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Review

Osteonecrosis in children and adolescents with cancer – An adverse effect of systemic therapy

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ARTICLE INFO

Article history:
Received 27 June 2006
Received in revised form
11 October 2006
Accepted 1 November 2006
Available online 13 December 2006

Keywords:
Adolescent
Child
Neoplasms
Osteonecrosis

ABSTRACT

Osteonecrosis (ON) is recognised increasingly as a complication of the treatment of cancer in children and adolescents. It is especially prevalent among survivors of acute lymphoblastic leukaemia and non-Hodgkin lymphoma, in whom as many as 1/3 may be affected, likely reflecting the cumulative exposure to glucocorticosteroid therapy. The pathogenesis is complex and includes suppression of bone formation, expansion of the intra-medullary lipocyte compartment and a direct effect on nutrient arteries. Children $\geqslant$10 years of age are at particular risk and the disorder is substantially more common in Whites than in Blacks. Genetic predispositions have been identified. ON is often multi-articular and bilateral, affecting weight-bearing joints predominantly. Surgical management options are of concern in young growing subjects, although injection of autologous marrow into affected sites offers promising results. Other novel approaches include the use of anti-resorptive drugs and strategies for prevention, such as with lipid-lowering agents, are being explored.

1. Introduction

Aseptic osteonecrosis, also known as avascular necrosis of bone or simply osteonecrosis (ON), is a disorder characterised by segmental death of one or more osseous sites. Several categorisations/classification schemes have been described,[1–7] based on radiological features (Table 1). The most sensitive and specific non-invasive assessment is provided by magnetic resonance imaging (MRI)[8] which has been used by investigators at St. Jude Children's Research Hospital (SJCRH) to devise a reliable system for diagnosis and to grade the severity of ON affecting the knee in children with leukaemia and lymphoma[9,10] (Figs. 1A and 1B).

With the exception of its occurrence in children with Legg-Calve-Perthes disease, non-traumatic ON is an uncommon finding in young people[11,12] (Table 2). However, the true incidence and prevalence of the disorder are unknown, for reasons described below. Nevertheless it has been reported increasingly in children and adolescents treated for acute lymphoblastic leukaemia (ALL), as better chemotherapeutic regimens are developed and survival rates continue to improve. In fact, although clinically manifest (symptomatic) ON was first described in such children at diagnosis almost 25 years ago,[13] and was reported as a complication of treatment as long ago as 1977,[14] a wider appreciation of the relationship between ALL and ON has resulted only from the

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[d] Dr. Sala received an American Cancer Society/ UICC International Fellowship for Beginning Investigators.
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doi:10.1016/j.ejca.2006.11.002

Table 1 – Categorisation systems for osteonecrosis – based on radiological features

First author	Joint	Technique
Marcus[1]	Hip	Plain radiograph
Koshino[2]	Knee	Plain radiograph
Ficat[3]	Hip	Plain radiograph
Ohzono[4]	Hip	Plain radiograph
ARCO[5a]	Hip	Plain radiograph/MRI[b]
Shimizu[6]	Hip	MRI
Steinberg[7]	Hip	MRI
Karimova[9,10]	Knee	MRI

a ARCO, Association Research Circulation Osseous.
b MRI, magnetic resonance imaging.

