Aseptic Osteonecrosis in Children and Adolescents Treated for Hemato-Oncologic Diseases

A 13-Year Longitudinal Observational Study

Herwig Lackner, MD, Martin Benesch, MD,* Andrea Moser, MD,* Freya Smolle-Jüttner, MD,† Wolfgang Linhart, MD,‡ Johann Raith, MD,§ and Christian Urban, MD**

Summary: Aseptic osteonecrosis (AON) is a serious long-term complication of childhood cancer therapy. A retrospective study was undertaken to describe treatment and long-term follow-up of patients with AON. Between 1990 and 2003, 630 consecutive children with various malignancies were treated at the University Children's Hospital in Graz, Austria. In nine of these patients presenting with skeletal symptoms, MRI revealed AON. All nine had hematologic malignancies. The median age at diagnosis of malignancy was 15.8 years (range 13.7–18.6 years), and the median interval between diagnosis of malignancy and onset of osteonecrosis-related symptoms was 16 months (range 6–53 months). All patients had received previous corticosteroid therapy. Treatment of AON included restriction of weight-bearing, physiotherapy, and analgesics. Three patients were treated with hyperbaric oxygen therapy combined with the prostacyclin analog iloprost, and one patient also received pamidronate, a second-generation bisphosphonate. This conservative treatment resulted in alleviation of symptoms in all patients. One patient had to undergo bilateral hip replacement and two had to undergo arthrotomy with sequestrotomy due to subsequent deterioration of symptoms. Close monitoring for skeletal symptoms is mandatory during follow-up of patients with hematologic malignancies. Previous corticosteroid treatment and age older than 10 years seem to be major risk factors. Early detection of AON leading to prompt intervention may prevent more severe morbidity.

Key Words: aseptic osteonecrosis, children, hematological malignancies, therapy

(*J Pediatr Hematol Oncol* 2005;27:259–263)

Received for publication September 25, 2004; accepted March 10, 2005.

From the *Division of Pediatric Hematology/Oncology, Department of Pediatrics and Adolescence Medicine, Medical University of Graz, Graz, Austria; †Division of Thoracic and Hyperbaric Surgery, Department of Surgery, Medical University of Graz, Graz, Austria; ‡Division of Pediatric Orthopedics, Department of Pediatric Surgery, Medical University of Graz, Graz, Austria; and §Department of Radiology, Medical University of Graz, Graz, Austria.

Reprints: Martin Benesch, Division of Pediatric Hematology and Oncology, Department of Pediatrics, Medical University of Graz, Auenbruggerplatz 30, A-8036 Graz, Austria (e-mail: martin.benesch@klinikum-graz.at).

Aseptic osteonecrosis (AON), also known as avascular necrosis, is a rare long-term complication of childhood cancer therapy that can result in significant morbidity and alteration of quality of life. There are only a few reports of AON in patients with lymphoma or leukemia in the literature, most of them describing the incidence, risk factors, and diagnostic studies.[1–7] Incidence rates vary widely depending on the time the study was conducted and the methods used for diagnosis. Mattano et al reported a 3-year cumulative incidence of 9% in children treated for acute lymphoblastic leukemia (ALL).[8] In another study using MRI screening, AON was detected in 9 of 24 patients (38%) with ALL, 6 of whom were asymptomatic.[9] As AON can be detected in completely asymptomatic patients, the true incidence remains unknown.

Pathogenetically, corticosteroids are considered the main etiologic factor for AON in children with malignancies.[4–8] As AON may also occur following chemotherapy not containing steroids,[3,10–12] other factors such as cytostatic drugs, immobilization, or the malignancy itself may contribute to the development of this disease. The clinical spectrum of AON ranges from asymptomatic patients to patients with significant bone pain and loss of function, sometimes necessitating total joint replacement.[6,8,9] Since data on the long-term outcome of pediatric cancer patients with AON are rare, additional information is urgently needed. The present retrospective, observational study describes a single-center experience with AON over a period of 13 years.

