Osteonecrosis in Children and Adolescents With Acute Lymphoblastic Leukemia: Early Diagnosis and New Treatment Strategies

GIADA BIDDECI¹, GERARDO BOSCO², ELENA VAROTTO¹, MARCO CORRADIN³,
GIULIA GERANIO¹, GLORIA TRIDELLO⁴, MARTA PILLON¹, ELISA CARRARO¹,
GIACOMO GARETTO⁵, ROYA ASSADI⁵, COSIMO GIGANTE³ and MARIA CATERINA PUTTI¹

¹Department of Women's and Children's Health, Pediatric Haemato-Oncology, University of Padua, Padua, Italy;

²Department of Biomedical Sciences, University of Padua, Padua, Italy;

³Pediatric Orthopedic Unit, Orthopedic Surgery Department, University of Padua, Padua, Italy;

⁴Pediatric Hematology Oncology, University Hospital, Verona, Italy;

⁵ATIP Hyperbaric Medical Center, Biomedical Science Department, Padua, Italy

Abstract. *Background/Aim:* In the last few decades, treatment strategies for acute lymphoblastic leukemia (ALL) have been associated not only with improvement of prognosis, but also with an increasing rate of late complication as osteonecrosis (ON). Herein, the cumulative incidence, risk factors, new conservative therapeutic strategies as hyperbaric oxygen therapy (HBO), and outcome of symptomatic ON were studied in pediatric patients with ALL. *Patients and Methods:* Between 2000 and 2017, 495 children and young adolescents with a diagnosis of ALL were evaluated. All the symptomatic patients underwent magnetic resonance imaging (MRI) to detect bone vascularization and structure. *Results:* Twenty-three out of 495 patients presented ON (4.6%). ON was associated with an older age ($p<0.0001$) and a higher steroid dose ($p=0.0013$). All the patients underwent standard therapies and HBO was performed in 8 of 23 patients. During the follow-up, 15 patients were stable: 6 were totally asymptomatic, 5 complained of pain during activity, and 4 presented mild function limitation. *Conclusion:* Our data highlight the importance of early diagnosis of ON by screening MRI in asymptomatic patients, in order to start conservative treatment strategies. Moreover, HBO could have beneficial effects on ON patients.

Correspondence to: Gerardo Bosco, MD, Ph.D., Environmental Physiology and Medicine Laboratory, Department of Biomedical Sciences, University of Padova, Via Marzolo, 3, 35131 Padua, Italy. Tel: +39 0498275297, Fax: +39 0498275301, e-mail: gerardo.bosco@unipd.it

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Osteonecrosis (ON) is one of the most disabling late complications of pediatric acute lymphoblastic leukemia (ALL) treatment, with an incidence up to 17.6% in pediatric (1). Depending on the stage of ON, symptoms can range from asymptomatic to highly debilitating, with severe pain, limited range of joint motion up to joint destruction (2).

ON in children with ALL has a multifactorial origin; the necrosis of bone tissues due to vascular causes is considered important. The presumed pathogenic mechanism lies in altered bone vascularization, which leads to a demineralization and trabecular thinning of bone structure, causing mechanical failure (1). Glucocorticoid therapy has been identified as the main contributing factor to ON. Steroid dose and administration rate (continuous *versus* intermittent) seem to be important, whereas the role of different steroid potency, *e.g.* dexamethasone (DXM) compared to prednisone (PDN), is not clear (3, 4). According to many authors, DXM is not associated with increased incidence of ON (5). Moreover, L-asparaginase treatment may contribute to the impairment of blood circulation in the bone, as a consequence of a hypercoagulable state (2, 6, 7).

ON is more frequent in older children, especially over 10 years of age and is associated with Caucasian ethnicity and impairment of ACP1, PAI-1 genes (8, 9). The impact of gender is still not clear; according to some studies, female gender is associated with increased risk of ON (1). With an incidence of 1.4% up to 17.6% (1, 4), ON is more frequent after hematopoietic stem cell transplantation (HSCT), probably due to the high dose of steroids administered for this therapy (4). Moreover, ON rate is higher in screening studies (22%), where magnetic resonance imaging (MRI) is performed in asymptomatic patients at fixed time points (10). ON is usually localized in the lower limbs joints, primarily knee and hip. This suggests that avascular necrosis mostly affects weight-bearing

epiphyseal bone with a vulnerable blood supply (11). Multiple joint involvement is also common (4).