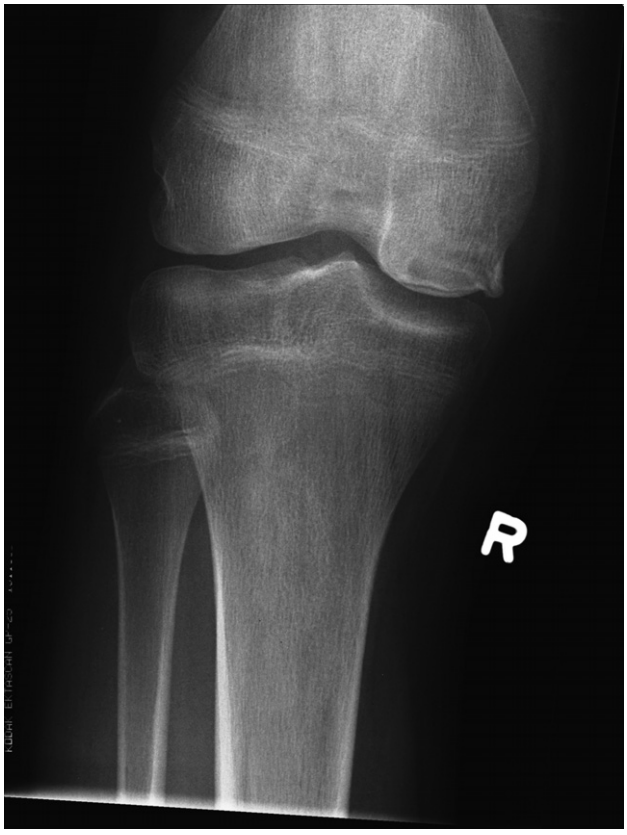

Fig. 1A – Plain radiograph of the knee in a male teenager at the completion of therapy for non-Hodgkin lymphoma. There are subchondral linear lucencies in the distal femur consistent with osteonecrosis.

published results of large co-operative group clinical trials in the past 5 years. The association of ON with ALL and non-Hodgkin lymphoma (NHL) in particular[15] has highlighted the important aetiological role of glucocorticosteroids (GCS), but asparaginase,[16] high-dose methotrexate[17] and cyclophosphamide[18] may contribute additional bony injury.

The association between steroid use and the development of ON has been known for 50 years.[19] It may be a 'price' of bipedal locomotion as the disorder occurs very seldom in quadrupedic animals.[19] Although ON has been reported in association with systemic lupus erythematosus, rheumatoid

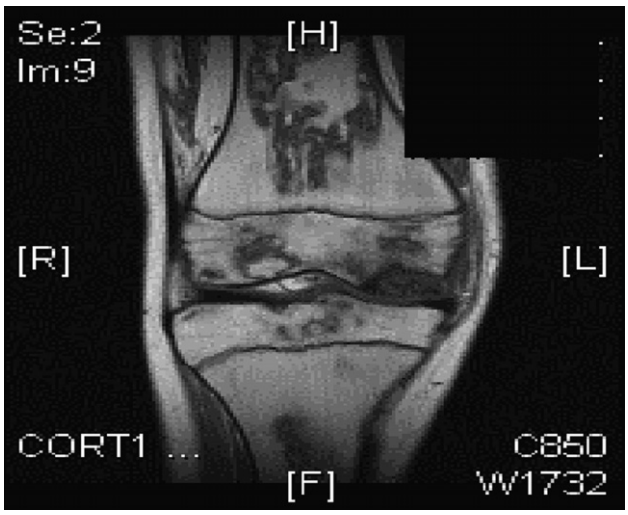

Fig. 1B – Coronal T1-weighted spin echo magnetic resonance image of the same knee. The distal femur and proximal tibia exhibit several areas of serpiginous low signal demarcation consistent with infarction of bone.

Table 2 – Conditions associated with osteonecrosis in children and adolescents

Legg-Calve-Perthes disease
Congenital dysplasia of the hip
Slipped capital femoral epiphysis
Gaucher disease
Sickle cell haemoglobinopathies, especially SC disease
Haemophilia
Renal failure with osteodystrophy
Disorders treated with prolonged use and/or high doses of glucocorticosteroids

arthritis, inflammatory bowel disease and solid organ transplantation in children and adolescents – in all of which circumstances patients may receive GCS – it is in the context of cancer in this age group that ON has been recognised more often, especially in relation to haematopoietic stem cell transplantation.[20]

2. Pathogenesis

The pathogenesis of ON appears to be complex[21] and has been reviewed comprehensively.[22] It includes suppression of osteoblasts, apoptosis of osteocytes, intra-medullary lipocyte proliferation and hypertrophy (compromising the sinusoidal circulation), adverse effects on nutrient arteries contributing to thrombosis and fat embolism, and damage to endothelial and smooth muscle cells of the venous system promoting further vascular stasis and ischaemia. The supporting bony architecture within the volume of infarction becomes weakened by resorption of subchondral bone along the reactive interface. The continued stress and motion of weight-bearing can result in subchondral bone plate fracture with buckling of the focal articular cartilage. Ultimately the patient has progressive joint collapse and degenerative joint disease develops.

