Surgical Oncology 28 (2019) 214–221

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

# Osteonecrosis in pediatric cancer survivors: Epidemiology, risk factors, and treatment

Sandesh S. Rao[a], Jad M. El Abiad[a], Varun Puvanesarajah[a], Adam S. Levin[b], Lynne C. Jones[a], Carol D. Morris[b,*]

[a] Department of Orthopaedic Surgery, The Johns Hopkins University, Baltimore, MD, USA
[b] Division of Orthopaedic Oncology, Department of Orthopaedic Surgery, The Johns Hopkins University, Baltimore, MD, USA

ARTICLE INFO

*Keywords:*
Chemotherapy
Late effects
Osteonecrosis
Pediatric cancer
Radiation

ABSTRACT

Several treatment regimens for childhood malignancies have been associated with the development of osteonecrosis, including radiation therapy, glucocorticoid medications, immunotherapy (including anti-angiogenic agents), and several chemotherapeutic agents. Adolescents older than 10 years are at greatest risk of developing osteonecrosis within 1 year of initiating therapy. Screening with magnetic resonance imaging in this high-risk population may be a useful method for detecting osteonecrosis. Surgery may be required for lesions that have progressed substantially despite nonoperative interventions.

## 1. Introduction

Treatment of childhood malignancies can have toxic effects on the musculoskeletal system [1–4]. Osteonecrosis is observed in patients with a history of childhood cancer and can cause severe pain and diminished quality of life, presumably for decades. Osteonecrosis is thought to occur because of disrupted vascular supply to the bone, causing apoptosis of bone marrow cells and osteocytes, with resulting marrow edema and necrotic bone [5]. Several cancer treatment regimens have been associated with the development of osteonecrosis, including radiation therapy; glucocorticoid medications; immunotherapy, including anti-angiogenic agents; and several chemotherapeutic agents. Screening options to detect lesions at risk of collapse and requiring surgery are vital [6]. The goal of this review is to summarize findings regarding the epidemiology and hypothesized pathophysiology of osteonecrosis as it pertains to several cancer treatment regimens and to discuss osteonecrosis screening strategies.

## 2. Epidemiology

Osteonecrosis predominantly affects adults; however, children with a history of cancer treatment are also at increased risk for developing osteonecrosis [1–4]. Much of the existing data assessing osteonecrosis in children have been collected from patients with acute lymphoblastic leukemia (ALL). ALL is the most prevalent pediatric malignancy with a cure rate greater than 90%, resulting in a large population of survivors who are at risk for developing sequelae secondary to treatment. Also steroid therapy, which has known associations with osteonecrosis, is critical to treatment regimens for ALL [7–12]. Despite the relative rarity of other malignancies in children, other pediatric cancers have been associated with later development of osteonecrosis. Such cancers include other hematologic malignancies, head and neck cancers, soft-tissue and primary bone sarcomas, neuro- and nephroblastomas, and primary central nervous system tumors [13–17].

Unfortunately, there is great heterogeneity in the definitions of early osteonecrosis in the literature. Study definitions vary widely and include diagnosis based on a combination of patient symptoms and radiographic confirmation, radiographic confirmation alone, patient surveys, or physician surveys [11,13,15,18,19]. The lack of a unifying definition based on strict criteria contributes to the complexity of identifying the disease process and is a potential reason for the wide range of cumulative incidence rates reported. This may be why so many theories on the pathophysiology of osteonecrosis exist. Much remains to be elucidated regarding osteonecrosis in children after cancer therapy, including eventual determination of the best course of treatment [20].

Osteonecrosis is usually observed in the femoral head, though the humeral head, distal femur, and proximal tibia are also common locations [2,15]. When considering joints, both knees and hips are commonly affected [11]. Other areas of involvement included the clavicle, wrist, and jaw [13,17]. Weightbearing joints and long bones are

* Corresponding author. Division of Orthopaedic Oncology, Department of Orthopaedic Surgery, The Johns Hopkins Hospital, 601 North Caroline Street, Baltimore, MD, 21287, USA.
*E-mail address:* cmorri61@jhmi.edu (C.D. Morris).

https://doi.org/10.1016/j.suronc.2019.02.001
Received 21 August 2018; Received in revised form 25 January 2019; Accepted 2 February 2019
0960-7404/ © 2019 Elsevier Ltd. All rights reserved.

commonly involved [7–12,15,17,18,20–22].

Sixteen major classification systems have historically been used to describe and classify and osteonecrosis. The most commonly used systems are the Ficat classification [23], the University of Pennsylvania system [24], the ARCO system [25], and the Japanese Orthopaedic Association system [26]. Although no one system has been established as the "gold standard," most systems, and hence most clinicians, consider the following criteria when staging osteonecrosis: symptoms, evidence of hyperemic bone, sclerosis, and subchondral fractures on imaging. Late-stage disease is identified universally across all classification systems as joint collapse and progression to arthritis.

The incidence of osteonecrosis in children varies considerably depending on the subset of patients being studied [15]. The most comprehensive study to date was conducted by Kadan-Lottick et al. [15], who observed a 20-year cumulative incidence of osteonecrosis of 0.43% by self-reporting in 9261 pediatric cancer patients with at least 5-year survival. Osteonecrosis incidence was significantly higher in patients with a history of cancer compared with siblings with no such history, who had an analogous incidence of 0.03% at 20 years. Patients treated for childhood cancer had a 5.6-times greater likelihood of having osteonecrosis. Even in ALL, which is the most prevalent childhood malignancy, osteonecrosis incidence varies widely, from less than 1.8%–71.8% [2,6,11,13,15,18]. Irrespective of cancer type and osteonecrosis definition, adolescent patients older than 10 years have a significantly higher incidence of osteonecrosis compared with younger patients who underwent equivalent treatment [1,2,6,10–12,15,16].

In patients with ALL, those younger than 10 years at the time of cancer diagnosis had a cumulative incidence of osteonecrosis of 0.2%–10%; whereas, those older than 10 years at diagnosis had a cumulative incidence of 2.8%–44.6% [6,11,15,18]. Although certain studies found a higher cumulative incidence in girls versus boys, especially at a younger age, boys older than 15 years had a higher incidence than girls. This indicates that puberty may play a role in the development of osteonecrosis [11,18], possibly in relation to physeal closure and changes in vascular supply with maturation. Additionally, patients with hematologic malignancies who received allogenic stem cell transplants developed osteonecrosis at rates of 3.9%–44% [15,27–29]. This subset of patients was exposed to total body radiation, as well as considerably higher doses of corticosteroids to prevent rejection of the transplant and combat graft-versus-host disease [2,7–12,18]. Notably, median time to diagnosis of osteonecrosis ranged from 14 to 25 months [13,18], with osteonecrosis occurring as soon as 3 months after initiating therapy. Among patients who developed osteonecrosis, those who underwent stem cell transplants developed osteonecrosis within 1 year of initiating therapy [15].

Genetic studies have identified several single nucleotide polymorphisms (SNPs) associated with the risk of developing of osteonecrosis. Common pathways identified include lipid metabolism and differentiation of osteoblasts and osteoclasts. Karol et al. found that, in patients younger than 10 years, those with SNPs in *BMP7* (bone morphogenetic protein 7) have 15-fold greater odds of developing osteonecrosis compared with those who do not have such SNPs ($p = 0.049$) [30]. The authors hypothesized that bone morphogenic proteins are implicated in differentiation of mesenchymal stem cells into osteoblasts and inhibition of formation of osteoclasts. Moreover, BMP7 is known to be toxic to vascular smooth muscle [31] and may be implicated in local arteriopathy, contributing to osteonecrosis via direct toxic effects on local bone vasculature. Furthermore, SNPs in *PROX1* (prospero homeobox 1) were associated with greater odds of developing osteonecrosis. *PROX1* has been shown to control the differentiation of lymphatic endothelial cells from vascular endothelial cells and is downregulated in familial combined hyperlipidemia. Thus, it has been hypothesized that SNPs in *PROX1* result in reduced clearance of plasma lipids [32,33], causing an increase in lipids in the bone marrow, which was identified by Kawedia et al. as a risk factor for osteonecrosis [6]. They found that patients with polymorphisms in *ACP1* (acid phosphatase 1), which secretes a protein regulated in lipid levels and osteoblast differentiation, were 5 times as likely to develop osteonecrosis than those without these polymorphisms.

## 3. Associations with oncologic treatment modalities

On the basis of demographics, epidemiology, and therapy regimens, several pathophysiologic explanations have been proposed for the development of osteonecrosis in children.

