Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia

MAURIZIO ARICÒ, MARIE FRANCE PINTA BOCCALATTE, DANIELA SILVESTRI, ELENA BARISONE, CHIARA MESSINA, ROBERT CHIESA, NICOLA SANTORO, PAOLO TAMARO, ALMA LIPPI, DOMENICO GALLISAI, GIUSEPPE BASSO, GIULIO DE ROSSI, PER LA ASSOCIAZIONE ITALIANA DI EMATOLOGIA ED ONCOLOGIA PEDIATRICA (AIEOP)

Background and Objectives. Osteonecrosis (ON) is a potentially disabling complication of combination chemotherapy including high doses of steroids. The incidence and main risk factors for symptomatic ON have been investigated in a large group of children treated with high-dose steroids, prednisone and dexamethasone for childhood acute lymphoblastic leukemia (ALL).

Design and Methods. From May 1995 to December 1999, 1421 patients <18 years old, with newly diagnosed non-B ALL, were registered in the AIEOP-ALL 95 study. Their data were reviewed to identify patients who developed symptomatic ON. For those who were positively identified additional data were requested concerning ON-related symptoms, treatment and outcome.

Results. Overall, 15 of the 1421 patients developed symptomatic ON (1.1%) in a total of 29 sites. The estimated 5-year cumulative risk for clinically diagnosed ON was 1.6% (SE 0.4). The incidence was significantly higher among females (p=0.01) and older patients, with a peak rate of 7.4% (2.3) among those aged 10 to 17 years (p<0.0001). When the two factors, i.e. age and gender were combined, there was a striking increase in the risk among female patients aged 10 to 17 years. The median time between the diagnosis of ALL and that of ON was 17 months (range 8-45). The hip was the most frequently involved (19/29) site.

Interpretation and Conclusions. Symptomatic ON occurred in only 1.1% of patients treated with BFM-type, intensive chemotherapy for childhood ALL. Female adolescents appear to be the subset of patients with the highest risk of ON, especially when categorized as having high risk leukemia and thus administered higher cumulative doses of dexamethasone.

Key words: acute lymphoblastic leukemia, dexamethasone, osteonecrosis.

Haematologica 2003; 88:747-753
http://www.haematologica.org/2003_07/747.htm

©2003, Ferrata Storti Foundation

From the OncoEmatologia Pediatrica, Ospedale dei Bambini "G. Di Cristina", Palermo, Italy.

Correspondence: Maurizio Aricò, OncoEmatologia Pediatrica, Ospedale dei Bambini "G. Di Cristina", via Benedettini 1, 90134 Palermo, Italy.
E-mail: arico@ospedalecivicopa.org

Recent advances in intensive multiagent chemotherapy along with adequate supportive care have produced remarkable improvements in long-term survival of children affected by acute lymphoblastic leukemia (ALL), so that over 70% of such individuals are currently likely to be cured.[1,2] On the other hand, as a drawback of more aggressive therapies, some late sequelae of treatment are expected to become more apparent.

Osteonecrosis (ON) is a potentially disabling complication of cancer treatment.[3-11] Although its etiopathogenesis is not fully established, steroids are considered one main cause.[12-15] Steroids are an essential component of chemotherapy for ALL. Along with more intensive use of prednisone, the current trend toward wider use of dexamethasone, which has proved to have both more potent antileukemic and side effects than prednisone,[16-18] is expected to increase the frequency of ON. Better knowledge of predisposing factors could offer clinicians the possibility of identifying subgroups of ALL patients at higher risk of ON. These patients might deserve specific evaluation and follow-up, or even therapy adjustments in order to reduce their excessive risk of ON.

In order to define the risk of ON associated with modern chemotherapeutic regimens better, we investigated the overall incidence and the factors associated with an increased risk of developing ON in patients treated front-line, and before bone marrow transplantation, in the AIEOP-ALL 95 study. The results of this survey are reported here.

Design and Methods

Patients

From May 1995 to December 1999, 1421 eligible and evaluable untreated patients less than 18 years old, with newly diagnosed non-B ALL, were registered in the AIEOP-ALL 95 study. According to presenting features, patients were assigned to standard risk (SR), intermediate risk (IR), or high risk (HR) groups.[19] The SR group included patients with all of the following criteria: age between 1 and 5 years, non-T ALL, leukocyte count less than 20,000/mm^3, DNA index between 1.16 and 1.60, prednisone good response (PGR: less than 1,000/mm^3 blasts in the peripheral blood after 7 days of steroids and one injection of intrathecal methotrexate),[20] absence of t(9;22) or t(4;11) clonal translocations, and complete remission after the first six weeks of induc-

Table 1. Treatment schedule for childhood ALL in the AIEOP-ALL-95 study.