This complexity has prompted a unifying theory[23] of 'accumulative cell stress' based on three main components: anatomic location, systemic illness and often GCS exposure. In this hypothesis, GCS play a 'necessary but not sufficient' role, but the influence of GCS on fat cells is clearly important.[24] Studies *in vitro* have shed further light on the mechanisms underlying ON associated with cancer chemotherapy, notably including the enhanced GCS-induced differentiation of mesenchymal stem cells into lipocytes at the expense of osteogenesis,[25] although this has not been a uniform observation.[26]

3. Risk factors

Several risk factors for ON have been identified in the cancer context. ON is more common in adolescents than in children[27–33] and those more than 15 years of age represent the population at highest risk,[28,32] perhaps reflecting the vulnerability of rapidly growing bone for the disorder is reported rarely in adults. Of the patients who developed ON, 12/15 (80%), 107/111 (96%), 28/31 (90%) and 8/13 (61%) were $\geqslant$10 years of age in the Associazione Italiana di Ematologia Oncologia Pediatrica (AIEOP), Children's Cancer Group (CCG), Berlin-Frankfurt-Munster (BFM) and Dana Farber Cancer Institute (DFCI) studies, respectively.

The disorder occurs more frequently in Whites than in Blacks.[28,34] Whites accounted for 97/111 (87%) and 23/25 (92%) in the CCG and SJCRH studies, respectively. In the CCG study, the three year incidence rate of ON was 16.7% in Whites, 3.3% in Blacks and 6.7% in other ethnic groups. There is no clear consensus on a risk differential between males and females, even among co-operative group studies involving thousands of patients.[28–30,32] A predominance of girls was observed by the Italian consortium[30] (12/15–80%), but not in the German collaborative study[32] that used essentially the same treatment regimen. Even in those groups experiencing the highest rates of occurrence of ON, there are disparate results in this regard; the CCG[28] reported the disorder more frequently in females (60/111–54%), while the DFCI ALL Consortium[29] and studies at SJCRH[15] found no such gender difference. This lack of agreement may reflect, in part, the retrospective nature of these surveys and the low incidence of ON in the ALL population overall.

Likewise there is no obviously higher risk of the disorder with the administration of dexamethasone than prednisone, although the results of a formal comparison are awaited,[29] and ON was reported infrequently in patients with ALL prior to the institution of delayed intensification therapies containing dexamethasone. However, there does appear to be a correlation between the risk of ON and the cumulative dose of GCS received. But this is confounded by risk categorisation (for ALL treatment assignment) that includes age as a factor.

In a pharmacogenetic study, Relling and colleagues at SJCRH[34] demonstrated that the thymidylate synthase low activity 2/2 enhancer repeat genotype and the vitamin D receptor FokI start site CC genotype were independent risk factors for ON of the hip in children undergoing treatment for ALL. The former polymorphism is associated with increased sensitivity to methotrexate and hyperhomocystinemia, while the latter could lead to perturbation of GCS metabolism. A triad of risk factors for ON (the two polymorphisms combined with age >10 years) had 82% specificity and 96% sensitivity for the disorder.

