INTRODUCTION

Currently, ~90% of children and adolescents affected with acute lymphoblastic leukaemia (ALL) can be cured and become long-term survivors. Thus, long-term side-effects of treatment become increasingly relevant. Osteonecrosis (ON) is one of the most common and debilitating therapy-related sequelae of anti-leukaemic treatment. Incidence of ON has been investigated in many studies, but results differ substantially, from 1.6%, as reported in the Associazione Italiana di
Ematologia e Oncologia Pediatrica (AIEOP)-ALL 95, to 25% in the German Co-operative Study Group childhood acute lymphoblastic leukaemia (CoALL)-07-03 trials. The ON incidence rises up to 59% in the Total XV protocols, which planned a systematic screening in all patients regardless of symptoms. Reported incidence rates in ALL studies may depend on age eligibility, treatment strategy (cumulative dose of steroids and other drugs) and diagnostic approach, which can be limited to severely symptomatic patients or patients with mild symptoms or even include screening procedures. In addition, censoring or not patients upon stem cell transplantation (SCT) and/or relapse may contribute substantially to the load of this complication.

Besides variations in diagnostics, what is still lacking is a universally accepted classification useful to predict clinical evolution and guide management and therapy. There are many radiological classification systems, developed with the aim to assess clinical relevance and consequences of ON lesions (Arlet-Ficat, Steinberg, and Association Research Circulation Osseous [ARCO] classification are among the most common), but the major weakness of these scoring systems is joint specificity for the femoral head, whereas patients with cancer often have multiple sites in various bones involved by the ON process.

The Niinimäki classification has been proposed as a universal classification system for oncological patients, suitable for all joints, regardless of the site of injury.

In our study the incidence of ON was assessed in a cohort of paediatric patients with ALL during the whole observation time, not only during front-line chemotherapy, but also after relapse and/or SCT. This approach may help to define the real risk of developing ON in a paediatric patient with ALL upfront, through the different stages of the disease and its therapy. We analysed sites and frequency of ON lesions and classified them according to radiological features. The aim of ON treatment is to avoid lesion progression that can lead to articular collapse, therefore a better understanding of the features that would possibly correlate with the lesion prognosis could play a crucial role.

**PATIENTS AND METHODS**

**Patients**

All 256 consecutive patients diagnosed with ALL in our Institution, between October 2010 and December 2016, were eligible for this analysis. Patients were allocated to the AIEOP-Berlin-Frankfurt-Münster (BFM) ALL 2009 Study, except for four patients with Philadelphia-chromosome positive ALL, who proceeded according to the European intergroup study of post-induction treatment of Philadelphia-chromosome-positive ALL (EsPhALL) Study, with the addition of the tyrosine-kinase inhibitor (TKI). The AIEOP-BFM ALL 2009 (European Union Drug Regulating Authorities Clinical Trials Database [EudraCT] number 2007–004270–43) study was approved by the institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Patients entered the study after informed consent was obtained from parents or legal guardians.

Demographics and clinical variables regarding the diagnosis of ALL were extracted from the AIEOP ALL national registry.

Diagnostic magnetic resonance imaging (MRI) of the lower limbs were performed in the case of symptoms suggestive for ON, including pain or gait abnormality. In a few patients, MRI of upper limbs was also performed in the case of pain in the upper limbs. Additionally, in adolescents proceeding to haematopoietic SCT (HSCT), MRI of the lower limbs might be performed as screening pre-HSCT. Clinical data of the 41 patients with a diagnosis of ON were obtained from medical records and radiological imaging digital archive.

**The ALL treatment is described in the Supplementary Materials**

**Radiological revision of ON lesions**

All the MRIs performed in the affected patients were evaluated by dedicated orthopaedists, ON lesions have been classified and studied over time.

A full hip and lower limb MRI was planned for patients diagnosed with lower limb ON.

Assessed sites for possible ON lesions are described in the Table S1. A total of 10 joints per patient (five bilateral: hip, knee, ankle, shoulder, elbow) were considered. In each area (including joints and diaphysis, as per description in Table S1) multiple sites of lesions could be detected. Sites of lesions were classified as diaphysis, convex or concave surface for the purpose of the study analysis (Table S1). The diagnosis of ON was based on radiological criteria: oedema is a pre-osteonecrosis stage and is characterised by a low signal in T1-weighted images and a high signal in T2-weighted images. When ON is diagnosed most often a crescentic, ring-like or well-defined band of low signal within the superior portion of the subchondral bone marrow is present in T1-weighted images. In T2-weighted images, the subchondral lesion shows a high signal intensity inner border with a low signal intensity peripheral rim. This is termed the ‘double-line’ sign, which is specific for the diagnosis of ON.