	Standard risk (SR)		*Intermediate Risk (IR)*		*High Risk (HR)*	
	mg/m²	*Day*	*mg/m²*	*Day*	*mg/m²*	*Day*
Induction						
VCR	1.5	8,15,9,22,2	1.5	8,15,22,29	1.5	8,15,22,29
PDN	60	1-28°	60	1-28°	60	1-28°
DNM			30	8,15,22,29	30	8,15,22,29
L-ASP	10,000°°	19,22,26,28,31,34,37,40	10,000°°	19,22,26,28,31,34,37,40	10,000°°	19,22,26,28,31,34,37,40
CPM	–	–	1,000	43,71	1,000	43,71
6-MP	–	–	60	43-70	60	43-70
ARA-C	–	–	75	45-48, 52-55,59-62,66-69	75	45-48,52-55,59-62,66-69
MTX it	by age*	1	by age*	1	by age*	1
TIT	by age*	15, 29	by age*	15, 29, 45,59	by age*	15, 29, 45,59 **
Consolidation***						
MTX iv	2,000	8,22,36,50	5,000	8,22,36,50	See legend	See legend
CF (levo)	7.5	42,48#	7.5	42,48		
TIT	by age*	8,22,36,50	by age*	8,22,36,50		
6-MP	25	1-56	25	1-56		
Reinduction ***						
DXM	10	1-21°	10	1-21	10	1-21
VCR	1.5	8,15,22,29	1.5	8,15,22,29	1.5	8,15,22,29
DXR	30	8,15, 22,29	30	8,15,22,29	30	8,15,22,29
L-ASP	10,000°°	8,11,15,18	10,000°°	8,11,15,18	10,000°°	8,11,15,18
6-TG	60	36-49	60	36-49	60	36-49
CPM	1,000	36	1,000	36	1,000	36
ARA-C	75	38-41,45-47	75	38-41,45-47	75	38-41,45-48
TIT	by age*	38,45	by age*	38,45	by age*	38,45 (only during 1st reinduction)
CRT	–		-		****	By age
Continuation						
6-MP	50	Daily	50	Daily	50	1-21
MTX im	20	weekly	20	Weekly	20	1,8,15
VCR	–		–		1.5	22
PDN	–		–		40	22-26
TIT	by age*	q 8 weeks	by age*	q 8 weeks	–	

*VCR: vincristine; PDN: prednisone; DNM: daunorubicin; L-ASP: L-asparaginase; CPM:cyclophosphamide; 6-MP: 6-mercaptopurine; ARA-C: cytarabine; MTX: methotrexate; CF: citrovorum factor; DXM: dexamethasone; ADM: adriamycin; 6-TG: 6-thioguanine; ° then tapered; °° (IU/m²); *Age-adjusted doses of TIT for MTX, ARA-C and PDN were, respectively, as follows: <1 year 6/16/4 mg, >1<2 years 8/20/6 mg, >2<3 years 10/26/8 mg, >3 years 12/30/10 mg. Patients with CNS leukemia had additional TIT on days 8 and 22. ***Consolidation phase for HR patients consisted of block therapy as follows: Block 1: VCR 1.5 mg/m² days 1 and 8, DXM 20 mg/m2 days 1-5, 6-MP 100 mg/m² days 1-5, MTX 5 g/m² day 1, CF: 7.5 mg/m² (levo) at 36, 42, 48 hrs after MTX infusion start, ARA-C 2+2 g/m² day 5, L-ASP 25,000 IU/m² day 6, TIT day 1. Block 2: Vindesine 3 mg/m² day 1, DXM 20 mg/m² days 1-5, 6-TG 100 mg/m² days 1-5, MTX 5 g/m² day 1, CF 7.5 mg/m² (levo) at 36, 42, 48 hrs after MTX infusion start; DNM 50 mg/m² day 5, L-ASP 25,000 IU/m² day 5, CPM 150 mg/m2 days 1-5, TIT day 1. Block 3: DXM 20 mg/m² days 1-5, ARA-C 2+2 g/m² days 1-2, L-ASP 25,000 IU/m² day 6, etoposide 150 mg/m² days 3-5, TIT day 5. # hours after HD-MTX infusion start. ***Protocol II was repeated after a 6-week interim maintenance phase during which the patients received 6-MP and MTX as in the following maintenance; ****Cranial radiotherapy was administered once during the interim maintenance at the following doses: age >1<2 years 12 Gys (18 Gys if CNS+ at diagnosis); age >2 years 18 Gys (24 if CNS+); for high risk with age <1 year extended triple intrathecal therapy during maintenance was substituted for cranial radiotherapy.*

