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Assessment of Corticosteroid-induced Osteonecrosis in Children Undergoing Chemotherapy for Acute Lymphoblastic Leukemia: A Report From the Japanese Childhood Cancer and Leukemia Study Group

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Summary: Steroid-induced osteonecrosis (ON) is a challenging complication encountered during modern chemotherapy for childhood acute lymphoblastic leukemia (ALL). We retrospectively assessed the incidence of ON and its risk factors in a total of 1095 patients enrolled in 3 consecutive Japanese Children's Cancer and Leukemia Study Group ALL studies (ALL941 [1994 to 2000], n = 464; ALL2000 [2000 to 2004], n = 305; and ALL2004 [2004 to 2010], n = 326). ON was diagnosed in 16 patients, of whom 15 were symptomatic. The cumulative incidence of ON was 0.76% in ALL941, 0.35% in ALL2000, and 3.6% in ALL2004. The incidence of ON in ALL941/2000, in which only prednisolone was administered as a steroid, was significantly lower than that in ALL2004, in which dexamethasone was used as a partial substitute for prednisolone ($P < 0.01$). In ALL2004, sex and age were significantly correlated with the incidence of ON (1.3% in boys vs. 6.7% in girls, $P = 0.0132$; 0.42% for age < 10 y vs. 15.6% for age ≥ 10 y, $P < 0.0001$), suggesting that girls aged 10 years and above are at a greater risk of ON onset. These results indicate that the risk of ON should be considered when administering dexamethasone as part of ALL protocol treatment in girls aged 10 years and above.

Key Words: acute lymphoblastic leukemia, osteonecrosis, corticosteroid, dexamethasone

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Recent advances in treatment strategies for childhood acute lymphoblastic leukemia (ALL) have improved the overall survival rate by 80% to 90%.[1–3] Enhanced chemotherapeutic agents, refined risk classification criteria, and improved supportive care have contributed to these high cure rates, but significant toxicity remains a major risk factor that causes long-term morbidity and decreased quality of life. Osteonecrosis (ON) has been increasingly documented in pediatric ALL and presents a challenging complication during modern chemotherapy.[4–7] ON can result in joint dysfunction and subsequent impairments in activities of daily living among long-term survivors.[8,9] Well-known risk factors for ON include age above 10 years, female sex, and use of dexamethasone (DEX).[5,7] Although the precise pathophysiology of ON remains unknown, corticosteroid administration has been shown to induce ischemia, upregulate apoptosis of osteoblasts and osteocytes, and prolong osteoclast lifespans.[10]

Most previous studies regarding ON in children with ALL have been limited to European and North American study groups, as there is little data concerning Japanese or Asian patients. Therefore, the aim of the present study was to assess the incidence, risk factors, and morbidity of corticosteroid-induced ON in ALL studies conducted by the Japanese Childhood Cancer and Leukemia Study Group (JCCLSG). We retrospectively analyzed the data of 1095 patients enrolled in 3 consecutive ALL studies (ALL941, ALL2000, and ALL2004) conducted by the JCCLSG. Prednisolone (PSL) was used as the primary corticosteroid in all studies, with DEX acting as a partial substitute for PSL in ALL2004. ON patients were practically identified by symptoms and ON was confirmed with imaging studies in all patients.

MATERIALS AND METHODS

Patients and Treatment

ALL941, ALL2000, and ALL2004 were conducted between 1994 and 2000, 2000 and 2004, and 2004 and 2010, respectively. The therapies on these studies were risk adjusted but not randomized. Patients enrolled in ALL941 and ALL2000 were aged 1 to 15 years, whereas those enrolled in ALL2004 were aged 1 to 18 years. All participants were newly diagnosed with B-precursor ALL or T-cell ALL, and those with a mature B-cell phenotype and Philadelphia chromosome-positive ALL were excluded. All studies were conducted across 18 hospitals that were members of the JCCLSG. The study protocol was approved by the institutional review board of each study,

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and written informed consent was provided by the patients or their legal guardians before treatment.