All the lesions were stratified according to the Niinimäki classification.

**Statistical analysis**

The association between ON and age, immunophenotype, gender and final risk group was analysed using a univariate Cox regression approach on the cause-specific hazard of ON; p values were calculated according to the likelihood ratio test. The Cox regression model was applied to investigate the impact of age, immunophenotype and final risk group on the risk of developing ON during front-line chemotherapy.
and, separately, during the whole observation time (i.e., after relapse or SCT, when appropriate). In these latter models, relapse and HSCT, respectively, were added as time-dependent variables in two different models. The cumulative incidence was estimated, accounting for death as a competing event for ON episodes occurring during the whole observation time, including post-relapse or -transplant, or during front-line treatment only, for which patients were censored upon relapse or transplant.

Data analyses were performed using the Statistical Analysis System (SAS), version 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient data were updated as of May 2019.

RESULTS

Incidence of ON

Osteonecrosis was diagnosed in 41 of the 256 analysed patients with ALL (16.0%). Detailed patient characteristics are summarised in Table 1. The median (interquartile range [IQR]) follow-up time after ALL diagnosis was 50 (39–63) months. The median (IQR) time of clinical follow-up after ALL diagnosis was 50 (39–68) months. The median (IQR) follow-up time after ALL diagnosis was 50 (39–63) months. The median (IQR) time of clinical follow-up after ALL diagnosis was 50 (39–68) months.

In all, 32 (78.0%) of the 41 patients developed ON during front-line treatment: 15 during consolidation or re-induction after the diagnosis of ON was 32 (78.0%) of the 41 patients developed ON during second-line chemotherapy during Protocol II or III, 14 during maintenance and three (CR)1 or CR2 (Figure S1).

After relapse and five (12.2%) after SCT in complete response (CR)1 or CR2 (Figure S1).

A lower limbs MRI was planned for ON screening in older patients undergoing HSCT. Seven of the 14 patients undergoing SCT in CR1 had a ‘screening’ MRI and four were positive; six out of the 23 patients undergoing SCT in CR2 had a ‘screening’ MRI (two patients were already diagnosed with ON) and four were positive. Among the eight patients diagnosed with ON in an asymptomatic phase (screening pre-HSCT), only two never developed symptoms and were not tested again by MRI, both of them had only diaphyseal lesions (tibial and femoral); the remaining six developed symptomatic ON.

The mean (SE) cumulative incidence of ON overall was 12.3 (2.1)% at 2 years, 14.8 (2.2)% and 16.3 (2.4)% at 3 and 5 years respectively (Figure 1A).

The mean (SE) cumulative incidence of ON accounting only for ON diagnosed during or after the front-line AIEOP-BFM ALL 2009 protocol, after censoring at relapse or SCT, was 11.2 (2.0)% and 12.7 (2.1)% at 2 and 5 years respectively (Figure 1B).

The mean (SE) cumulative incidence of ON among patients undergoing either SCT in CR1 or chemotherapy ± SCT after relapse, was 15.0 (5.0)% and 18.5 (5.7)% at 2 and 5 years respectively (Figure 1C).

Risk factors

The percentage of patients with ON was 18.0% (n = 27) in males and 13.2% in females (n = 14; p = 0.30); 30 (46.2%) of the 65 patients aged ≥10 years developed ON, 11 of whom (47.8%) were aged ≥15 years (patient characteristics in Table 1). Age distribution between the group of patients with and without ON was statistically significant (p < 0.001). According to immunophenotype, the percentage of ON patients with T-immunophenotype versus those with B-lineage ALL was 28.2% (n = 11) versus 13.6% (n = 29; p = 0.02). In high-risk patients, there were 23 cases of ON (35.9%), compared with 18 (9.4%) in non-high-risk patients (p < 0.001). These results were confirmed also when only the 32 ON occurring during front-line treatment were considered. Detailed patient characteristics are summarised in Table 1.