©Ferrata Storti Foundation

tion therapy (protocol Ia). The criteria for inclusion in the HR group were: prednisone poor response (PPR), or failure to achieve complete remission (CR) after protocol Ia, or evidence at the prospective screening of the t(9;22) translocation, or, in infants, the presence of the t(4;11) translocation or CD10-negative immunophenotype. The IR group included all the remaining patients.

Criteria for diagnosis of osteonecrosis

These criteria were not standardized in the protocol. Only patients who complained of symptoms potentially related to bone necrosis underwent diagnostic studies including plain X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). Although the onset of ON had to be prospectively reported in the routine protocol data collection, an *ad hoc* data recall was performed on May 1, 2000 for each AIEOP center on all recruited patients. For those patients reported to have developed ON, additional information was requested, and the disease course was evaluated as of April 1, 2003.

Diagnostic studies

The diagnosis of ALL was based on standard morphologic, cytochemical and immunophenotypic criteria.[22,23]

Treatment

Treatment schedules are summarized in Table 1. In brief, all patients received seven days of prednisone pre-phase and induction therapy with protocol Ia.[2] Thereafter SR patients received consoli-

dation therapy with high dose methotrexate (HD-MTX), 2 g/m^2, reinduction therapy with protocol II, and continuation therapy with extended triple intrathecal therapy (TIT); IR patients received protocol Ib, consolidation therapy with HD-MTX, 2 g/m^2, (except for T-ALL, or patients with CNS or testicular involvement, who had 5 g/m^2) reinduction therapy (protocol II), and continuation therapy with extended TIT. Patients with T-ALL presenting with a leukocyte count exceeding 100,000/mm^3 also received cranial irradiation. IR patients were also randomized to receive or not 2 weekly doses of vincristine and one week of dexamethasone (6 mg/m^2) q 10 weeks during maintenance therapy. Induction therapy for HR patients[19] consisted of the entire protocol I and was followed by consolidation therapy with three BFM blocks[23] with non-cross-resistant chemotherapeutic agents including either high dose methotrexate (HD-MTX, 5 g/m^2), or high dose cytarabine (HD-ARAC, 3 g/m^2). Reinduction therapy consisted of protocol II, followed by an interim maintenance phase during which cranial irradiation (18 Gys if aged >1<2 years, or 24 Gys if older than 2 years, in 12 or 14 fractions) was delivered, and by a second protocol II without intrathecal therapy. For the low-risk group continuation therapy consisted of oral 6-mercaptopurine (50 mg/m^2, daily), weekly methotrexate (20 mg/m^2), and nine TIT injections (q 8 weeks); in the intermediate risk group, the patients were randomized to receive or not, on top of the above described antimetabolite-based and TIT (6 injections) chemotherapy, a total of six pulses (q 10 weeks) with two doses of vincristine (1.5 mg/m^2, day 1 and 8) and one week of oral dexamethasone (6 mg/m^2 days 1-7); patients in the high risk group received 28-day cycles of: oral 6-mercaptopurine (50 mg/m^2, day 1-21), methotrexate (20 mg/m^2 day 1, 8, 15), vincristine (1.5 mg/m^2, day 22) and prednisone (40 mg/m^2 days 22-26). The duration of treatment was 24 months for all groups. Children with central nervous system leukemia at diagnosis received two additional doses of TIT during protocol Ia and CRT, given after reinduction therapy. For children younger than 1 year at the time of irradiation, extended TIT was substituted for CRT.

Cumulative doses of steroids, i.e. prednisone and dexamethasone, calculated as prednisone equivalent, were 3,250 mg/m^2 for the standard risk and for the intermediate risk patients who were randomized not to receive the vincristine/steroid pulses during continuation therapy, 4,762 mg/m^2 for those who received the pulses, and 6,460 mg/m^2 for the high risk group.

Statistical analysis

The incidence of ON during frontline treatment was estimated according to Kaplan-Meier analysis. The time to ON was calculated from diagnosis.

