REVIEW ARTICLE

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Chemotherapy-Associated Osteonecrosis in Cancer Patients with Solid Tumours

A Systematic Review

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Contents

Abstract

Non-traumatic osteonecrosis of bone is recognized as a potential complication in solid-tumour cancer patients receiving treatment with cytotoxic chemotherapy. This review summarizes recent reports of osteonecrosis associated with chemotherapy in cancer patients, and describes the possible underlying pathophysiology and options available for its diagnosis, prevention and treatment. Fifty-four reported cases of non-traumatic osteonecrosis in adult patients with solid tumours receiving chemotherapy were identified by searching for reports in the medical literature. Osteonecrosis was observed most commonly in men receiving chemotherapy for testicular cancer. Osteonecrosis was also seen in patients receiving chemotherapy for breast, ovarian, small-cell lung cancer and osteosarcoma. Most patients had received corticosteroids, had femoral head involvement and had delayed onset of osteonecrosis. It appears that patients at higher risk for oste-

onecrosis with chemotherapy are identifiable. As the long-term survival of patients with solid tumours receiving chemotherapy increases, the prevalence of treatment-related osteonecrosis may also increase. Patients should be informed that osteonecrosis is a potential complication of cancer treatment. Measures to reduce risk should be taken, and patients should be monitored for early symptoms. Routine screening for chemotherapy-associated osteonecrosis is not recommended; however, a high index of clinical suspicion in patients at risk may allow for early intervention and preservation of the joints.

Non-traumatic osteonecrosis is well recognized as a complication of corticosteroid exposure in benign diseases. Non-traumatic osteonecrosis has also been reported in patients with haematological malignancies, in patients undergoing allogeneic bone marrow transplantation, and in those receiving radiotherapy. Only recently has it been recognized as a potential complication in patients with solid tumours receiving chemotherapy.[1] Solid tumours are much more common than haematological cancers, and the use of chemotherapy is increasing as more agents are approved for use and the indications for adjuvant chemotherapy are expanding.[2] Thus the absolute number of cancer patients at risk for cancer chemotherapy-associated osteonecrosis (CCON) is increasing dramatically.

The use of bisphosphonates has recently been associated with osteonecrosis of the maxilla and mandible.[3] Although bisphosphonate use is common in cancer patients, the focus of this article will be on patients with solid tumours who have received cytotoxic chemotherapy.

This review describes case reports of CCON in the literature, then discusses hypotheses for its underlying pathophysiology, its prevalence, diagnosis and the options available for prevention and treatment.

1. Reports in the Literature

1.1 Literature Search Strategy

A previous systematic review identified 12 reports and describes 38 adult, solid-tumour patients with CCON.[1] The cases identified in this previous review are included in this current paper, and in addition we searched for reports and reviews published since the previous review using the MEDLINE (1998–January 2008) and EMBASE (1998–January 2008) electronic databases, and carried out a bibliographical review of relevant citations. The searches were unrestricted by language and used the major topic headings of 'osteonecrosis' (MEDLINE) and 'bone necrosis' (EMBASE) in combination with the term 'chemotherapy'. Paediatric patients (age <18 years), patients with histories of prior surgery or radiotherapy to the sites of osteonecrosis, haematological neoplasms, osteonecrosis affecting solely the mandible or maxilla and those using concurrent bisphosphonates were excluded. Clinical information for each case, including age, sex, cancer diagnosis, chemotherapy treatment, cumulative corticosteroid dose during chemotherapy, timing of osteonecrosis diagnosis and treatment of osteonecrosis was recorded. Corticosteroid doses were converted to, and are reported as, the oral prednisone equivalent dose.

1.2 Literature Search Findings

In addition to the cases already published,[1,4-15] 9 reports describing 14 unique patients with non-traumatic osteonecrosis after chemotherapy for solid tumours were identified.[16-24] Patient age ranged from 24 to 68 years. Ten of these newly reported patients were men with testicular cancer, three were women with ovarian cancer and one was a woman with breast cancer. In total, 54 cases of non-traumatic osteonecrosis in patients with solid tumours receiving chemotherapy were identified (table I).

