

General

A Current Review in the Orthopedic Management of Osteonecrosis of the knee Secondary to Treatment of Pediatric Hematologic Malignancy

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Acute Lymphoblastic Leukemia is the most prevalent pediatric hematologic malignancy. The treatment for this illness has advanced significantly, now touting a 90% cure rate. Although these patients often become disease free, treatment can leave devastating effects that last long after their disease burden is alleviated. A commonly experienced result of treatment is osteonecrosis (ON), often occurring in weight bearing joints. Uncertainty exists in the optimal treatment of this cohort of patients. In this review, we describe the etiology and suspected pathogenesis of ON, as well as treatment options described in the literature.

INTRODUCTION

Hematologic cancer are the most prevalent cancers afflicting the pediatric population with, acute lymphoblastic leukemia (ALL) being most common.^{1,2} Every year there are approximately 4,000 new diagnoses of ALL in the United States with about two thirds of those arising in the pediatric and adolescent population.^{2,3} Over the last 60 years, the advent and optimization of various chemotherapies has brought with it the ability to cure a once fatal set of diseases.^{2,3} Current literature cites a cure rate of over 90% for ALL.^{1,4,5} Although this is undeniably optimistic, treatment brings with it the potential of debilitating side effects. The most common of which is osteonecrosis (ON), with a reported incidence as high as 72%.^{1,6,7}

Osteonecrosis, or avascular necrosis, is a process of cell death and subsequent bone resorption that leads to structural compromise and often gross deformity.⁸ ON often presents in subchondral bone associated with weight bearing joints such as the hip or knee.⁶ The pathophysiology is thought to be due to disruption in the microcirculation.⁸ It is most commonly seen in adults between 20-50 years old, affecting between 10,000-20,000 patients annually.^{1,9} There is also a predilection for ON in pediatric patients treated for hematologic malignancies, particularly those between 11 and 13 years old.^{10,11}

Ongoing investigation into causes, predispositions, and treatments for ON is tenuous despite its devastating consequences. Currently, both medical and surgical management strategies are employed, with most literature focusing on treatment of only the hip. Here, we give a brief review of the characteristics of osteonecrosis and look at the efficacy of core decompression as a treatment modality concerning ON of the knee secondary to ALL.

PATHOGENESIS

The etiology of this condition is still somewhat speculative and multifactorial, but there are several proposed hypotheses that offer sound insight into potential causes. Glucocorticoids, a staple in the treatment of ALL, are a dose and length of exposure dependent risk factor in the development of ON.

^{1,4-} The mechanism may result from fat emboli causing embolic micro-occlusions in the vessels supplying the bone.⁸ Other theories posit a hypercoagulable state that manifests from the interaction of asparaginase and exogenous corticosteroids, a down-regulation of VEGF receptors leading to localized hypoperfusion and ischemia, glucocorticoid-induced suppression of osteoblasts with apoptosis of osteocytes, or lipocyte proliferation and hypertrophy within the medullary canal.^{12,13} All current theories are putative explanations for a reduction in blood flow secondary to increased intraosseous pressure accounting for ischemia.^{11,14}

In regard to other offending agents, methotrexate is believed to contribute to this process through the depletion of folate, a necessary component in the metabolism of homocysteine. The ensuing homocysteinemia imparts a state of hypercoagulability from endovascular damage, concomitantly increasing the risk for ON by venous vascular occlusion.¹⁰

Glucocorticoids and methotrexate are oncologic therapeutics, partially explaining the increased risk that cancer patients have in developing ON. As far as explanations for why adolescents are more likely to be affected, the rapid maturation of the skeleton or increased intraosseous pressure secondary to closure of the physis are proposed plausible explanations that increase likelihood of developing ON.