MRI is the gold-standard diagnostic tool to identify early stage ON, when direct radiography is still negative (12, 13). Different radiological classifications have been proposed, but Association Research Circulation Osseus (ARCO) grading score is the most used (14, 15).

A standardized protocol treatment for ON does not exist (2). Anti-inflammatory drugs, vitamin D, and bisphosphonate play a role as supportive therapies. Nevertheless, 20-22% of patients with ON need a surgical approach after an average time of 2.2 years from diagnosis (16, 17). Surgery may decrease pain and improve mobility. In adults with ON, joint decompression may be effective in preventing subsequent joint collapse (18). Recently, implantation of autologous osteogenic cells or osteochondral grafting has been described (14, 19). Moreover, hyperbaric oxygen therapy (HBO) has a beneficial impact on ON providing a higher oxygen concentration to all tissues and ischemic bone cells as well (20, 21). There is no evidence that HBO acts on tumor growth and recurrence, *in vitro*, while *in vivo* and clinical studies suggest a neutral effect of HBO on tumor growth (22). Instead, putative mechanisms and benefits have been found by modulating antioxidant and inflammatory responses (23-25).

ON treatment is still controversial and undefined. Given the uncertainties in this field, clinical and real-life reports are warranted. Randomized studies are difficult, due to the small number of affected patients and their heterogeneity. Herein, we studied the cumulative incidence, risk factors, new conservative therapeutic strategies, and outcome of symptomatic ON in pediatric patients with ALL. The prevalence and risk factors of ON in homogeneously treated children with ALL, were retrospectively analyzed to identify strategies for early diagnosis and precocious conservative treatment with HBO.

Patients and Methods

Patients. We retrospectively evaluated 495 children and young adolescent ALL patients, diagnosed and treated at the Clinic of Pediatric Hematology-Oncology of Padua University Hospital between September 2000 and February 2017. Patients were treated according to the Protocols used in Associazione Italiana di Emato-Oncologia Pediatrica (AIEOP) Centers: AIEOP ALL 2000 Protocol from 2000 to 2011 and AIEOP-BFM ALL 2009 Protocol from 2012 to February 2017. Informed consent was obtained from parents and adolescent patients, as approved by the local Ethical Committee. Age at diagnosis, gender, immunophenotype, treatment risk arm, HSCT in first remission, death or relapse, number and site of ON, and bone lesions at diagnosis were recorded for each patient.

Both chemotherapy protocols had similar backbones. Two different steroids were administered: PDN in the initial Induction phase and DXM later in the Delayed Intensification phase (Table I). Patients with a more aggressive leukemia, defined as "high risk" (HR), were treated with more intensive chemotherapy and higher doses of

steroids. Each ALL patient presenting with symptoms (joint pain, functional limitation) underwent X-Ray and MRI examination. A pediatrician and an orthopedic surgeon independently classified ON radiological signs according to ARCO criteria. Controversial cases were monitored and re-evaluated within one to three months according to a flow-chart protocol developed in our Center (Figure 1). Radiological evaluation was repeated every 3-6 months, depending on severity and treatment. Clinical presentation of ON was graded using CTCAE criteria (26). At first, patients were treated with conservative methods, usually weight discharge. HBO therapy was administered using DRASS Galeazzi Model device (Livorno, Italy), as follows: daily administration of 3 fractions of 25 min at O₂ 100% alternated with 5 min of air at 2.5 absolute atmospheres (A.T.A), for at least 30 consecutive sessions. Surgical core decompression was performed for persisting pain or radiological images worsening. Joint replacement was chosen in case of progressive disease (27).