### 3.1. Corticosteroid therapy

Corticosteroids play a key role in the treatment of oncologic disease in children. However, this treatment modality involves a complex balance of benefits and risks [1–4,6–13,15–18,20,21,27–29]. Steroids function by inducing apoptosis in lymphocytes, making them integral to the treatment of several hematologic neoplasms. Steroids are effective in decreasing malignancy- or treatment-associated symptoms, such as inflammation and nausea [2,7–12,34–39]. Their therapeutic and adverse effects as they pertain to childhood cancers have been studied primarily in children with ALL [1,3,4,7–11,13,15,22].

Several theories exist regarding the pathophysiology of how steroid exposure induces osteonecrosis and likely affects bone metabolism and health (Fig. 1). One theory describes the direct toxic effects to osteoblasts and osteoclasts, resulting in apoptosis and impaired bone turnover [20,40,41]. Another theory describes increased intraosseous and intramedullary pressure leading to ischemia and eventual necrosis. Elevated pressure in this compartment is thought to be caused by lipid infiltration within the bone marrow and lipocyte hypertrophy [20,40,41]. Additionally, there is concern for embolic disease from fat-emboli in arteries resulting in ischemic insults [14,42]. Genetic studies have found associations between single-nucleotide polymorphism in the acid phosphatase 1 and *SH3YL1* gene locus that were associated with increased risk of developing both osteonecrosis and hyperlipidemia [6]. Other theories involve a hypercoagulable state with associated vascular insult causing ischemia and inhibiting angiogenesis [43–46].

Current treatment regimens for ALL include a 28-day course of prednisone for induction therapy, followed by intermittent 5-day regimens to maintain remission [2,7,9–12,39]. Compared with continuous steroid dosing regimens, intermittent regimens may be associated with a lower incidence of osteonecrosis, particularly for patients with ALL [2,15]. Dexamethasone is also used in addition to, or instead of, prednisone in these regimens, according to disease profile, because of dexamethasone's superior central nervous system penetration [39]. Larsen et al. reported that patients with ALL who were younger than 10 years and who received dexamethasone during induction had superior outcomes compared with those who received prednisone [47]. In contrast, older patients did not derive the same benefit from dexamethasone and experienced higher rates of osteonecrosis [47]. However, several head-to-head randomized controlled trials have shown equivalent long-term survival benefits [39,48,49]. Mattano et al. showed cumulative dexamethasone dosing to be a risk factor for the development of osteonecrosis [11]. Similarly, Kadan-Lottick et al. noted a 30% higher likelihood of developing osteonecrosis after dexamethasone compared with prednisone treatment, irrespective of age at treatment or timing of treatment (induction versus post-induction) [15]. Furthermore, timing of response to treatment was identified by Moricke et al. as a factor influencing survival benefit [50]. They found that, among pediatric ALL patients, superior overall survival benefit was achieved in patients with appropriate early treatment who were taking dexamethasone during induction, compared with prednisone. However, age may play a role when considering the osteonecrosis risks associated with dexamethasone versus prednisone, in addition to steroid potency. Vrooman et al. reported that patients treated with induction dexamethasone at ages 10–18 years were approximately four

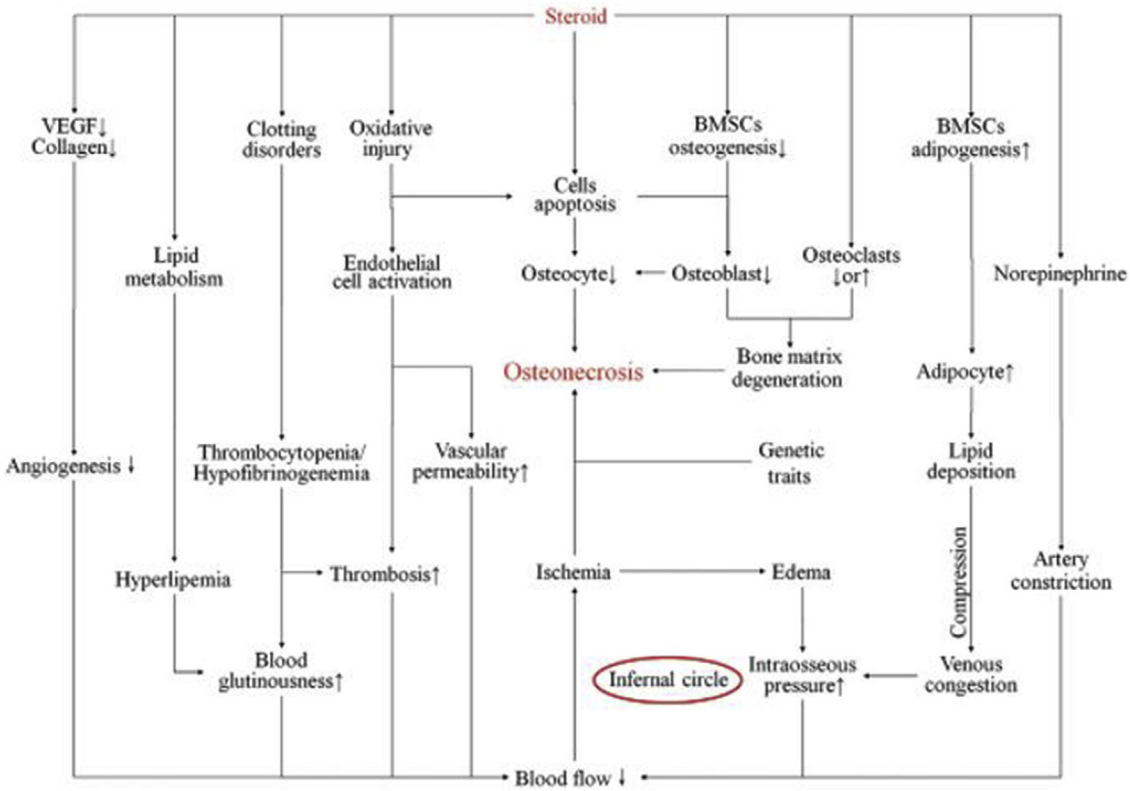


**Fig. 1.** Pathophysiology of steroid-associated osteonecrosis with different pathways (summarized from published work by other authors). BMSC, bone marrow stem cell; VEGF, vascular endothelial growth factor. (Preprinted with permission from Elsevier, Xie XH, Wang XL, Yang HL, Zhao DW, Qin L. Steroid-associated osteonecrosis: epidemiology, pathophysiology, animal model, prevention, and potential treatments (an overview). J Clin Orthop Transl. 2015; 3(2):58–70.).

times as likely to develop osteonecrosis compared with patients younger than 10 years when treated with dexamethasone (13.5% versus 4.5%, respectively) and were approximately five times as likely to develop osteonecrosis than patients of the same age treated with prednisone (23% versus 4.7%, respectively) [51]. However, Strauss et al. found no difference in osteonecrosis incidence when comparing ALL treatment with dexamethasone versus prednisone during remission therapy in children [52]. Frequency of dosing was also identified as influencing the incidence of osteonecrosis. Mattano et al. found that, among pediatric patients with ALL, alternate-week dexamethasone administration significantly reduced the incidence of osteonecrosis (8.7%) compared with continuous dexamethasone administration (17%) [53].

Steroid therapy, which is commonly used as a primary cytotoxic treatment for hematologic malignancies, is rarely indicated for solid tumors. Instead, steroids, including dexamethasone, are used to treat symptoms such as swelling and nausea [54]. In a study by Niinimaki et al., no cases of osteonecrosis were identified in patients with solid tumors; however, the patients were young, with a mean age of less than 6 years [54]. These patients did not receive prednisone, but some received dexamethasone. One possible explanation for why osteonecrosis is rare in patients with solid tumors is that treatment duration is usually much shorter or intermittent and on an as-needed basis, even if the total dosage received is high compared with treatment for hematologic neoplasms, in which patients receive lower doses of steroids for an extended period [6,11,54].

### 3.2. Chemotherapy

Several chemotherapeutic agents have been associated with osteonecrosis in children [14,55,56]. Almost all of these agents have been used in conjunction with high doses of steroids, so it is difficult to assess how much these agents influence osteonecrosis development independent of corticosteroids [1–4,6–13,15,17–19]. However, several studies and case reports describe osteonecrosis in children who had not received radiation or steroid therapy [4,14,55,57–61]. This section will explore some of these chemotherapeutic agents and describe independent effects leading to osteonecrosis, as well as synergistic effects in the setting of corticosteroid therapy that have led to the development of osteonecrosis in children.

#### 3.2.1. L-Asparaginase

The amino acid asparagine is in high demand in metabolically active neoplastic cells, especially lymphatic cells, and thus plays a key role in cell survival in hematologic neoplasms [59]. L-asparaginase is an enzyme that is used in conjunction with several chemotherapeutics and steroids to treat hematologic neoplasms, particularly ALL, for its role in depleting asparagine levels and aiding in cell death [4,7–12,22,59].