EPIDEMIOLOGY

Osteonecrosis is generally a disease of middle age and elderly patients. However, adolescents receiving treatment for hematologic malignancy have the highest risk for ON.^{10,15} Additionally, adolescents with ON are more likely to be symptomatic and more likely to experience bony collapse, with one study demonstrating a 40% likelihood of collapse in adolescents while younger patients demonstrated only a 4% likelihood of collapse.¹¹ Reasons for the higher risk of development and increased symptom severity in this population are not understood. One speculative explanation is susceptibility of the adolescent joint to osteochondral shear fracture.

DETECTION AND IMAGING

As previously stated, patients undergoing treatment for hematologic malignancies including chronic glucocorticoids and methotrexate are at increased risk for developing ON, as are children treated with stem cell transplants.¹ Early imaging in this group has become more common, as early intervention can alter the disease course. The best modalities for imaging appear to be MRI, which has the highest sensitivity in detecting early changes of bone marrow edema and inflammation. CT is another viable imaging modality because of its sensitivity in identifying sub-chondral collapse.^{1,16,17}

OSTEONECROSIS OF THE KNEE

In a 2010 publication investigating ON of the knee, Sharma et al reported that this was the most common sites of involvement of ON in children receiving bone marrow transplant.¹⁸ Both the distal femur and the proximal tibia were involved. It is unclear if this holds true in patients with ON resulting from cancer therapy.

TREATMENT STRATEGIES FOR ON IN ALL

Because exact causes are enigmatic and literature sparse, there is neither an agreed-upon guideline nor consensus on best practices in the treatment of ALL patients. Management is therefore location and provider dependent. Because it is now becoming more routine to image asymptomatic patients who are being treated for ALL with MRI, more information and treatment strategies are emerging on potential regimens for early intervention.

Kawedia et al demonstrated osteoedema (ASCO stage 1) to be a common finding with 25% progressing to later stages.⁷ Tools for addressing this finding include having the patient remain non-weight bearing and serial monitoring with MRI, although no evidence has shown this to be effective in ON from ALL.⁶ Medical management includes vitamin D and calcium supplementation, anti-inflammatories, prostacyclin analogs, statin therapy, bisphosphonates, and anticoagulation, specifically with low-molecular weight heparin (LMWH). Although literature exists discussing the

various roles that these might play in ON of varying etiologies, there is no literature that current medical therapies affect the progression of ON in ALL.⁶

BISPHOSPHONATES

Antiresorptive therapies such as bisphosphonates have been implicated in the prevention and treatment of ON.¹⁹⁻²⁶ Bisphosphonates have both anti-inflammatory and anti-resorptive properties that inhibit osteoclast activity and prevent osteocyte and osteoblast apoptosis.¹⁹ Corrado et al reported a case of an elderly woman with osteonecrosis of the knee treated with intramuscular neredronate (25mg/monthly) and daily calcitriol (0.50 µg) and aspirin (100mg). At 2 months, the patient's pain and functional impairment had resolved, and at 4 months MRI revealed significant improvement in previous necrotic areas.²³ Kraenzlin et al. reported a prospective observational study of 28 adult patients who developed osteonecrosis of the knee (22 post arthroscopic surgery; 6 SONK) and were subsequently treated with IV pamidronate (120mg over 2 weeks) and oral alendronate (70 mg weekly for 4-6 months). Twenty-six of the 28 patients demonstrated improved VAS scores after treatment and 2 patients required arthroplasty. This study did not assess functional outcomes, but an improved quality of life and improved mobility was subjectively reported by the patients.²⁴ Jureus et al compared bisphosphonate treatment to no treatment for SONK in 17 adult patients. These patients had radiographic indications of knee osteonecrosis and were treated with oral alendronate (70 mg/weekly for a minimum of 6 months). Ten of 17 patients did not develop osteoarthritis, 4 patients developed mild osteoarthritis, and 3 patients experienced joint surface collapse.²⁵ In 2013, Breer et al reported a case series of 5 adult patients with early stage osteonecrosis of the knee (Koshino Stage I) that were treated with high dose vitamin D (20,000 IU weekly for 4 months) and low dose ibandronate (3 mg i.v. every 8 weeks for 16 weeks). All 5 patients reported significantly lower VAS scores and had no evidence of osteonecrosis on MRI at follow up.²⁶ In a double blind, placebo-controlled study, Meier et al did not show clinical or pain relief benefits when comparing ibandronate and anti-inflammatory medications in patients with spontaneous osteonecrosis of the knee. This study followed 30 patients with only 20 completing the study (9-treatment and 11-placebo) and there were no significant differences in pain relief (VAS score) or functionality measured using WOMAC score and IKDC questionnaire.²⁷ A case report described two cases for which short-term alendronate was introduced 6 months after diagnosis of ON of the hip. These two patients were both diagnosed with ON secondary to corticosteroid use and both reported absence of pain and fully functioning joint mobility at 6.5 and 7 year follow up.²² Padhye et al. showed that IV administration of zoledronic acid at 3 month intervals after the development of ON reduced pain in all 20 patients, and 5 out of 8 patients with predominant knee involvement remained radiologically stable (ARCO II or III).²¹ However, 8 out of 9 patients with predominant hip joint involvement progressed