Even with this relatively small number of reported cases, some clinical associations are evident. Over 70% of reported cases of CCON have involved men. Reported cases in adults have largely been restricted to four solid cancer types: testicular cancer, breast cancer, ovarian cancer and osteosarcoma. Where reported, 90% of patients received cortico-

Table I. Adult cases of osteonecrosis associated with chemotherapy for solid tumours

Publication	No. of cases	Age (y), sex	Cancer diagnosis	Chemotherapy treatment	Cumulative corticosteroid dose (g) [prednisone equivalent]	Onset	Site(s)	Treatment
Obrist et al.[4]a	1	48 F	Breast	CMF	0	Subacute	Humeral head	NR
Perloff and Lesnik[5]a	2	62 F, 47 F	Breast	CMFVP	1.2, 1.5	Delayed	R femoral head, bilateral femoral heads	TRHR, TBHR
Harper et al.[6]a	1	23 M	Testis	VeB + VAC, PVB	0	Subacute	Multiple	NSAID, PT
Marymont and Kaufmann[7]a	1	40 F	Breast	Melphalan, FAC	0	Delayed	Bilateral femoral condyles	Decompression, bone graft
Kolin and Sherry[8]a	3	48 F, 62 F, 43 F	Breast	CMFVP	1.5, 1.2, NR	Delayed	Femoral heads	TBHR, TRHR, R Jewitt nail
Meneghello et al.[9]a	2	32 M, 32 F	1 testis, 1 OS	PVB, VAC	NR, 0.1	Delayed	Bilateral femoral heads	NR
Wuisman et al.[10]a	1	18 F	OS	Adriablastin, methotrexate, ifosfamide, cisplatin	NR	Acute	Proximal L tibia	NR
Forrai et al.[11]a	19	31–52 M	Testis	PVB	Range 1.7–8.1, average 3.6	2 subacute, 17 delayed	6 one femoral head, 13 bilateral femoral heads	NR
Jones[12]a	1	53 M	Small-cell lung	EC, EP	>1.7	Subacute	Multiple	ORIF of undisplaced fracture
Gogas and Fennelly[13]a	1	61 F	Ovary	Multiple	4.3	Delayed	Bilateral femoral heads	Bilateral core decompression
Besson et al.[14]a	1	47 F	Breast	Multiple	2.7	Subacute	Multiple	Joint replacement
Cook et al.[15]a	5	29–33 M	Testis	BEP	2.9, 2.5, 3.3	Delayed	2 bilateral femoral heads, 1 R femoral head	2 patients had TBHR, 1 conservative mgmt

Continued next page

Table I. Contd

Publication	No. of cases	Age (y), sex	Cancer diagnosis	Chemotherapy treatment	Cumulative corticosteroid dose (g) [prednisone equivalent]	Onset	Site(s)	Treatment
Winquist et al.[1]a	2	20 M, 37 M	Testis	1 PVB, 1 BEP	2.8, 3.2	Delayed	Femoral heads	TBHR
Coles and Williams[17]	1	24 M	Testis	BEP	1.9	Delayed	Bilateral femoral heads	TLHR
Cook et al.[16]	2	NR	Testis	BEP	3.0, 2.5, 3.3, 1.5	Delayed	Femoral heads	NR
Dawson et al.[18]	1	68 F	Breast	CMF	1.1	Delayed	Bilateral femoral heads	TRHR
Magné et al.[19]	1	42 M	Testis	EP, ECI	2.4	Subacute	Multiple	TBHR
Virik et al.[20]	1	34 M	Testis	BEP	3.2	Delayed	Bilateral femoral heads	Conservative mgmt
Bojko et al.[21]	2	49 F, 39 F	Ovary	Multiple, including PBSCT	NR	Delayed	Femoral heads	TBHR
van den Berkmortel et al.[22]	3	28–29 M	Testis	BEP	2.2, 2.6, 1.2	Delayed	Femoral heads	TRHR, L bone grafting after removal of osteonecrotic bone; conservative mgmt; R hip decompression
Beckmann et al.[23]	1	61 F	Ovarian	Carboplatin	0	Delayed	L scaphoid	Resection scaphoid, arthrodesis
Kaila and Wolman[24]	2	25 M, 36 M	Testis	BEP	0.64, 0.64	Delayed	R femoral head, L femoral head	Both patients had surgical decompression and resurfacing

a Cases described previously in Winquist et al.[1]

BEP = bleomycin, etoposide, cisplatin; **CMF** = cyclophosphamide, methotrexate, fluorouracil; **CMFVP** = cyclophosphamide, methotrexate, fluorouracil, vincristine, prednisone; **EC** = etoposide, carboplatin; **ECI** = etoposide, carboplatin, ifosphamide; **EP** = etoposide, cisplatin; **F** = female; **FAC** = fluorouracil, doxorubicin, cyclophosphamide; **L** = left; **M** = male; **mgmt** = management; **NR** = not reported; **ORIF** = open reduction internal fixation; **OS** = osteosarcoma; **PBSCT** = peripheral blood stem cell transplant; **PT** = physiotherapy; **PVB** = cisplatin, vinblastine, bleomycin; **R** = right; **TBHR** = total bilateral hip replacement; **TLHR** = total left hip replacement; **TRHR** = total right hip replacement; **VAC** = vincristine, dactinomycin, cyclophosphamide; **VeB** = vinblastine, bleomycin.

steroids with chemotherapy, and the range of cumulative corticosteroid dose was 0–8.12 g prednisone equivalent. The median cumulative corticosteroid dose was 2.2 g, and over 85% of patients received a cumulative dose of at least 1.0 g. Nearly 95% of patients had involvement of the femoral head, often bilaterally. Finally, 90% of patients had delayed onset (more than 6 months after chemotherapy) or diagnosis of osteonecrosis. The remainder had subacute onset (within 6 months of chemotherapy), except one patient with acute osteonecrosis of the proximal tibia in association with intra-arterial chemotherapy.