Three out of the four patients with Philadelphia (Ph)-positive ALL and treated with additional TKI (imatinib or dasatinib) developed symptomatic ON during maintenance of front-line chemotherapy (two cases, both had no SCT in CR1), whereas the third patient was diagnosed with ON after SCT in CR1. The patient without ON died in remission during consolidation, therefore he was only partially evaluable.

The multivariate analyses assessed that the risk of ON diagnosis, when also ON after relapse and SCT were considered, was significantly higher in high-risk patients and in patients aged ≥10 years. A significant impact of SCT could not be demonstrated in this patient series (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.33–2.67; p = 0.91; Table 2, Model A), whereas the impact of relapse was associated with a significant increased risk of ON (HR 2.91, 95% CI 1.25–6.78; p = 0.01; Table 2, Model B). The risk of ON diagnosis exclusively during or after front-line treatment was fivefold higher in

### Table 1

| Characteristics of patients with and without osteonecrosis. Data are reported as absolute numbers and percentages | With ON, n (%) | Without ON, n (%) | Total, N | p |
|---|---|---|---|---|
| **TOTAL** | 41 (16.0) | 215 (84.0) | 256 | 0.31 |
| **Gender** |  |  |  |  |
| Male | 27 (18.0) | 123 (82.0) | 150 |  |
| Female | 14 (13.2) | 92 (86.8) | 106 |  |
| **Age, years** |  |  |  | < 0.001 |
| 1–9 | 11 (5.8) | 180 (94.2) | 191 |  |
| 10–14 | 19 (45.2) | 23 (54.8) | 42 |  |
| 15–17 | 11 (47.8) | 12 (52.2) | 23 |  |
| **Immunophenotype** |  |  |  | 0.01 |
| B-lineage | 29 (13.6) | 185 (86.4) | 214 |  |
| T-ALL | 11 (28.2) | 28 (71.8) | 39 |  |
| Other | 1 | 2 | 3 |  |
| **Final risk group** |  |  |  | < 0.001 |
| No high risk | 18 (9.4) | 174 (90.6) | 192 |  |
| High risk | 23 (35.9) | 41 (64.1) | 64 |  |
high-risk patients, compared with standard- and intermediate-risk patients (HR 5.39, 95% CI 2.61–11.12; $p < 0.001$) and 10-fold higher in patients aged ≥10 years (HR 10.31, 95% CI 4.54–23.44; $p < 0.001$), whereas no significant impact of immunophenotype could be demonstrated (Table 2, Model C).

**Radiological assessment**

A total of 177 MRI were evaluated (median [range] 4 [1–10] MRI/patient).

Upon the first positive MRI for each of the 41 patients, a total of 293 lesions were detected, with a median (range, IQR) of 6 (1–20, 3–10) lesions/patient, with 101 of them affecting convex surfaces only (i.e., diaphyseal and concave surface lesions not taken into account).

Five patients had had a single MRI at the time of last follow-up (two deaths, two resolutions of symptoms, one follow-up for ON in another centre). Thus, the radiological evolution of ON lesions could be assessed in 36 patients of the 41 diagnosed with ON. The median (range, IQR) time elapsed between the first and last radiological imaging (time between first and last MRI) was 25 (4–60, 13–44) months.

When the MRI detecting the highest number of lesions was considered for each patient, 375 lesions (140 lesions on convex surfaces, 96 on concave surfaces and 139 on diaphyses) were counted, accounting for the maximum number of lesions simultaneously detected per patient anytime. The median number of lesions increased over time from 6 to 8/patient (3–4 on convex surfaces) (range 1–20, IQR 5–12). A total of 131 joints were affected with ON, with a median (range) of 4 (1–7) joints/patient involved in the 37 patients assessed over time.

The knee was the most affected joint, being affected in 33 patients (80%), with 107 lesions detected, involving either left or right femoral medial or lateral condyle, tibial plate and patella, assessed as single different lesions. The second most affected joint was the ankle, with 64 lesions found in 24 patients (59%) and the hip was affected by 27 lesions in 17 patients (41%). In the foot, 26 lesions were found in 13 patients (32%). Five lesions were found at the shoulders, one at the elbow and none in the humeral diaphysis, but the upper limbs were radiologically assessed only in a very few patients who were symptomatic at that level. Diaphyses of the lower limbs were found to be affected with several lesions, 87 in the tibia (29 patients, 71%) and 52 in the femur (28 patients 68%).