PATIENTS AND METHODS

Patients

From 1990 to 2003, 630 consecutive children with various malignancies were treated at the University Children's Hospital in Graz, Austria. Diagnosis was ALL in 116 patients, acute myelogenous leukemia (AML) in 50 patients, Hodgkin's disease (HD) in 45 patients, non-Hodgkin's lymphoma (NHL) in 28 patients, and a solid tumor in 391 patients. Treatment was carried out according to the respective national and international cooperative therapy studies.[13–17] After completion of cancer therapy, all patients entered a detailed follow-up program including careful clinical and tumor-specific examinations at yearly intervals to evaluate possible tumor- and treatment-related side effects, as previously described.[18]

During the observation period of 13 years, 9 of the 630 patients developed symptoms suspicious of AON, including

bone pain or impairment of joint function. All MRI examinations were performed on a 1.5-Tesla device (Siemens Magneton Symphony or Philips Gyroscan Intera ACS-NT). Longitudinal and axial T2-weighted and unenhanced and gadolinium-enhanced T1-weighted sequences with and without fat saturation of the clinically indicated region of interest were acquired. The images were reviewed and analyzed in consensus by two radiologists. Geographically margined lesions within the bone marrow with a typical low-intensity rim on T1-weighted sequences[9,19] were interpreted as AON.

Informed consent was obtained from the patients and/or their parents before entering this follow-up program.

All patients with radiographically confirmed AON received conservative first-line treatment including restricted weight-bearing (crutches and/or wheelchair), physical therapy, and administration of nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with unacceptable bone pain or severe impairment of joint function not responding to initial treatment were considered for alternative treatment including hyperbaric oxygen (HBO) therapy or administration of the prostacyclin analog iloprost (Ilomedin; Schering Vienna, Vienna, Austria) and/or pamidronate, a second-generation bisphosphonate (Aredia; Novartis Pharma, Vienna, Austria). HBO was applied as suggested for osteoradionecrosis.[20,21] It was delivered for 90 minutes at 2.4 bar absolute pressure with two breaks of 10 minutes, during which the patients breathed pressured air. HBO therapy was administered once a day for 30 consecutive days. Iloprost was given intravenously at a dose of 50 μg/d over 6 hours on 5 consecutive days.[22,23] Pamidronate was administered intravenously at a dose of 45 mg every third day, three times.[24] Patients whose symptoms further deteriorated on conservative treatment underwent surgical treatment including joint replacement or arthrotomy with sequestrotomy.

RESULTS

Patients

Of 630 children, 9 (7 boys, 2 girls) (1.4%) developed AON (Table 1). The median age at diagnosis of malignancy was 15.8 years (range 13.7–18.6 years). The underlying malignancies were ALL (n = 4), NHL (n = 2), HD (n = 2), and AML (n = 1). Compared with the whole study cohort, AON occurred in 4 of the 116 patients (3.4%) with ALL, 2 of the 28 patients (7.1%) with NHL, 2 of the 45 patients (4.4%) with HD, and 1 of the 50 patients (2%) with AML. For patients older than 10 years of age, the incidence rates were as follows: ALL 19% (4/21), NHL 10% (2/20), HD 4.9% (2/41), and AML 4.5% (1/22).

The median interval between diagnosis of malignancy and clinical manifestation of AON was 16 months (range 6–53 months). In all patients, AON was located in weight-bearing extremities (femur or tibia). In three patients (patients 2–4), AON also involved the upper extremities. Seven patients had multiple bone lesions (Fig. 1), and two patients (patient 1 and 5) had single lesions.

Treatment

Table 2 summarizes treatment and outcome data. Oncologic treatment was carried out according to the cooperative treatment protocols ALL-BFM 90 and 2000, NHL-BFM 90 and 95, GPOH-HD 95, AML-BFM 98, ALL-REZ BFM PILOT 2002, and AML-BFM 98 and AML-BFM REZ 97.[13–17] All patients had received prednisone at a median dose of 1,980 mg/m^2 (range 480–4,200 mg/m^2); six patients had also received dexamethasone at a median dose of 270 mg/m^2 (range 270–1,080 mg/m^2).

Treatment of AON consisted of restriction of weight-bearing, physiotherapy, and NSAIDs in all patients. Three patients also received HBO therapy combined with intravenous iloprost (patients 5, 7, and 9); one patient in addition received intravenous pamidronate (patient 7). Conservative treatment led to significant subjective improvement of symptoms in all patients, although follow-up MRI studies remained unchanged so far. Deterioration of symptoms resulted in bilateral hip replacement in one patient (patient 4) and arthrotomy with sequestrectomy in two patients (patients 2 and 5). Despite AON, oncologic treatment was not altered in any of the patients. None of the study patients received steroids after the diagnosis of AON.

