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# Manifestations et complications orthopédiques dans la leucémie aiguë lymphoblastique de l'enfant : étude épidémiologique et thérapeutique

Pauline Savidan

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**THÈSE POUR LE DIPLÔME D'ÉTAT  
DE DOCTEUR EN MÉDECINE**

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**Par Madame Pauline SAVIDAN**

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**MANIFESTATIONS ET COMPLICATIONS  
ORTHOPÉDIQUES DANS LA LEUCÉMIE AIGUË  
LYMPHOBLASTIQUE DE L'ENFANT**

***ÉTUDE ÉPIDÉMIOLOGIQUE ET THÉRAPEUTIQUE***

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# INTRODUCTION

La leucémie aiguë lymphoblastique (LAL) de l'enfant peut initialement se manifester par des douleurs osseuses et se compliquer par des atteintes squelettiques au cours de son évolution et de son traitement, qui nécessitent une prise en charge orthopédique. En effet, grâce aux progrès de la science, cette maladie est devenue une maladie curable et la question de la qualité de vie est alors devenue primordiale.

Le but de ce travail multicentrique était de répertorier l'ensemble des différentes atteintes osseuses révélatrices de la maladie ainsi que les complications orthopédiques survenant lors du traitement ou du suivi afin de réaliser une cartographie de ces lésions, d'identifier des facteurs de risque puis d'évaluer leur prise en charge et leur évolution à long terme. En effet, l'objectif principal était de fournir une analyse rétrospective longitudinale reposant sur une base de données de plus de 1000 patients traités et suivis depuis 10 ans dans 3 centres différents afin de mieux appréhender les risques et la prise en charge des complications orthopédiques dans la LAL de l'enfant et de pouvoir ainsi donner des informations supplémentaires aux patients et à leurs parents lors de leur survenue.

## *i.1 Epidémiologie*

La leucémie aiguë est le cancer le plus fréquent de l'enfant et représente environ 29% d'entre eux (1). Chez l'enfant, les formes aiguës de la maladie sont les plus fréquentes (90% des leucémies) et 80% d'entre elles sont les formes lymphoblastiques (LAL), les autres correspondent aux leucémies aiguës myéloblastiques (LAM), aux leucémies chroniques myéloblastiques et aux leucémies myélomonocytaires juvéniles (2). En France, l'incidence de cette hémopathie est de 3,4 pour 100000 enfants âgés de moins de 15 ans par an, avec un pic d'incidence entre l'âge de 1 et 6 ans (1,3,4).

Les protocoles thérapeutiques, notamment les chimiothérapies, ont considérablement amélioré la survie de ces enfants depuis les 30 dernières années avec un taux de survie globale de presque 90% actuellement alors qu'il était quasiment nul avant 1970 (5).



## **i.2 Physiopathologie**

La leucémie aigüe résulte d'une prolifération clonale non contrôlée de précurseurs hématopoïétiques (Annexe 1). Ces précurseurs lymphoïdes (LAL) ou myéloïdes (LAM) sont bloqués à un certain stade de différenciation. Dans les LAL, les cellules immatures concernées peuvent appartenir à différentes lignées donnant naissance à des LAL de type B ou T.

## **i.3 Facteurs de risque**

Les causes des leucémies restent encore inconnues et sont probablement multifactorielles. Il existe une prédominance masculine (55% des garçons contre 45% des filles) et elle est principalement présente dans les populations caucasiennes (5 nouveaux cas pour 100 000 enfants âgés de 0 à 14 ans dans la population caucasienne, contre 3 enfants pour 100000 enfants dans les populations asiatiques et africaines) (2,4). Certaines maladies génétiques ont également été identifiées comme facteur de risque de LAL (l'anémie de Fanconi, le syndrome ataxie-télangiectasie, la trisomie 21) avec des risques pouvant être multipliés par 20 (2-4). Des facteurs environnementaux ont également été identifiés comme les radiations ionisantes, certains pesticides et les solvants organiques tout particulièrement lors de la grossesse (2,4). Néanmoins, dans 90% des cas, la cause n'est jamais identifiée et d'après *Greaves et coll.*, elle serait la conséquence d'une réponse immunologique anormale à une infection sur une altération génétique préalable (6,7).

## **i.4 Classifications**

Les leucémies aigües lymphoblastiques réunissent un groupe hétérogène de leucémies avec différentes manifestations cliniques et des pronostics variables. Plusieurs classifications ont été proposées mais deux sont principalement utilisées dans la littérature (8).

La première est issue d'un travail Franco-Américano-Britannique : la classification FAB (4,9,10). Elle est fondée sur des critères morphologiques (taille des cellules, forme des noyaux, visibilité des nucléoles, caractéristiques du cytoplasme) qui divise la maladie en 3 sous-groupes : L1, L2 et L3 (Annexes 2 et 3). La LAL L1 est le groupe le plus fréquent chez l'enfant (85% des cas), la L2 est plus fréquente chez l'adulte (15% chez l'enfant) et la L3 représente moins de 5% des cas chez l'enfant (4,9).

La seconde est une classification immuno-phénotypique fondée sur l'identification des antigènes de surface exprimés lors de la différenciation qui permettent de déterminer le stade auquel s'est arrêté la cellule leucémique (Annexes 4). Pour les cellules lymphoïdes l'immuno-phénotypage permet de différencier les cellules issues de la lignée B de celles issues de la lignée T (10-15% chez l'enfant). Pour les cellules de la lignée B, 3 sous-groupes peuvent être distingués : les cellules pré pré-B (early pre-B) (65-70%), les pré-B (pre-B) (15-20%) et les cellules B (10-15%) (3,9).

### ***1.5 Signes cliniques de découverte de la maladie***

Les symptômes sont liés à la prolifération clonale des cellules dans la moelle osseuse et à l'infiltration des tissus non hématopoïétiques par les cellules leucémiques.

Les principaux signes cliniques sont l'altération de l'état général avec l'asthénie et la pâleur présents en moyenne respectivement dans 35% et 79% des cas (11). De nombreux organes peuvent également être atteints avec ou sans manifestations cliniques et/ou biologiques : système ganglionnaire (70,7% par des adénopathies), foie et rate (75% par une hépatosplénomégalie), reins (3 à 5%), cœur (13,5%), poumons (37%), yeux (6,1%), peau (30% par un purpura), muqueuses (25 % de manifestations hémorragiques), tube digestif (13%), système nerveux central (5%) et glandes sexuelles (1%) (1,4,11-16).

Les manifestations orthopédiques sont particulièrement fréquentes avec une incidence pouvant aller jusqu'à 50% chez l'enfant pour 2 raisons: (1) l'intégralité de la moelle osseuse est hématopoïétique avec une involution adipeuse dans les os longs qui se fait progressivement lors de la croissance et (2) le métabolisme osseux est sous la dépendance des hormones stéroïdes et de différents facteurs de croissance qui n'existent que pendant la croissance (17-19) .

Trois manifestations orthopédiques ont été décrites comme mode de révélation : les douleurs osseuses, l'arthrite et les fractures pathologiques.