Seventy percent of the adult patients were males with testicular cancer,[1,9,11,15-17,19,20,22,24] and the median age of this subset of patients was 29 years (range 20–42 years). All received treatment with combinations of cisplatin, bleomycin, vinblastine and/or etoposide. One patient did not receive corticosteroids with chemotherapy, and the median cumulative prednisone equivalent dose was 2.24 g (range 0–8.108 g). Excess alcohol consumption was identified as a potential risk factor in two patients in two reports and, interestingly, both had also received lower cumulative doses of corticosteroids (1.16 g and 1.45 g).[16,22] This association was also identified in an earlier report using case-control methodology.[11] Use of alcohol and other patient characteristics such as body mass index were not consistently reported. Where reported, the femoral heads were involved in all patients, with bilateral involvement occurring in 75% of cases. One patient developed multifocal osteonecrosis involving both femoral heads, the right humeral head and both scapulae. He had also received radiotherapy to the mediastinum and both subclavicular regions, but not the hips.

With the exception of a patient with osteosarcoma, all women with CCON had either breast cancer or ovarian cancer. The nine breast cancer patients had a median age of 47 years (range 40–68 years).[4,5,7,8,14,18] Six had received adjuvant chemotherapy, and one patient had metastatic disease. All of these patients had received cyclophosphamide, methotrexate and fluorouracil-based chemotherapy, except one patient who was treated first with melphalan and then with fluorouracil, doxorubicin and cyclophosphamide. All but two of the patients had received corticosteroids with chemotherapy (median cumulative prednisone equivalent dose 1.35 g, range 0–2.7 g). Although five breast cancer patients had femoral head involvement, other sites were also affected, including the humeral head and femoral condyles. Four women with ovarian cancer were identified.[13,21,23] The median age of the patients with ovarian cancer was 55 years at diagnosis (range 39–61 years). Except for one patient treated with carboplatin alone, all had received multiple regimens for metastatic disease. All but one were reported to have received corticosteroids with chemotherapy. Only one case report specified the total dose of corticosteroid given, a cumulative prednisone equivalent dose of 4.32 g given along with chemotherapy in the 61-year-old woman who later developed bilateral osteonecrosis of the femoral heads. Three of the ovarian cancer patients had femoral head involvement, but one patient who had received carboplatin alone (without corticosteroids) had osteonecrosis of the scaphoid bone of wrist.

Two patients with osteosarcoma and osteonecrosis were reported.[9,10] One 32-year-old patient developed bilateral femoral head osteonecrosis following chemotherapy with vincristine, doxorubicin and cyclophosphamide chemotherapy. The other patient (age 18 years) had multiple prior chemotherapy regimens and developed acute osteonecrosis of the proximal tibia following intra-arterial cisplatin therapy in the ipsilateral leg. A single patient with lung cancer (small-cell type) was identified,[12] and developed CCON after ten cycles of platinum/etoposide chemotherapy as well as intravenous dexamethasone given for the treatment of brain metastases.

2. Pathophysiology

There are many well established risk factors for the development of osteonecrosis that may occur either alone or in combination. The emphasis of this review is non-traumatic osteonecrosis. Risk factors for osteonecrosis include alcoholism, radiation exposure, chemotherapy, corticosteroid use and haematological disorders.[25] For a more extensive list, please see table II. Hypotheses regarding the aetiology of osteonecrosis in cancer patients include altered fat metabolism, intravascular coagulation, inhibition of angiogenesis and primary cell death (apoptosis).