to ARCO stage III/IV despite treatment. In a study focusing solely on zoledronic acid treatment for ON secondary to treatment of ALL, this same group reported that all 6 patients with hip involvement progressed to ARCO stage III or IV and 3 of those patients underwent joint replacement surgery. Of the 6 patients with predominant knee involvement, three had minimal or no joint destruction and 3 have radiologic evidence of joint deformity.²⁸ Leblcq et. al. reported that IV pamidronate for treatment of ON secondary to chemotherapy reduced pain in 10 of 14 patients and radiologic improvements, based on MRI evaluation, in 5 patients with mild ON and 1 patient with severe ON.¹⁹ Kotecha et al. reported 9 patients who underwent bisphosphonate therapy for ON secondary to ALL treatment.²⁰ All 9 patients demonstrated an improvement of functional range of motion, and only 1 patient required continued analgesics for pain control after bisphosphonate therapy. Radiological evaluation using the ellipsoid method did not demonstrate a benefit of bisphosphonate therapy. Due to the limitations of these studies including small sample sizes, study design, limited control patients and variable treatment times it is difficult to conclude the role of bisphosphonates in preventing or slowing the progression of ON secondary to ALL, however, this therapy may provide clinically relevant pain relief.¹⁹⁻²²

PROSTACYCLIN ANALOGUES

Other non-surgical management strategies have been developed targeting prostacyclin analogues contingent on the theory that ON is caused by localized ischemia from insufficient supply through the marrow.²⁹ Iloprost, a prostacyclin analogue, has been shown to have antiplatelet, antiproliferative and vasodilatory properties, capable of blood flow restoration to the ischemic area.^{30,31} Jager et. al. followed 95 patients through a clinical trial for an average of 33 months and found reduction in pain from an average of 5 to 2 on visual analogue scores (VAS). Additionally, improvement in mobility as measured by Harris hip score from 52 to 79 was reported.³⁰ Claben et al treated 108 patients with osteonecrosis in varying joints (hip, ankle, knee) and varying etiologies (steroid-induced, idiopathic, traumatic) with iloprost. This cohort consisted of patients of varying ages (11-92 years) and varying stages of osteonecrosis (ARCO I-IV). 75% of patients reported improvements in subjective pain scores and symptoms. 16% of the patients underwent subsequent joint replacement with a majority (59%) of those being from ARCO III or ARCO IV stages prior to treatment. Of those patients with ARCO stage I (69% of patients) only 4% required joint replacement surgery after treatment.³² Similar to bisphosphonates, the data suggest that prostacyclin analogues have a role in improving clinical outcomes in earlier stages of ON and bone marrow edema, but have no appreciable effect on advanced staged of ON.³⁰