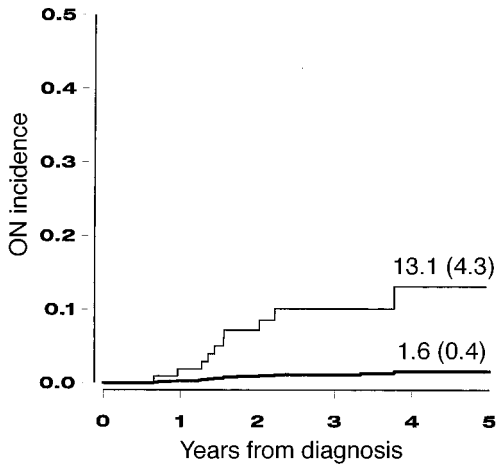

Figure 1. Cumulative risk of osteonecrosis in 1421 patients with childhood acute lymphoblastic leukemia treated in study AIEOP-ALL 95 (bold line) and in 115 females aged 10-17 years (thin line).

Patients who underwent BMT in first CR or had a failure (resistance, relapse, death in CR) before the onset of ON or did not develop ON were censored at that time. The Cox model was applied to analyze the effect of three regressors (age, sex and cancer risk group) on the risk of developing ON. Application of the Cox model should be considered with caution, given the relatively low number of events (ON). Follow-up was updated as of the end of year 2000.

Results

Overall, 15 of the 1421 patients with childhood ALL who entered this study developed symptomatic ON, accounting for 1.1% of the entire population. The estimated cumulative incidence for clinically diagnosed ON at five years is 1.6% (SE 0.4) (Figure 1).

Diagnosis, treatment and outcome of ON

The first symptoms related to ON consisted of pain in 12 patients and of limp alone in 3 patients. A total of 29 sites were involved by ON; three patients had a single site involved. The most frequently affected site was the hip, this site being involved in 19 cases in 10 patients; the ankle was affected 5 times in three patients (Table 2).

The median time between the diagnosis of ALL and the diagnosis of ON was 17 months (range, 8-45 months). The diagnosis of ON was based on plain, X-rays in all but one case; CT scan was reported as diagnostic in 3 of the 7 patients test-

©Ferrata Storti Foundation

Table 2. Characteristics of the 15 patients with childhood acute lymphoblastic leukemia in study AIEOP-ALL 95 who developed osteonecrosis.

Case	Gender/Age (yrs)	Risk group	Treatment phase (months from ALL diagnosis)	Characteristics at onset of ON				Diagnostic study			Current status (months from ON)
				PDN (mg/m^2)	DXM (mg/m^2)	Symptom	Involved sites	RX	CT	MR	
1	M/17	IR	Cont (15)	1830	237	Hip pain	Femoral head R	+	–	+	Pain and disability at month +25. Dead of disease after relapse.
2	F/11	HR	Cont (16)	3008	548	Pain	Humerus, femoral head B	+	–	+	58+ months, asymptomatic after NWB and PKT
3*	F/11	IR	Cont (27)	1418	236	Foot pain	Astragalus L	+	NP	+	34+ months, minimal pain
4**	M/2	SR	Off (40)	1418	236	Pain	Femoral head B	+	+	NP	47+ months, NWB,
5	F/14	IR	Cont (9)	1680	236	Pain,limp	Femoral head B	+	NP	+	35+ months, NWB (Sticks), pregnant
6	F/12	IR	Reind (8)	1820	233	Leg pain	Knee L, tibia R, humerus R	–	NP	+	48+ months, progression (femoral head B); arthroprothesis hip R, planned L.
7	F/13	IR	Cont (24)	2837	550	Hip pain	Femoral head B	+	NP	+	38+ months, minimal pain, no disability, PKT, MT
8	F/12	HR	Cont (19)	2285	692	Hip pain	Femoral head B	+	NP	+	45+ months, mild pain under prolonged walking
9	F/9	IR	Cont (10)	1898	236	Foot pain	Astragalus B	+	–	–	46+ months, no disability
10	F/11	HR	Reind2 (15)	1537	492	Limp	Femoral head B	+/–	+	+	Progression to humerus B → NWB, FKT, improved; 36+ months only mild limping.
11	M/14	IR	Cont (21)	1820	240	Knee pain	Femoral + tibia R	+	+	+	43+ months, asymptomatic
12	F/12	HR	Off (45)	4579	707	Pain, limp	Femoral head B	+	–	–	NWB, aledronate, FKT, MT; at 30+ months: free walking.
13	F/15	HR	Cont (18)	2800	1072	Limp	Femoral head L	+	NP	NP	48+ months, asymptomatic, PKT
14	F/12	IR	Cont (18)	2216	604	Limp	Femoral head B	+	NP	+	50+ months, asymptomatic, PKT
15	F/9	IR	Reind (8)	1837	236	Pain, limp	Ankle B, calcaneus L	+	NP	+	Bilateral pain, limited disability 34+ months