The use of L-asparaginase has been linked to the development of osteonecrosis in children treated for hematologic malignancies [44,59,61]. Theories on how L-asparaginase leads to osteonecrosis involve independent properties of the enzyme, as well as its synergistic properties with dexamethasone [57,58,60,61]. Toxic effects of L-asparaginase that may contribute to osteonecrosis include its induction of a hypercoagulable state by decreasing levels of antithrombin III, plasminogen, protein C and protein S, which eventually leads to thrombosis in the effected bone, possibly contributing to osteonecrosis [62–66]. Similarly, L-asparaginase has been associated with cerebrovascular thrombosis, hyperlipidemia, and arteriopathy, resulting in osteonecrosis [44,58,60,67,68]. Furthermore, treatment of mice with both asparaginase and dexamethasone has produced a higher rate of arteriopathy (58%) compared with dexamethasone alone (17%) [44]. A known adverse effect of L-asparaginase is hypoalbuminemia, thought to be a surrogate marker for hepatic dysfunction, and resulting in

dysfunctional protein synthesis [59,69]. Hepatic dysfunction then leads to an increase in circulating plasma levels of dexamethasone, secondary to diminished clearance, and has been associated with increased incidence of osteonecrosis [69,70]. Patients can develop antibodies to L-asparaginase rapidly, and the anti-immune effects of steroids are thought to prevent this. This is another reason for treatment with both modalities that may inadvertently and synergistically increase the incidence of osteonecrosis [59,70].

The use of L-asparaginase with dexamethasone has also been shown to increase event-free survival [70–72]. Additionally, adolescents with hematologic neoplasms are more resistant than are young children to steroid therapy and thus require higher doses [38,39,48]. Achieving therapeutic dosing and event-free survival while avoiding long-term sequelae of treatment is a major challenge.

#### 3.2.2. Other chemotherapeutic Agents

Other chemotherapeutic agents have also been implicated. Ishii et al. described the development of osteonecrosis in two 3-year-old boys who were treated for neuroblastoma [14]. One patient received cyclophosphamide exclusively, whereas the other patient received cyclophosphamide, vincristine, and doxorubicin. Both developed osteonecrosis of the femoral head within weeks of therapy initiation, highlighting the rapid cytotoxic effects of these agents, particularly cyclophosphamide [14]. The development of osteonecrosis after treatment with vincristine and anthracyclines or doxorubicin and daunorubicin has been reported in adults and children in the absence of steroid or radiation treatment. Thus, the contribution of these agents to osteonecrosis cannot be diminished [2,7,9–12,14,73,74].

A case report by Bernbeck et al. describes a 9-year-old girl with nephroblastoma who developed osteonecrosis of the tibia 8 months after receiving treatment with dactinomycin, vincristine, and doxorubicin [55]. Similarly, Ghosh et al. described a 12-year-old girl who developed osteonecrosis 6 months after treatment for acute myeloid leukemia with daunorubicin and cytarabine [73]. These cases highlight the fact that much is unknown about the causes and pathophysiology of osteonecrosis in children who have undergone chemotherapy [1–4,6–13,15,17–19].

### 3.3. VEGF inhibitors

Targeted therapies have become a novel option to treat pediatric and adult malignancies [75]. However, given the infancy of the field, much is still unknown regarding the toxicity and resulting long-term effects after therapy [22,75,76].

Bevacizumab is one such antiangiogenic therapy used to treat solid tumors. It is a humanized monoclonal antibody against all isoforms of human vascular endothelial growth factor [77,78]. Vascular endothelial growth factor is vital in osteogenic differentiation and vascular proliferation [79,80]. The anti-angiogenic properties of bevacizumab help block the development of new vasculature, thus decreasing vascular permeability and increasing cell apoptosis [80,81].

Fangusaro et al. reported three patients with recurrent central nervous system tumors treated with bevacizumab and irinotecan who subsequently developed osteonecrosis involving the lunate, bilateral proximal femur, and bilateral knees (distal femur and proximal tibia), respectively [21]. Two of the three patients were receiving corticosteroids. Although corticosteroids may have contributed to the development of osteonecrosis, the antiangiogenic, prothrombotic, and osteocyte disruptive properties of bevacizumab were thought to have played a role as well [77–81]. Interestingly, the increased susceptibility to osteonecrosis caused by VEGF inhibitors has been linked to VEGF-634C/G polymorphisms in a recent meta-analysis by Wang et al. [82]. Conversely, bevacizumab has been used in conjunction with cyclophosphamide and vincristine to treat other pediatric cancers without any recorded cases of osteonecrosis to date [77–81,83,84]. As the use of target therapies expands and gains popularity, we will better understand the pathophysiology of their toxicities [76].

### 3.4. Radiation therapy

Radiation therapy for treatment of cancer is thought to be a risk factor in the development of osteonecrosis in children [2,9,11,15]. Radiation therapy to endocrine organs involved in bone homeostasis, especially the gonads, as well as the bony regions irradiated, increases the risk of developing osteonecrosis [15]. Studies also indicate that dose per fraction, total fractions received, volumes irradiated, and the method of radiation delivery are all risk factors for adverse musculoskeletal outcomes, including avascular necrosis, fractures, and alterations in bone growth [15,85–88]. Children are particularly susceptible to long-term effects at lower doses compared with adults [85]. Younger children may be at greater risk for adverse effects as a result of radiation therapy compared with adults and older children [85]. Unfortunately, there are limited data on the effects of radiation therapy on the pediatric musculoskeletal system because the skeletal system is less likely to be considered a dose-limiting factor in treatment regimens compared with healthy soft tissues [85].

A proposed cause of osteonecrosis secondary to radiation therapy involves damage to existing osteoblasts, osteoclasts, and progenitor cells, resulting in impaired bone metabolism and pathologic bone formation [87,89–92]. Another contributing factor is thought to be local ischemic injury to bone occurring from fibroblast and macrophage aggregation within the microvasculature leading to fibrosis of the vessels [87,93]. All studies assessing risk of osteonecrosis from radiation therapy have been in the context of a combination of chemotherapy, steroid treatment, and surgery [1–4,7–13,15,18,20]. Hanif et al. investigated 5278 children with cancer treated between 1974 and 1991 and found 15 cases of femoral head osteonecrosis [13]. Five of those 15 patients received radiation therapy, and four of the five received localized therapy of 35 Gy or higher to the pelvis and surrounding soft and bony tissue. However, these patients were also treated with various chemotherapeutic agents associated with the development of osteonecrosis. Additionally, three of the five patients were treated with steroids. Prosnitz et al. assessed osteonecrosis in patients with Hodgkin disease treated with combined-modality therapy and found no cases of osteonecrosis among the 92 patients who received only radiation therapy [3]. However, of the nine patients who developed osteonecrosis, all received radiation therapy of at least 20 Gy or higher, in addition to prednisone and chemotherapy. Lastly, Mattano et al. prospectively assessed the development of osteonecrosis among 1409 children with ALL [11]. Patients who were rapid responders to therapy (as shown by a decrease in blast percentage below 25% within 7 days of induction) were randomized to receive cranial radiation in addition to maintenance therapy or maintenance therapy alone. Incidence of osteonecrosis was the same in both groups (8.4% in those who received radiation therapy versus 8.9% in those who did not). Although an association between radiation therapy and development of osteonecrosis in children is likely, the exact causes and incidence remain unclear [13].

## 4. Early detection and screening for osteonecrosis

Currently, there is no consensus on the best screening approach or time to screen for children at risk of developing osteonecrosis [6,19,94,95]. Kaste et al. prospectively used magnetic resonance imaging (MRI) as a screening tool to identify patients with extensive asymptomatic osteonecrosis of the femoral head, defined as greater than 30% of epiphyseal involvement, in children newly diagnosed with ALL [95]. Extensive osteonecrosis was chosen as the screening severity level because of its strong likelihood of needing further intervention, with 80% of these patients progressing to joint collapse within 2 years [6]. Children older than 10 years were more likely to develop extensive osteonecrosis (24%) compared with children younger than 10 years

(6.5%). Nineteen of the 40 lesions in older patients were eventually treated with total hip arthroplasty, with the remaining 21 not demonstrating improvement. All lesions in the younger cohort resolved or remained asymptomatic and did not progress. The authors found that in patients older than 10 years, a mean of 3.8 patients must be screened to discover an extensive osteonecrotic lesion [95].

Te Winkel et al. prospectively assessed symptomatic osteonecrosis (confirmation on MRI) in 35 patients with newly diagnosed and treated ALL who were followed for an average of 5 years after diagnosis [19]. Half of patients had persistent pain, while 40% had complete resolution. Given the unpredictable clinical course of symptomatic osteonecrosis, combined with young age, the authors stressed caution before pursuing surgery.