A familial form of ON, inherited in an autosomal dominant fashion, has been described in Taiwan[35] involving the type II collagen gene (*COL2A1*) on chromosome 12q13. Other genetic profiles seem to carry a higher risk of sporadic ON in different patient populations. It is important to emphasise that the majority of these studies were conducted in adults. There may be a predisposition to the idiopathic ('primary') form occurring among the elderly in those with thrombophilic disorders such as the Factor V Leiden mutation, as reported from Sweden.[36] This association was not observed in a smaller Turkish study of renal allograft recipients[37] and it has not been reported in young people with cancer. Homozygosity for the 4G polymorphism of the plasminogen activator inhibitor –1 gene, leading to hypofibrinolysis, was reported to be twice as common in patients with 'primary' ON as in the general population,[38] but this difference was not seen in patients with the steroid-associated disorder. Again, homozygosity for the 677 C $\rightarrow$ T mutation in the methyl-tetrahydrofolate reductase (*MTHFR*) gene, that leads to prothrombotic hyperhomocystinemia, was identified in 26% of Greek patients with idiopathic ON compared to a prevalence of 10% in the general population,[39] but this association was not seen in the Turkish study[37] and *MTHFR* polymorphisms did not distinguish children in Germany with ALL who developed ON from those who did not.[40]

4. Clinical features

The clinical impact of ON is highly variable. In some patients the disorder is asymptomatic but in many there is pain, limping and limitation of movement. It is important to exercise a low threshold of diagnostic suspicion and undertake MRI examination of symptomatic joints. Although spontaneous resolution may occur,[28] particularly with small lesions,[41] and a proportion of asymptomatic patients appear to have stable disease, other asymptomatic patients and probably all of those with symptoms have a progressive disorder, the culmination of which is collapse of the affected joints.[41] ON is often multi-articular and commonly bilateral, especially when associated with the use of GCS.[42] The hips and knees are the joints affected most frequently, but involvement of the ankles is well-recognised.[43] Functional assessment of morbidity can be accomplished with tools such as the Harris hip score[44] which addresses the elements of pain, functional capacity, range of motion and deformity.

Most reports addressing the prevalence of ON in children and adolescents with cancer focus on ALL and suggest that the disorder occurs uncommonly. The true prevalence is almost certainly underestimated by the majority of these reports, for they are almost all retrospective analyses limited to patients with symptoms. Furthermore, incidence rates vary widely depending on the time the study was conducted and the methods used for the diagnosis of ON. Nevertheless, it does seem clear that the great majority of cases of ON occur within three years of initiation of therapy for ALL.[28–33] In a prospective survey[15] of a cohort of 116 patients with ALL and NHL, who were treated with a single regimen at SJCRH,

Ribeiro and colleagues observed that, in those who had received at least one year of chemotherapy, 15% had evidence of ON on MRI. The knee was the site involved most frequently. Numerous patients were asymptomatic and the majority appeared to have a benign disorder on short-term follow-up despite the continued administration of GCS, with only one individual requiring surgical intervention. In smaller cross-sectional[45] and serial studies[46] from Finland, one-third or more of children with ALL exhibited radiological evidence of ON. The majority were asymptomatic, some showed regression and a few even complete resolution of the disorder. However, in the experience of large co-operative groups,[28,32] 24–42% of those with symptomatic osteonecrosis in the context of ALL have undergone some form of orthopaedic surgery. In asymptomatic patients it may be reasonable to undertake MRI examination of both hips and both knees at the completion of anti-leukaemic therapy. For patients with no abnormality, a repetition of these examinations one year later could be considered.

5. Treatment options

Decisions on treatment are confounded by the variable natural history of the disorder. It appears appropriate to simply observe and monitor asymptomatic patients who have small lesions.[47] For those with more extensive disease, especially when associated with pain, some form of intervention is warranted,[47] in addition to discontinuation of physical activity, avoiding weight-bearing and the use of analgesic drugs.