**Les douleurs osseuses** sont les manifestations les plus fréquentes et sont présentes jusque dans 59% des enfants atteints de leucémie aigüe (20). Elles touchent la plupart du temps les extrémités du squelette et sont bien localisées (fémur et tibia dans 30% des cas, le rachis dans 25% des cas) (20). La cause de ces douleurs est attribuée par certains soit à l'ostéolyse liée à l'envahissement, soit aux atteintes du périoste richement innervé, soit à l'augmentation de la pression intra-médullaire également lié à l'envahissement néoplasique (20,21). Les radiographies, généralement réalisées devant ces douleurs, peuvent trouver quatre types de

lésions : les bandes claires métaphysaires, l'ostéopénie, l'ostéolyse et les réactions périostées (Annexe 5).

Les bandes claires métaphysaires sont les anomalies les plus fréquentes (7,5 à 70% des cas) (22). Il s'agit d'étroites bandes de 2 à 15 mm d'épaisseur, parallèle à l'épiphyse. Elles sont dues à un trouble de l'ostéogénèse au niveau des épiphyses et traduisent l'apposition de l'os sain formé à partir de la physe tandis que celui-ci est soulevé par la lésion sous-jacente (23). Elles surviennent le plus souvent au niveau des os longs et plus particulièrement dans les zones de croissance rapide (genoux, poignets, chevilles).

L'ostéopénie (13 à 40% des cas) est liée à la diminution en nombre et en taille des travées osseuses en raison de la prolifération clonale (22). Au niveau de l'os cortical, l'ostéopénie est due à un élargissement des canaux de Havers et de Volkmann et elle est proportionnelle au degré d'infiltration par les cellules leucémiques.

Les lésions ostéolytiques surviennent dans 19 à 38% des cas, avec des lésions de taille variables (<5mm) qui peuvent mimer les signes radiologiques d'une ostéomyélite aiguë hémotogène (ostéolyse mouchetée) (22,23).

Les réactions périostées (2 à 19%) sont dues à l'infiltration du périoste par les cellules leucémiques qui le soulève (22). Le nouvel os formé apparaît comme une ligne de densité augmentée, parallèle au fût diaphysaire.

**L'arthrite** est le 2<sup>nd</sup> mode de manifestation orthopédique initial dans les LAL. Elles sont retrouvées dans 12 à 15% des nouveaux cas de leucémie aiguë avec les mêmes symptômes qu'une arthrite infectieuse ou inflammatoire (impotence fonctionnelle ou boiterie, fièvre et limitation des amplitudes articulaires) (20,23). Pour les articulations superficielles, il existe parfois des signes inflammatoires locaux (rougeur, chaleur). Ces arthrites sont causées par l'infiltration des cellules leucémiques au niveau du périoste métaphysaire, à proximité de la capsule articulaire, provoquant une inflammation de la synoviale qui sécrète alors du liquide et donc un épanchement articulaire. Les grosses articulations sont le plus souvent concernées (genoux, poignets, chevilles, coudes, épaules et hanches) (19).

Enfin, les **fractures pathologiques** sont la 3<sup>ème</sup> manifestation orthopédique de la leucémie aiguë chez l'enfant et sont révélatrices dans 2 à 10% des cas (22). L'infiltration de la moelle osseuse conduit à une augmentation du volume de la cavité médullaire intra osseuse avec un amincissement de la corticale qui est alors fragilisée. Ces fractures se manifestent souvent au décours d'un traumatisme mineur et sont le plus souvent localisées au niveau du rachis (16%) plutôt qu'au niveau des membres (3 à 8%) (11,22,24). Dans plus de la moitié des cas les fractures vertébrales sont asymptomatiques chez l'enfant (24).

### **i.6 Diagnostic paraclinique**

Lorsqu'une leucémie aiguë est suspectée, notamment devant les signes cliniques précédemment cités, une numération formule sanguine (NFS) est alors demandée et elle pourra retrouver une pancytopenie (66% de cas) ou une hyperleucocytose ( $100 \cdot 10^9/L$  leucocytes/ $mm^3$ ) (4,11). La recherche de blastes est alors réalisée, mais leur présence dans la circulation sanguine n'est pas systématique. Le diagnostic est alors confirmé avec certitude par la ponction-biopsie de moelle osseuse qui va mettre en évidence les cellules leucémiques (par définition, >20% des cellules normales de la moelle osseuse) (1). Le diagnostic précis est ensuite établi avec l'immunophénotypage des cellules leucémiques par la cytométrie en flux qui va permettre de déterminer la lignée des cellules qui est atteinte (lymphoïde ou myéloïde) et leur appartenance à un sous-groupe en fonction des classifications précédemment citées (3,9). Une analyse cytogénétique est ensuite réalisée, comprenant un caryotype et d'autres analyses génétiques plus performantes telles que l'hybridation fluorescente in situ (FISH), le caryotypage spectral et le CGH-Array (l'analyse génomique comparative par hybridation). Toutes ces analyses génétiques sont réalisées non seulement à visée diagnostique et pronostique mais également pour déterminer la localisation des lésions moléculaires à l'origine de la transformation et de la prolifération des cellules leucémiques (3). L'analyse biomoléculaire quant à elle, permet la détection de la maladie résiduelle après le début de la chimiothérapie.

### **i.7 Traitements**

Une fois le diagnostic confirmé, un traitement par chimiothérapie intensive doit être débuté en urgence. Les protocoles thérapeutiques des dernières décennies ont considérablement amélioré la survie des enfants atteints de LAL. Ils sont essentiellement composés de glucocorticoïdes (dexaméthasone et prednisone) et de chimiothérapies : la vincristine, l'asparaginase, le méthotrexate, la mercaptopurine et parfois des anthracyclines. Ce traitement est divisé en 3 phases : une **phase d'induction-rémission** (5 semaines), une **phase de consolidation** (6 à 12 mois) et une **phase d'entretien** (24 mois) dans lesquelles les différentes molécules précédemment citées sont associées à des dosages différents (1).

La 1<sup>ère</sup> phase a pour but d'éradiquer plus de 99% des cellules leucémiques initiales et de restaurer une hématopoïèse normale (6). La 2<sup>nde</sup> phase a pour objectif d'éradiquer les cellules leucémiques résiduelles résistantes au traitement afin de diminuer le risque de récurrence. La 3<sup>ème</sup> est plus controversée, mais semble nécessaire pour prévenir une récurrence ou maintenir la

rémission. *Toyoda et coll.* ont montré que 2/3 des enfants pourraient être guéris avec seulement 12 mois de chimiothérapie au total (25). Cependant, jusqu'à ce jour, aucune technique ne permet d'identifier avec certitude les enfants qui seraient en rémission au bout d'un an. C'est pourquoi la durée moyenne totale du traitement pour une LAL est de 2,5 ans.

Trois protocoles ont principalement été utilisés en France et dans notre étude : FRALLE 2000, CAALL F01 et INTERFANT 06.