*R: right; L: left; B: bilateral. NP: not performed. NWB: non-weight bearing. *This patient had a bilateral orthopedic prosthesis for congenital pes valgus; **this patient had congenital bilateral coxa vara. PKT: physiokinesiotherapy; MT: magnetotherapy.*

©Ferrata Storti Foundation

ed, while MR confirmed the diagnosis in 11 of the 13 patients tested. The majority of patients (n=10) developed ON during continuation therapy and none before reinduction therapy.

Only two patients were reported to have received no specific ON-directed treatment due to minimal clinical symptoms. Physiokinesiotherapy was given to 7 patients. Non-weight bearing was prescribed to 7 patients.

At a median time of 26 months (range, 16-53 months), local pain was still reported in 10 patients, of whom 6 showed a variable level of disability, although surgery for arthroprothesis has not been performed in any so far.

Analysis of risk factors

The 5-year probability of developing ON during the front-line chemotherapy regimen was not uniform among the different categories of patients; in particular it was significantly higher among females than among males (p=0.01) and in older patients, with a peak rate of 7.4% (SE 2.3) among those aged 10 to 17 years (p<0.0001) (Table 3). When the two factors, i.e. age and gender were combined, there was a striking increase in the risk among female patients aged 10 to 17 years (Table 4 and Figure 1). Notably, of the 11 patients who were female, 10 to 17 years old and in the HR group, 5 developed ON. According to the Cox model, both older age (p=0.0001) and female sex (p=0.01) retained their impact on the risk of ON, after adjusting for treatment group.

Discussion

Symptomatic ON occurred in 1.1% of patients with childhood ALL enrolled in the AIEOP-ALL 95 study. The estimated 5-year incidence of ON during front-line chemotherapy was 1.6%. This incidence is lower than that reported by others. First,

a reporting bias should be taken into account. Since ON was not prospectively screened but only recorded in patients with clinical manifestations, we acknowledge that some cases of ON may have been underdiagnosed. In a recent prospective MR study of 24 children (11 girls) with childhood ALL treated with dexamethasone-containing regimens, the authors found that 9 patients (38%), four of whom were older than 10 years, developed MR findings compatible with ON.[11] Yet only 3 patients had symptoms, which were always mild and self-limiting, so that none of the patients had needed any specific therapy.[11]

More important is that the present incidence of symptomatic ON is lower than that observed in two recent reports by the CCG[24] and the DFCI Consortium.[25] In the retrospective study of 1409 children aged up to 20 years, treated in the protocol CCG-1882, the 3-year incidence of ON was 9.3%,[24] while in 176 children aged up to 18 years treated in the DFCI- consortium between 1987 and 1995 a 5-year incidence of 7% was observed.[25] One likely explanation for this lower incidence is that the AIEOP-ALL-95 chemotherapy regimen included a lower cumulative dose of steroids (3,250-6,460 mg/m^2) compared to that in the CCG (cumulative dose 5,8,85-9,050 mg/m^2) and the DFCI (cumulative dose of steroid 7,600-21,240 mg/m^2) studies.

Altogether these data suggest that use of higher cumulative doses of steroids, which may contribute to better leukemia control, appear to be responsible for an increased risk of developing ON in patients cured from ALL with different, contemporary, intensive chemotherapy regimens. A cost-benefit balance must keep into consideration that the high risk group of the present study AIEOP-ALL-95 achieved, with a median follow-up of 3.2 years, a remarkably satisfactory 4-year EFS and survival (standard error, SE) of 56.5%(3.9) and 62.8%(3.9) respectively.[19]

Two characteristics were significantly associated with the risk of developing ON in this series, i.e. age over 10 years and female gender. Although based on 33 patients, ON was not observed in infants (<1 year), and only 2 patients developed ON among the over 1200 diagnosed when aged 1 to 10 years. On the basis of our study, symptomatic ON seems to be a complication mainly pertaining to adolescents, and even more so, female adolescents. Although based on a small number of observations, we were particularly worried by the fact that when adolescent females qualified for and were treated in the high-risk group, 3 of these 11 patients developed ON, compared with 1 of the 25 comparable males. Although ON is not a life-threatening complication, it can cause non-trivial morbidity and frequently needs surgical repair. This should be considered when planning future treatment schedules.