Ribeiro et al. prospectively evaluated whether MRI could screen for osteonecrosis beginning 1 year after initiation of cancer therapy in children with ALL and non-Hodgkin lymphoma [96]. The authors reported a 15% incidence of osteonecrosis (17 patients), predominantly involving the knee. Of these 17 patients, eight were asymptomatic without evidence of progressive disease on imaging, seven had mild symptoms that did not affect daily living, one patient had pain requiring analgesics daily, and one patient required hip arthroplasty. Additionally, severity on MRI did not correlate with disease progression. On the basis of the findings, they were unable to determine the clinical utility of MRI screening.

These three studies represent the largest prospective series assessing MRI screening techniques for osteonecrosis using different definitions [19,95,96]. Reaching consensus on the most clinically relevant definition of osteonecrosis and then determining the optimal method for early detection using prediction models will be vital as pediatric cancer survival rates continue to improve [97,98].

Kubota et al. prospectively evaluated 42 patients with MRI-confirmed osteonecrosis of the femoral head [99]. The purpose of their study was to evaluate the relationship between the maximum standardized uptake value (SUVmax) using F-fluoride positron emission tomography (PET), and the Ficat classification system using MRI. They found that SUVmax increased according to progression of the Ficat classification stage and estimated a cutoff SUVmax of 6.45 (sensitivity 0.80, specificity 0.92) for prediction of femoral head collapse. The authors hypothesized that F-fluoride PET may reflect accelerated bone metabolism caused by micro-collapse of the femoral head, which may not be detected on plain radiography and should be considered as an additional screening tool.

## 5. Treatment

Treatment of osteonecrosis in children is challenging because many definitive surgical interventions are more comfortably used in adults. Treatment can also encompass nonoperative strategies (Table 1). For instance, after a diagnosis is made, the affected joint should be made nonweight bearing, though this is likely to be ineffective as a standalone therapy [16,100,101].

**Table 1**
Proposed treatments for osteonecrosis in children.

| |
|---|
| Pharmacologic |
| Prostacyclin analogs |
| Low-molecular-weight heparin |
| Statins |
| Bisphosphonates |
| Nonoperative |
| Extracorporeal shockwave therapy |
| Hyperbaric oxygenation |
| Non-weightbearing |
| Single-pulsed electromagnetic fields |
| Surgical |
| Core decompression |
| Mesenchymal stem cell implantation |
| Autologous chondrocyte grafting |
| Joint resurfacing |
| Joint arthroplasty |

Various pharmacologic treatments have been proposed, often targeting presumed pathophysiologic mechanisms that may be implicated in osteonecrosis development in this patient population. For example, low-molecular-weight heparin, prostacyclin analogs, and statins have been suggested as possible treatment or prevention options for osteonecrosis. Low-molecular-weight heparin, which is intended to target osteonecrosis secondary to thromboembolism, may be less effective in this patient population in whom glucocorticoid-mediated osteonecrosis may be the more prevalent mechanism. Prostacyclin analogs, which likely serve in a vascular dilatory role in preventing osteonecrosis, have not been researched extensively in this patient population. Jager et al. reported pain and functional improvements in eight patients with chemotherapy-associated osteonecrosis treated with iloprost [102]. However, five of the eight patients were treated with surgical measures before or after iloprost administration. Statins, with their lipid-lowering effects, have been shown to prevent osteonecrosis in rabbits treated with steroids [103], though no studies have shown their positive role in children treated for childhood malignancy.

Lastly, it remains unclear whether bisphosphonates affect osteonecrosis development or progression in this patient population [104,105], although pamidronate may improve pain and function [105]. Kotecha et al. reported on 17 patients who developed osteonecrosis after therapy for ALL. Nine patients were treated with intravenous pamidronate or oral alendronate [105]. Clinical improvement, defined as improvement in pain and reduced need for analgesia, was observed in three of six patients treated with oral alendronate. Two of these patients had significant improvement in function and range of motion. The other three patients who did not show clinical improvement were then treated with intravenous pamidronate. These patients, in addition to three patients who were treated with pamidronate only, all showed improvement. In contrast, only one of the eight patients not treated with bisphosphonates did not deteriorate clinically.

Other nonsurgical therapies that have been investigated include hyperbaric oxygenation, extracorporeal shockwave treatment, and single-pulsed electromagnetic field therapy, all with low-level evidence. Little research into these methods has been performed in children. Bernbeck et al. found that hyperbaric oxygen therapy appeared to benefit children younger than 10 years, although the treatment effect was difficult to quantify because of limited data [106]. Regarding extracorporeal shockwave treatment and single-pulsed electromagnetic field therapy, only data from adults [107–110] and animals [111] are currently available.

In severe cases of osteonecrosis, surgery may be required. Core decompression, whereby holes are drilled into the necrotic area of bone to create new vascular networks and reduce intraosseous pressure, is a salvage method to avoid joint replacement and is favored in patients with early-stage disease. In a systematic review of osteonecrosis of the femoral head, Mont et al. found that patients who underwent core decompression had significantly lower rates of subchondral collapse and better clinical improvement compared with those treated nonoperatively [112]. Core decompression has been combined with implantation of mesenchymal stem cells, which has showed favorable results in adults [113–116]. Mesenchymal progenitor cells induce bone formation (although the clinical relevance of this in osteonecrotic bone is unclear), and their numbers and activity are thought to be decreased in osteonecrotic bone. Therefore, their local application is thought to regenerate the affected bone. Hernigou et al. reported that, among 145 patients with early-stage osteonecrosis of the femoral head, those treated with core decompression and bone marrow grafting had a femoral head survival rate of 93% at 5 years [117]. However, functional improvements with this adjunctive technique have not been observed. In a randomized prospective trial, Pepke et al. observed no radiographic or functional differences when comparing patients who underwent core

decompression with those who underwent core decompression and bone marrow implantation [113]. Core decompression may also be combined with cancellous bone grafting and implant stabilization with good results in children with early-stage lesions [118]. Autologous chondrocyte grafting is another surgical technique that has been reported to delay arthroplasty [119].

Although patients in the final stage of osteonecrosis with major joint destruction would benefit from arthroplasty, this treatment should be avoided for as long as possible because very young patients are expected to outlive their prostheses by many years. Resurfacing arthroplasty may be allow delay of total hip arthroplasty by 3–7 years [120]. Ultimately, the estimated cumulative incidence of total joint arthroplasty in patients treated for leukemia or lymphoma is 0.4%–4.5% at 20 years [121]. Currently, there is no definitive research pertaining to long-term outcomes after joint arthroplasty in children with osteonecrosis.

## 6. Conclusion

Osteonecrosis in children represents a clinical challenge. Much of the existing data are from children with hematologic malignancies in which treatment regimens are complex and involve multimodal approaches. Therefore, many factors may contribute to the development of osteonecrosis. Determining which imaging findings are clinically relevant, and hence actionable, is a diagnostic challenge that requires further investigation. A plethora of treatment options with variable clinical outcomes further complicates the decision-making process in managing these complex patients. Future prospective trials should focus on long-term solutions for this condition that substantially diminishes patients' quality of life.

## Declarations of interest

None.

## Acknowledgments

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements) that might pose a conflict of interest in connection with the submitted article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors thank Rachel Box and Jenni Weems for their editorial assistance.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.02.001.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References