The treatment protocols adopted in ALL941 and ALL2000 were reported previously.[11,12] The patients were stratified according to leukocyte count and age at the time of diagnosis into standard-risk (SR), high-risk (HR), and high-high-risk (HHR) groups. The ALL941 and ALL2000 study protocols were almost identical except for the addition of doxorubicin administration to patients with a leukocyte count $<10{,}000/\mu L$ and age below 5 years in ALL2000. Treatment schedules and adopted drugs are briefly described in the supplement (see Supplemental Digital Content 1, Table 1,http://links.lww.com/JPHO/A55).

The ALL2004 treatment protocols are described in Figure 1 and Table 1. Previous risk classification criteria were modified according to the National Cancer Institute criteria,[13] resulting in a shift from HR to SR in 6- to 9-year-old patients with leukocyte counts of 5000 to 10,000 cells/μL. After a 7-day PSL regimen, induction therapy in the SR and HR groups was almost identical to that in previous studies.[11,12] In the HHR group, cyclophosphamide was added on day 8. After achieving complete remission, all risk groups received the same intensification therapy (Int-1). At week 15, SR patients with MRD levels $<10^{-3}$ received further intensification therapy (Int-2) that was followed by maintenance therapy (M-1 and M-2) until week 110. In the HR and HHR groups, patients with MRD levels $<10^{-3}$ at week 15 received 2 cycles of reinduction/intensification therapy (Rc1/Int-2 and Rc1/Int-3 in HR, Rc2/Int-4 and Rc2/Int-5 in HHR group) that was followed by the same maintenance therapy (M-3 and M-4) until week 165. Patients with MRD levels $\geq 10^{-3}$ at week 12 in the SR and HR/HHR groups were assigned to salvage arms 1 and 2, respectively. In the salvage regimen, patients received intensification therapy comprising 2 cycles of Rc-2/etoposide + cytarabine + L-asparaginase. For CNS prophylaxis, SR and HR patients received extended TIT injections beginning from day 1. When IT was combined with a high dose of methotrexate, only cytarabine and hydrocortisone were injected (double intrathecal [DIT] injection). TIT injections were repeated every 6 weeks in the first year, every 8 weeks in the second year, and every 12 weeks in the third year. The HHR group patients included in salvage arm 2 received 18 Gy of CRT in addition to 6 and 7 doses of TIT injections until week 22 and 32 of therapy, respectively.

Cumulative doses of the corticosteroids administered in ALL941/2000 and ALL2004 are listed in Table 2.

Identification of ON Patients

Because the significance of this therapy-related toxicity had not been fully appreciated until the early 2000s, case report form in the 3 studies did not request data regarding ON. Thus, cases with ON were collected by the questionnaire specified for ON to the investigators of JCCLSG. Most of the ON patients were identified based on clinical symptoms such as bone pain and further confirmed with diagnostic imaging studies (x-ray/magnetic resonance imaging [MRI]) by the each institutional radiologists, except one who was asymptomatic and diagnosed by imaging studies at the discretion of primary physician.

Statistical Analysis

Differences in the categorical variables of patient characteristics were analyzed using the χ^2 test. The cumulative incidence of ON during the study period was estimated using Kaplan-Meier analysis. The median follow-up periods were 147.4, 100.3, and 43.6 months for patients enrolled in ALL941, ALL2000, and ALL2004, respectively (median follow-up period, 78.7 mo for all patients). Differences in cumulative incidence between patient subsets were tested using the log-rank test.

RESULTS

A total of 1095 patients were enrolled in the present study (ALL941, n = 464; ALL2000, n = 305; and ALL2004, n = 326). Sixteen of 1095 patients developed ON during or after treatment, 4 (0.86%), 2 (0.65%), and 10 (3.1%) were in ALL941, ALL2000, and ALL2004, respectively. In patients with ON, the median age at diagnosis of ALL was 11.5 years (range, 5 to 16 y) and the male to female ratio was 1:3. When patients were evaluated by risk classification, only 1 patient in the SR group and 15 patients in the HR/HHR groups developed ON.