Statistical analysis. Demographic and clinical characteristics of patients were represented through descriptive methods: absolute frequencies and percentages were used for dichotomous and categorical variables, whereas continuous variables were expressed by median, range, mean, and standard deviation. We studied the association between the analyzed variables (age ≤ 10 years or >10 years, gender, therapeutic risk group) and the onset of ON using the Chi-square test or Fisher test for categorical variables. Variables that were significant by univariate analysis were further studied by multivariate logistic regression analysis. Wilcoxon test was used to compare the dose of steroid received by patients with ON. Variables with a p -value <0.05 were considered significant. The statistical analysis was performed using SAS v 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

The main demographic, hematological and clinical features of our patients (age, immunophenotype, risk group, bone injuries at leukemia onset, HSCT, relapse or death) are reported in Table II. Most of the ALL patients (76.2%) were under 10 years of age [$p=0.001$; Odds ratio (OR)=13.25, CI=5.84-30.07]. Seventy-six children (15.3%) received HR therapy. Median follow-up was 38.3 months (range=8-170) at the time of this study. We identified ON in 23/495 patients (4.6%); of them, 20 were over 10 years of age. The prevalence of ON was significantly higher in older children (16.9% vs. 0.8%, $p<0.0001$), while it did not differ between the two genders. We found that 43% of ON patients had reached puberty (stage 3) and 13% had body mass index (BMI) >15 ; statistical significance could not be analyzed, since information about BMI were available only for ON patients.

HR patients showed an increased prevalence of ON (9/76, 11.8%) compared to NHR patients (11/419, 2.6%, $p=0.0013$) (Table II). The mean dose of DXM received was significantly higher in HR patients ($p=0.0015$) compared to NHR group. Moreover, the mean PDN doses received by HR and NHR patients with ON were comparable. Transplanted patients represent a peculiar group; they received a significantly higher dose of PDN compared to the NHR and HR groups ($p=0.012$),

Table I. Steroids used in the treatment of ALL children: doses and length of administration.

	PDN	DXM
Pre-phase		
Dose	60 mg/m ²	-
Duration	7 days	-
Induction		
Dose	60 mg/m ²	10 mg/m ²
Duration	28 days	28 days
		(in T ALL NHR in Protocol 2009)
Consolidation (HR patients)		
Dose	-	20 mg/m ²
Duration	-	5 days, 3 times
Delayed Intensification		
Dose	-	10 mg/m ²
Duration		NHR: 4 weeks
		HR: 3 weeks, 3 times

ALL, Acute lymphoblastic leukemia; PDN, prednisone; DXM, dexamethasone; HR, high risk; NHR, non-high risk.

and a similar dose of DXM compared to the HR group. Three patients presented ON after bone marrow transplantation: the prevalence of ON in this population is not significantly higher compared to other patients ($p=0.47$), probably due to the exiguity of the sample. Two of 3 transplanted patients received very high doses of PDN (5700 mg/m² and 4090 mg/m², respectively) after HSCT because of graft *versus* host disease (GVHD); the third patient did not receive any additional dose of steroids; he had total body irradiation (TBI) as part of conditioning therapy (Table II).

The majority of patients presented ON in the last part of the chemotherapy period (Delayed Intensification or Maintenance) or after stopping chemotherapy: median time of onset was 17 months (range=8-63) from diagnosis of ALL. At the time of diagnosis (Table III), all patients were symptomatic, usually severely: 5 patients presented only pain (CTCAE 2) and 18 patients presented pain and functional limitation (CTCAE 3). Most patients were classified in advanced radiological stages (ARCO 3-4:12 patients) at first examination. Six out of 23 children (26%) showed a single site of ON, whereas 17 (74%) presented multiple sites at onset. Lower limbs were most frequently involved, in particular hips, knees and ankles.

Five patients with ON presented further additional sites at a subsequent time-point; clinical evolution during follow-up is also shown in Table III.

All patients were at first treated using conservative therapy. Joint discharge was prescribed to all children but was accomplished only in 13/23 (56.5%) of them; 10/23 (43.4%) received anti-inflammatory drugs; occasional children received other therapies (vitamin D and calcium

Figure 1. Diagnostic flow chart for osteonecrosis. MRI, Magnetic resonance imaging; ARCO, Association Research Circulation Osseus.

supplementation, physiotherapy, magneto-therapy) (Table IV). Only transient symptomatic improvement was obtained in some patients. In 8/23 children (34.8%) we administered HBO therapy, according to the availability of the procedure. Four out of the 8 children presented severe lesions (3 patients with ARCO 3, 1 patient with ARCO 4), 4 patients had mild-grade ON (3 patients with ARCO 2 and 1 patient with ARCO 1). Outcome of HBO therapy differed according to initial grading: 3 patients with mild grade of ON were stable at MRI controls; the 4 patients with severe lesions worsened and underwent joint replacement, one patient died early of a second neoplasia (mutation of p53 protein).