Table II. Conditions associated with non-traumatic osteonecrosis (reproduced from Jones Jr,[25] with permission)

Category	Condition
Familial thrombophilia	APC resistance, protein C deficiency, protein S deficiency, antithrombin III deficiency, hyperhomocysteinaemia
Hyperlipaemia and embolic lipid	Alcoholism, carbon monoxide poisoning, diabetes mellitus, fat emulsion therapy, hypercortisolism, hyperlipaemia (types II and IV), C-reactive protein increased, obesity, pregnancy (fatty liver), disrupted adipocytes, dysbaric phenomena, haemaglobinopathies, pancreatitis (lipase), severe burns, unrelated fractures
Hypersensitivity reactions	Anaphylactic shock, antiphospholipid antibodies, immune complexes, immune globulin therapy, serum sickness, systemic lupus erythematous, anticardiolipin antibodies, lupus anticoagulant
Hypofibrinolysis	Dysfibrinogenaemia, plasminogen deficiency, t-PA decreased, PAI-1 increased
Infections	Bacterial endotoxic reactions (e.g. *Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli*, others), bacterial polysaccharides (e.g. intravenous drug abuse, septic abortion, toxic shock, *Staphylococcus* exotoxin), viruses (e.g. cytomegalovirus, hepatitis, human immunodeficiency, rubella, others)
Proteolytic enzymes	Pancreatitis (trypsin), snake venom
Tissue factor release	Inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis), malignancies (e.g. acute leukaemias, Hodgkin's disease, metastatic carcinoma, pancreatitic carcinoma, others), chemotherapy, neurodamage (e.g. brain injury/surgery, spinal injury/surgery), pregnancy (e.g. amniotic fluid embolism, fatty liver of pregnancy, normal pregnancy, retained fetus *in utero*, toxaemia, pre-eclampsia, eclampsia)
Other prethrombotic conditions	Acidosis, anorexia nervosa, oestrogens, cigarette smoking, decompression sickness, diabetic angiopathy, haemolytic-uraemic syndrome, haemolysis, hepatic failure, hyperfibrinogenaemia, hypertension, hypertrophic fatty marrow, hyperviscosity, hypotension (shock), immobilization, lipoprotein (a), nephrotic syndrome, patent foramen ovale, polycythaemia, postoperative states, Raynaud's phenomenon, sickle-cell crisis, storage diseases, Fabry-Anderson disease, Gaucher disease, polyvinylpyrrolidone, thrombocytosis, thrombocytopenia purpura, vasoconstriction, vascular disorders, aneurysms, arteriosclerosis, giant haemangioma, vasculitis

APC = activated protein C; **PAI-1** = plasminogen activator inhibitor 1; **t-PA** = tissue-type plasminogen activator.

2.1 Corticosteroids

The use of dexamethasone and other corticosteroid agents is common in patients with cancer, both as part of an anti-neoplastic regimen and for palliation of symptoms. However, the use of dexamethasone is associated with hyperlipidaemia and the accumulation of lipids in bone, particularly in the femoral head.[26] As bone is an inextensible compartment, expansion of the nonvascular content leads to compromise the vascular compartment and subsequent critical ischaemia.

Animal autopsy studies have examined the size of bone marrow fat cells in osteonecrosis of the femoral head. These studies have suggested that enlargement of fat compartments within the femoral head is an early event in the pathogenesis of osteonecrosis and that this expansion of fat compartments is promoted by administration of corticosteroids.[27] *In vitro* studies suggest that corticosteroids may shunt uncommitted osteoprogenitor cells in bone marrow from osteoblastic differentiation into the adipocytic pathway, eventually leading to osteonecrosis.[28,29]

2.2 Intravascular Coagulation

Intravascular coagulation is now recognized as a central event in the pathogenesis of osteonecrosis.[25] It is obvious from table II that most of the conditions associated with non-traumatic osteonecrosis are also associated with either disseminated intravascular coagulation or hypercoagulability. Cancer and its treatments are linked with hypercoagulability. The overall rate of clinical venous thromboembolism in cancer patients is approximately 15% (range 3.8–30.7%), compared with an incidence of 2.5% in the general population.[30] Several mechanisms for thrombophilia in the cancer patient have been proposed.[30] There is limited direct information regarding the incidence of thrombosis in patients with osteonecrosis, and therefore it remains unclear if those at increased risk for thrombosis are also at elevated risk for osteonecrosis.

Support for the concept of thrombophilia as a key factor in the pathogenesis of osteonecrosis can be taken from the work of Zalavras et al.[31] These investigators measured haematological indices in 68 patients with osteonecrosis and 36 healthy controls. The osteonecrosis patients had increased von Willebrand factor, protein C and protein S concentrations compared with normal controls. Wada et al.[32] randomized rats to receive either water with warfarin or plain water. In the rats treated with warfarin, the incidence of osteonecrosis was significantly lower than in the plain water group (10% vs 53%). Predictably, coagulation time was significantly longer in the warfarin group. The finding that warfarin lowers the incidence of osteonecrosis supports the hypothesis that hypercoagulability plays an important role in the pathogenesis of osteonecrosis.