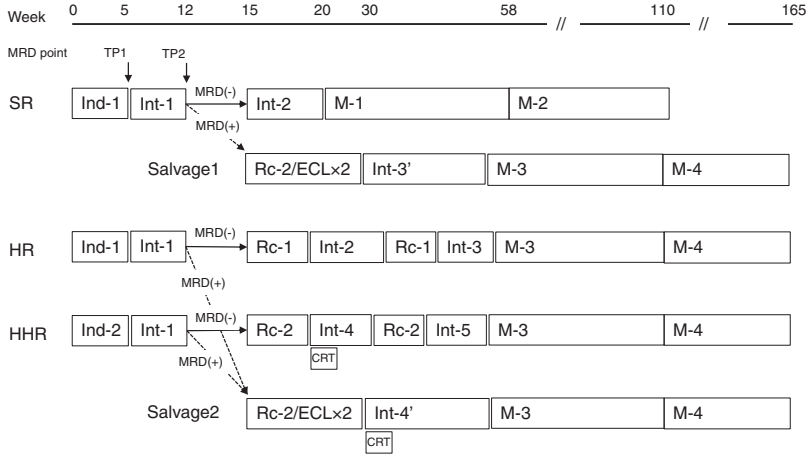

FIGURE 1. Treatment framework and minimal residual disease (MRD) stratification in the ALL2004 study. Patients with MRD levels $\geq 10^{-3}$ at week 12 received salvage therapy (dotted arrows), whereas the remainder continued to receive the initial risk-adapted therapy (solid arrows). Treatment schedules are shown in Table 1. CRT indicates cranial radiotherapy; HR, high-risk group; HHR, high-high-risk group; SR, standard-risk group.

TABLE 1. Drug Dosage and Schedule for ALL2004

	Regimen	Daily Dose	Administration	Days
Induction phase				
Ind-1	VCR	2 mg/m^2	IV	8, 15, 22, 29
	LASP	2000 U/m^2	IM	9-34 (3/wk)
	PSL*	60 mg/m^2	Oral	1-28
	DOX	25 mg/m^2	IV	8, 15, 22
Ind-2	Same as in Ind-1 except for CY (1200 mg/m^2)			8
Intensification phase				
Int-1				
AA	THP	20 mg/m^2	IV	1, 43
	VCR	2 mg/m^2	IV	1, 43
	PSL	120 mg/m^2	Oral	1-5, 43-47
	6MP	250 mg/m^2	Oral	1-5, 43-47
C	CY	400 mg/m^2	IV	15
	CA	50 mg/m^2 × 2	IV	15-18
	6MP	125 mg/m^2	Oral	15-19
BH	MTX	3000 mg/m^2	IV	29
Weekly LASP	LASP	6000 U/m^2	IM	1-50 (1/wk)
Int-2				
C + BH × 3 + A	VCR	2 mg/m^2	IV	43
	PSL	120 mg/m^2	Oral	43-47
	6MP	250 mg/m^2	Oral	43-47
Int-3				
CH + BH × 3	CY	500 mg/m^2	IV	1, 15
	CA	75 mg/m^2 × 2	IV	1-4, 15-18
	6MP	60 mg/m^2	Oral	1-28
AA + C + BH†				63-91
Weekly LASP†				63-98 (1/wk)
Int-4				
CHs	CY	500 mg/m^2	IV	1, 15
	CA	75 mg/m^2 × 2	IV	1-4, 15-18
	6MP	30 mg/m^2	Oral	1-28
AA + C + BI‡	MTX	500 mg/m^2	IV	63
Weekly LASP‡				35-70 (1/wk)
Int-5				
ECL + AA + C + BI	E	100 mg/m^2	IV	1-4
	CA	2000 mg/m^2 × 2	IV	1-4
	LASP	6000 U/m^2	IM	5
Weekly LASP				21-98 (1/wk)
Reinduction phase				
Rc-1	VCR	2 mg/m^2	IV	1, 8, 15, 22
	LASP	2000 U/m^2	IM	2-20 (3/wk)
	DEX*	10 mg/m^2	Oral	1-14
	DNR	25 mg/m^2	IV	1, 8, 15
Rc-2	VCR	2 mg/m^2	IV	1, 8, 15, 22
	LASP	6000 U/m^2	IM	9-20 (3/wk)
	DEX*	10 mg/m^2	Oral	1-14
	DNR	40 mg/m^2	IV	1, 8, 15
	CY	1200 mg/m^2	IV	1
Maintenance phase				
M-1 (C + B + A)	MTX	225 mg/m^2	IV	15
	LASP	2000 U/m^2	IM	15
M-2 (B + As)	VCR	2 mg/m^2	IV	15
	PSL	80 mg/m^2	Oral	15-19
M-3 (AA-C-B)				1-29
M-4 (Bs + As)	MTX	225 mg/m^2	IV	1
CNS prophylaxis				
TIT	MTX	12 mg/m^2	IT	
	CA	30 mg/m^2		
	HDC	50 mg/m^2		
DIT	Same as TIT except for methotrexate			