OSTEOCHONDRAL ALLOGRAFT TRANSPLANTATION

Osteochondral allograft transplantation (OATs) involves the transplantation of fresh mature hyaline cartilage allograft or. Common harvesting sites include lateral femoral condyle, tibiotalar joint, patella, and humeral head.³³ The graft contains viable chondrocytes with an intact matrix in order to provide a functional unit to replace diseased tissue.³⁴⁻³⁶ Gortz et al reported retrospective data on 28 knees in 22 patients who underwent osteochondral allografts for steroid induced osteonecrosis. They reported an 89% survivorship of the implants, and postoperative improvements of the D'Aubigne and Postel score, International Knee Documentation Committee pain and function score, and the Knee Society function scores.³⁷ Murphy et al reported a case series of osteochondral allograft transplants in the adolescent population. Of the 39 patients in the study, 7 had a primary diagnosis of avascular necrosis of the knee. All patients in this study reported being "extremely satisfied" or "satisfied" postoperatively and only one of the 7 patients underwent subsequent revision allograft surgery.³⁵ Early et al reported retrospective data on 33 knees in 25 patients under the age of 50, who underwent osteochondral allograft transplantation of femoral condyles for osteonecrosis (modified Ficat/Arlet stage III/IV) secondary to steroid-use. This study showed a survivorship rate of 82% at 10 years and improved postoperative clinical outcomes measured by Merle-d'Aubigne-Postel scores.³⁶

HYPERBARIC TREATMENT AND OTHER MODALITIES

Hyperbaric oxygen has been experimented with in this population but has proven to be equally fruitless according to the literature. There are instances in the literature of hyperbaric treatment in osteonecrosis of the knee in adults as well as spontaneous osteonecrosis of the knee in a 24 year old male that have shown some promise in both subjective relief and MRI signal intensity reduction but nothing purporting similar findings in chemotherapy induced osteonecrosis of the knee in the pediatric population.^{55,56} Additionally, other modalities such as statins, LMWH, Vitamin D/Calcium supplementation and anti-inflammatories have been reported to be attempted but none have been presented as compelling and replicable treatment strategies. Many of these therapies are aimed at addressing the putative mechanisms of ON previously discussed, such as micro thromboembolisms or lipoembolisms, reduction in oxygenation of the bone, and loss of osteocytes.

CORE DECOMPRESSION

Surgical core decompression (CD) has been shown to be an efficacious intervention in ALL induced ON. The technique for core decompression involves drilling one or more holes into the necrotic bone, thereby decompressing the intraosseous pressure caused by the edema as well as poten-

tially encouraging healing by catalyzing angiogenesis and increasing nutrient delivery to the area. The success of this is dependent on several factors such as size and location of the defect.^{6,38-40} This treatment strategy has shown greater efficacy when paired with administration of mesenchymal stem cell therapy (MSC) as reported by Muller et al and corroborated by several studies.⁴⁰⁻⁴⁵ These cells are able to combat the deficiencies in the microenvironment and encourage the restoration of an orthotopic environment. The majority of studies conducted have shown benefit to combination CD with MSC over CD alone.⁴⁰⁻⁴⁵ The caveat is the majority of investigation has been in ON of the femoral head, very little had been done looking at it in the knee. Muller et al has shown safety and efficacy in CD with MSC in treating ON of both the distal femur and the proximal tibia.⁴⁶ Should all other treatments fail, arthroplasty remains the only option.

CONCLUSION

Pediatric patients with hematologic malignancies are at high risk for developing osteonecrosis in weight bearing joints and treatment of these malignancies increases this risk. This condition can be debilitating for a young patient and there is a relative sparsity of literature on the management of these patients. The majority of literature discusses management of ON in the femoral head, but there is little discussing management of ON in the knee which develops in a majority of patients. Additionally, Karimova

et al found that 22% of patients with symptomatic ON of the knee experienced joint collapse in a study investigating long term follow up of ON about the knee.¹¹ A review of the literature shows the most promise using core decompression with mesenchymal stem cells to treat ON in this population. More investigation into treatment of this disease process as well as mitigation strategies to prevent its development is needed.

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Caleb Gottlich: Concept development, Data collection, Manuscript drafting

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DISCLOSURE

There are no disclosures to present from any of the authors.

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