Table 3. Incidence of osteonecrosis among 1421 patients with childhood acute lymphoblastic leukemia treated in the AIEOP-ALL 95 study, overall and according to some presenting features.

Category	*No. of patients*	*No. of patients with osteonecrosis*	*5-year probability of developing ON % (SE)*
Total	1421	15	1.6 (0.4)
Gender			
Female	669	12	2.5 (0.8)
Male	752	3	0.7 (0.5)
p-value=0.01			
Age (years)			
0-5	877	1	0.3 (0.3)
6-9	295	2	0.7 (0.5)
10-17	249	12	7.4 (2.3)
p-value<0.0001			
Risk group			
Standard	98	1	2.4 (2.4)
Intermediate	1121	9	1.0 (0.3)
High	202	5	5.8 (2.9)
p-value=0.02			

Table 4 . Frequency of osteonecrosis among 1421 patients with childhood acute lymphoblastic leukemia treated in the AIEOP-ALL 95 study according to age, gender and treatment group.

	0-5 years			*6-9 years*		*10-17 years*		*Total*	
Gender	SR	IR	HR	IR	HR	IR	HR	SR+IR	HR
Female	0/52	0/315	0/56	2/117	0/12	5/106	5/11	7/590	5/79
Males	1/46	0/328	0/80	0/14	0/22	2/111	0/21	3/629	0/123
Total	1/98	0/643	0/136	2/261	0/34	7/217	5/32	10/1219	5/202

In an attempt to reduce the incidence of ON among the subgroup at highest risk of this complication, in the current AIEOP-BFM-ALL 2000 study we have decided to give adolescents a one-week break in the course of their 3-week exposure to dexamethasone during protocol II. Although this reduces the chemotherapy intensity to some extent, we hope that this will not allow a significant increase of the risk of relapse while at least some patients could be spared from non-trivial bone morbidity or even the need of surgical repair for treatment-induced ON.

In a recent report, Zalavras *et al.* found that the 677C-T mutation in the methylene-tetrahydrofolate reductase (MTHFR) gene was present in 26.1% of 66 patients with idiopathic ON but in only 10%

©Ferrata Storti Foundation

of controls.[26] This suggests that some genetic factors might play a significant role in determining predisposition to ON. Whether this might justify, in the future, screening for such genetic variants in patients exposed to additional, treatment–related, risk factors for ON, remains to be discussed.