The median follow-up for all patients was 28.5 months (8-170 months). Sixteen patients were stable throughout the years: 6 are now asymptomatic, 5 present only pain during physical activity and 4 have mild functional limitations.

Six out of 23 patients (26%) presented at follow-up radiological and clinical worsening; another patient also complained of pain and functional limitation, in the presence of stable radiological findings. They all were considered CTCAE grade 4; 6 underwent joint replacement and one had articular drilling of femoral head. These 7 patients did not significantly differ from other ON patients in terms of age, puberty, gender and BMI.

Table II. Main clinical features of acute lymphoblastic leukemia (ALL) patients; comparison with children affected by osteonecrosis (ON).

	ALL patients	ON patients	Statistical significance [Method]
Total patients (n)	495	23	
Age (years)			
Median age	5.2	13.9	
Range	(1.1-19.8)	(5.2-19.1)	
Age<10 years, n (%)	377/495 (76.2%)	3/23 (0.8%)	$p=0.001$
Age >10 years, n (%)	118/495 (23.8%)	20/23 (86.9%)	[Multivariate analysis]
Gender			
Female	224/495 (45.2%)	11/23 (4.9%)	$p=0.8$ [Chi-square]
Male	271/495 (54.8%)	12/23 (52.1%)	
Immunophenotype			
B	431/495 (87%)	20/23 (87%)	$p=0.76$ [Chi-square]
T	64/495 (13%)	3/23 (13%)	
Bone injuries at diagnosis	11/495 (2.2%)	0	
Risk group			
HR	76/495 (15.3%)	9/23 (39%)	$p=0.0013$ [Chi-square]
NHR	419/495 (84.7%)	14/23 (61%)	
HSCT in 1st remission	46/495 (9.3%)	3/23 (13%)	$p=0.47$ [Chi-square]
Death/ALL relapse	49/495 (9.9%)	1/23 (4.3%)	
Steroid doses (mean dose)			
PDN mg/m ²			
HR		1698	Mean dose of PDN
NHR		1840	in HSCT > in NHR
HSCT		3863	$p=0.01$ [Wilcoxon test]
DXM mg/m ²			
HR		527	Mean dose of DXM
NHR		234	in HR > in NHR
HSCT		550	$p=0.0015$
			in HSCT > in NHR
			$p=0.0015$ [Wilcoxon test]

HR, High-risk; NHR, non-high risk; HSCT, hematopoietic stem cell transplantation; PDN, prednisone; DXM, dexamethasone.

Discussion

The global prevalence of osteonecrosis in our monocentric series was similar to what is reported by other Groups, both after chemotherapy (1.4-7.6%) and after HSCT (6.8%) (3, 4, 28, 29).

Since all our patients were diagnosed at onset of symptoms, in our report the incidence of ON at earlier stages is probably underestimated. Indeed, some studies have reported higher incidence (22% after chemotherapy and 44% after HSCT), when radiological examinations were used as screening early in the course of treatment, especially among those patients older than 10 years (10, 28).

Literature describes female gender, age over 10 years, and high doses of steroids as risk factors for the development of ON. It was speculated that the increase in estrogens in females could have a procoagulant effect, predisposing them to avascular necrosis (1). We could not confirm this finding, being females affected in the same rate of males in our series. In the present study, most patients with ON were older than 10 years and only occasionally ON was diagnosed

at a younger age (5.7 and 9 years). This difference was statistically significant also in multivariate analysis, underlying the importance of age as a risk factor for ON (OR=13.25, CI=5.84-30.07). We then can confirm the importance of older age as risk factor, irrespectively of gender (1, 4). This can be explained by the peculiar modalities of bone growth at adolescence, when the epiphyseal and metaphyseal vascular zones are separated by growth plates, with a reduced blood supply. Hormonal factors also contribute to modifying vascular resistance and consequently vascularization (1).

ON in our cohort was severe both clinically and radiologically. Moreover, it involved multiple sites at onset and spread to other sites at follow-up. Not only classical weight bearing bones were affected, but also foot, ankle and upper limbs, causing severe impairment and difficult treatment approach (Table IV). None of the children described by Salem had foot and arm involvement, while 10% of upper limbs involvement is described in the literature (11).