Conventionally this has meant a surgical procedure ranging from core decompression,[48] based on the demonstration of intra-osseous hypertension and venous congestion in bones affected by ON,[49] to arthrodesis and joint replacement. While these are clearly efficacious in the short-term, there is valid concern[50] about coring procedures in growing subjects with open physes and arthrodeses in patients with bilateral disease, and joint replacement in young people is not an attractive option given the (albeit improving) longevity of these prostheses. The use of bone grafts, especially if vascularised,[51] is technically demanding and the long-term outcomes of such undertakings remain uncertain. Recent innovations have included the combination of core decompression with the insertion of human bone morphogenetic protein.[52]

Based on the evidence that mesenchymal cells are reduced in number and function in areas of ON,[53] and on the multipotentiality of embryonic stem cells in the adult human subject, two groups of investigators in Europe have injected autologous bone marrow into sites affected by ON.[54] In one study that included a small number of adolescents,[55] the outcome appeared to be an appreciable retardation of early disease progression and gain in Harris hip scores, with an average follow-up of 7 years, compared to the historical experience in patients not so treated. The other study was conducted in a smaller number of patients,[56] all of whom had early disease, and employed the same procedure. However, this was double-blinded although not randomised; all of the patients having core decompression and half of them assigned to receive autologous bone marrow. Although the follow-up was only 2 years, in the transplanted group the volume of the necrotic lesion diminished by more than a third and only one patient had progressive disease. Among those not transplanted more than half experienced deterioration. Similar claims for the value of this approach have been made recently from China.[57]

Therapeutic strategies that avoid all surgical interventions are also being explored. Some of these, such as external electrical stimulation/capacitance coupling[58,59] and the use of hyperbaric oxygen (of no clear benefit),[60] are non-pharmacological, but most involve the use of agents administered systemically. It was reported more than 15 years ago[61] that pain was reduced in patients with ON, but not in those with osteoarthritis, by the use of the anti-hypertensive agent nifedipine, presumptively on the basis of elevated intra-osseous pressure in the former group, but this observation has not been confirmed. Administration of low molecular weight heparin, in a single arm study to patients with early stages of ON,[62] seemed to inhibit progression in those with the 'primary' disorder but not in those with steroid-related disease; an outcome predictable on the basis of the different proportions of those affected by thrombophilia.[35]

An anti-bone resorption strategy has prompted the use of bisphosphonates[63] which, at first glance, may appear to be a double-edged sword, for these agents have been associated with ON of the jaw in adult patients with cancer[64] when administered intravenously. However, these patients had multiple myeloma or carcinoma metastatic to the skeleton, and 60% of the cases of ON were preceded by a dental surgical procedure. Moreover this serious side-effect has not been described in younger subjects. In a large single arm study of adult patients conducted in India,[65] the use of a third generation bisphosphonate – alendronate – seemed to avoid the need for early surgical intervention in most patients. A non-randomised study in Japan[66] appeared to show similar gains from the use of this drug. A randomised controlled trial performed in Taiwan[67] showed clear benefit from weekly oral alendronate therapy for ON, some of which was steroid-induced. Many of the patients in the control arm had falling Harris hip scores and progressed to hip replacement, while in the experimental arm, the Harris hip scores improved overall and only one patient underwent joint replacement. The use of alendronate offers an added advantage in children and adolescents with ALL or malignant lymphoma in whom osteopenia is a common problem[68,69] that is ameliorated by bisphosphonate therapy.[70] Some of these patients were symptomatic when alendronate was started. In rat models of Perthes disease[71] and traumatic ON of the hip[72], there is demonstrable benefit in the use of another bisphosphonate (zoledronic acid) for preserving the integrity of the femoral head.

An entirely different approach has been pursued in a rabbit model. Using an adenoviral vector, the vascular endothelial growth factor (*VEGF*) gene was used to transduce endothelial cells in the animals' saphenous arteries which were then placed into necrotic iliac crest bone *in vivo*.[73] The extent of neo-angiogenesis was significantly greater in the *VEGF* group than in the control group of animals. Given the demonstrated relevance of *VEGF* expression in human osteonecrotic lesions,[74] the experimental interventional study may have clinical applicability.

