficacy was superior. In 1982, another German group reported on osteonecrosis: *Aseptic Osteonecrosis in Children Treated for ALL and Aplastic Anemia*. 4 of the 5 patients observed were treated by the BFM therapy from the reinforced reinduction study; this was the first hint that a problem may lie in the toxicity of treatment.

The current forms of successful therapy in the treatment of ALL present components that are risk factors for developing osteonecrosis; toxic components are glucocorticoid, asparaginase, and methotrexate. Other risk factors include patient aspects which include age, puberty, gender, marrow, and genetic polymorphisms, such as bone metabolism, hypercoagulation, corticoid sensitivity, drug metabolism and clearance. These patient risk factors support research that indicates the adolescent age group has the highest predilection for osteonecrosis among young patients.

Osteonecrosis is the death of a segment of bone. It presents itself as either asymptomatic, which affects the trabecular bone, or symptomatic, that affects the cortical bone, in ALL patients. The
signs and symptoms for osteonecrosis include joint swelling with/without pain, a limited range of motion, antalgic gait, and joint collapse/arthritus. Multifocal osteonecrosis, in which the disease affects three or more anatomic sites, is commonly developed in young ALL patients. Common sites are the hips, knees, and ankles with affected regions being the epiphyseal, metaphyseal, and/or diaphyseal.

**Bone and Bone Cell Physiology**

One of the therapeutic agents used to treat ALL is glucocorticoids. However, results show that glucocorticoid administration and aging reduce bone interstitial fluid and solute transport. However, the reduction can be prevented by blocking glucocorticoid action on osteoblasts and osteocytes. If osteoblasts and osteocytes are not protected from endogenous glucocorticoids, they will experience apoptosis.

Collapse of the femoral head, also known as aseptic, avascular, or ischemic necrosis, was first observed in 1957 and is an accompaniment of long-term glucocorticoid therapy. It is now developed in 10-25% of patients receiving long-term therapy. The risk increases with dose and duration of therapy, but even short-term exposure to glucocorticoid excess can lead to osteonecrosis. Osteonecrosis has been attributed to vascular interruption, venous occlusion, thrombosis and emboli with air or fat, and microvascular tamponade of the blood vessels by marrow fat or fluid retention and slowly mending fatigue fractures.

However, research indicates that cell swelling and inflammation typical of necrosis did not occur with glucocorticoids; therefore, glucocorticoid-induced osteonecrosis may actually be osteocytes apoptosis, a cumulative and unreparable defect that would uniquely disrupt that mechanosensory role of the osteocytes-canalicular network, and thus promote collapse of the femoral head. Glucocorticoid-induced osteocytes apoptosis would also explain the correlation between total steroid dose and the incidence of osteonecrosis and its occurrence after glucocorticoid administration has ceased.

**Risk Factors**

There are a variety of risk factors for the development of osteonecrosis in the treatment of ALL. These factors include increased body mass, Caucasian race, age, steroid dose, mutations in the PAI-1 gene, and L-asparaginase procoagulant effects. Through research, a hypothesis has been formed which states that familial thrombophilias, hypofibrinolysis, and possibly reduced production of nitric oxide through the eNOS (endothelial nitric oxide synthase) gene mutation interact with the high dose, long term corticosteroid L-asparaginase therapy of ALL to produce osteonecrosis.

In the future with additional research, pharmacogenetics could help identify risk factors that may elucidate biology. Dosing regimens could be modified if genetic risk factors reveal drug-target associations that can be ameliorated without decreasing efficacy.
Animal Models

Animal models would allow the incidence of ALL to be observed and studied, as well as the models of human disease, such as pathogenesis, diagnosis, and treatment. One of the current goals is to define the treatment and host-related risk factors for osteonecrosis in children with ALL, so that less toxic regimens can be designed, without compromising efficacy. For animal models to prove to be efficient, the researcher must ask the correct questions to determine what models would be best to use: what is the question, what approach is the best (i.e. which animal and which outcome), how does it relate to the human disease, and the age, gender, physiology, and lifespan must be taken into consideration.

Animal models do present some limitations in studying osteonecrosis that should be taken into account. Humans are bipedal and the easiest animals to test upon, mice, are quadripedal, the difference in thickness of the articular cartilage, animals metabolize corticosteroids differently, etc.

The efficacy of continuous dexamethasone versus discontinuous dexamethasone has been studied in mice for the treatment of leukemia. No significant difference was found in cure rates, however, there were trends for lower leukemic burden at the time of sacrifice with continuous dexamethasone, indicating that there is a need for more definitive studies with an adequate sample size and for more than one ALL model to be tested.

Osteonecrosis in the Non-Leukemic Setting

The pathophysiology of osteonecrosis is poorly understood; to gain a better understanding of this disease, the natural history and etiologies were studied. Also, observing osteonecrosis in other disease settings, such as solid tumors, HIV, Crohn’s disease, and juvenile idiopathic arthritis, it may be easier to determine causes and develop treatment strategies by taking into account what is already in practice.