Appendix

The following institutions enrolled patients in the AIEOP-ALL 95 study, which was chaired by Prof. G.Masera (Monza): Ancona, Clinica Pediatrica (Dr. L. Felici, Dr. P. Pierani); Ancona, Divisione di Pediatria (Prof. G. Caramia, Dr. Iorini); Bari, Clinica Pediatrica I (Prof. F. Schettini, Dr. N. Santoro); Bari, Clinica Pediatrica II (Prof. N. Rigillo, Dr. ssa S. Bagnulo); Bergamo, Div. Pediatria (Prof. F. Bergonzi, Dr. P. E. Cornelli), Ematologia (Prof. T. Barbui). Bologna, Clinica Pediatrica (Prof. G. Paolucci, Dr. A. Pession, Dr. R. Rondelli); Bologna, Divisione di Pediatria, Ospedale Maggiore (Prof. G. Ambrosioni); Brescia, Clinica Pediatrica (Prof. A. G. Ugazio, Dr. A. Arrighini); Cagliari, Servizio di Oncoematologia Pediatrica (Prof. P. F. Biddau, Dr. ssa R. Mura); Catania, Divisione di Onco-Ematologia Pediatrica (Prof. G. Schilirò, Dr. L. Lo Nigro); Catanzaro, Div. di Ematologia (Prof. S. Magro, Dr.ssa C. Consarino); Firenze, Ospedale Meyer, Dipartimento di Pediatria, U.O. Oncoematologia Pediatrica (Prof.ssa G. Bernini, Dr.ssa A. Lippi); Genova, Ist. "G. Gaslini" (Prof. P. G. Mori, Dr.ssa C. Micalizzi); Genova Galliera (Prof. A. Rasore Quartino, Dr. M. Cominetti); Modena, Clinica Pediatrica (Prof.ssa F. Massolo, Dr.ssa M. Cellini); Monza, Clinica Pediatrica (Prof. G. Masera, Dr. V. Conter, Dr. C. Rizzari, Dr. M. Jankovic); Napoli, Ospedale Pausilipon (Prof. V. Poggi, Dr.ssa M.F. Pintà Boccalatte); Napoli, II Università, Dipartimento di Pediatrica, Servizio Autonomo di Oncologia Pediatrica, (Prof.ssa M. T. Di Tullio, Dr.ssa F. Casale, Dr.ssa A. Murano); Napoli, Clinica Pediatrica II (Prof. S. Auricchio, Dr. A. Fiorillo, Dr.ssa R. Migliorati); Napoli, Ospedale SS. Annunziata (Prof. F. Tancredi, Dr. A. Correra); Padova, Clinica Pediatrica II (Prof. L. Zanesco, Prof. G. Basso, Dr.ssa C. Messina); Palermo, Clinica Pediatrica I (Prof.ssa M. Lo Curto, Dr.ssa G. Fugardi); Parma, Clinica Pediatrica (Dr. G. Izzi, Dr.ssa P. Bertolini); Pavia, Clinica Pediatrica (Prof.ssa F. Severi, Dr. F. Locatelli, Dr. M. Aricò); Perugia, Divisione di Oncoematologia Pediatrica, Ospedale Silvestrini (Dr. A. Amici, Dr. P. Zucchetti); Pescara, Divisione di Ematologia (Dr. A. Di Marzio, Dr. R. Di Lorenzo, Prof. G.Torlontano); Pisa, Clinica Pediatrica III (Prof. P. Macchia, Dr. C. Favre); Reggio Calabria, Divisione di Ematologia, Ospedali Riuniti (Prof. F.Nobile, Dr.ssa M. Comis); Roma, Divisione di Ematologia Pediatrica, Ospedale "Bambino Gesù" (Prof. G. De Rossi, Dr. M.Luciani); Roma, Cattedra di Ematologia (Prof. F. Mandelli, Dr.ssa A.M. Testi); Roma, Clinica Pediatrica (Prof. G. Multari, Dr.ssa B. Werner); S.Giovanni Rotondo, "Casa Sollievo della Sofferenza", Divisione di Pediatria, Sezione di Ematologia ed Oncologia Pediatrica (Prof. M. Carotenuto, Dr. S. Ladogana); Sassari, Clinica Pediatrica (Prof. D. Gallisai, Dr. C. Cosmi); Siena, Clinica Pediatrica (Prof. G. Morgese, Dr. A. Acquaviva, Dr. A. D'Ambrosio); Torino, Clinica Pediatrica (Prof. E. Madon, Prof. R. Miniero, Dr.ssa E. Barisone); Trieste, Clinica Pediatrica (Prof. P. Tamaro, Dr. G. A. Zanazzo); Varese, Clinica Pediatrica (Prof. L. Nespoli, Dr.ssa S. Binda); Verona, Clinica Pediatrica (Prof. L. Tatò, Dr. Marradi).