In the group of older children and adolescents, who experience fair percentages of event-free-survival (about

Table III. Clinical features of osteonecrosis (ON) at onset and at follow-up.

	at Onset	at Follow-up (8-170 months)
Site		
Single	6/23 (26%)	5/23 (21.7%)
Multiple	17/23 (74%)	18/23 (78.3%)
Lower limbs		
Hip	10/23 (43.5%)	11/23 (47.8%)
Knee	13/23 (56.5%)	15/23 (65.2%)
Pelvis	2/23 (8.7%)	2/23 (8.7%)
Ankle	5/23 (21.7%)	6/23 (26%)
Foot	2/23 (8.7%)	3/23 (13%)
Upper limbs		
Elbow	2/23 (8.7%)	3/23 (13%)
Shoulder	0	3/23 (13%)
ARCO		
1	3/23 (13%)	2 (8.7%)
2	8/23 (34.8%): 3 grade 2c	8 (34.8%): 6 grade 2c
3	11/23 (47.8%)	10 (43.5%)
4	1/23 (4.4%)	3 (13%)
Total n. of worsened lesions		6 (26%)
CTCAE		
1	0	6 (26%)
2	5 (21.7%)	5 (21.7%)
3	18 (78.3%)	4 (17.4%)
4	0	7 (30.5%)
Lost to follow-up		1 (4.4%)

ARCO, Association Research Circulation Osseus; CTCAE, Common Terminology Criteria for Adverse Events.

80%), ON represents a significant collateral burden in terms of chronic pain, impaired daily activities and quality of life (30). The high prevalence found in older children supports the necessity for specific diagnostic and therapeutic intervention in this age group.

Another relevant feature in our series is the incidence of ON in children treated in HR arm of our protocols. In particular, 11.8% of patients at HR experienced ON *versus* 2.6% of NHR patients. This difference was statistically significant in univariate analysis, but not in multivariate analysis, probably due to the differences regarding age of patients and steroid doses between the two groups. HR patients were significantly older than NHR; considering ON only in HR patients >10 years, the prevalence is 30.4% (7/23). Moreover, HR patients received higher doses of DXM than NHR, but the same dose of PDN. The importance of steroid therapy has been reported to be one of the main causes of ON, both in leukemia patients and in other diseases (2, 3). Glucocorticoid therapy induces a hypercoagulable state and interacts with other chemotherapy agents (L-asparaginase, methotrexate) (2, 6). The role of the different potency of steroid drugs in the development of ON is controversial. In fact some authors state that DXM is associated with a higher

Table IV. Conservative and surgical therapies in patients with osteonecrosis (ON).

Therapies	Patients with ON (n=23)
Conservative therapies	23/23 (100%)
- Joint discharge	13 (56.5%)
- Anti-inflammatory therapies	10 (43.5%)
- Vitamin D/calcium	5 (21.7%)
- Hyaluronic acid	2 (8.7%)
- Physiotherapy	3 (13%)
- Magneto therapy	1 (4.3%)
Hyperbaric therapy	8 (34.8%)
Surgery	
- Articular drilling	1 (4.3%)
- Joint prosthesis	6 (26%)

incidence of ON: the COG group only found a difference in incidence of ON when using DXM during induction phase for patients over 10 years (31, 32). On the other hand, the BFM group found no difference between patients receiving PDN and DXM (3, 4). In our experience all patients received both PDN and DXM in two different time points of treatment. All children received similar doses of PDN, while HR patients received a higher dose of DXM. Moreover, DXM was given to HR in multiple courses over a period of about 6 months. Both doses and modality of administration can be responsible for the ON effect (33).

Forty-six patients of our series underwent HSCT in first remission; 3 of them (6.5%) experienced ON. All of them were HR patients and had received higher doses of DXM. Two had received additional steroid therapy (usually PDN) as a treatment of transplant-related complications (28, 34).