[1] D.C. Ihde, V.T. DeVita, Osteonecrosis of the femoral head in patients with lymphoma treated with intermittent combination chemotherapy (including corticosteroids), Cancer 36 (5) (1975) 1585–1588.
[2] S.C. Kaste, E.J. Karimova, M.D. Neel, Osteonecrosis in children after therapy for malignancy, AJR Am. J. Roentgenol. 196 (5) (2011) 1011–1018.
[3] L.R. Prosnitz, J.P. Lawson, G.E. Friedlaender, L.R. Farber, J.F. Pezzimenti, Avascular necrosis of bone in Hodgkin's disease patients treated with combined modality therapy, Cancer 47 (12) (1981) 2793–2797.
[4] D.L. Sweet Jr., D.G. Roth, R.K. Desser, J.B. Miller, J.E. Ultmann, Avascular necrosis of the femoral head with combination therapy, Ann. Intern. Med. 85 (1) (1976) 67–68.
[5] K.N. Shah, J. Racine, L.C. Jones, R.K. Aaron, Pathophysiology and risk factors for osteonecrosis, Curr Rev Musculoskelet Med 8 (3) (2015) 201–209.
[6] J.D. Kawedia, S.C. Kaste, D. Pei, J.C. Panetta, X. Cai, C. Cheng, G. Neale, S.C. Howard, W.E. Evans, C.H. Pui, M.V. Relling, Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia, Blood 117 (8) (2011) 2340–2347 quiz 2556.
[7] P.S. Gaynon, W.A. Bleyer, P.G. Steinherz, J.Z. Finklestein, P.S. Littman, D.R. Miller, G.H. Reaman, H.N. Sather, G.D. Hammond, Modified BFM therapy for children with previously untreated acute lymphoblastic leukemia and unfavorable prognostic features. Report of Children's Cancer Study Group Study CCG-193P, Am. J. Pediatr. Hematol. Oncol. 10 (1) (1988) 42–50.
[8] P.S. Gaynon, R.H. Lustig, The use of glucocorticoids in acute lymphoblastic leukemia of childhood. Molecular, cellular, and clinical considerations, J. Pediatr. Hematol. Oncol. 17 (1) (1995) 1–12.
[9] P.S. Gaynon, P.G. Steinherz, W.A. Bleyer, A.R. Ablin, V.C. Albo, J.Z. Finklestein, N.J. Grossman, L.J. Novak, A.F. Pyesmany, G.H. Reaman, et al., Improved therapy for children with acute lymphoblastic leukemia and unfavorable presenting features: a follow-up report of the Childrens Cancer Group Study CCG-106, J. Clin. Oncol. 11 (11) (1993) 2234–2242.
[10] G. Henze, H.J. Langermann, J. Ritter, G. Schellong, H. Riehm, Treatment strategy for different risk groups in childhood acute lymphoblastic leukemia: a Report from the BFM study group, Haematol. Blood Transfus. 26 (1981) 87–93.
[11] L.A. Mattano Jr., H.N. Sather, M.E. Trigg, J.B. Nachman, Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the children's cancer group, J. Clin. Oncol. 18 (18) (2000) 3262–3272.
[12] C.M. Niemeyer, A. Reiter, H. Riehm, M. Donnelly, R.D. Gelber, S.E. Sallan, Comparative results of two intensive treatment programs for childhood acute lymphoblastic leukemia: the Berlin-Frankfurt-Munster and Dana-Farber Cancer Institute protocols, Ann. Oncol. 2 (10) (1991) 745–749.
[13] I. Hanif, H. Mahmoud, C.H. Pui, Avascular femoral head necrosis in pediatric cancer patients, Med. Pediatr. Oncol. 21 (9) (1993) 655–660.
[14] E. Ishii, N. Yoshida, S. Miyazaki, Avascular necrosis of bone in neuroblastoma treated with combination chemotherapy, Eur. J. Pediatr. 143 (2) (1984) 152–153.
[15] N.S. Kadan-Lottick, I. Dinu, K. Wasilewski-Masker, S. Kaste, L.R. Meacham, A. Mahajan, M. Stovall, Y. Yasui, L.L. Robison, C.A. Sklar, Osteonecrosis in adult survivors of childhood cancer: a report from the childhood cancer survivor study, J. Clin. Oncol. 26 (18) (2008) 3038–3045.
[16] H. Lackner, M. Benesch, A. Moser, F. Smolle-Juttner, W. Linhart, J. Raith, C. Urban, Aseptic osteonecrosis in children and adolescents treated for hemato-oncologic diseases: a 13-year longitudinal observational study, J. Pediatr. Hematol. Oncol. 27 (5) (2005) 259–263.
[17] H. Zietz, S. Berrak, H. Ried, K. Weber, M. Maor, N. Jaffe, The clavicle: a vulnerable bone in pediatric oncology, Int. J. Oncol. 18 (4) (2001) 689–695.
[18] B. Padhye, L. Dalla-Pozza, D. Little, C. Munns, Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL), Cancer Med 5 (5) (2016) 960–967.
[19] M.L. te Winkel, R. Pieters, W.C. Hop, H.A. de Groot-Kruseman, M.H. Lequin, I.M. van der Sluis, J.P. Bokkerink, J.A. Leeuw, M.C. Bruin, R.M. Egeler, A.J. Veerman, M.M. van den Heuvel-Eibrink, Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia, J. Clin. Oncol. 29 (31) (2011) 4143–4150.
[20] M.L. te Winkel, R. Pieters, E.J. Wind, J.H. Bessems, M.M. van den Heuvel-Eibrink, Management and treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia, Haematologica 99 (3) (2014) 430–436.
[21] J. Fangusaro, S. Gururangan, R.I. Jakacki, S.C. Kaste, S. Goldman, I.F. Pollack, J.M. Boyett, L.E. Kun, Bevacizumab-associated osteonecrosis of the wrist and knee in three pediatric patients with recurrent CNS tumors, J. Clin. Oncol. 31 (2) (2013) e24–27.
[22] S. Katsenos, C. Christophylakis, K. Psathakis, Osteonecrosis of the jaw in a patient with advanced non-small-cell lung cancer receiving bevacizumab, Arch. Bronconeumol. 48 (6) (2012) 218–219.
[23] R.P. Ficat, Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment, J Bone Joint Surg Br 67 (1985) 3–9.
[24] D.R. Steinberg, M.E. Steinberg, The University of Pennsylvania classification of osteonecrosis, in: K.H. Koo, M.A. Mont, L.C. Jones (Eds.), Osteonecrosis, Springer, Heidelberg, 2014, pp. 201–206.
[25] J. Gardeniers, A new international classification of osteonecrosis of the ARCO committee on terminology and classification, ARC News 4 (4) (1992) 41–46.
[26] N. Sugano, T. Atsumi, K. Ohzono, T. Kubo, T. Hotokebuchi, K. Takaoka, The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head, J. Orthop. Sci. 7 (5) (2002) 601–605.
[27] M. Faraci, M.G. Calevo, E. Lanino, S. Caruso, C. Messina, C. Favr, A. Iori, S. Santaron, S. Bonanomi, R. Rondelli, G. Dini, R. Haupt, Osteonecrosis after allogeneic stem cell transplantation in childhood. A case-control study in Italy, Haematologica 91 (8) (2006) 1096–1099.
[28] S.C. Kaste, T.J. Shidler, X. Tong, D.K. Srivastava, R. Rochester, M.M. Hudson, P.D. Shearer, G.A. Hale, Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation, Bone Marrow Transplant. 33 (4) (2004) 435–441.
[29] S. Sharma, S. Yang, R. Rochester, L. Britton, W.H. Leung, J. Yang, M.D. Neel, K.K. Ness, S.C. Kaste, Prevalence of osteonecrosis and associated risk factors in children before allogeneic BMT, Bone Marrow Transplant. 46 (6) (2011) 813–819.
[30] S.E. Karol, L.A. Mattano Jr., W. Yang, K.W. Maloney, C. Smith, C. Liu, L.B. Ramsey, C.A. Fernandez, T.Y. Chang, G. Neale, C. Cheng, E. Mardis, R. Fulton, P. Scheet, F.A. San Lucas, E.C. Larsen, M.L. Loh, E.A. Raetz, S.P. Hunger, M. Devidas, M.V. Relling, Genetic risk factors for the development of osteonecrosis in children