Utilisé depuis les années 2000, le protocole FRALLE 2000 est destiné aux enfants âgés de plus de 1 an. Il se divise ensuite en 3 groupes selon l'âge de l'enfant et le type de leucémie : le protocole FRALLE 2000 A (enfants < 10 ans) et FRALLE 2000 B (enfants > 10 ans) pour les LAL B et le protocole FRALLE T pour les LAL T (26). Ces différents protocoles sont ensuite divisés en sous-groupe selon la réponse thérapeutique initiale (27). Le protocole INTERFANT 06 est utilisé depuis 2006, pour les enfants âgés de moins de un an (28). Il est également divisé en sous-groupes selon la réponse au traitement. Enfin, le protocole CAALL F01 est actuellement en cours d'essai thérapeutique (depuis 2016) et tend à remplacer le protocole FRALLE 2000 afin de diminuer l'usage des anthracyclines qui sont cardiotoxiques et d'améliorer la survie avec une nouvelle molécule appelée la peg-asparaginase. Il est composé de deux groupes selon le type de leucémie B ou T (29). Chaque groupe est divisé en sous-groupe selon le risque de la leucémie déterminé en fonction de l'âge, du taux de leucocytes au diagnostic, de la présence d'une atteinte du système nerveux central, d'éventuelles anomalies génétiques et de la réponse initiale au traitement.

### **i.8 Complications orthopédiques des thérapeutiques**

Bien que très efficaces, les chimiothérapies et les glucocorticoïdes ont de nombreux effets secondaires aigus et à long terme. Sur le plan général, le principal effet secondaire est l'aplasie, avec un risque accru d'infections, auquel s'ajoutent les risques d'hémorragies et les syndromes de lyse tumorale. Les autres effets secondaires tels que vomissements, mucites et alopecie, sont communs aux autres chimiothérapies. Sur le plan orthopédique, les complications sont principalement l'ostéonécrose et l'ostéopénie (11,22).

**L'ostéonécrose** représente la principale complication orthopédique avec une incidence >17,6% dans la population pédiatrique, surtout chez les enfants de plus de 10 ans (30,31). L'explication physiopathologique est incertaine, bien que certains facteurs tels que les changements hormonaux et la croissance osseuse puissent jouer un rôle (31). Le mécanisme présumé est la

survenue d'une ischémie osseuse, conduisant à une déminéralisation osseuse avec une altération de la structure trabéculaire qui devient plus fine et plus fragile (32). Le traitement par les glucocorticoïdes est le principal facteur prédisposant aux ostéonécroses avec 3 mécanismes expliquant l'interruption de la vascularisation osseuse.

- L'apoptose des cellules endothéliales et l'hyperviscosité sanguine favorisant le développement des micro thrombi (33).
- La diminution du nombre d'ostéoblastes et la stimulation de l'apoptose des ostéocytes altèrent le processus de régénération osseuse (33).
- La stimulation de la prolifération et l'hypertrophie des adipocytes dans la moelle osseuse conduisent à une augmentation de la pression intramédullaire favorisant l'ischémie (33).

L'asparaginase est également responsable d'ostéonécrose, car elle réduit la clairance de la dexaméthasone et potentialise ainsi les effets ostéonécrotiques des glucocorticoïdes (32,34). Les ostéonécroses affectent le plus souvent des zones épiphysaires, en zone portantes et/ou avec une vascularisation vulnérable. Les articulations les plus touchées sont les hanches, les genoux, les épaules et les chevilles (35).

La seconde complication orthopédique est **l'ostéopénie et/ou l'ostéoporose**. Elle peut résulter de l'hémopathie elle-même, mais également des thérapies anti leucémiques (chimiothérapie, glucocorticoïdes) avec comme effets secondaires principaux la dénutrition, la diminution de la masse musculaire et les carences en vitamine D (22). Les glucocorticoïdes, principaux responsables de cette complication, agissent selon deux mécanismes.

Premièrement les corticoïdes agissent sur 5 points de la formation osseuse :

- Ils entraînent une diminution de la production des facteurs de croissance (IGF-1 et TGF-B) qui sont indispensables au fonctionnement des ostéoblastes.
- Ils réduisent la capacité de synthèse osseuse des ostéoblastes ainsi que leur différenciation et stimule leur apoptose.
- Ils altèrent la fonction musculaire en induisant des myopathies, qui réduisent elle-même la mobilité et donc les sollicitations mécaniques sur l'os.
- Ils augmentent transitoirement le taux d'ostéoclastes.
- Ils induisent un hypogonadisme par inhibition directe des hormones gonadiques et de l'axe hypothalamo-hypophysaire, lui-même responsable d'une moindre stimulation osseuse.

Deuxièmement, les corticoïdes réduisent l'absorption intestinale de calcium et sa réabsorption rénale, entraînant donc une hypocalcémie et un hyperparathyroïdie secondaire (36). Le rachis

est particulièrement atteint par ces effets secondaires des glucocorticoïdes, provoquant des fractures pathologiques qui peuvent modifier les paramètres radiologiques normaux de la statique rachidienne. Il est important de les diagnostiquer et de les prendre en charge dès l'enfance. En effet, ces modifications des paramètres radiologiques, surtout dans le plan sagittal, ont des effets bien connus dans la littérature sur la qualité de vie à long terme mais ils ont été essentiellement décrits dans d'autres pathologies et principalement chez l'adulte (37,38).

### ***i.9 Organisation de nos études***

A la vue de ces différentes problématiques orthopédiques de la LAL en pédiatrie, notre travail a été articulé en 3 parties et suivant trois études.

Dans la **première étude**, nous avons décrit les différentes manifestations orthopédiques révélatrices de la maladie, leurs incidences et leurs localisations au sein de notre population d'étude. Il s'agissait d'une étude purement épidémiologique dans le but de cartographier les atteintes orthopédiques de l'enfant dans la LAL.

Dans la **seconde étude**, nous avons analysé les complications survenues au cours des traitements dans le but d'identifier des facteurs de risques liés aux thérapeutiques ou aux caractéristiques de la maladie.

Dans la **troisième étude**, nous avons étudié les complications rachidiennes (tassements vertébraux) en analysant les paramètres radiologiques initiaux, leurs différentes prises en charge (traitement symptomatique, traitement orthopédique et chirurgical) et leur évolution radiologique à long terme.

# **I PART 1**

## **Clinical and radiological orthopaedic manifestations in children with acute lymphoblastic leukemia - A multicentric demographic study**

### **I.1 INTRODUCTION**

Acute lymphoblastic leukemia (ALL) is a malignant blood disorder resulting from the uncontrolled clonal proliferation of hematopoietic precursors with cellular maturation suspended at a particular stage of differentiation and it is the most common pediatric neoplasia (approximately 30%) with an overall incidence of 3.4 for 100 000 children younger than 15 years old per year (1). Physical symptoms are related to the proliferation of the clonal cells in the bone marrow with disruption of normal hematopoiesis and the infiltration of non-hematopoietic tissues by leukemic cells. Common clinical manifestations at initial diagnosis include asthenia (35%), anorexia (27%), pallor (79%) and fever (56%) (11). Many organs can be touched with or without clinical and/or biological manifestations: nodal system (lymphadenopathy in 70%), liver and spleen (hepatosplenomegaly in 75%), lungs (37%), skin (purpura 30%), mucous membranes (hemorrhages 25%), heart (13.5%), gastro-intestinal tract (13%), eyes (6%), kidney (3 to 5%), central nervous system (5%) and sexual organs (1%) (1,4,12–16).