References

1. Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med 1998;339:605-15.
2. Reiter A, Schrappe M, Ludwig WD, Hiddemann W, Sauter S, Henze G, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. Blood 1994; 84: 3122-33.
3. Murphy RG, Greenberg ML. Osteonecrosis in pediatric patients with acute lymphoblastic leukemia. Cancer 1990; 65:1717-21.
4. Bomelburg T, von Lengerke HJ, Ritter J. Incidence of aseptic osteonecrosis following the therapy of childhood leukemia. Hamatol Bluttranfusion 1990;33:577-9.
5. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med 1992;326:1473-9.
6. Hanif I, Mahmoud H, Pui CH. Avascular femoral head necrosis in pediatric cancer patients. Med Pediatr Oncol 1993; 21:655-60.
7. Chan-Lam D, Prentice AG, Copplestone JA. Avascular necrosis of bone following intensified steroid therapy for acute lymphoblastic leukemia and high-grade malignant lymphoma. Br J Haematol 1994;86:227-30.
8. Thornton MJ, O'Sullivan G, Williams MP, Huges PM. Avascular necrosis of bone following an intensified chemotherapy regimen including high dose steroids. Clin Radiol 1997; 52:607-12.
9. Körholz D, Bruder M, Engelbrecht V. Aseptic osteonecrosis in children with acute lymphoblastic leukemia. Pediatr Hematol Oncol 1998;15:307-15.
10. Vaidya S, Saika S, Sirohi B, Pai S, Advani S. Avascular necrosis of bone: a complication of aggressive therapy for acute lymphoblastic leukemia. Acta Oncol 1998;3:175-7.
11. Ojala AE, Pääkkö E, Lanning FP, Lanning BM. Osteonecrosis during the treatment of childhood acute lymphoblastic leukemia: a prospective MRI study. Med Pediatr Oncol 1999; 32:11-7.
12. Bockman RS, Weinerman SA. Steroid-induced osteoporosis. Orthop Clin North Am 1990;21:97-107.
13. Chang CC, Grenspan A, Gershwin ME. Osteonecrosis. Current perspectives on pathogenesis and treatment. Semin Arthritis Rheum 1993;23:47-69.
14. Schroer WC. Current concepts on the pathogenesis of osteonecrosis of the femoral head. Orthop Review 1994;23: 487-97.
15. Gaynon PS, Lustig RH. The use of glucocorticoids in acute lymphoblastic leukemia of childhood. Molecular, cellular and clinical considerations. J Pediatr Hematol Oncol 1995;17:1-12.
16. Ito C, Evans WE, McNinch L, Coustan-Smith E, Mahmoud H, Pui CH, et al. Comparative cytotoxicity of dexamethasone and prednisolone in childhood acute lymphoblastic leukemia. J Clin Oncol 1996;14:2370-6.
17. Pieters R, Kaspers GJL, van Wering ER. Dexamethasone is much more potent than prednisolone in the assumed equivalent doses in childhood leukemia. Proc Am Soc Clin Oncol 1992; 11:282[abstract].
18. Veerman AJ, Hahlen K, Kamps WA, Van Leeuwen EF, De Vaan GA, Solbu G, et al. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol 1996; 14:911-8.

©Ferrata Storti Foundation

19. Aricò M, Valsecchi MG, Conter V, Rizzari C, Pession A, Messina C, et al. Improved outcome in high-risk childhood acute lymphoblastic leukemia defined by prednisone-poor response treated with double Berlin-Frankfurt-Muenster protocol II. Blood 2002;100:420-6.
20. Riehm H, Reiter A, Schrappe M, Berthold F, Dopfer R, Gerein V, et al. Corticosteroid-dependent reduction of leukocyte count in blood as a prognostic factor in acute lymphoblastic leukemia in childhood (therapy study ALL-BFM 83). Klin Pädiatr 1987;199:151-60.
21. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukemias. French-American-British Cooperative group. Br J Haematol 1976;33:451-8.
22. van der Does-van den Berg A, Bartram CR, Basso G, Benoit YC, Biondi A, Debatin KM. Minimal requirements for the diagnosis, classification, and evaluation of the treatment of childhood acute lymphoblastic leukemia (ALL) in the "BFM Family" Cooperative Group. Med Pediatr Oncol 1992;20:497-505.
23. Schrappe M, Reiter A, Ludwig WD, Harbott J, Zimmermann M, Hiddemann W, 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;95:3310-22.
24. Mattano LA, Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Study Group. J Clin Oncol 2000;18:3262-72.
25. Strass A, Su JT, Kimball Dal ton VM, Gelber RD, Sallan SE, Silverman LB. Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 2001;19:3066-72.
26. Zalavras CG, Malizos KN, Dokou E, Vartholomatos G. The 677C→T mutation in the methylene-tetrahydrofolate reductase (MTHFR) gene in the pathogenesis of osteonecrosis in the femoral head. Hematologica 2002;87:111-2.

Pre-publication Report & Outcomes of Peer Review

Contributions

MA, VC: design of the study, writing the paper; DS: data management and analysis; MB, EB, CM, GDR, NS, PT, AL: contributed to the conception of the study, slection and clinical evaluation of patients, interpretation of results; GB: head of the biology group of the AIEOP-ALL group; CM: co-ordinator of the CSS-ALL group of AIEOP.

The authors are grateful to Prof. M. G. Valsecchi for her critical evaluation of the study design, for reading the manuscript and advising in data analysis.

Funding

This work was partly supported by MURST (grant 2001068982-007), Fondazione Tettamanti, Città della Speranza and other charities and parents associations.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received January 13, 2003; accepted May 20, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

Osteonecrosis is a potentially disabling complication of combination chemotherapy including high doses steroids, which is typically employed in children with childhood acute lymphoblastic leukemia.

What this study adds

Female adolescents receiving high doses of dexamethasone are the subset of patients at highest risk of osteonecrosis.

©Ferrata Storti Foundation