under age 10 treated for acute lymphoblastic leukemia, Blood 127 (5) (2016) 558–564.
[31] S. Zhang, I. Fantozzi, D.D. Tigno, E.S. Yi, O. Platoshyn, P.A. Thistlethwaite, J.M. Kriett, G. Yung, L.J. Rubin, J.X. Yuan, Bone morphogenetic proteins induce apoptosis in human pulmonary vascular smooth muscle cells, Am. J. Physiol. Lung Cell Mol. Physiol. 285 (3) (2003) L740–L754.
[32] N.C. Johnson, M.E. Dillard, P. Baluk, D.M. McDonald, N.L. Harvey, S.L. Frase, G. Oliver, Lymphatic endothelial cell identity is reversible and its maintenance requires Prox1 activity, Genes Dev. 22 (23) (2008) 3282–3291.
[33] A. Horra, J. Salazar, R. Ferre, J.C. Vallve, M. Guardiola, R. Rosales, L. Masana, J. Ribalta, Prox-1 and FOXC2 gene expression in adipose tissue: a potential contributory role of the lymphatic system to familial combined hyperlipidaemia, Atherosclerosis 206 (2) (2009) 343–345.
[34] O. Alvarez, A. Freeman, A. Bedros, S.K. Call, J. Volsch, O. Kalbermatter, J. Halverson, L. Convy, L. Cook, K. Mick, et al., Randomized double-blind crossover ondansetron-dexamethasone versus ondansetron-placebo study for the treatment of chemotherapy-induced nausea and vomiting in pediatric patients with malignancies, J. Pediatr. Hematol. Oncol. 17 (2) (1995) 145–150.
[35] P.A. Cassileth, E.J. Lusk, S. Torri, N. DiNubile, S.L. Gerson, Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy, Arch. Intern. Med. 143 (7) (1983) 1347–1349.
[36] J. Dietrich, K. Rao, S. Pastorino, S. Kesari, Corticosteroids in brain cancer patients: benefits and pitfalls, Expert Rev. Clin. Pharmacol. 4 (2) (2011) 233–242.
[37] C.W. Distelhorst, Recent insights into the mechanism of glucocorticosteroid-induced apoptosis, Cell Death Differ. 9 (1) (2002) 6–19.
[38] A.S. Fauci, D.C. Dale, J.E. Balow, Glucocorticosteroid therapy: mechanisms of action and clinical considerations, Ann. Intern. Med. 84 (3) (1976) 304–315.
[39] H. Inaba, C.H. Pui, Glucocorticoid use in acute lymphoblastic leukaemia, Lancet Oncol. 11 (11) (2010) 1096–1106.
[40] S.S. Shim, H.E. Hawk, W.Y. Yu, The relationship between blood flow and marrow cavity pressure of bone, Surg. Gynecol. Obstet. 135 (3) (1972) 353–360.
[41] T.M. Zizic, D.S. Hungerford, M.B. Stevens, Ischemic bone necrosis in systemic lupus erythematosus. II. The early diagnosis of ischemic necrosis of bone, Medicine (Baltim.) 59 (2) (1980) 134–142.
[42] D.E. Fisher, W.H. Bickel, K.E. Holley, Histologic demonstration of fat emboli in aseptic necrosis associated with hypercortisonism, Mayo Clin. Proc. 44 (4) (1969) 252–259.
[43] M.A. Kerachian, C. Seguin, E.J. Harvey, Glucocorticoids in osteonecrosis of the femoral head: a new understanding of the mechanisms of action, J. Steroid Biochem. Mol. Biol. 114 (3–5) (2009) 121–128.
[44] C. Liu, L.J. Janke, J.D. Kawedia, L.B. Ramsey, X. Cai, L.A. Mattano Jr., K.L. Boyd, A.J. Funk, M.V. Relling, Asparaginase potentiates glucocorticoid-induced osteonecrosis in a mouse model, PLoS One 11 (3) (2016) e0151433.
[45] G. Motomura, T. Yamamoto, K. Miyanishi, S. Jingushi, Y. Iwamoto, Combined effects of an anticoagulant and a lipid-lowering agent on the prevention of steroid-induced osteonecrosis in rabbits, Arthritis Rheum. 50 (10) (2004) 3387–3391.
[46] C. Zalavras, S. Shah, M.J. Birnbaum, B. Frenkel, Role of apoptosis in glucocorticoid-induced osteoporosis and osteonecrosis, Crit. Rev. Eukaryot. Gene Expr. 13 (2–4) (2003) 221–235.
[47] E.C. Larsen, M. Devidas, S. Chen, W.L. Salzer, E.A. Raetz, M.L. Loh, L.A. Mattano Jr., C. Cole, A. Eicher, M. Haugan, M. Sorenson, N.A. Heerema, A.A. Carroll, J.M. Gastier-Foster, M.J. Borowitz, B.L. Wood, C.L. Willman, N.J. Winick, S.P. Hunger, W.L. Carroll, Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from children's oncology group study AALL0232, J. Clin. Oncol. 34 (20) (2016) 2380–2388.
[48] Y. Bertrand, S. Suciu, Y. Benoit, A. Robert, B. Nelken, A. Uyttebroeck, P. Lutz, A. Ferster, A. Baruchel, L.A. Norton, G. Margueritte, P. Rohrlich, M. Munzer, D. Plantaz, F. Millot, P. Boutard, N. Sirvent, C. Hoyoux, L. Baila, J. Otten, Dexamethasone(DEX)(6mg/sm/d) and prednisolone(PRED)(60mg/sm/d) in induction therapy of childhood all are equally effective: results of the 2nd interim analysis of EORTC trial 58951, Blood 112 (11) (2008) 8-8.
[49] S. Igarashi, A. Manabe, A. Ohara, M. Kumagai, T. Saito, Y. Okimoto, T. Kamijo, K. Isoyama, M. Kajiwara, M. Sotomatsu, K. Sugita, K. Sugita, M. Maeda, H. Yabe, A. Kinoshita, T. Kaneko, Y. Hayashi, K. Ikuta, R. Hanada, M. Tsuchida, No advantage of dexamethasone over prednisolone for the outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in the Tokyo Children's Cancer Study Group L95-14 protocol, J. Clin. Oncol. 23 (27) (2005) 6489–6498.
[50] A. Moricke, M. Zimmermann, M.G. Valsecchi, M. Stanulla, A. Biondi, G. Mann, F. Locatelli, G. Cazzaniga, F. Niggli, M. Arico, C.R. Bartram, A. Attarbaschi, D. Silvestri, R. Beier, G. Basso, R. Ratei, A.E. Kulozik, L. Lo Nigro, B. Kremens, J. Greiner, R. Parasole, J. Harbott, R. Caruso, A. von Stackelberg, E. Barisone, C. Rossig, V. Conter, M. Schrappe, Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000, Blood 127 (17) (2016) 2101–2112.
[51] L.M. Vrooman, K.E. Stevenson, J.G. Supko, J. O'Brien, S.E. Dahlberg, B.L. Asselin, U.H. Athale, L.A. Clavell, K.M. Kelly, J.L. Kutok, C. Laverdiere, S.E. Lipshultz, B. Michon, M. Schorin, M.V. Relling, H.J. Cohen, D.S. Neuberg, S.E. Sallan, L.B. Silverman, Post induction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study-Dana-Farber Cancer Institute ALL Consortium Protocol 00-01, J. Clin. Oncol. 31 (9) (2013) 1202–1210.