However, in children, osteoarticular manifestations are particularly frequent at initial stage (up to 50% of the cases) for 2 reasons. First, the entire bone marrow is involved in the hematopoiesis process (including long bones) conversely to adults (sternum, skull, ribs iliac bone and femoral head only). Second, bone metabolism, depending on steroids hormones and growth factors, is much more active during growth (17–19). Three particular musculo-skeletal manifestations can reveal the disease: bone pain, arthritis and pathological fractures.



Bone pain is the most frequent symptom (up to 59% of children with ALL) (20). Standard antero-posterior and lateral side views X-rays are usually performed and might show several anomalies, such as, radiolucent metaphyseal bands (7.5 à 70% of cases), osteopenia (13% to 40%), focal osteolysis (19 % to 38% of cases) and periosteal reactions (2% to 19% of cases) (22). Joint effusion is the 2<sup>nd</sup> most frequent revealing symptom found in 12% to 15% of the cases, with no difference allowing distinction between septic and rheumatoid arthritis (limping/functional impotence, fever, limited range of motion) (23). Diagnosis is only possible after joint fluid anatomopathologic analysis, but generally other signs are associated on blood cell count (23). Finally, the 3<sup>rd</sup> orthopaedic revealing manifestation are pathological fractures (2% to 10%), due to the infiltration of the bone marrow by leukemic cells, that progressively fill the medullary cavity, making the cortical thinner until breaking and usually occurring after a minor traumatism (22).

To the best of our knowledge, while orthopaedic revealing manifestations are well-known and well-described in the literature, a specific mapping correlated to clinical and radiological symptoms among a large population of children with ALL was not investigated yet (11).

Therefore, the aim of this study was to provide an accurate demographic overview of clinical and radiological orthopaedic manifestations in children affected by acute lymphoblastic leukemia.

## **I.2 MATERIAL AND METHODS**

### ***1.2.1 Study design***

A multicentric (3 pediatric university hospitals) and retrospective study was conducted between 2007 and 2017 including all children, diagnosed and treated for an ALL. All data were collected after approval by local ethic committees. All medical records and X-rays of children < 18 years

old, diagnosed for ALL were reviewed in order to identify patients with initial symptomatic osteoarticular manifestations, associated or not to a loss of conditions (asthenia, anorexia), pallor, purpura and lymphadenopathy. Patients suffering from another type of leukemia were excluded (myeloblastic leukemia, Burkitt lymphoma and biphenotypic leukemia) as well as ALL secondary to a syndrome (Down syndrome, Fanconi anemia).

### ***1.2.2 Clinical and radiological orthopaedic manifestations***

Three different types of orthopaedic manifestations were recorded: (1) bone pain, (2) joint effusion and (3) pathological fractures.

Initial X-rays (antero-posterior and lateral views) focused on painful location, were recorded and verified by one senior pediatric orthopaedic surgeon. Systematic X-rays were not performed at initial medical consultation in the absence of specific location. Only a blood cell count was collected. Interpretation of all X-rays was performed by a senior radiologist. Four different types of lesions were explored: (1) radiolucent metaphyseal bands (RMB), (2) focal osteolytic lesions (FO), (3) periosteal reactions (PR) and (4) osteopenia. All these signs were not considered as pathognomonic of leukemia in the literature but were frequently found in the disease (23). Any other complementary radiological exams were also recorded as well as their results (ultrasounds, bone scintigraphy, CT-scan and MRI).

### ***1.2.3 Statistical analysis***

Statistical analyses were performed using SPSS statistics 23.0 (SPSS Inc., Armonk, NY, USA). Continuous numeric data was expressed as Mean  $\pm$  Standard Deviation (SD) and ranges [min-max]. Descriptive qualitative data was expressed as rates (%).

## I.3 RESULTS

### I.3.1 Patients

Between 2007 and 2017, 1293 patients were treated for an ALL in 3 pediatric institutions. Mean age at diagnosis was  $6.8 \pm 0.1$  [0.08-20.5] year-old, (y.o), range from 1 month to 20 years (726 males and 567 females). A total of 138 patients (10.7%, mean age  $7.4 \pm 0.4$  [0.42-18] y.o n=25 < 3 y.o) had some orthopaedic manifestations at initial diagnosis, including bone pain, pathological fractures and arthritis in respectively 8.2%, 1.8% and 0.7% of the total number of children diagnosed with an ALL. Bone pain was expressed by limping in 12 children (11.3%) and by sciatica in 6 patients (5.7%). Biological diagnosis of the malignant blood disease was made on the bone-marrow biopsy (Table 1).

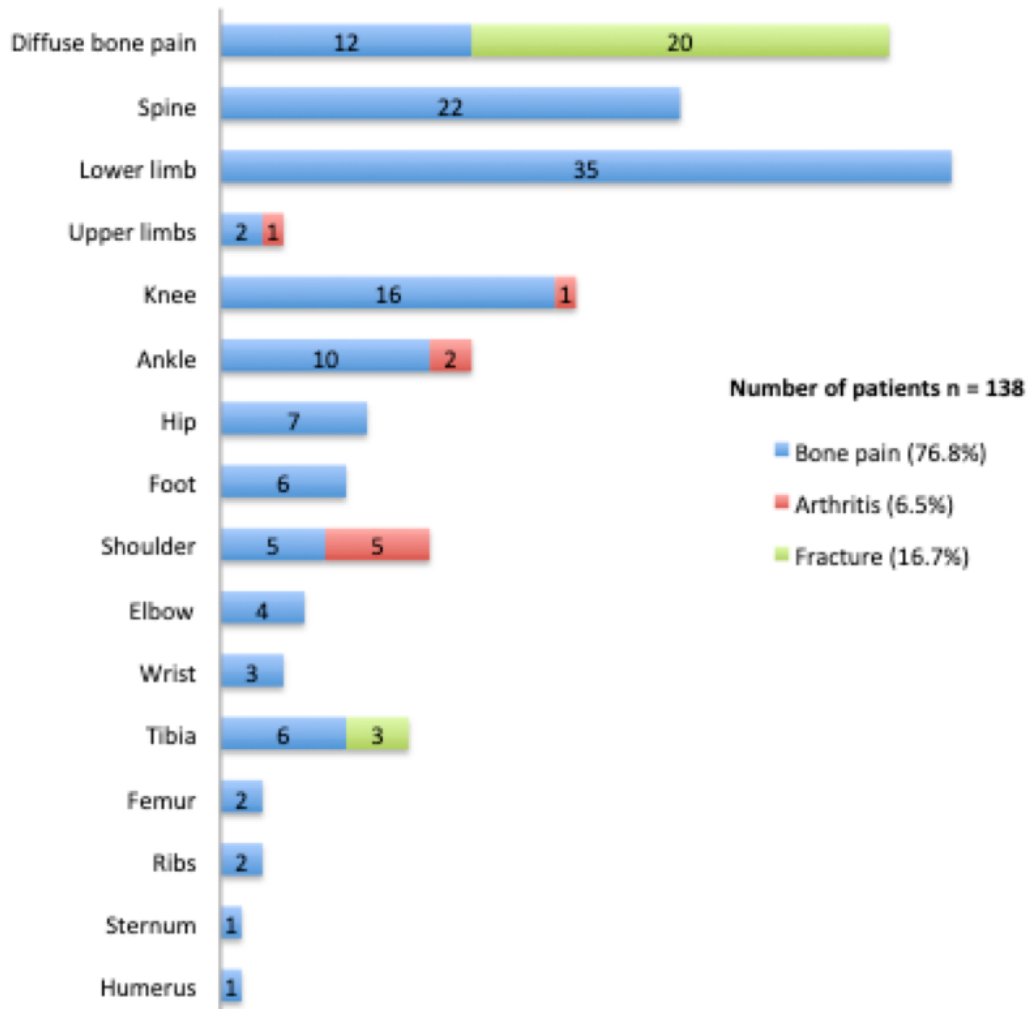
Table 1: Patients with musculo-skeletal manifestations demographics (n=138).