2.3 Angiogenesis

The normal bone turnover process involves angiogenesis, the formation of new blood vessels. A hypothesis that the pathogenesis of osteonecrosis is at least partly based on inhibition of angiogenesis has been proposed.[33] Evidence for this hypothesis includes the angiographical studies of the femoral head in patients with osteonecrosis. *In vivo* rat studies have afforded some insight into the mechanisms by which angiogenesis contributes to the early reparative phase of osteonecrosis.[34] In one study, investigators experimentally cut off vascular supply to the femoral heads of rats and resulting osteonecrosis was observed. During the repair phase, synovial fibroblasts were found to express vascular endothelial growth factor (VEGF), an important mediator of the angiogenesis process. Similarly, work by Yang et al.[35] and Nakame et al.[36] show that angiogenic factors (VEGF and basic fibroblast growth factor) can enhance the repair of avascular necrosis of the femoral head in rabbits.

Hypoxia-inducible factor (HIF)-α is also an important component of the biological pathways that regulate angiogenesis. In a Korean study, certain genetic polymorphisms of HIF-α were found to be tightly associated with the incidence of idiopathic osteonecrosis of the femoral head in human studies.[37]

Anti-angiogenic therapy has recently been a focus of interest in cancer research. It should be noted, however, that many 'traditional' chemotherapeutic agents have anti-angiogenic properties. Such agents include alkylating agents (cyclophosphamide, melphalan), antimetabolites (methotrexate, fluorouracil), anthracyclines (doxorubicin, epirubicin, mitoxantrone), topoisomerase inhibitors (irinotecan, topotecan), taxanes (paclitaxel, docetaxel), vinca alkaloids and cisplatin.[38] These agents may inhibit angiogenesis wherever it occurs, whether it is at the site of tumour, a surgical incision or an osteonecrotic femoral head. Furthermore, although the newer, 'targeted' anti-angiogenic therapies (e.g. bevacizumab, sorafenib, sunitinib) have not yet been linked with osteonecrosis in patients, it is a theoretical concern.

2.4 Osteocyte Death

The theory has been forwarded by Wong et al.[39] that the death of osteocytes may in fact be a cause of osteonecrosis rather than a result. Pathological studies have shown that, in the 'timeline' of osteonecrosis, osteoblast death may precede other histological changes in bone tissue.[26,40] In any event, the death (by either necrosis or apoptosis) of osteoblasts is a crucial event in the pathogenesis of osteonecrosis. Calder et al.[41] studied the rate of osteoblast apoptosis in the femoral heads of patients undergoing total hip arthroplasty. Of 20 patients with osteonecrosis, 15 showed findings indicative of osteoblast apoptosis. No patients in the control group (patients with osteoarthritis) exhibited this finding. If the osteoblast death was due to ischaemia alone, the predominant histopathological finding should have been necrosis, rather than apoptosis. Gangji et al.[42] also noted abnormalities in the replicative capacity of osteoblasts taken from the femoral head of patients with osteonecrosis.

Several authors have studied the effects of cytotoxic chemotherapy on bone cells. Banfi et al.[43] found that chemotherapy in patients with non-Hodgkin's lymphoma and breast cancer was associated with dose-dependent toxicity to bone marrow stromal osteoprogenitors. An *in vitro* study by Davies et al.[44] assessed the effects of chemotherapy on primary human osteoblast-like cell numbers and apoptosis. They noted a reduction in osteoblast numbers with exposure to various chemotherapeutic

agents. Finally, rat studies have shown that fluorouracil induces apoptosis in metaphyseal bone.[45]

3. Incidence

Cook et al.[16] followed a cohort of 103 patients with testicular cancer undergoing chemotherapy to determine the prevalence of avascular necrosis. Of 103 patients, 4 had evidence of avascular necrosis identified using MRI, an overall prevalence of 3.8% (95% CI 1, 10). Winquist et al.[1] estimated the overall crude incidence of osteonecrosis in testicular cancer patients at 1.5% (95% CI 0.9, 2.1).

As a reference point, in *non-cancer* (renal transplant) patients taking high doses of corticosteroids MRI evidence of osteonecrosis of the femoral head was seen in 6–9% of patients.[46,47] It should be noted, however, that most of these patients were taking long-term, daily doses of prednisone in excess of 0.25 g. Koo et al.[48] reported that in 22 patients who had received corticosteroids and were diagnosed with non-traumatic osteonecrosis, the mean cumulative dose ranged from 1.8 to 15.5 g, with a mean of 5.9 g prednisone equivalents. Further to this, Griffith et al.[49] noted that in patients with severe acute respiratory syndrome treated with corticosteroids, a cumulative corticosteroid dose of <3 g was associated with a 0.6% risk of osteonecrosis, while a cumulative dose of >3 g resulted in a 13% risk.