TABLE 1. Clinical Characteristics of Nine Patients With Aseptic Osteonecrosis

Pt. No.	Sex	Diagnosis of Malignancy	Age at Diagnosis of Malignancy	Interval Between Diagnosis of Malignancy and Clinical Manifestation of AON	Localization of AON
1	M	NHL	16	24	Left femoral head
2	M	ALL	17	15	Both femoral and tibial condyles, left distal humerus
3	F	HD IIIB	15	53	Both femoral and tibial condyles, left distal humerus
4	F	ALL	16	26	Both femoral and humerus heads
5	M	AML relapse	16.7	21	Right femoral head
6	M	HD IVB	18	6	Both tibial condyles and right femoral shaft
7	M	NHL IV	13.7	10	Both femoral and tibial condyles
8	M	ALL relapse	18.6	16	Both femoral and tibial condyles
9	M	ALL	15.8	10	Both femoral and tibial condyles

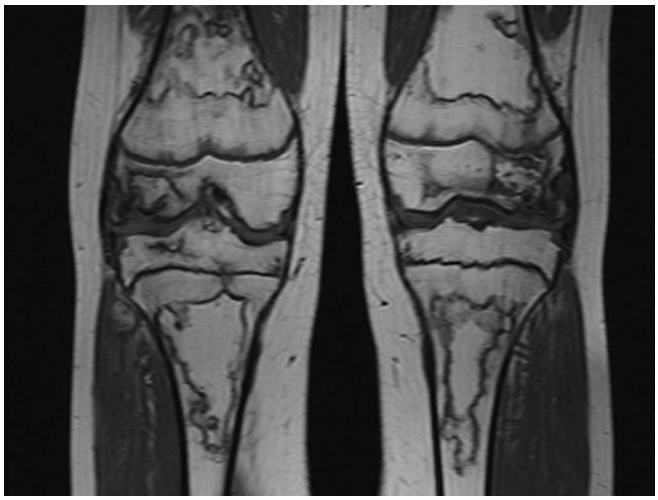

FIGURE 1. Patient 7 presented with bone pain and impaired joint function of both knees during reinduction therapy for NHL. Coronal T1-weighted MRI (1.5 T; SE, TR 707 msec/TE 20 msec) of the knees showed bilateral circumscribed osteonecrotic lesions in both femoral and tibial condyles and in the adjacent metaphysis of the distal femur and the proximal tibia.

Outcome

By January 2004, all patients were alive in first remission (7/9 patients) or second remission (2/9 patients). Median follow-up since diagnosis of malignancy was 2.6 years (range 1.5–11.3 years), with two patients still receiving oncologic therapy (patients 8 and 9). Six patients were completely asymptomatic, whereas AON-related symptoms improved in the other three patients. The median duration of follow-up after initial improvement was 2 years (range 0.7–9.5 years).

DISCUSSION

In this series, AON was observed in 1.4% of the entire study population: 3.4% of patients with ALL, 7.1% of patients with NHL, 4.4% of patients with HD, and 2% of patients with AML. These data are consistent with earlier reports describing incidence rates of 1% to 9%.[4,6,8] Since diagnostic studies were done only in symptomatic patients, the true incidence might be higher. Furthermore, some of our patients may still develop AON during further follow-up. However, when only patients older than 10 years of age were considered, incidence rates ranged from 4.5% (AML) to 19% (ALL).

MRI has been proven to be the technique of choice to identify AON in pediatric cancer patients with bone pain.[9,19] Whether MRI screening should be introduced in regular follow-up programs is a matter of debate. In our institution, early MRI is done in every patient with bone pain or impaired joint function, but general MRI screening is not proposed.

Most of the reports on children with malignancies and AON suggest corticosteroids to be the main pathogenetic factor for AON.[1,2,4–6,8] In this context dexamethasone is considered to be more toxic to the skeletal system than prednisone.[6,8] In this study all nine patients with AON had