		Number of children (%)
Type of leukemia	Pre-B	81 (58.7)
	Early pre-B	29 (21)
	B	17 (12.3)
	T	11 (8)
Orthopaedic manifestations	Bone pain	106 (76.8)
	Pathological fractures	23(16.7)
	Arthritis	9 (6.5)
Sex	Male	69(50)
	Female	69(50)

### ***1.3.2 Cartography of initial orthopedic manifestations***

Regarding bone pain, 134 anatomical localizations were found among the 106 children, meaning that 19.8 % of the children had multiple localizations (Figure 1).

Figure 1: Orthopaedic manifestations localizations



Most of the patients localized their pain at lower-limb (51.2%). Pain was diffuse in 36.6% of the cases (lower-limb > full-body > upper-limb), involved one specific joint in 38% of the children (knee > ankle > hip > shoulder > foot > elbow > wrist), was at the spine level in 16.4% and was at a specific bone location in 9% (tibia > femur > ribs > humerus = sternum).

Among the 9 patients with arthritis, localizations were elbow (n=5), hip (n=2), knee (n=1) and ankle (n=1) (Figure 1). A total of 6 patients were initially treated like septic arthritis combining surgery (4 arthrotomy, 2 puncture) and intravenous antibiotherapy (Table 2).

Table 2: Initial blood cell count of the patients with arthritis treated surgically.

	Age (years)	Type of Leukemia	Hb (g/dl)	Thrombocytes (/mm <sup>3</sup> )	Leucocytes (/mm <sup>3</sup> )	Neutrophils (/mm <sup>3</sup> )	Lymphocytes (/mm <sup>3</sup> )	Reticulocytes (/mm <sup>3</sup> )	Blasts
Patient 1	4	Pre-B	9.6	165000	3270	70	2130	4430	+
Patient 2	8	Pre-B			23000		19000		+
Patient 3	10	Pre-B	9.2	31000	5900				+
Patient 4	2	Pre-B	9.8	150000	1900	610	1000	204000	
Patient 5	5	Pre-B			34500				
Patient 6	9	B	12.3	327000	6400	5250			

Hb: hemoglobin

The lack of clinical improvement and of bacteriological identification made look at anatomopathological results and closer look to the blood cell count that gave the diagnosis subsequently. Among the 23 patients with pathological fractures, the spine was most frequently involved (n=20) followed by lower-limb fractures (n=3) (Figure 1). Eleven patients were treated orthopedically by cast or brace immobilization without instrumentation (mean time of treatment  $7.9 \pm 0.4$  months) and the remaining 9 patients were treated symptomatically. All spinal fractures, were vertebral compression fractures (n=89 at the thoracic level and n=49 at the lumbar level). Lower-limb fractures were all femoral fractures (one femoral neck fracture and 2 distal metaphyseal fractures).

### 1.3.3 Radiological analysis

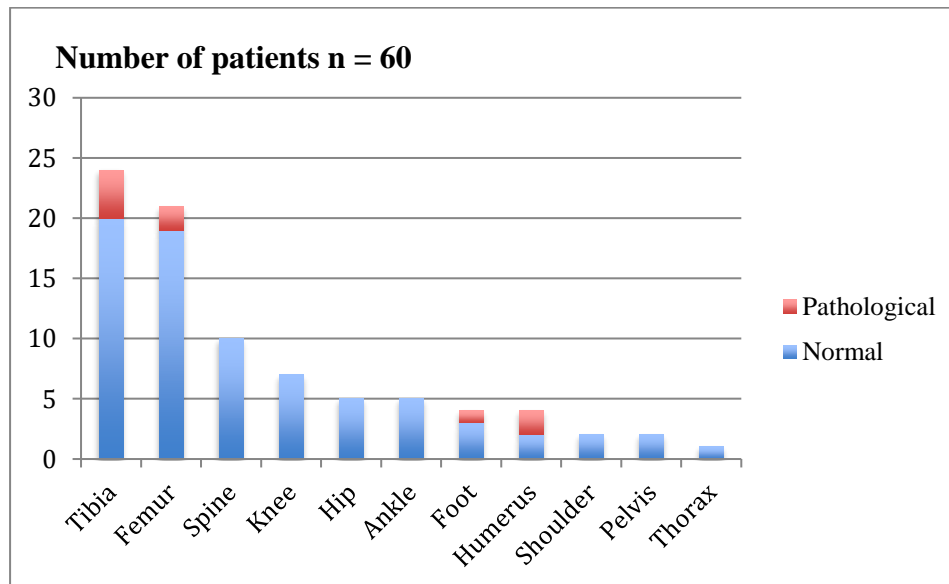
A total of 118 radiological exams (X-rays, CT-scan, ultrasound, MRI, bone scintigraphy) were performed in front of orthopaedic symptoms and found no anomaly in most of the cases (Table 3).

Table 3: Radiological exams (n=118). Data is expressed in number of exam performed with the corresponding number of pathological lesions found on these exams into brackets.

	X-rays	MRI	Ultrasound	CT-scan	Bone scintigraphy
Bone pain	60 (22)	15 (14)	3 (0)	2 (1)	2 (1)
Arthritis	9 (9)	0	7 (7)	0	2 (2)
Fractures	24 (24)	0	0	0	0

Among the 106 children with bone pain, 60 patients had a localized pain investigated by centered X-rays (Figure 2).

Figure 2: X-rays demographics



Diagnosis of arthritis was made on ultrasound in 7 out of 9 patients. In the remaining 2 patients, the diagnosis of arthritis secondary to the malignant blood disease was suspected on a bone scintigraphy that found multiple hyperfixation, excluding the diagnosis of septic and rheumatoid disease.

Amongst the 60 painful patients, 18 patients had X-rays or MRI with radiological anomalies (Table 4).