Of the 54 patients we identified, most received concomitant corticosteroids at a mean cumulative dose below the level commonly associated with increased risk for osteonecrosis in non-cancer patients.[48,49] The incidence of CCON was highest in men with testicular cancer. This is somewhat unusual as many cancer patients with more common malignancies are treated with chemotherapy but with far fewer reported cases of CCON. Possible explanations for this apparent increased risk include more prolonged or higher corticosteroid exposure, specific effects of the cytotoxic agents commonly used for treatment of testicular cancer, or an age-vulnerability effect related to bone growth or metabolism. The latter may be perhaps most influential as other groups of cancer patients receive very similar drug exposures with few reports of CCON. For example, only one patient with lung cancer has been reported with osteonecrosis[12] despite use of agents very similar to those used in the treatment of testicular cancer and cumulative corticosteroid doses. As the clinical presentation of CCON is dramatic, it is unlikely that under-diagnosis is responsible, but it is possible that CCON is simply under-reported. Another final possibility relates to the historical use of chemotherapy predominantly in solid-tumour patients with metastatic disease. As CCON has a delayed onset, it is possible that patients may succumb to their cancer before developing symptoms of CCON or these symptoms may be mistaken for those of metastatic disease. Adjuvant chemotherapy for breast cancer also involves the treatment of patients potentially cured of their cancer (similar to testicular cancer), so it is interesting to note that breast cancer was the second most common cancer associated with CCON, and six of the nine reported cases had received chemotherapy in the adjuvant setting.

4. Diagnosis

As osteonecrosis usually affects the hips, early diagnosis and management is essential to avoid long-term morbidity and to improve the chances of preserving the affected joints. Typically patients are asymptomatic for weeks to years after the initial vascular insult. The pathophysiology of this is unknown, with insidious presentation resulting in delayed diagnosis being typical of the disease.

4.1 History and Physical Examination

The most common symptom patients present with is pain, usually localized to the inguinal region but may also involve the buttock or upper thigh. The pain is brought on by activity, especially weight bearing, but it can also occur at rest in up to two-thirds of patients.[50] Occasionally, osteonecrosis occurs at multiple sites, and will present with multiple joint complaints. On examination, a limp may be observed, and there is usually decreased range of motion, especially with forced internal rotation and abduction.[50]

4.2 Radiographic Investigations

Several imaging modalities are available to diagnose osteonecrosis; however, their sensitivity and specificity depend heavily on the stage of the dis-

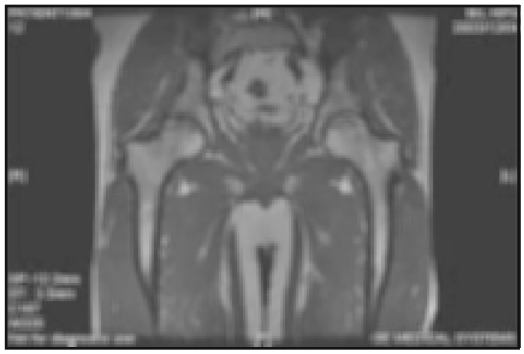

Fig. 1. T1-weighted magnetic resonance imaging (MRI) scan showing areas of peripheral serpiginous low signal with osteonecrosis affecting approximately 75% of the articular surface on the right and 50% on the left, without femoral head collapse, in a testicular cancer patient with delayed non-traumatic osteonecrosis following chemotherapy (figure 1 and figure 2 show the same patient).

ease. Cancer patients presenting with new-onset hip pain usually first undergo standard radiographic evaluation. Plain radiographs of both hips may take weeks to months to show changes consistent with osteonecrosis, which is initially manifested as areas of radiolucency and sclerosis within the femoral head.

MRI should be performed if osteonecrosis is suspected despite normal plain films. Both hips should be imaged as more than 50% of cases of non-traumatic osteonecrosis are bilateral.[50] The most common MRI finding is a line of low signal in the anterior superior portion of the femoral head on T1-weighted sequences, which is well demarcated by a serpiginous line (figure 1). On the T2-weighted images, there is also a decreased signal that is surrounded by a high signal circumscribing the necrotic area in the upper part of the femoral head (figure 2). In the early stages, this necrotic area exhibits the normal bone marrow fatty signal. In the late stages, it exhibits a low signal on both sequences. MRI has been found to be superior to computed tomography (CT) and bone scintigraphy for diagnosis of osteonecrosis.[51]

4.3 Differential Diagnosis

When a patient presents with a history of pain consistent with osteoarticular origin and imaging findings are suggestive of osteonecrosis, the differential diagnosis is limited. The other main diagnostic possibility is transient bone marrow oedema syndrome (TMES).[52-54] In both osteonecrosis and TMES, there is a pattern of bone marrow oedema: low signal intensity on T1-weighted MR images and high signal intensity on T2-weighted MR images. This is often described in the femoral head and neck. However, osteonecrosis usually shows a well demarcated area surrounded by a serpiginous line, whereas in bone marrow oedema there is a low-diffuse signal. Causes of bone marrow oedema may include bone bruise, infection, epiphyseal stress fracture and neoplasm. TMES is a rare disorder that involves hip pain along with femoral head and neck osteopenia. It is a self-limiting disorder, usually resolving both clinically and radiologically within 6–24 months, which has a unique histopathology, and is most common in pregnant women and middle-aged men who lack osteonecrosis risk factors.[52]