*PSL and DEX were tapered off (PSL; 30 mg/m^2 for 3 d and 15 mg/m^2 for 4 d, DEX; 5 mg/m^2 for 3 d and 2.5 mg/m^2 for 4 d).
†Repeat 2 cycles in Int-3′ for salvage 1.
‡Repeat 3 cycles in Int-4′ for salvage 2.
6MP indicates 6-mercaptopurine; CA, cytarabine; CY, cyclophosphamide; DEX, dexamethasone; DNR, daunorubicin; DOX, doxorubicin; E, etoposide; HDC, hydrocortisone; LASP, L-asparaginase; MTX, methotrexate; PSL, prednisolon; THP, pirarubicin; VCR, vincristine.

TABLE 2. Cumulative Dose of Corticosteroid in Trials ALL941/2000 and ALL2004

	ALL941/2000		ALL2004	
	PSL (mg/m^2)	DEX (mg/m^2)	PSL (mg/m^2)	DEX (mg/m^2)
Induction	1830	—	1830	—
Reinduction				
SR	—	—	—	—
HR/HHR	1830	—	—	330
Intensification				
SR	600	—	1200	—
HR/HHR	1200	—	2400	—
Maintenance				
SR	18,000	—	9200	—
HR/HHR	15,000	—	12,200	—
Total*				
SR	20,430		12,230	
HR/HHR	19,860		18,575	

*Calculated in PSL equivalents (1 mg of DEX = 6.5 mg of PSL).
DEX indicates dexamethasone; HHR, high-high risk; HR, high risk; PSL, prednisolone; SR, standard risk.

Comparisons of the characteristics of patients with and without ON are presented in Table 3, which shows a predominance of females aged 10 years and above, treatment with ALL2004, and high risk ($P < 0.01$) in patients with ON. Notably, 9 of the 12 female and 3 of the 4 male patients with ON were aged 10 years and above, the latter was marginally significant ($P = 0.044$). ON was diagnosed at median treatment weeks 56.5 (range, 32 to 264) and 66 (range, 37 to 120) in ALL941/2000 and ALL2004, respectively. The median cumulative corticosteroid doses at the time of ON onset were as follows: PSL, 5700 mg/m^2 (range, 3480 to 13,880 mg/m^2) in ALL941/2000 and PSL, 6030 mg/m^2 (range, 3480 to 13,800 mg/m^2) and DEX, 330 mg/m^2 (range, 240 to 330 mg/m^2) in ALL2004. As described in Table 2, SR patients in ALL2004 originally did not receive DEX, and despite the cumulative dose of PSL far exceeded the median doses for patients with ON at onset, none of them eventually developed ON. To obtain total PSL equivalents, DEX was multiplied by a conversion factor of 6.5[14]; therefore, a relatively higher steroid dose