[52] A.J. Strauss, J.T. Su, V.M. Dalton, R.D. Gelber, S.E. Sallan, L.B. Silverman, Bony morbidity in children treated for acute lymphoblastic leukemia, J. Clin. Oncol. 19 (12) (2001) 3066–3072.
[53] L.A. Mattano Jr., M. Devidas, J.B. Nachman, H.N. Sather, S.P. Hunger, P.G. Steinherz, P.S. Gaynon, N.L. Seibel, Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial, Lancet Oncol. 13 (9) (2012) 906–915.
[54] R.A. Niinimaki, A.H. Harila-Saari, A.E. Jartti, R.M. Seuri, P.V. Riikonen, E.L. Paakko, M.I. Mottonen, M. Lanning, Osteonecrosis in children treated for lymphoma or solid tumors, J. Pediatr. Hematol. Oncol. 30 (11) (2008) 798–802.
[55] B. Bernbeck, K.A. Krauth, A. Scherer, V. Engelbrecht, U. Gobel, Aseptic osteonecrosis in a child with nephroblastoma healed by hyperbaric oxygen therapy, Med. Pediatr. Oncol. 39 (1) (2002) 47–48.
[56] A.M. Newland, A.P. Lawson, V.R. Adams, Complications associated with treatment of malignancies: a focus on avascular necrosis of the bone, Orthopedics 33 (6) (2010) 413–416.
[57] G. Goyal, V.R. Bhatt, L-asparaginase and venous thromboembolism in acute lymphocytic leukemia, Future Oncol. 11 (17) (2015) 2459–2470.
[58] T. Hanada, Y. Horigome, M. Inudoh, H. Takita, Osteonecrosis of vertebrae in a child with acute lymphocytic leukaemia during L-asparaginase therapy, Eur. J. Pediatr. 149 (3) (1989) 162–163.
[59] K.B. McCredie, D.H. Ho, E.J. Freireich, L-asparaginase for the treatment of cancer, Ca - Cancer J. Clin. 23 (4) (1973) 220–227.
[60] S.K. Parsons, S.X. Skapek, E.J. Neufeld, C. Kuhlman, M.L. Young, M. Donnelly, J.D. Brunzell, J.D. Otvos, S.E. Sallan, N. Rifai, Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia, Blood 89 (6) (1997) 1886–1895.
[61] L. Yang, J.C. Panetta, X. Cai, W. Yang, D. Pei, C. Cheng, N. Kornegay, C.H. Pui, M.V. Relling, Asparaginase may influence dexamethasone pharmacokinetics in acute lymphoblastic leukemia, J. Clin. Oncol. 26 (12) (2008) 1932–1939.
[62] N. Anderson, J.J. Lokich, J.L. Tullis, L-asparaginase effect on antithrombin-III levels, Med. Pediatr. Oncol. 7 (4) (1979) 335–340.
[63] A.C. Homans, M.E. Rybak, R.L. Baglini, C. Tiarks, M.E. Steiner, E.N. Forman, Effect of L-asparaginase administration on coagulation and platelet function in children with leukemia, J. Clin. Oncol. 5 (5) (1987) 811–817.
[64] N.K. Ramsay, J.R. Priest, A.J. Bennett, W. Krivit, J.R. Edson, The effect of L-asparaginase on antithrombin, plasminogen, and plasma coagulation during therapy for acute lymphoblastic leukemia, J. Pediatr. 100 (6) (1982) 990–995.
[65] E. Truelove, A.K. Fielding, B.J. Hunt, The coagulopathy and thrombotic risk associated with L-asparaginase treatment in adults with acute lymphoblastic leukaemia, Leukemia 27 (3) (2013) 553–559.
[66] S. Vigano'D'Angelo, L. Gugliotta, M. Mattioli Belmonte, M.L. Cascione, E. Pattarini, A. D'Angelo, L-asparaginase treatment reduces the anticoagulant potential of the protein C system without affecting vitamin K-dependent carboxylation, Thromb. Res. 59 (6) (1990) 985–994.
[67] B. Dubashi, A. Jain, L-Asparginase induced cortical venous thrombosis in a patient with acute leukemia, J. Pharmacol. Pharmacother. 3 (2) (2012) 194–195.
[68] N.A. Wani, T. Kosar, N.A. Pala, U.A. Qureshi, Sagittal sinus thrombosis due to L-asparaginase, J. Pediatr. Neurosci. 5 (1) (2010) 32–35.
[69] A. Kashuba, J. Park, A. Persky, K. Brouwer, Drug metabolism, transport and influence of hepatic disease, in: M. Burton, L. Shaw, J. Shentag, W. Evans (Eds.), Applied Pharmacokinetics & Pharmacodynamics: Principles of Therapeutic Drug Monitoring, Lippincott Williams & Wilkins, Philadelphia, PA, 2006, pp. 135–142.
[70] J.D. Kawedia, C. Liu, D. Pei, C. Cheng, C.A. Fernandez, S.C. Howard, D. Campana, J.C. Panetta, W.P. Bowman, W.E. Evans, C.H. Pui, M.V. Relling, Dexamethasone exposure and asparaginase antibodies affect relapse risk in acute lymphoblastic leukemia, Blood 119 (7) (2012) 1658–1664.
[71] M.D. Amylon, J. Shuster, J. Pullen, C. Berard, M.P. Link, M. Wharam, J. Katz, A. Yu, J. Laver, Y. Ravindranath, J. Kurtzberg, S. Desai, B. Camitta, S.B. Murphy, Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study, Leukemia 13 (3) (1999) 335–342.
[72] L.B. Silverman, R.D. Gelber, V.K. Dalton, B.L. Asselin, R.D. Barr, L.A. Clavell, C.A. Hurwitz, A. Moghrabi, Y. Samson, M.A. Schorin, S. Arkin, L. Declerck, H.J. Cohen, S.E. Sallan, Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01, Blood 97 (5) (2001) 1211–1218.
[73] J. Ghosh, Y.C. Manjunatha, S. Thulkar, S. Bakhshi, Avascular necrosis of femoral head in childhood acute myeloid leukemia: complication of chemotherapy without steroids, Pediatr. Blood Canc. 51 (2) (2008) 308–309.
[74] P.G. Harper, C. Trask, R.L. Souhami, Avascular necrosis of bone caused by combination chemotherapy without corticosteroids, Br. Med. J. 288 (6413) (1984) 267–268.
[75] C.M. Capitini, M. Otto, K.B. DeSantes, P.M. Sondel, Immunotherapy in pediatric malignancies: current status and future perspectives, Future Oncol. 10 (9) (2014) 1659–1678.
[76] F. Francini, A. Pascucci, E. Francini, S.T. Miano, G. Bargagli, G. Ruggiero, R. Petrioli, Osteonecrosis of the jaw in patients with cancer who received zoledronic acid and bevacizumab, J. Am. Dent. Assoc. 142 (5) (2011) 506–513.
[77] N. Ferrara, K.J. Hillan, W. Novotny, Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy, Biochem. Biophys. Res. Commun. 333 (2) (2005) 328–335.
[78] Y.S. Lin, C. Nguyen, J.L. Mendoza, E. Escandon, D. Fei, Y.G. Meng, N.B. Modi, Preclinical pharmacokinetics, interspecies scaling, and tissue distribution of a humanized monoclonal antibody against vascular endothelial growth factor, J. Pharmacol. Exp. Therapeut. 288 (1) (1999) 371–378.
[79] C.L. Estilo, M. Fornier, A. Farooki, D. Carlson, G. Bohle 3rd, J.M. Huryn,