Table 4: Patients with radiological anomalies (n=18)

	Age (years)	ALL diagnosis	Location of pain	Region	X-ray anomaly	MRI anomaly
Patient 1	5	B	Ankle	Tibia Distal metaphysis	FO	BMN
Patient 2	6	Pre-B	Elbow	Humerus distal metaphysis	FO	
Patient 3	2	B	Elbow	Humerus distal epiphysis	PR	
Patient 4	3	Pre-B	Lower-limb	Femur distal metaphysis Tibia proximal metaphysis	RMB RMB	
Patient 5	13	T	Lower-limb	Tibia distal and proximal metaphysis	RMB	
Patient 6	2	Pre-B	Foot	Foot 5 <sup>th</sup> metatarsal diaphysis	FO	
Patient 7	4	Pre-B	Lower-limb	Femur distal metaphysis Tibia and fibula proximal metaphysis	RMB RMB	
Patient 8	12	Pre-B	Lower-limb	Femur Spine	- -	Myositis BMN
Patient 9	8	T	Lower-limb	Distal femur	-	Myositis + EN
Patient 10	14	Early Pre-B	Diffuse	Spine	Normal	BMN
Patient 11	9	Early Pre-B	Knee	Femur	-	BMN + EN
Patient 12	13	B	Sciatica	Pelvis (sacrum)	-	BMN
Patient 13	3	Pre-B	Spine	Spine	-	BMN
Patient 14	3	Early Pre-B	Ankle	Distal tibia	-	BMN
Patient 15	3	Early Pre-B	Foot	Foot	-	BMN
Patient 16	9	Pre-B	Lower-limb and sciatica	Spine and pelvis	-	BMN
Patient 17	17	Pre-B	Sciatica	Spine	-	BMN
Patient 18	16	Early Pre-B	Shoulder	Proximal humerus	Normal	FO

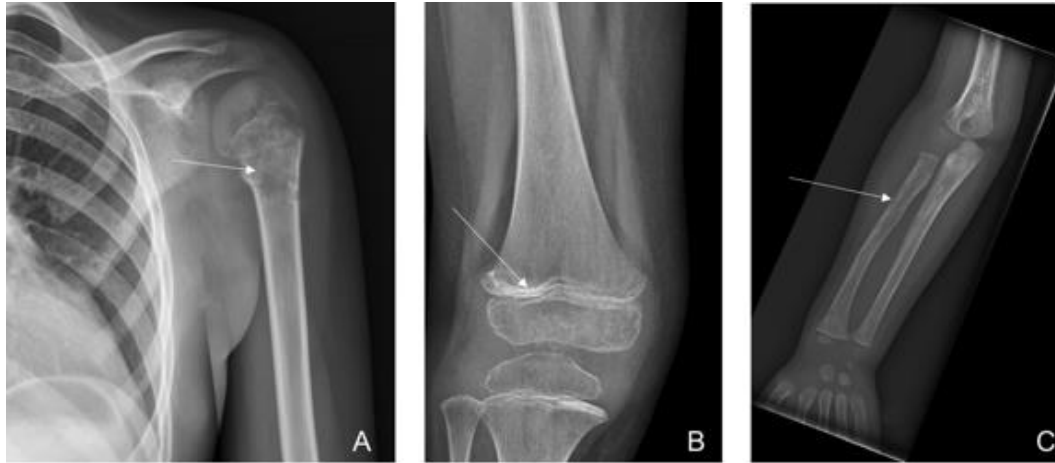
Lesions on radiographs FO: focal osteolysis; MRB: metaphyseal radiolucent bands; PR: periosteal appositions

Lesions on MRI BMN: bone marrow necrosis; ON: osteonecrosis; Myositis;

- no X-ray performed

Focal osteolysis, radiolucent metaphyseal bands and periosteal reaction were found in respectively 3, 3 and 1 cases (Figure 3). No case of osteopenia was found.

Figure 3: Radiological anomalies



A: Proximal humerus focal osteolysis

B: Distal femur radiolucent metaphyseal bands

C: Radius periosteal reaction.

In one patient, proximal focal osteolysis of the humerus was found as initial symptom of a recurrence of the disease (Figure 3). Fifteen MRI (12 children) were performed and found bone marrow necrosis, epiphyseal necrosis and myositis that were not associated to radiographic anomalies in most of the cases (Figure 4).



Figure 4: Illustrations of MRI anomalies.



A: 14-y-o boy with spinal bone marrow necrosis at T11, L2-L5 and S1 characterized by hyper-signal in T2-weighted sequences suggesting abnormal bone marrow activity.

B: 14-y-o girl with femoral epiphyseal necrosis of the right proximal femur characterized by hypo-signal in the femoral epiphysis on T1-weighted sequence.

C: 9-y-o girl with a femoral osteonecrosis and epiphyseal osteonecrosis characterized by an iso-signal lesion surrounded by hypo-signal on T1-weighted sequence.

## I.4 DISCUSSION

This large retrospective series of children diagnosed with an ALL found that orthopaedic manifestations were symptomatic at initial diagnosis in 10% of the patients although associated to other symptoms. However, these musculo-skeletal manifestations were associated to radiographic anomalies in less than 5% of the children.

### *1.4.1 Clinical presentation at initial diagnosis*

Conversely to previous reports, the incidence of orthopaedic symptoms at initial presentation was lower (10% vs. 20%) (11,39). However, most series had a small number of patients included (< 200 patients), making the current study the largest study ever performed to the best

of our knowledge (11,39,40). Furthermore, 1 out of 5 patients (18.1 %) were under 3-y-o, meaning that localization of complaints might be difficult to detect in many cases. Nonetheless, musculoskeletal manifestations remained overall a common symptom. It should be noted that musculo-skeletal manifestations were sufficiently symptomatic to be reported at initial presentation for the present patients. Besides, other symptoms were frequently associated such as loss of consciousness, cutaneous signs (pallor, purpura) and lymphadenopathy, which are the most frequent signs of malignant blood disease, since they are directly related to the perturbation of hematopoiesis (11). Finally, most of the patients were addressed by their general practitioner at the emergency departments in front of these symptoms without any complementary explorations.

The 3 manifestations were bone pain, pathological fractures and arthritis, which pathophysiology has been largely described in prior literature (11,20,39). Bone pain was the most frequent skeletal symptom (8.2%) followed by pathological fractures (1.8%) and arthritis (0.7%). These rates were far below from those reported in prior studies (11,39,41). Regarding arthritis, reported rates in the literature are ranged from 12% to 15% at initial diagnosis (23). An ultrasound was performed in most of the children consulting for functional impairment associated with fever and reduced range of motion, which are the cardinal signs of a joint effusion. Although these symptoms mimicked septic or rheumatoid arthritis, a blood cell count was also performed, orientating towards a possible malignant blood disease. Nonetheless, 6 patients had surgery because the effusion was considered as a septic arthritis and final diagnosis was secondary confirmed by anatomopathological analysis (Table 2).

Finally, regarding pathological fractures, even though current rates were in the lowest of those reported in the literature (range from 5.7 to 10 %), localizations were similar, with a frequent involvement of the spine (16.2%) (11,42).