TABLE 3. Comparison of Patient Characteristics Between With and Without ON

	Patients With ON (%)	Patients Without ON (%)	P (χ^2)
All	16	1079	
Sex			< 0.01
Male	4 (25)	606 (56)	
Female	12 (75)	473 (44)	
Age (y)			< 0.01
Male			0.044
1-5	1 (6)	345 (32)	
6-9	0	124 (11)	
>10	3 (19)	137 (13)	
Female			< 0.01
1-5	0	271 (25)	
6-9	3 (19)	102 (10)	
>10	9 (56)	100 (9)	
WBC			
< 10,000	6 (38)	571 (53)	
10,000-100,000	9 (56)	398 (37)	
> 100,000	1 (6)	110 (10)	
Immunophenotype			
BCP	9 (56)	739 (68)	
T	3 (19)	99 (9)	
Others	3 (19)	158 (15)	
NK	1 (6)	90 (8)	
Treatment			0.015
ALL941	4 (25)	460 (43)	
ALL2000	2 (12)	303 (28)	
ALL2004	10 (63)	316 (29)	
Risk			< 0.01
SR	1 (6)	629 (58)	
HR/HHR	15 (94)	450 (42)	

BCP indicates B-cell precursor; HHR, high-high risk; HR, high risk; NK, not known; ON, osteonecrosis; SR, standard risk; WBC, white blood cell count.

was used in ALL2004 compared with that used in ALL941/2000.

The cumulative 5-year incidence of ON was 0.76% (SE, 0.43%), 0.35% (SE, 0.35%), and 3.6% (SE, 1.1%) in ALL941, ALL2000, and ALL2004, respectively (Fig. 2), with a significant difference between ALL2004 and ALL941/2000 ($P < 0.01$). To assess the contribution of sex and age to ON incidence in patients receiving DEX-containing protocols, the cumulative incidence of ON was estimated in ALL2004 (Figs. 3A, B). Both sex and age were significantly associated with the 5-year ON incidence rate ($P < 0.01$), whereas female sex and age 10 years and above were HR factors for ON. The cumulative 5-year incidence of ON for girls over 10 years of age was 25.6% (SE, 8.4%), which was extremely higher than the rest of patients in ALL2004 ($P < 0.0001$) (Fig. 3C).

The characteristics of the 16 patients who eventually developed ON are listed in Table 4. All patients showed typical imaging findings on MRI except 1 (case 941-3) who underwent only x-ray that showed bilateral flattened femoral head. The most commonly affected joints and bones were the hip joint (44%), the knee joint (25%), and the femur (13%). Three patients (19%) exhibited multiple lesions. Nine (56%) continued to receive the planned steroid therapy despite the diagnosis of ON, whereas the doses were decreased or withdrawn in 7 (44%). ON management varied for each patient depending on the physician discretion. Most patients (75%) received supportive care only and were advised to avoid lifting heavy weights (grade 2 according to Common Terminology Criteria for Adverse Event version 4.0). Three patients (19%) underwent surgical intervention (grade 3) and 1 was treated with oral bisphosphonates (grade 2). With the median follow-up times of 33 months (range, 4 to 194), the clinical outcomes of ON were as follows: 12 with amelioration of ON and 3 with stable disease, except 1 who suffered a relapse of leukemia.