When the first positive MRI was performed, five of the 41 patients (12%) had a single ON lesion (four on a convex surface), while during follow-up all but one patient did develop additional lesions, thus 98% of the affected patients had multiple lesions detected by MRI at some point.
Among the 17 patients with ON of the hip, eight had bilateral involvement (47%). The bilateral involvement was more frequent in the knee 24/33 (73%) and for 23/24 (96%) patients with ON in ankles. Regarding the diaphyses, the tibia was involved in both sides in 26 of 29 patients (90%), whereas bilateral involvement of the femoral diaphysis was found in 24 of 28 patients (86%).

Of the 13 patients screened with lower-limbs MRI before transplant, eight were found to be positive and only two never developed symptomatic ON. Both of them had only diaphyseal lesions.

### Radiological classification and outcome of lesions

All the ON lesions were stratified according to the Niinimäki classification. Progression of the lesions over time according to the Niinimäki score is represented in Table 3, with grading detected at first MRI and at worst MRI (highest grade detected) per patient. This approach allowed us to describe the evolution of each lesion over time, either towards an improvement or a worsening, of both joints as well as diaphyseal lesions.

Diaphysis only had Grade 0 (absence of lesion) or Grade 2 (presence of lesion) as per classification, as Grade 1 in diaphyses refers only to non-weight-bearing bones. Diaphyseal lesions completely disappeared in 28% of the cases at the last follow-up (Table 3). None of the patients reported a pathological fracture related to ON of diaphyses. Lesions involving concave surfaces had little clinical significance, with 54% of the lesions resolved or improving during follow-up, while 53% of the lesions that progressed more than one grade or reached Grade 4 were located on convex surfaces (Table 3).

The mean (SE) cumulative incidence of ON in convex surfaces, considered as the lesions at worst evolution, was 15.2 (2.4)% at 5 years after the first osteonecrotic lesion in a convex surface was detected (Figure S2).
DISCUSSION

Our study matched its aim to assess ON incidence, type, grade and identify risk factors in a cohort of patients with ALL from their diagnosis until last follow-up.

The mean (SE) cumulative incidence of ON at 5 years during the whole observation time, including post-relapse and -transplant observations was 18.5 (5.7)%. Incidences of symptomatic ON reported in the literature vary widely, up to 25%, according to the level of vigilance among physicians in charge, experience of radiologists and orthopaedists and different front- and second-line treatment.5,6 Adverse events such as ON may be under reported in national or international studies compared with single institution studies, committed towards optimising toxicity early diagnosis and management. In our series, most of the patients (78%) were diagnosed with ON during front-line chemotherapy.

The multivariate analysis assessed that the risk of ON during front-line treatment was fivefold higher in high-risk patients and 10-fold higher in patients aged ≥10 years. This result confirms the major risk factors known from the literature.4,15,16 Female gender was not a risk factor in our cohort, whereas in the literature there is no consensus on this.5,17,18 The T-immunophenotype was not confirmed as a risk factor in the multivariate analysis per se, which is likely explained by the fact that T-immunophenotype is strongly associated with older age and high-risk features, which are associated with ON risk.5,6

Another Cox model, accounting for all ON diagnoses including those occurring after relapse and SCT showed that the risk of ON remained significantly higher in high-risk patients (HR 3.2; p = 0.0005) and in patients aged ≥10 years (HR 9.8; p < 0.0001), while a significant impact of SCT could not be confirmed (HR 0.9; p = 0.91), as the majority of ON in the transplanted patients had already been diagnosed prior to SCT. This shows that a high-risk treatment protocol is a risk factor for ON per se, regardless of the fact that it is more frequently associated with relapse and/or SCT, as confirmed by the increased incidence of ON during the observation time limited to the front-line protocol. It could be speculated that SCT might act as a confounding factor, being often associated with high-risk features and relapses. Furthermore, the diagnosis can be delayed and therefore it is difficult to clearly assess the time of onset of the ON. Patients with high-risk features have an older median age compared to rest of the population, therefore the interaction between age and a high-risk treatment protocol is certainly relevant to the probability of developing ON. Our results are comparable to the high prevalence of ON found by Sharma et al.9,19 before transplant, which did not increase relevantly after SCT. The inclusion of few pre-symptomatic ON diagnoses in our cohort, due to a pre-transplantation screening or early imaging upon initial symptoms, essentially did not increase the final overall incidence of ON, as virtually all early detected cases would have been diagnosed anyway later on, due to the symptoms that were subsequently reported in all but two of these eight patients. The possibility that also patients not eligible for transplantation, therefore not screened with MRI, could have had asymptomatic ON could not be ruled out. Having ON diagnosed upon SCT before specific symptoms occurred might help patient management during the post-SCT course, in terms of limiting the use of steroids in the case of graft-versus-host disease (i.e., starting a combined therapy to facilitate an early steroid tapering), facilitating the diagnosis of ON lesion worsening and referring patients to the orthopaedist to optimise treatment timing. Of the four patients with ALL carrying the BCR/ABL translocation in our Institution, three developed ON, while the fourth was not evaluable due to early death during consolidation. Two of the three cases had already developed ON before SCT and one after SCT in CR1. Treatment within the high-risk protocol stratum must have contributed to ON, but the young age of one patient (<6 years) and the severity of the lesions suggest that additional treatment with TKI, as planned in Ph-positive patients, may contribute to ON onset and severity, although it has not been reported in the literature to date. Furthermore the impact of TKI on bone mineral metabolism is well known.20–22