Bone marrow necrosis is a distinct clinicopathological entity associated with haematological malignancy, sickle cell disease, infection and some medications. It is often accompanied by pancytopenia. In bone marrow necrosis (unlike osteonecrosis), the spicular architecture of bone is preserved, while the reticular structure is destroyed. Histologically, necrosis of myeloid tissue and medullary stroma are seen. Patients often have severe back pain, fever, pancytopenia and elevated lactate dehydrogenase levels.[55]

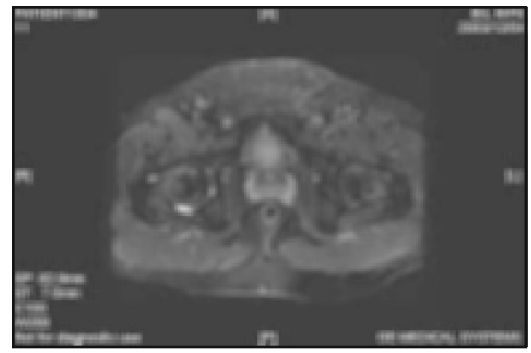

Fig. 2. T2-weighted magnetic resonance imaging scan showing areas of high signal in the femoral heads bilaterally, along with peripheral serpiginous low signal (figure 1 and figure 2 show the same patient).

4.4 Staging

At least five staging systems for osteonecrosis are in common use.[56] One of the more commonly used systems is that of the Association Internationale de Recherché sur la Circulation Osseuse (ARCO).[57] The ARCO staging system is drawn from several previous osteonecrosis staging systems, and also adds the characteristic of lesion size:

Stage 0:

- Only bone biopsy shows avascular necrosis, all other tests normal.

Stage 1:

- Plain radiographs and CT normal.
- MRI or scintigraphy positive, extent of involvement of femoral head categorized as A, B or C (<15%, 15–30% and >30%, respectively).

Stage 2:

- Radiographs show osteosclerosis, osteopenia, cystic or mottled femoral head without collapse or acetabular involvement.
- MRI or scintigraphy positive.
- Extent of involvement A, B or C.

Stage 3:

- Radiographs show crescent sign, early flattening of dome.
- May need CT or tomograms.
- Extent of involvement A, B or C with further characterization by amount of depression (<15% involvement or <2-mm depression of femoral head, 15–30% involvement or 2- to 4-mm depression of femoral head, >30% involvement or >4-mm depression of femoral head).

Stage 4:

- Radiographs show flattened articular surface, joint space narrowing, acetabular changes, osteophytosis.

5. Prevention

Minimization of exposure to known risk factors for osteonecrosis in patients at risk should reduce incidence. It is not clear whether specific chemotherapy agents may increase risk. Within the realm of solid tumours, osteonecrosis has been most commonly reported in testicular cancer patients receiving combination chemotherapy containing cisplatin, bleomycin and etoposide.[1] Attribution of risk to these drugs is confounded by concomitant exposure to corticosteroids and a cohort of patients at a vulnerable age for osteonecrosis.

The risk of osteonecrosis is increased with both exposure to corticosteroids and total cumulative corticosteroid dose. This suggests that the ubiquitous use of dexamethasone for prophylaxis of emesis may need to be reassessed in some patients. However, younger patients are at higher risk for chemotherapy-related nausea and vomiting, leaving the feasibility of omitting corticosteroids open to question. Efforts to minimize the total dose are sensible, and omission of corticosteroids may become more practical with the emergence of effective alternative noncorticosteroid antiemetics.

In order to minimize concomitant risk factors, patients should also be cautioned regarding excessive alcohol use and smoking as these behaviours may increase the risk of osteonecrosis. Fat compartment expansion is implicated in the pathogenesis of osteonecrosis,[27] and statin-type drugs may have beneficial effect.[58] Therefore, in patients with hyperlipidaemia, the use of lipid-lowering agents might be considered. Experimental evidence suggests that intravascular coagulation is a factor in osteonecrosis.[31,32] Therefore, correction of hypercoagulable states (e.g. in patients with documented thromboembolic events) may also, theoretically, lower the risk of osteonecrosis.