### ***1.4.2 Cartography of the symptoms***

Musculo-skeletal complaints had various and non-uniform localizations in the current study (Figure 1). However, 18.1% of the patients were under 3-year-old at diagnosis and exact location of pain could be difficult (36.6% of diffuse pain). Most frequent location was lower-limb in 51.2% of cases, followed by spine 16.4% and upper-limb in 11.1%, which corresponded to previous reports (11,20). Indeed, *Thomas et al.* showed that bone pain affected preferably the lower-limb (50%) and spine (20%), as well as *Sinigaglia et al.*, that reported same locations but with different rates (18.8% and 9% respectively) (11,20).

According to *Roux et al.*, arthritis sites were similar to those reported in the present study (19). As a matter of fact, the biggest joints were affected, but not in the same proportion (Figure 1) (19). *Roux et al.* indicated that arthritis concern big joints, especially knee but also wrists, ankle, elbow, shoulder and hip (19). Elbow arthritis were particularly frequent in the current study without followed by hip.

Finally, pathological fractures did affect the spine more frequently than long-bones, which is similar to prior reports (11,39). Indeed, spine is essentially constituted of trabecular bone, which is a risk for osteopenia (22).

### ***1.4.3 Radiological analysis***

A total of 67% radiographic lesions amongst symptomatic patients was reported, which corresponded to rates reported in literature (from 40.2 to 75%) (11,43,44) even if X-rays were not systematically performed conversely to several studies. Only symptomatic patients, with a specific location of pain, had an X-ray performed. All X-rays have been read by a senior radiologist, that allow the authors to exclude errors. As previously reported, osteolytic lesions (2.8%) and radiolucent metaphyseal bands (2.8%) were the most frequent observed anomalies followed by periosteal reactions (0.9%). Osteolytic lesions (range from 10% to 38%) were

preferably localized in the long bones metaphysis but may occur in other bones and could be associated to periosteal reactions (22). Interference with normal epiphyseal growth due to the invasion by leukemic cells are responsible for radiolucent metaphyseal bands (11,23,45). They were reported in only 2.8% compared to 7.5% to 70% in the literature (22). However, 18.1 % of the children were under 3-y.o and according to *Gunz et al.*, this sign is more specific after 2 years (45). Periosteal reactions were the least frequent anomaly (0.9%) rates varying from 2% to 50% in the literature and were located along long bones diaphysis (20,22,44). Finally, osteopenia was not described on radiographs either on MRI. Presence of some kind of osteopenia was diagnosed on MRI 's, under the form of bone marrow necrosis (8.5%), whereas X-rays found no anomaly, which is not described in prior studies, since MRI are not usually performed. Bone marrow necrosis have been reported in the literature by *Thomas et al.* but after anatomopathological analysis (20).

#### ***1.4.4      Limitations***

The main limitation of this study was its retrospective nature that did not ensure a complete data recovering. However, reason for consultation was reported in all cases and orthopaedic manifestations were therefore, mentioned on initial medical record. Furthermore, compared to other studies, the current series is the largest one ever performed. The second limitation was the poor number of radiographs performed. A recent prospective study by *Sinigaglia et al.* found a total rate of 40.2% radiological lesions at initial diagnosis (11). However, radiological anomalies would not have changed initial management that required urgent chemotherapy and corticoids and performing systematic X-rays increase radiation exposure rates, which should be taken into consideration. Further radiological exams are usually performed during treatment, when symptomatic osteoarticular complications occur.

In conclusion, orthopedic manifestations are a frequent means of revelation in children with ALL. Therefore, clinicians (general practitioner, pediatricians) should be aware that faced to a patient with loss of condition and musculo-skeletal symptoms, the child should be urgently referred to a pediatric hospital in order to initiate biological (complete blood cell count) and radiological exams if symptomatic. However, in the absence of radiological anomalies, the diagnosis should not be reject, since radiographic signs are rare and not specific and only the bone-marrow biopsy will confirm the final diagnosis.

## **II PART 2:**

### **Risk factors of orthopaedic complications in children with acute lymphoblastic leukemia**

#### **II.1 INTRODUCTION**

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer (1). Once the diagnosis is confirmed by a bone marrow biopsy, the treatment by chemotherapy and corticoids must be urgently started. Treatment modalities significantly improved global survival in childhood ALL over the last decades with nearly 90% of 5-year survival rates compared to almost no survival before 1970 (5). Recent reports also found a 85% event-free survival rates (5). However, treatments must be aggressive to eradicate all tumor cells at the expense of numerous complications such as infections, internal bleeding and tumor lysis syndrome, but also orthopaedic problems that occurred in up to 47% of the cases (46).

Two skeletal complications have been described: osteonecrosis (ON) and osteopenia (OP) (11,22). Bone osteonecrosis is the most frequent complication with a mean incidence of 17.6% in children, particularly in those older than 10 years old (30,31). Hormonal changes and bone growth might play a role, but the exact physiopathology is uncertain (31). The principal mechanism causing osteonecrosis is the alteration of bone vascularization leading to a demineralization and trabecular thinning of bone structures, responsible for mechanical failure (32). Corticoids and asparaginase have been identified as the main contributing factors for osteonecrosis, and do frequently affect weight-bearing lower-limb joints (hip, knee and ankle) and also epiphysis with vulnerable blood supply such as shoulder (30,32–35). The 2<sup>nd</sup> orthopedic complication is osteopenia (defined as osteoporosis if Z-score < -2.5 SD) with an incidence range from 13% to 40%, which is probably caused by the blood disease itself but also by the cytotoxic therapeutics (chemotherapies and glucocorticoids) and their side effects

(undernutrition, poor muscle mass and vitamin D deficiency) (22,42,47). Spine and long bones are particularly involved by this complication, rates varying from 9% to 16% and 3 à 8% respectively (11,22,24,46). Since ALL is currently a curable disease in children, it is of utmost importance to predict risk of orthopaedic treatment-related morbidities in order to prevent from potential fractures and chronic pain that might altered quality of life during adulthood.

The aim of the study was therefore, to report orthopaedic morbidities during treatment, their characteristics and risk factors in children treated for an acute lymphoblastic leukemia.

## **II.2 MATERIAL AND METHODS**

### ***II.2.1 Study design***

A multicentric (3 pediatric university hospitals) and retrospective study was conducted between 2007 and 2017 including all children treated for an ALL in these institutions. All data was collected after approval by local ethic committees. All medical records and radiological exams of the children < 18 years old treated for an ALL were reviewed in order to identify treatment-related osteoarticular complications and evolution during follow-up. Patients suffering from another type of leukemia were excluded (myeloblastic leukemia, Burkitt lymphoma and biphenotypic leukemia) as well as ALL secondary to a syndrome (Down syndrome, Fanconi anemia).

### ***II.2.2 Treatment protocols***

Three different protocols were used during the study period: FRALLE 2000, (since 2000), INTERFANT-06 (since 2006) and CAALL F01 (since 2016). Two classes of therapeutic were used in the 3 protocols: glucocorticoids (prednisolone and dexamethasone), and chemotherapies (vincristine, asparaginase, methotrexate, mercaptopurine and in some cases anthracyclines) (Table 1).