Osteonecrosis in patients with ALL is almost always characterised by multiple lesions, with a median of six lesions/patient at diagnosis in our cohort and as already reported by others.14 The most frequent site of ON in our population was the knee, consistent with other studies in paediatric ALL, and not the hip, as reported mainly in adults.7,16

Available radiological classifications of ON have several limitations, the Niinimäki scoring system, proposed for patients with cancer and first published in 2015, allowed us to compare different types of ON lesions: convex surface, concave surface, diaphysis. Diaphyseal lesions (especially tibial and femoral) were very common in our patients but following diaphyseal lesions over time was found not clinically relevant as none of the patients developed complications, such as pathological fractures, and 28% of the lesions disappeared spontaneously. Moreover, two of the eight patients diagnosed with asymptomatic ON who never developed symptoms had only diaphyseal lesions (tibial and femoral). The involvement of convex surfaces had the worst prognostic impact, as the majority of the lesions worsened during follow-up (more than Grade 2 or reaching Grade 4) were located on convex surfaces.

According to our study, assessment and classification of the involvement of convex surfaces allowed us to detect the most critical lesions. This is consistent with the disease pathogenesis, as described in the literature. In the convex articular surfaces, subchondral bone is thinner than in the concave surfaces, making the convex articular surface stiff and resistant. In addition, the shape of the surface plays a role: during load, convex surfaces are subjected to convergent forces whereas concave/plane surfaces are subjected to divergent or parallel forces. These convergent forces can more easily lead to vaso-occlusion and subsequent ON development in the convex articular sides.23 In this perspective radiological classification focussed on convex surfaces seems to help to better identify lesions potentially with a worse prognosis. The Steinberg classification is more focussed on the damage of convex surfaces, but was available only for the femoral head, thus our orthopaedists developed an adaptation for
the knee and ankle. The adaptation followed the analysis of the convex surface of femoral heads reported in the original Steinberg classification (Table S2) and could be useful for future managing of ON lesions.

CONCLUSION

Our study detected a high prevalence of ON in paediatric patients with ALL, mostly occurring during front-line treatment and generally presenting with multiple lesions. Diaphyseal lesions were very common in our patients, but over time had little clinical relevance as none of the patients’ developed complications, such as pathological fractures, and 28% of the lesions disappeared. The lesions with a higher probability of worsening over time involved convex surfaces, being the most relevant to be followed-up over time.

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ALL, acute lymphoblastic leukaemia; ON, osteonecrosis. ALL, acute lymphoblastic leukaemia; CI, confidence interval; HR, hazard ratio; Immunoph., immunophenotype HSCT, haematopoietic stem cell transplantation. Max., maximum; MRI, magnetic resonance imaging. Open Access Funding provided by Universita degli Studi di Milano-Bicocca within the CRUI-CARE Agreement. [Correction added on 26 March 2022, after first online publication: CRUI funding statement has been added.]