6. Treatment

Much remains to be learned about the optimal treatment of non-traumatic osteonecrosis. Early investigation and involvement of an orthopaedic surgeon is imperative. The femoral head is the most common and important joint affected, and management of osteonecrosis of the femoral head has been recently reviewed.[51,59,60] A summary of the various therapeutic approaches can be found in table III. An extensive review of orthopaedic techniques is beyond the scope of this article.

6.1 Non-Operative Approaches

A non-operative approach may be justified in patients with other serious co-morbidities that are likely to limit their medical operability and lifespan (e.g. metastatic malignancy). Small pre-collapse lesions seen on MRI that are asymptomatic (e.g. on

Table III. Treatment for osteonecrosis of the femoral head (reproduced from Mont et al.,[51] with permission from *The Journal of Bone and Joint Surgery*, Inc.)

Stage	Treatment
I (no radiographic changes)	Core decompression, percutaneous drilling
II (pre-collapse)	Core decompression, percutaneous drilling, bone-grafting, osteotomies
III (subchondral fracture, collapse)	Bone-grafting, hemi-resurfacing, total hip arthroplasty
IV (joint deformity, acetabular involvement)	Total hip arthroplasty, metal-on-metal total hip resurfacing arthroplasty

the contra-lateral hip of an affected patient) have a better prognosis. However, many patients with asymptomatic osteonecrosis will become symptomatic with pain. A further 73% may have femoral head collapse at a mean of 11 years after diagnosis.[61]

Other than appropriate analgesia and the avoidance of weight-bearing activities, there are no standard non-operative therapies. Investigational treatments include lipid-lowering agents ('statins'), anticoagulants, vasodilators, bisphosphonates, shock wave therapy, hyperbaric oxygen and pulsed electromagnetic fields.[51]

6.2 Operative Procedures

For patients with early stage disease (no radiographical changes or pre-collapse lesions), core decompression may have successful results, although a small, randomized study found no difference in rates of femoral head collapse following core decompression compared with conservative treatment.[62] The procedure generally involves a single drilling with a large-diameter trephine, although drilling multiple times with a small-diameter trephine has also been proposed.[51] In patients without significant collapse, the results of core decompression may be superior if combined with vascular bone grafting or autologous stem-cell grafting.[63,64]

Osteotomy moves the segment of necrotic bone away from the weight-bearing regions. This surgery has a high potential for morbidity, including non-union of the bone surfaces. This approach also makes subsequent total hip replacements technically difficult.[51]

For patients with a collapse of the femoral head, total hip arthroplasty is the treatment of choice. However, there are concerns about the long-term results of total hip arthroplasty, and as most patients with osteonecrosis are young, approaches intending to preserve the joint by supporting the subchondral bone have been explored. These include nonvascular and vascular bone grafting procedures, cementation and the implantation of porous metal rods.[51,60]

7. Conclusions

We have reported on 54 patients who received cancer chemotherapy, and in whom non-traumatic osteonecrosis of the bone has been diagnosed. Although most of the patients described received concomitant corticosteroids (a known risk factor for osteonecrosis), the mean cumulative corticosteroid dose was similar to the dose associated with osteonecrosis in non-cancer patients.[48,49] As men with testicular cancer were most commonly affected, one might speculate that the agents commonly used to treat this cancer might be responsible for an increased risk. However, despite use of agents very similar to those used in the treatment of testicular cancer, including corticosteroids, the development of osteonecrosis has only been reported in one patient with lung cancer. The increased risk observed in patients with testicular cancer could also represent an age-vulnerability rather than an effect of specific drugs. Therefore, a reasonable theory is that the increased risk of osteonecrosis in these populations is due to a combination of the effects of chemotherapy treatment, the malignancy itself and patient factors.

Another theory for the demographics observed would be a 'survivor phenomenon', as the diagnosis of osteonecrosis is usually delayed and, in the past, chemotherapy has been mainly used in solid-tumour patients with incurable cancer (vs the higher rates of cure in men treated for testicular cancer and women treated for adjuvant breast cancer). If true, then the increased treatment of solid tumours with chemotherapy will increase the absolute number of patients at risk for osteonecrosis. Although only 17% of the patients identified in this review had breast cancer, this diagnosis is far more common in the population than testicular cancer and indications for chemotherapy are increasing. The use of chemotherapy con-

comitantly with radiotherapy has also increased, and this practice may reduce standard radiation dose thresholds and increase the risk of radiation-associated osteonecrosis.[65]

It is important that both patients and healthcare personnel have an improved awareness of this disabling complication of treatment and cancer patients at risk should be informed about the risk of osteonecrosis as a complication of chemotherapy and corticosteroids. The use of alternatives to corticosteroids for prophylaxis of emesis, if available, to minimize exposure would seem sensible. A high index of clinical suspicion may allow early intervention and therefore preservation of the joints. Routine screening for CCON, however, is not currently supported by prospective evidence.

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