TABLE 2. Treatment Data and Outcomes

Pt. No.	Treatment Protocol	Cumulative Corticosteroid Dose (mg/m^2)	Treatment of AON	Outcome	Follow-up Since Initial Improvement (years)
1	NHL-BFM 90	PRED 1980 DXM 270	Restricted weight bearing, analgesics	First remission asymptomatic	9.5
2	ALL-BFM 90	PRED 1980 DXM 270	Restricted weight bearing, analgesics, arthrotomy with sequestrotomy (left knee)	First remission, minimal residual complaints during exercise	7.0
3	GPOH-HD 95	PRED 4200	Restricted weight bearing, analgesics	First remission, asymptomatic	4.3
4	ALL-BFM 90	PRED 1980 DXM 270	Restricted weight bearing, analgesics, bilateral hip replacement	First remission, asymptomatic	6.4
5	AML-BFM 98, AML-BFM REZ 97, auto-PSCT	PRED 1200	Restricted weight bearing, analgesics, HBO therapy, iloprost, arthrotomy with sequestrotomy (left knee)	Second remission, asymptomatic	1.0
6	GPOH-HD 95	PRED 4200	Restricted weight bearing, analgesics	First remission, asymptomatic	1.3
7	NHL-BFM 95	PRED 1980 DXM 270	Restricted weight bearing, analgesics, HBO therapy, iloprost, pamidronate	First remission, improvement	2.0
8	ALL-BFM REZ PILOT 02	PRED 2280 DXM 1080	Restricted weight bearing, analgesics	Second remission, asymptomatic	1.0
9	ALL-BFM 2000	PRED 480 DXM 550	Restricted weight bearing, analgesics, HBO therapy, iloprost	First remission, minimal residual complaints	0.7

DXM, dexamethasone; PRED, prednisone; PSCT, peripheral stem cell transplantation.

received prednisone (median cumulative dose 1,980 mg/m^2), and six of the nine were also given dexamethasone (median cumulative dose 270 mg/m^2). Our data support the hypothesis that corticosteroid administration is a major risk factor for the development of AON. Treatment intensification with dexamethasone, as proposed by the BFM protocols, may therefore result in an increased incidence of AON in patients with ALL and NHL in the future. Age older than 10 years at diagnosis of malignancy has been recognized as another important risk factor for AON.[6,8] Some authors argue that the maturing bones of adolescents might be more susceptible to the development of AON.[6,8] The age distribution of our study population was in accordance with published data[1,8] showing that mostly adolescents older than 10 years old develop AON. This indicates that younger children, even those with high steroid exposure, seem less likely to be affected. AON is reported to occur predominantly in females,[8,9,19] but in our series AON was more common in boys than girls. Due to the small number of patients in our study, however, no definitive epidemiologic conclusions can be drawn.

Data concerning the optimal treatment of AON in childhood cancer patients are rare. Most investigators propose conservative treatment including relief of weight-bearing structures, physiotherapy, and NSAIDs, followed by surgical therapy in severe cases.[1,4,10,19] Other conservative treatment options (eg, HBO, iloprost, or bisphosphonates) have been only sporadically reported. The rationale for HBO treatment is that due to the high ambient pressure with the patient breathing 100% oxygen, the latter dissolves in the plasma. The solubilized oxygen supplies areas within AON where reduced blood flow impedes oxygenation by hemoglobin-bound O_2. Osseous repair induced by HBO alone has been reported.[12,19–21] Iloprost, a prostacyclin analog, has been used to treat juvenile bone marrow edema of the talus and the acetabulum, and it seems to cause dilatation of arterioles and venules and reduction in the permeability of capillaries.[22,23] Bisphosphonates might be another therapeutic option to improve bone mineralization and to reduce corticosteroid-induced osteoporosis.[24] Statin therapy and coagulation studies have been performed in adults, but the efficacy and safety of these treatment modalities in children with AON have yet to be determined.[25,26] In our series, three patients (patients 5, 7, and 9) with deterioration of symptoms and severe impairment of joint function despite physical therapy and NSAIDs received HBO treatment combined with iloprost. One of them (patient 7) also was treated with pamidronate, and another one (patient 5) also underwent arthrotomy with sequestrotomy. In all three patients dramatic improvement of clinical symptoms was observed, although MRI findings remained unchanged.

Although our observations suggest that multimodal treatment of AON led to clinical response and durable improvement of AON-related symptoms, the small number of patients and the relatively short duration of follow-up do not allow us to make definitive recommendations for the treatment of AON. Large-scale prospective studies evaluating HBO therapy and the administration of iloprost in addition to the generally applied conservative treatment (physical therapy, NSAIDS), probably in a randomized design, would be helpful to identify appropriate therapy for patients with AON.

The goal of this observational study was to increase the physician's awareness of the diagnosis of AON in long-term survivors of childhood cancer therapy. AON is a rare but serious complication in these patients, sometimes resulting in significant alteration of quality of life. Early recognition and initiation of adequate therapy are necessary to prevent morbidity, but the optimal treatment of AON remains to be defined.