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REFERENCES

1. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, et al. Childhood acute lymphoblastic leukaemia: progress through collaboration. J Clin Oncol. 2015;33:2938–48.
2. Girard P, Auquier P, Barlogis V, Contet A, Poiree M, Demeocq F, et al. Symptomatic osteonecrosis in childhood leukaemia survivors: prevalence, risk factors and impact on quality of life in adulthood. Haematologica. 2013;98:1089–97.
3. Schmiegelow K, Attarbaschi A, Barzilai S, Escherich G, Frandsen TL, Halsey C, et al. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. Lancet Oncol. 2016;17:e231–e9.
4. Arico M, Boccalatte MF, Silvestri D, Barisone E, Messina C, Chiesa R, et al. Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukaemia. Haematologica. 2003;88:747–53.
5. Kuhlen M, Moldovan A, Krull K, Meisel R, Borkhardt A. Osteonecrosis in paediatric patients with acute lymphoblastic leukaemia treated on co-ALL-07-03 trial: a single centre analysis. Klin Padiatr. 2014;226:154–60.
6. Kunstreich M, Kummer S, Laws HJ, Borkhardt A, Kuhlen M. Osteonecrosis in children with acute lymphoblastic leukaemia. Haematologica. 2016;101:1295–305.
7. Inaba H, Cao X, Chang JY, Karol SE, Panetta JC, Ness KK, et al. Incidence of hip and knee osteonecrosis and their associations with bone mineral density in children with acute lymphoblastic leukaemia. Br J Haematol. 2020;189:e177–81.
8. Padhye B, Dalla-Pozza L, Little D, Munns C. Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukaemia (ALL). Cancer Med. 2016;5:960–7.
9. Sharma S, Leung WH, Deqing P, Yang J, Rochester R, Britton L, et al. Osteonecrosis in children after allogeneic hematopoietic cell transplantation: study of prevalence, risk factors and longitudinal changes using MR imaging. Bone Marrow Transplant. 2012;47:1067–74.
10. Niinimaki T, Harilla-Saari A, Niinimaki R. The diagnosis and classification of osteonecrosis in patients with childhood leukaemia. Pediatr Blood Cancer. 2015;62:198–203.
11. Steinberg ME, Hayken GD, Steinberg DR. A quantitative system for staging avascular necrosis. J Bone Joint Surg Br. 1995;77:34–41.
12. Mont MA, Marulanda GA, Jones LC, Saleh KJ, Gordon N, Hungerford DS, et al. Systematic analysis of classification systems for osteonecrosis of the femoral head. J Bone Joint Surg Am. 2006;88(Suppl 3):16–26.
13. Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. J Bone Joint Surg Br. 1985;67:3–9.
14. Niinimaki T, Niinimaki J, Halonen J, Hanninen P, Harila-Saari A, Niinimaki R. The classification of osteonecrosis in patients with cancer: validation of a new radiological classification system. Clin Radiol. 2015;70:1439–44.
15. Campbell S, Sun CL, Kurian S, Francisco L, Carter A, Kulkarni S, et al. Predictors of avascular necrosis of bone in long-term survivors of hematopoietic cell transplantation. Cancer. 2009;115:4127–35.
16. Mattano LA Jr, Devidas M, Nachman JB, Sather HN, Hunger SP, Steinherz PG, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. Lancet Oncol. 2012;13:906–15.
17. Mattano LA Jr, Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukaemia in children: a report from the Children’s cancer group. J Clin Oncol. 2000;18:3526–72.
18. Strauss AJ, Su JT, Dalton VM, Gelber RD, Sallan SE, Silverman LB. Bony morbidity in children treated for acute lymphoblastic leukaemia. J Clin Oncol. 2001;19:3066–72.
19. Sharma S, Yang S, Rochester R, Britton L, Leung WH, Yang J, et al. Prevalence of osteonecrosis and associated risk factors in children before and after allogeneic BM. Bone Marrow Transplant. 2011;46:813–9.
20. Milot F, Guilhot J, Baruchel A, Petit A, Leblanc T, Bertrand Y, et al. Growth deceleration in children treated with imatinib for chronic myeloid leukaemia. Eur J Cancer. 2014;50:3206–11.
21. Suttorp M, Eckardt L, Tauer JT, Milot F. Management of chronic myeloid leukaemia in childhood. Curr Hematol Malig Rep. 2012;7:116–24.
22. Tauer JT, Hofbauer LC, Jung R, Gerdes S, Glauche I, Erben RG, et al. Impact of long-term exposure to the tyrosine kinase inhibitor imatinib on the skeleton of growing rats. PLoS One. 2015;10:e0131192.
23. Simkin PA, Graney DO, Fiechtner JJ. Roman arches, human joints, and disease: differences between convex and concave sides of joints. Arthritis Rheum. 1980;23(11):1308.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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