DISCUSSION

In the 3 most recent JCCLSG ALL studies, we found that a significant number of patients developed ON during or after treatment. ALL2004 study was conducted to evaluate the efficacy of DEX usage as a corticosteroid in the context of intensification of reinduction phase, comparing with the preceding 2 studies wherein PSL was the only corticosteroid adopted. This strategy also enabled us to compare the DEX toxicity with that of PSL. The results clearly demonstrated the higher incidence of ON in

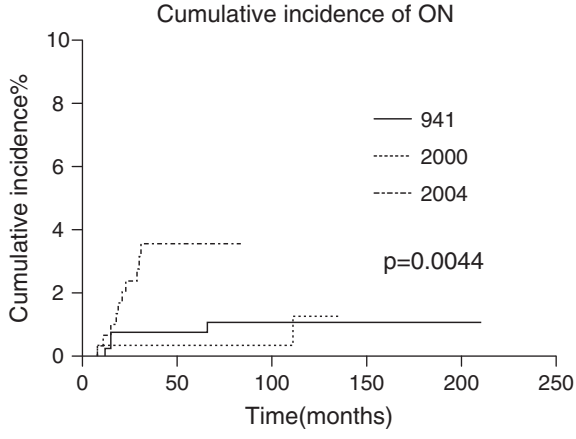

FIGURE 2. The cumulative incidence of osteonecrosis (ON) in the 3 Japanese Childhood Cancer and Leukemia Study Group studies on acute lymphoblastic leukemia (ALL). ALL941: 0.76%, SE, 0.43%; ALL2000: 0.35%, SE, 0.35%; ALL2004: 3.6%, SE, 1.1%.

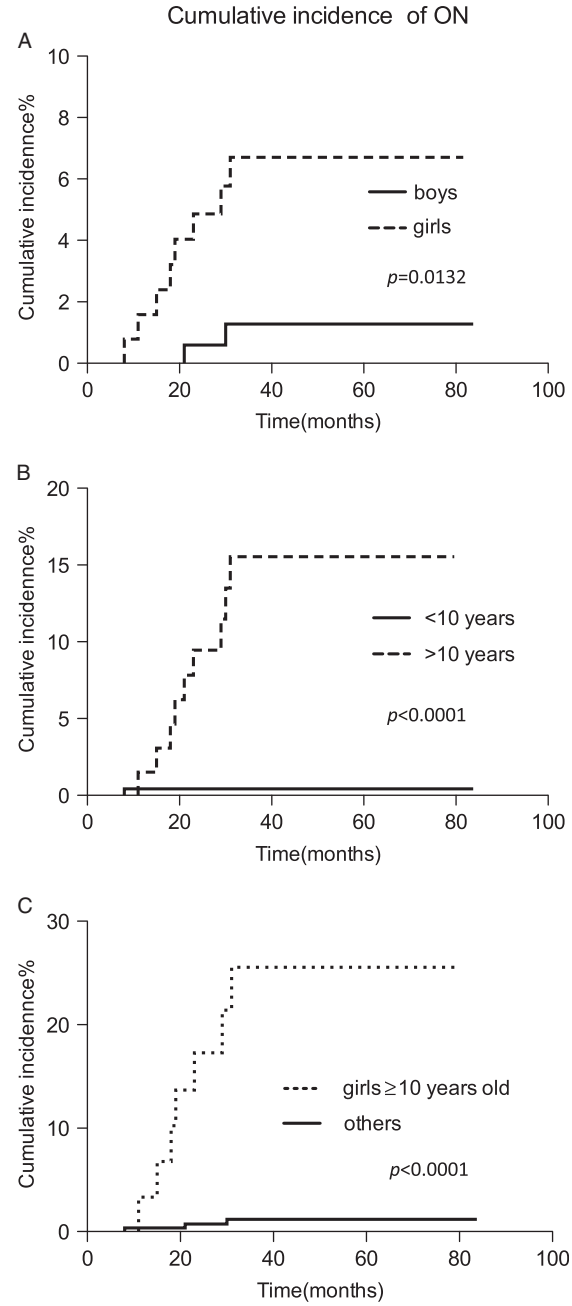

FIGURE 3. The cumulative incidence of osteonecrosis (ON) in ALL2004 according to sex (a), age (b), and combined (c). A, Boys (n = 2/190): 1.3%, SE, 0.9%; girls (n = 8/136): 6.7%, SE, 2.3%. B, Age below 10 years (n = 1/249): 0.42%, SE, 0.42%; age 10 years and above (n = 9/77): 15.6%, SE, 4.8%. C, Girls 10 years and above (n = 7/33): 25.6%, SE, 8.42%; others (n = 3/293): 1.19%, SE, 0.68%.