6. Prevention

Opportunities for prevention of ON in children and adolescents with cancer appear to be limited (Fig. 2). The rarity of the disorder in diseases other than ALL and NHL, reflecting the use of GCS therapy, precludes a comprehensive strategy for all young people with malignant disease. But high risk groups of patients are identifiable, such as patients over 10 years of age at diagnosis of ALL or NHL, allowing for targeted interventions.

Consideration could be given to inclusion of a statin or bisphosphonate, in prophylactic mode, for the duration of therapy for ALL and NHL, to those patients who are at appreciable risk of ON, potentially providing the further benefit of reducing other forms of bone morbidity in this group. A retrospective review[75] was undertaken of the records of 284 adult patients (34 of whom had malignant disease) who were taking statin drugs at the time they were started on 'high dose' GCS therapy – at least 20 G of prednisone-equivalent in 90 days or more. With a minimum follow-up of 5 years only three patients had developed confirmed ON; a proportion lower than was expected.

Unfortunately, the demonstrated efficacy of anticoagulation in adult patients with thrombophilia-associated ON does not provide an avenue to follow, for this phenotype does not characterise the steroid-induced disorder. Limiting the cumulative dose of GCS or giving it more intermittently in future protocols for the treatment of ALL and NHL is worth considering,[28,29] comparing the current regimens with those incorporating reduced exposure to steroids in randomised, controlled trials. This approach offers the added potential advantage of minimising other common steroid-related morbidities. However, the risks and benefits of reducing or discontinuing GCS exposure to patients on active treatment are not fully understood. This applies not only to the risks and severity of ON, but also to cancer-related event-free survival.

Several *in vitro* studies are ongoing. Using a multipotential cell line, it has been demonstrated that lovastatin enhanced osteoblast gene expression and inhibited adipocyte gene expression despite the presence of dexamethasone.[76] Steroid-treated chickens showed bone marrow adipogenesis and ON which were reduced and entirely prevented, respectively, by the co-administration of lovastatin.[19] In a canine model of cryosurgically induced ON of the femoral head, a randomised placebo-controlled study[77] revealed an increase in bone volume and trabecular thickness, as well as bone mineral density, in the perturbed femoral heads of the dogs treated with either simvastatin or alendronate, compared to those in control animals. Interestingly, in the contralateral femora of the treated dogs, these benefits were seen only in the animals which receive alendronate.

7. Closing comments

Notable gaps in current knowledge include the real frequency of clinically important (moderate, severe or progressive) ON and the efficacy of non-surgical interventions in young people with malignant disease. It will be essential to complement radiological outcome measures with good functional assessments and measures of health-related quality of life. Studies to fill these gaps will require rigorous design and a sufficiently long time frame.

Conflict of interest statement

None declared.

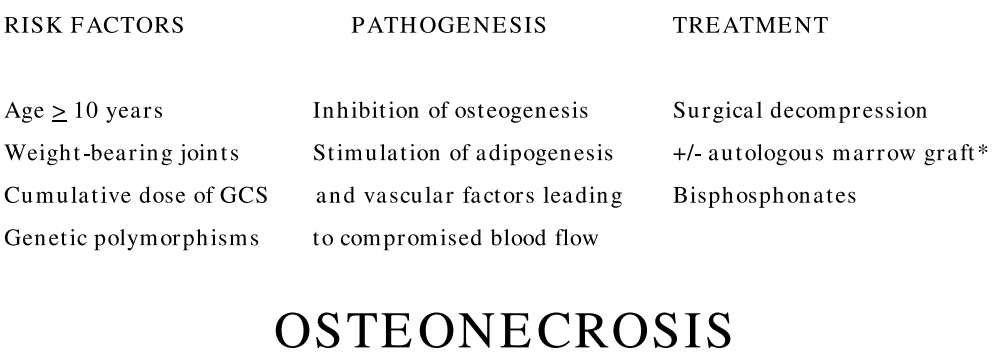

Fig. 2 – Glucocorticosteroid induced osteonecrosis.

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