REFERENCES

1. Prindull G, Weigel W, Jentsch E, et al. Aseptic osteonecrosis in children treated for acute lymphoblastic leukemia and aplastic anemia. *Eur J Pediatr*. 1982;139:48–51.
2. Felix C, Blatt J, Goodman MA, et al. Avascular necrosis of bone following combination chemotherapy for acute lymphocytic leukemia. *Med Pediatr Oncol*. 1985;13:269–272.
3. Ishii E, Yoshida N, Miyazaki S. Avascular necrosis of bone in neuroblastoma treated with combination chemotherapy. *Eur J Pediatr*. 1984;143:152–153.
4. Bömelburg T, von Lengerke HJ, Ritter J. Aseptic osteonecroses in the treatment of childhood acute leukaemias. *Eur J Pediatr*. 1989;149: 20–23.
5. Murphy RG, Greenberg ML. Osteonecrosis in pediatric patients with acute lymphoblastic leukemia. *Cancer*. 1990;65:1717–1721.
6. Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol*. 2001;19:3066–3072.
7. Levien MG. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *Clin Pediatr (Phila)*. 2002;41:63–64.
8. Mattano LA Jr, Sather HN, Trigg ME, et al. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol*. 2000;18:3262–3272.
9. Ojala AE, Lanning FP, Pääkkö E, et al. Osteonecrosis in children treated for acute lymphoblastic leukemia: a magnetic resonance imaging study after treatment. *Med Pediatr Oncol*. 1997;29:260–265.
10. Bojko P, Hilger RA, Ruehm SG, et al. Femoral head necrosis in three patients with relapsed ovarian cancer receiving high-dose chemotherapy followed by autologous peripheral stem cell transplantation. *Bone Marrow Transplant*. 2003;31:487–491.
11. Mascarin M, Giavitto M, Zanazzo GA, et al. Avascular necrosis of bone in children undergoing allogeneic bone marrow transplantation. *Cancer*. 1991; 68:655–659.
12. Bernbeck B, Krauth KA, Scherer A, et al. Aseptic osteonecrosis in a child with nephroblastoma healed by hyperbaric oxygen therapy. *Med Pediatr Oncol*. 2002;39:47–48.
13. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. *Blood*. 2000;95:3310–3322.
14. Reiter A, Schrappe M, Tiemann M, et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: a report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. *Blood*. 1999;94:3294–3306.
15. Dörffel W, Lüders H, Rühl U, et al. Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: analysis and outlook. *Klin Pädiatr*. 2003;215:139–145.
16. Attarbaschi A, Mann G, Dworzak M, et al. Malignant non-Hodgkin's lymphoma of childhood and adolescence in Austria: therapy results between 1986 and 2000. *Wien Klin Wochenschr*. 2002;114:978–986.
17. Reinhardt D, Langebrake C, Creutzig U, et al. Minimal residual disease in acute myeloid leukemia in children: standardization and evaluation of immunophenotyping in the AML-BFM-98 study. *Klin Pädiatr*. 2002;214: 179–187.

18. Lackner H, Benesch M, Schagerl S, et al. Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years. *Eur J Pediatr*. 2000;159:750–758.
19. Scherer A, Engelbrecht V, Krauth KA, et al. MRI follow-up study of aseptic osteonecrosis (AON) in children treated with chemotherapy for malignant diseases. *Klin Pädiatr*. 2001;213:56–62.
20. Marx RE. Clinical applications of hyperbaric oxygen. In: Kindwall EP, ed. *Hyperbaric Medicine Practice*. Arizona: Best Publishing, 1995:464–468.
21. Chavez JA, Adkinson CD. Adjunctive hyperbaric oxygen in irradiated patients requiring dental extractions: outcomes and complications. *J Oral Maxillofac Surg*. 2001;59:518–522.
22. Aigner N, Petje G, Steinboeck G, et al. Treatment of bone marrow oedema of the talus with the prostacyclin analogue iloprost. An MRI-controlled investigation of a new method. *J Bone Joint Surg [Br]*. 2001;83:855–858.
23. Aigner N, Petje G, Schneider W, et al. Juvenile bone-marrow oedema of the acetabulum treated by iloprost. *J Bone Joint Surg [Br]*. 2002;84:1050–1052.
24. Varenna M, Zucchi F, Binelli L, et al. Intravenous pamidronate in the treatment of transient osteoporosis of the hip. *Bone*. 2002;31:96–101.
25. Pritchett JW. Statin therapy decreases the risk of osteonecrosis in patients receiving steroids. *Clin Orthop*. 2001;386:173–178.
26. Glueck CJ, McMahon RE, Bouquot JE, et al. A preliminary pilot study of treatment of thrombophilia and hypofibrinolysis and amelioration of the pain of osteonecrosis of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85:64–73.