TABLE 4. Affected Joints and Clinical Course of Patients With ON

Cases	Affected Lesion	Corticosteroids	Management	Outcome
941-1	Right hip	Reduced	Avoidance of weight-bearing	Improve
2	Bilateral hips	Continue	Prohibit hard exercise	Stable
3	Bilateral hips	Continue	Avoidance of weight-bearing	Improve
4	Bilateral hips	Reduced	Avoidance of weight-bearing	Improve
2000-1	Left hip	Continue	Bracing	Improve
2	Bilateral knees, right talus	Withhold	Observation	Improve
2004-1	Bilateral hips	Withhold	Avoidance of weight-bearing	Stable
2	Bilateral hips	Withhold	Observation	Improve
3	Bilateral knees	Continue	Surgery	Improve
4	Left femur	Continue	Avoidance of weight-bearing	Improve
5	Right femur	Continue	Avoidance of weight-bearing	Improve
6	Bilateral hips and knees	Continue	Observation	ALL relapse
7	Right knee	Continue	Observation	Improve
8	Right knee	Withhold	Surgery	Improve
9	Bilateral hips and knees	Reduced	Bisphosphonate	Stable
10	Bilateral knees	Continue	Surgery	Improve

ALL indicates acute lymphoblastic leukemia; ON, osteonecrosis.

ALL2004, indicating DEX exposure was the risk for ON in ALL chemotherapy.

The overall incidence of ON was 1.5% (16/1095), which was comparable with that in a previous study by the Japan Association of Childhood Leukemia Study (JACLS) (2.4%, Hiroki H, Yasushi I, Teruaki H, Makoto Y, Megumi O, Tooru K, Shinichiro N, Junichi H, Keizo H, Keiko Y, and Tatsutoshi N; unpublished data). In studies from Europe and the United states, the ON incidence was highly variable (1% to 2% up to 9%) and dependent on patient characteristics and treatment intensity.[5–7] Furthermore, the detection methods of ON have significantly affected the incidence. Recent report from St Jude Total XV study showed that 17.6% of patients had the symptomatic ON, whereas the asymptomatic ON was detected in $>50\%$ of patients by the prospective screening with MRI test.[15] With regard to the effects of race, the incidence of ON is reportedly higher in whites than in patients of African descent.[7] Although it remains unclear whether the Asian race is related to an increased risk of ON, our results showed that the incidence of ON in Japanese children seemed to be comparable with that in European and American children. However, it should be taken into account the limitation of the present assessment: the possible missing of asymptomatic cases and the diagnosis partly depending on physician's discretion.

In this study, female sex, age 10 years and above, and the use of DEX as a corticosteroid were significant risk factors for ON. Of the 33 female patients aged over 10 years who received DEX, 7 developed ON (cumulative incidence, 25.6%). This was the extremely higher incidence of ON comparing with the rest of patients. Although females were found to be at a higher risk of developing ON in the Children's Cancer Study Group (CCG) and Italian studies,[5,7] there was no such correlation in studies performed in the UK and Germany and at the Dana Farber Cancer Institute (Boston, MA).[6,16,17] In addition, a Japanese study conducted by the JACLS failed to show a significant female predominance (male to female ratio, 7:9). Therefore, the effects of sex on ON pathogenesis remain unclear.

A significant contribution of age to ON onset has been robustly documented by most retrospective and prospective studies.[5–7,9,16,18–21] Among children aged 10 years and above, those aged 16 to 20 years were at the highest risk of ON. The eligible patient age was 1 to 15 years in ALL941/2000 and 1 to 18 years in ALL2004; therefore, we may have underestimated the incidence of ON. Further monitoring is necessary when ALL treatment protocols designed for children are extended to adolescence and young adulthood.