Through observation of a large population with osteonecrosis, it was observed that the onset of the disease is frequently within one year after a (BMT) transplant. Spontaneous regression only occurs in small infarcts; osteonecrosis does not grow or spread locally or among other bony sites. Making diagnosis more difficult, it can be an asymptomatic disease that can last many years at this stage. Pain may or may not precede a subchondral fracture of the hip. Diabetes is a strong negative predictor for osteonecrosis and its relationship between statins has not yet been confirmed.

Cancer chemotherapy-related osteonecrosis (CCON) is an uncommon complication of cytotoxic chemotherapy in adults with solid tumors. The femoral heads are usually affected, often bilaterally, and diagnosis is typically delayed. Corticosteroids are causally implicated, but patient factors and chemotherapy type probably contribute to the risk. It is possible that CCON will become more prevalent as chemotherapy indications expand and survival of adult solid tumor patients improves. Reduced use of corticosteroids may reduce the risk of osteonecrosis and early detection of the disease may allow for joint preservation to occur.
HIV-infected patients have an unexpectedly high occurrence of osteonecrosis. The asymptomatic disease has a prevalence of 4.4%, or 0.65 cases/100 patients per year over 3 to 4 years; the symptomatic disease has 0.26 cases/100 patients per year. Risk factors include corticosteroids, testosterone, and the presence of lipid or coagulation abnormalities. Short courses of corticosteroids appear to increase the risk of developing osteonecrosis. Follow-up studies are needed to further understand the natural history of osteonecrosis in the HIV population, evaluate risk factors, and to assess interventions to delay progression of the disease.

Bone density and structure were studied in several chronic childhood diseases: steroid-sensitive nephrotic syndrome, Crohn’s disease, juvenile idiopathic arthritis, and late effects in bone marrow transplantation. While observing the effects of treatment, it was found that glucocorticoids cause a decrease in trabecular BMD and an increase in cortical BMD. Inflammation causes a decrease in trabecular BMD, periosteal circumference, and muscles; an increase occurs in endosteal circumference. Anti-TNF-α therapy (tumor necrosis factor-alpha) causes an increase in trabecular BMD, growth, and muscle; a decrease in cortical BMD and endosteal circumference was observed.

**Diagnosis**

There are various imaging techniques available to detect osteonecrosis and bone abnormalities, each with its own advantages and disadvantages; those most widely used as radiographs (XR), ultrasound (US), computed tomography (CT), magnetic resonance imaging (MR), nuclear medicine imaging, and others categorized as “on the horizon”. “On the horizon” techniques include different MR approaches and fusion imaging, including MR-PET and MR-SPECT.

When using imaging to diagnose, the location of the lesion is important; epiphyseal lesions, especially those involving the articular surface, usually lead to collapse. The size of the lesion is also important; lesions involving >30% of the femoral head lead were found to lead to collapse while small lesions (<15% of the femoral head) rarely lead to collapse. In addition, surgical intervention is associated with the greater number of joints affected.

Future problems to identify and develop solutions include designing effective risk-adapted interventions to minimize development of, ameliorate, and optimize treatment of osteonecrosis without compromising care. It will be difficult to manage osteonecrosis that affects both the upper and lower extremities; also, the presence of bone mineral deficits, which is common in ALL survivors, will provide a challenge to manage.

**Treatment**

For the best treatment options to be provided, osteonecrosis must be diagnosed as soon as possible; also, the lesion needs to be staged early. Currently, a joint preserving strategy is needed in young age. In the older age, the current model of treatment includes implants in the following sequence: surface – short stem – long stem.

Deformity is common with this disease and more effective treatments need to be developed to prevent deformities from occurring. Once it is determined why the femoral head deforms, then
specific treatments can be developed to target the pathologic processes that contribute to the
development of the deformity. Current treatments do not specifically address the pathologic
processes. Specifically targeting the pathologic processes, such as bone resorption and
formation, appear promising in preventing this.

A possible risk reduction therapy could be the administration of a lipid-lowering agent; it has
been theorized that administering this agent during times of corticoid exposure will ameliorate
the development extent and severity of osteonecrosis through the reduction of marrow fat
expansion and lipid emboli.

Cellular therapies should also be explored as a strategy to minimize the invasiveness of surgical
interventions, to introduce healing potential exogenously, and to potentiate local healing process.
For this to be successful, the pathophysiology of osteonecrosis must be understood in the distinct
clinical conditions for “targeted” cellular therapy. A source of adult stem cells must be
established, as well as an animal model that can allow researches to determine adequate
osteonecrosis staging and read-outs for cellular therapy.

**Next Steps**

A manuscript based on the workshop will be developed in order to compile the data presented
and make others in the research community aware of issues related to osteonecrosis in the
pediatric, young, and adolescent ALL population. The meeting participants were charged to
promote awareness and research of issues related to osteonecrosis and ALL within their
institutions and among their colleagues.