In the experience of COG group any attempt to reduce the dose of steroids was successful in avoiding the onset of ON, but at the price of lower rates of cure. It showed a reduction in the ON incidence with the administration of intermittent DXM treatment instead of continuous steroids (days 1-7 and 15-21) at the same doses, but with higher rate of relapse (32). It is thus difficult to reduce ON without hampering the hematological results of chemotherapy protocols. However, by identifying children at higher risk of ON, it is possible to develop strategies for early screening. This might be useful only if successful treatment strategies are available.

There is no standard of care for the treatment of ON in children with ALL, especially for the early stages; meanwhile HBO showed itself to be safe and effective in most patients even those dose immunocompromised or critical ill (35, 36). Our preliminary experience in HBO (3

patients included in the present study and treated until 2014) suggested its implementation in our current treatment approach. Joint discharge, which was prescribed to all children, was not applied by almost 1/3 of them, who continued to lead almost normal activity. This suggests that, at least in some patients, pain and functional limitations were tolerable as demonstrated also at clinical follow-up. Others have found joint discharge is not useful in reducing the progression of ON (37). Analgesic therapy is also frequently used to reduce pain and functional limitation. The efficacy of bisphosphonates, used in adults for osteoporosis, arthrosis, algo-dystrophic syndrome and post-traumatic avascular necrosis, is still debated on children: pain reduction and functional improvement is described, but without radiological improvement (2, 13, 34). These drugs show a prolonged anti-osteoclastic effect; clodronate also has an anti-inflammatory effect with inhibition of cytokine release (38). However, their use does not show any effect on ON progression. In a previous study, we used bisphosphonate only rarely and we seldom found it effective (39).

Patients with severe symptomatic ON or progressive disease (30%) required surgical intervention. None of them have been subjected to revision until now. Most reported joint replacements are done within three years from ON diagnosis. A multicenter study showed that 37% of patients with joint replacement need a second surgery within 6 months from the first one (16). There is thus a general agreement to postpone hip replacement to a later age (40, 41). Articular drilling, core decompression together with stem cell therapy have been proposed (27). All these interventions require that ON is identified at early stages and their role is still not fully cleared.

In our experience, only children with early stage-ON could benefit from HBO treatment. Three out of 4 patients with mild ON (ARCO 1,2), treated by HBO therapy, did not evolve either clinically or at MRI. Half of our children were identified at late stages (ARCO 3-4) and most of them were highly symptomatic (CTCAE 3). Four of them received HBO therapy without success.

HBO is frequently used in adult patients for ON due to different causes. The mechanism of HBO action is still unclear, but seems to increase neo-vascularization in ischemic tissues, osteoblastic proliferation in ischemic bone modulating oxygen free radicals (42-44). Historically, it has been used to avoid dysbaric osteonecrosis and in osteomyelitis; it is well used in chronic bone pathology, as for osteoradionecrosis, bisphosphonate osteonecrosis of the jaw (45). HBO is prescribed in the treatment of non-healing lesions *via* reactive oxygen and nitrogen species modulation (44), but recently there is speculation that the underlying HBO mechanism is related to an augmented signaling for bone turnover and osteoclast differentiation (20, 43). In Europe, HBO is recognized with a level of evidence B and

regularly used in adults affected by idiopathic ON diagnosed at early stages (ARCO 1, 2a/b), obtaining the alleviation of pain, functional disabilities and radiological images (21, 46).

The stability of clinical and radiological picture after HBO that was observed in early stages ON suggests the use of HBO in combination with screening strategies. In fact, screening studies have shown a higher prevalence of radiological abnormalities during ALL treatment, most of which can evolve into overt ON (10, 47). Therefore, the combined use of early screening in a selected ALL population (older children and HR cases) together with HBO treatment, might be useful in avoiding the worsening of bone lesions at an early stage.

In conclusion, our experience shows the importance of ON as a mid-term complication of ALL therapy, with a strong impact on quality of life. Its detection could be improved by screening strategies, especially in older children and HR patients, for whom HBO could be considered a conservative treatment. However, HBO efficacy should be confirmed with further larger studies.

Conflicts of Interest

Authors have no conflict of interest to declare.

Authors' Contributions

GB, GBo and MCP conceived and designed the experiments. GR, RA, EV and MC performed the experiments. GGe, GT, MP and EC analyzed the data. CG, GG, RA contributed materials. GB, GBo and MCP wrote the paper. All authors approved the final version of the manuscript.

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