The potential effect of DEX on ALL is 6.5 times that of PSL, resulting in an increase in the use of DEX for ALL treatment. Because DEX is more toxic to bone tissues,[14,22] a higher incidence of ON has been a major concern in the design of treatment protocols. In ALL2004, DEX was incorporated only in the reinduction phase because an increased incidence of ON and mortality was reported with the use of DEX in the induction phase.[23] Nonetheless, our data revealed a higher cumulative incidence of ON associated with DEX administration; this finding was comparable with the results of the Dana Farber Consortium study DFCI 00-01, wherein DEX was used in postremission intensification therapy and/or in the maintenance phase.[24] Although the total corticosteroid dose (analyzed as PSL equivalents) at therapy completion were slightly lower in ALL2004 than in ALL941/2000 (Table 2), ON was most frequent in patients who had received only DEX in the HR group in ALL2004. These results suggest that DEX administration at any dose (as PSL equivalents) and in any treatment phase affects the incidence of ON. A recent report from the CCG found that DEX administration could influence the risk of ON[21] and that alternate-week DEX administration during delayed intensification therapy decreased ON incidence compared with continuous DEX. In our ALL2004 protocol, DEX was administered continuously for 2 weeks, and it would have been beneficial to modify the DEX schedule from continuous administration to alternate-week administration.

Recently, biological and genetical basis for ON development has been extensively investigated. Children's Oncology Group tested 12 polymorphisms of candidate genes and identified children with *PAI-1* GA/AA genotypes were significantly associated with ON.[25] Another study from St Jude Children's Research Hospital showed polymorphisms of *ACP1* were associated with risk of

symptomatic ON as well as with lower serum albumin and higher cholesterol levels.[15] These results suggest that some patients are prone to develop ON and individualized therapy should be needed in the future ALL studies.

In the present report, cases with ON were retrospectively collected by the questionnaire, and most of the ON patients were identified by symptoms and confirmed with imaging studies (x-ray/MRI) without central review. Despite such limitations, the clinical features of all 16 ON patients in our study were virtually comparable with those of patients in previous studies.[6,7,16] Weight-bearing joints were commonly affected, whereas asymptomatic lesions might have been overlooked.[15] Once ON is confirmed, the physician must decide whether steroids should be withheld or continued, considering that no consensus guideline is available thus far. Most of our patients were prescribed a planned dose of steroids without compromising functional outcomes after ON development. We believe that it may not be necessary to withhold steroids at the risk of leukemia relapse.

Bisphosphonates, which are structurally similar to pyrophosphates, inhibit osteoclast activity and bone turnover, thus exerting beneficial effects on bone mineralization.[26] Alendronate, a third-generation bisphosphonate, is reportedly effective in the prevention of femoral head collapse in ON patients.[27] Wiernikowski et al[28] showed that alendronate-induced changes in bone mineral metabolism/homeostasis benefited bone mineralization in children with ALL or non-Hodgkin lymphoma with steroid-induced osteopenia. Another bisphosphonate, pamidronate, was shown to be effective in the management of pain and motor function recovery in symptomatic ON occurring in children with ALL.[29] In the present study, alendronate was administered to 1 patient with symptomatic ON of the bilateral hip and knee joints; this resulted in no further deterioration of functional outcome and no treatment-induced side effects. However, further studies are required to clarify the potential benefits of concomitant bisphosphonate and steroid use for ON treatment.

In summary, the overall incidence of ON was 1.5% in the JCCLSG ALL studies, which was comparable with that reported in previous studies conducted in the Unites States and Europe. The known risk factors of age above 10 years, female sex, and DEX use were all significantly associated with an increase in the cumulative incidence of ON. In our future studies, we are intending to routinely screen for ON development with MRI test, especially those incorporating DEX in the treatment protocol. Although an ON management regimen remains to be established, steroids should not be withheld at the risk of ALL relapse.

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