Osteonecrosis of the jaw related to bevacizumab, J. Clin. Oncol. 26 (24) (2008) 4037–4038.
[80] R. Kerbel, J. Folkman, Clinical translation of angiogenesis inhibitors, Nat. Rev. Canc. 2 (10) (2002) 727–739.
[81] F. Yuan, Y. Chen, M. Dellian, N. Safabakhsh, N. Ferrara, R.K. Jain, Time-dependent vascular regression and permeability changes in established human tumor xenografts induced by an anti-vascular endothelial growth factor/vascular permeability factor antibody, Proc. Natl. Acad. Sci. U. S. A. 93 (25) (1996) 14765–14770.
[82] Y. Wang, C.J. Xia, B.J. Wang, X.W. Ma, D.W. Zhao, The association between VEGF -634C/G polymorphisms and osteonecrosis of femoral head: a meta-analysis, Int. J. Clin. Exp. Med. 8 (6) (2015) 9313–9319.
[83] F. Navid, S.D. Baker, M.B. McCarville, C.F. Stewart, C.A. Billups, J. Wu, A.M. Davidoff, S.L. Spunt, W.L. Furman, L.M. McGregor, S. Hu, J.C. Panetta, D. Turner, D. Fofana, W.E. Reddick, W. Leung, V.M. Santana, Phase I and clinical pharmacology study of bevacizumab, sorafenib, and low-dose cyclophosphamide in children and young adults with refractory/recurrent solid tumors, Clin. Canc. Res. 19 (1) (2013) 236–246.
[84] L. Wagner, B. Turpin, R. Nagarajan, B. Weiss, T. Cripe, J. Geller, Pilot study of vincristine, oral irinotecan, and temozolomide (VOIT regimen) combined with bevacizumab in pediatric patients with recurrent solid tumors or brain tumors, Pediatr. Blood Canc. 60 (9) (2013) 1447–1451.
[85] M.J. Krasin, L.S. Constine, D.L. Friedman, L.B. Marks, Radiation-related treatment effects across the age spectrum: differences and similarities or what the old and young can learn from each other, Semin. Radiat. Oncol. 20 (1) (2010) 21–29.
[86] P. Massin, J. Duparc, Total hip replacement in irradiated hips. A retrospective study of 71 cases, J Bone Joint Surg Br 77 (6) (1995) 847–852.
[87] L. Michalecki, D. Gabrys, R. Kulik, J. Wydmanski, K. Trela, Radiotherapy induced hip joint avascular necrosis-Two cases report, Rep. Practical Oncol. Radiother. 16 (5) (2011) 198–201.
[88] D.E. Peterson, W. Doerr, A. Hovan, A. Pinto, D. Saunders, L.S. Elting, F.K. Spijkervet, M.T. Brennan, Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strategies, and future studies, Support. Care Canc. 18 (8) (2010) 1089–1098.
[89] X. Cao, X. Wu, D. Frassica, B. Yu, L. Pang, L. Xian, M. Wan, W. Lei, M. Armour, E. Tryggestad, J. Wong, C.Y. Wen, W.W. Lu, F.J. Frassica, Irradiation induces bone injury by damaging bone marrow microenvironment for stem cells, Proc. Natl. Acad. Sci. U. S. A. 108 (4) (2011) 1609–1614.
[90] A. Chandra, S. Lan, J. Zhu, T. Lin, X. Zhang, V.A. Siclari, A.R. Altman, K.A. Cengel, X.S. Liu, L. Qin, PTH prevents the adverse effects of focal radiation on bone architecture in young rats, Bone 55 (2) (2013) 449–457.
[91] O. Gates, Effects of radiation on bone, cartilage and teeth, Arch. Pathol. 35 (1943) 323–340.
[92] P. Hasselbacher, H.R. Schumacher, Bilateral protusio acetabuli following pelvic irradiation, J. Rheumatol. 4 (2) (1977) 189–196.
[93] J.W. Ewing, Tissue reactions to radiation, Am. J. Roentgenol. 15 (1926) 93–115.
[94] D. Ippolito, A. Masetto, C.T. Franzesi, P.A. Bonaffini, A. Sala, A. Biondi, S. Sironi, Lower-limb MRI in the staging and re-staging of osteonecrosis in paediatric patients affected by acute lymphoblastic leukaemia after therapy, Skeletal Radiol. 45 (4) (2016) 495–503.
[95] S.C. Kaste, D. Pei, C. Cheng, M.D. Neel, W.P. Bowman, R.C. Ribeiro, M.L. Metzger, D. Bhojwani, H. Inaba, P. Campbell, J.E. Rubnitz, S. Jeha, J.T. Sandlund, J.R. Downing, M.V. Relling, C.H. Pui, S.C. Howard, Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids, J. Clin. Oncol. 33 (6) (2015) 610–615.
[96] R.C. Ribeiro, B.D. Fletcher, W. Kennedy, P.L. Harrison, M.D. Neel, S.C. Kaste, J.T. Sandlund, J.E. Rubnitz, B.I. Razzouk, M.V. Relling, C.H. Pui, Magnetic resonance imaging detection of avascular necrosis of the bone in children receiving intensive prednisone therapy for acute lymphoblastic leukemia or non-Hodgkin lymphoma, Leukemia 15 (6) (2001) 891–897.
[97] M.A. den Hoed, S.M. Pluijm, A.G. Uitterlinden, R. Pieters, M.M. van den Heuvel-Eibrink, Genetic biomarkers to identify the risk of osteonecrosis in children with acute lymphoblastic leukemia, Mol. Diagn. Ther. 20 (6) (2016) 519–522.
[98] S.E. Karol, W. Yang, S.L. Van Driest, T.Y. Chang, S. Kaste, E. Bowton, M. Basford, L. Bastarache, D.M. Roden, J.C. Denny, E. Larsen, N. Winick, W.L. Carroll, C. Cheng, D. Pei, C.A. Fernandez, C. Liu, C. Smith, M.L. Loh, E.A. Raetz, S.P. Hunger, P. Scheet, S. Jeha, C.H. Pui, W.E. Evans, M. Devidas, L.A. Mattano Jr., M.V. Relling, Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia, Blood 126 (15) (2015) 1770–1776.
[99] S. Kubota, Y. Inaba, N. Kobayashi, U. Tateishi, H. Ike, T. Inoue, T. Saito, Prediction of femoral head collapse in osteonecrosis using 18F-fluoride positron emission tomography, Nucl. Med. Commun. 36 (6) (2015) 596–603.
[100] M.A. Mont, J.J. Carbone, A.C. Fairbank, Core decompression versus nonoperative management for osteonecrosis of the hip, Clin. Orthop. Relat. Res. 324 (1996) 169–178.
[101] S. Okazaki, S. Nagoya, K. Tateda, R. Katada, K. Mizuo, S. Watanabe, T. Yamashita, H. Matsumoto, Weight bearing does not contribute to the development of osteonecrosis of the femoral head, Int. J. Exp. Pathol. 93 (6) (2012) 458–462.
[102] M. Jager, C. Zilkens, B. Westhoff, E.M. Jelinek, G. Kozina, R. Krauspe, Efficiency of iloprost treatment for chemotherapy-associated osteonecrosis after childhood cancer, Anticancer Res. 29 (8) (2009) 3433–3440.
[103] K. Pengde, P. Fuxing, S. Bin, Y. Jing, C. Jingqiu, Lovastatin inhibits adipogenesis and prevents osteonecrosis in steroid-treated rabbits, Joint Bone Spine 75 (6) (2008) 696–701.
[104] N.L. Amin, R.M. James, R. Phillips, QUESTION 1: should we be using bisphosphonates for osteonecrosis complicating childhood acute lymphoblastic leukaemia? Arch. Dis. Child. 101 (3) (2016) 287–290.
[105] R.S. Kotecha, N. Powers, S.J. Lee, K.J. Murray, T. Carter, C. Cole, Use of bisphosphonates for the treatment of osteonecrosis as a complication of therapy for childhood acute lymphoblastic leukaemia (ALL), Pediatr. Blood Canc. 54 (7) (2010) 934–940.
[106] B. Bernbeck, A. Christaras, K. Krauth, S. Lentrodt, H. Strelow, J. Schaper, G. Janssen, U. Modder, U. Gobel, Bone marrow oedema and aseptic osteonecrosis in children and adolescents with acute lymphoblastic leukaemia or non-Hodgkin-lymphoma treated with hyperbaric-oxygen-therapy (HBO): an approach to cure? - BME/AON and hyperbaric oxygen therapy as a treatment modality, Klin. Pädiatr. 216 (6) (2004) 370–378.
[107] D. Kusz, A. Franek, R. Wilk, P. Dolibog, E. Blaszczak, P. Wojciechowski, P. Krol, P. Dolibog, B. Kusz, The effects of treatment the avascular necrosis of the femoral head with extracorporeal focused shockwave therapy, Ortop. Traumatol. Rehabil. 14 (5) (2012) 435–442.
[108] F. Gao, W. Sun, Z. Li, W. Guo, W. Wang, L. Cheng, D. Yue, N. Zhang, A. Savarin, Extracorporeal shock wave therapy in the treatment of primary bone marrow edema syndrome of the knee: a prospective randomised controlled study, BMC Muscoskelet. Disord. 16 (2015) 379.
[109] C.J. Wang, J.H. Cheng, C.C. Huang, H.K. Yip, S. Russo, Extracorporeal shockwave therapy for avascular necrosis of femoral head, Int. J. Surg. 24 (Pt B) (2015) 184–187.
[110] C.J. Wang, F.S. Wang, J.Y. Ko, H.Y. Huang, C.J. Chen, Y.C. Sun, Y.J. Yang, Extracorporeal shockwave therapy shows regeneration in hip necrosis, Rheumatology 47 (4) (2008) 542–546.
[111] Y.C. Fu, C.C. Lin, J.K. Chang, C.H. Chen, I.C. Tai, G.J. Wang, M.L. Ho, A novel single pulsed electromagnetic field stimulates osteogenesis of bone marrow mesenchymal stem cells and bone repair, PLoS One 9 (3) (2014) e91581.
[112] M.A. Mont, D.S. Hungerford, Non-traumatic avascular necrosis of the femoral head, J Bone Joint Surg Am 77 (3) (1995) 459–474.
[113] W. Pepke, P. Kasten, N.A. Beckmann, P. Janicki, M. Egermann, Core decompression and autologous bone marrow concentrate for treatment of femoral head osteonecrosis: a randomized prospective study, Orthop. Rev. 8 (1) (2016) 6162.
[114] R.K. Sen, S.K. Tripathy, S. Aggarwal, N. Marwaha, R.R. Sharma, N. Khandelwal, Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study, J. Arthroplasty 27 (5) (2012) 679–686.
[115] P. Hernigou, M. Trousselier, F. Roubineau, C. Bouthors, N. Chevallier, H. Rouard, C.H. Flouzat-Lachaniette, Stem cell therapy for the treatment of hip osteonecrosis: a 30-year review of progress, Clin. Orthop. Surg. 8 (1) (2016) 1–8.
[116] D. Zhao, D. Cui, B. Wang, F. Tian, L. Guo, L. Yang, B. Liu, X. Yu, Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells, Bone 50 (1) (2012) 325–330.
[117] P. Hernigou, A. Poignard, O. Manicom, G. Mathieu, H. Rouard, The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone, J Bone Joint Surg Br 87 (7) (2005) 896–902.
[118] L. Wells, H.S. Hosalkar, E.A. Crawford, N. Agrawal, J. Goebel, J.P. Dormans, Thorough debridement under endoscopic visualization with bone grafting and stabilization for femoral head osteonecrosis in children, J. Pediatr. Orthop. 29 (4) (2009) 319–326.
[119] H. Clar, A. Pascher, N. Kastner, G. Gruber, T. Robl, R. Windhager, Matrix-assisted autologous chondrocyte implantation into a 14cm(2) cartilage defect, caused by steroid-induced osteonecrosis, Knee 17 (3) (2010) 255–257.
[120] E.J. Karimova, S.N. Rai, J. Wu, L. Britton, S.C. Kaste, M.D. Neel, Femoral resurfacing in young patients with hematologic cancer and osteonecrosis, Clin. Orthop. Relat. Res. 466 (12) (2008) 3044–3050.
[121] R. Niinimaki, L.M. Hansen, T. Niinimaki, J.H. Olsen, T. Pokka, R. Sankila, K. Vettenranta, H. Hasle, A. Harila-Saari, Incidence of severe osteonecrosis requiring total joint arthroplasty in children and young adults treated for leukemia or lymphoma: a nationwide, register-based study in Finland and Denmark, J. Adolesc. Young Adult Oncol. 2 (4) (2013) 138–144.