Table 1: Drug molecules total dose (mg/m<sup>2</sup> or UI/m<sup>2</sup>) during treatment. Data is expressed as mean ± Standard Error of the Mean (SEM) and their ranges [min-max].

		<b>FRALLE 2000</b>	<b>CAALL F01</b>	<b>INTERFANT-06</b>
	Number of patients	n=114	n=12	n=2
<b>Glucocorticoids</b>	Prednisolone (mg/m <sup>2</sup> )	4316.7 ± 1064.0 [420-5860]	1374 ± 389.5 [420-2010]	420
	Dexamethasone (mg/m <sup>2</sup> )	456.7 ± 153.0 [185-995]	418 ± 61.9 [300-635]	232.5 ± 55 [177-288]
<b>Chemotherapy</b>	Vincristine (mg/m <sup>2</sup> )	30.2 ± 1.41 [25.5-36]	21.3 ± 2.62 [12-27]	6 ± 0.0 [6-12]
	Asparaginase (UI/m <sup>2</sup> )	127 333 ± 9261.6 [108000-170000] <i>(L-asparaginase)</i>	12300 ± 2736.8 [6000-20000] <i>(Pegylated-asparaginase)</i>	60000 <i>(L-asparaginase)</i>
	Methotrexate (mg/m <sup>2</sup> )	20471.3 ± 4120.8 [1607-31444]	454.6 ± 37.0 [400-597]	57 ± 3 [54-60]
	Mercaptopurine (mg/m <sup>2</sup> )	4912.5 ± 1264.5 [2450-9450]	31924.5 ± 7276.3 [8350-44380]	3750 ± 1950 [1800-5700]
	Anthracycline (mg/m <sup>2</sup> )	243 ± 35.6 [155-365]	260 ± 47.8 [75-350]	135 ± 75 [60-210]

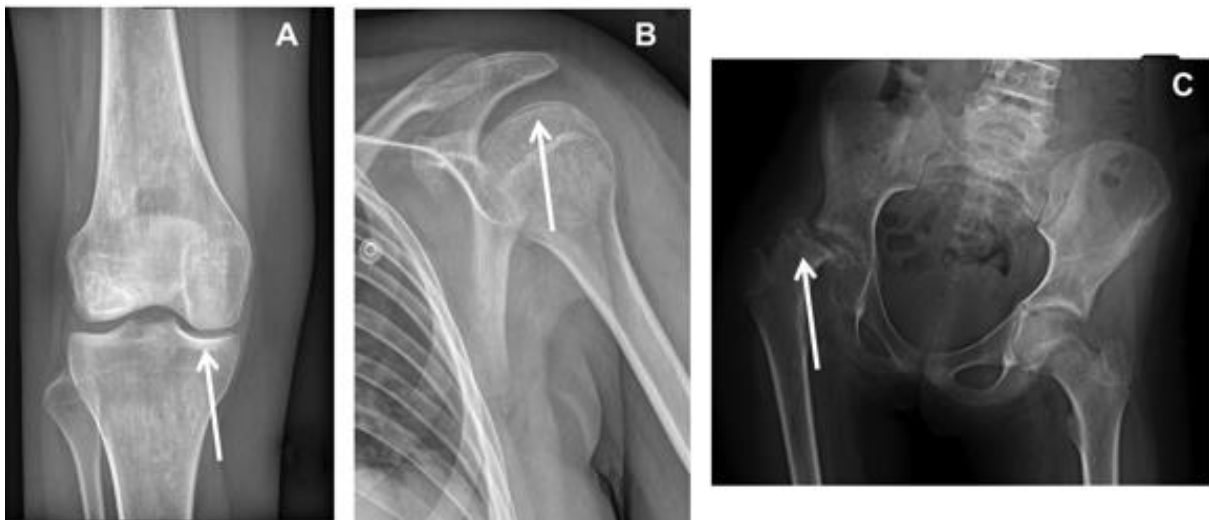
Each protocol was divided into 3 phases: (1) the induction phase (period of 2 weeks), which role is to eradicate > 99% of leukemic cells, (2) the consolidation phase (period of 20 to 50), which role is to eradicate residual leukemic cells and (3) the maintenance phase (period of 1 or 2 years), which prevent from relapses in order to obtain a complete remission. Patients who received a complementary treatment by bisphosphonates or bone marrow graft were also reported. After treatment and/or healing, all the patients were followed by a senior pediatric hematologist once a year and complementary radiological exams (X-rays, CT-scan, MRI or osteodensitometry) were exclusively performed in front of physical complaints and the patients were addressed, if required, to a pediatric orthopaedic surgeon for further management of orthopaedic complications.



### II.2.3 Osteonecrosis

The 1<sup>st</sup> orthopaedic complication was suspected in front of joint pain, limited range of motion (joint effusion) and limping or functional impairment. Radiological exams, usually performed to confirm the diagnosis and establish the severity of the impairment, were: X-rays, scintigraphy and/or MRI. Focused X-rays (anteroposterior and lateral side views) were prescribed first and looked for several anomalies (sub-chondral condensation, sub-chondral fracture with the crescent sign, or total collapsing) (Figure 1).

Figure 1: Illustration of X-rays anomalies during ALL treatment



A: 15-y-o girl that developed 17 months after treatment a sub-chondral condensation of the proximal tibia medial plate.

B: 14-y-o girl that developed 21 months after treatment, a proximal humerus sub-chondral fracture (crescent sign).

C: 10-y-o girl that developed 27 months after treatment a proximal femoral epiphysis resulting in collapsing and hip subluxation. The epiphysis did not reconstruct after ON.

MRI is the gold-standard for the detection of infra-radiological lesions and confirm the diagnosis by several sequences: T1-weighted, short inversion tau recovery (STIR) and T2-weighted (48). T2-weighted sequences were performed if the 2 other sequences showed

anomalies in order to delimitate the necrotic bone from the normal bone (49). Two anomalies are characterizing ON on T1-weighted sequences: a hypo-signal lesion or a lesion with normal signal bordered by a hypo-signal (rim sign). On STIR sequences, ON lesions are characterized by a hyper signal. On T2 sequences, the double line sign confirms the diagnosis of ON (hypo-signal line with an adjacent hyper-signal line) (Figure 2) (50).

Figure 2: Illustration of MRI anomalies induced by ALL treatments



A: 5-y-o boy 6 years after treatment, an epiphyseal osteonecrosis of the distal femur. T1-weighted sequence showing a normal signal bordered by a hypo-signal (rim sign) of the distal femur

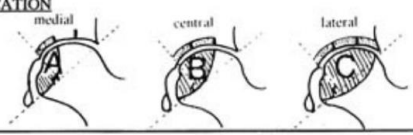
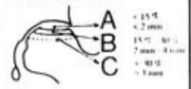
B: 5-y-o girl that developed 25 months after treatment, a bone marrow osteonecrosis of the femur. T2-weighted sequence showing the double line sign of the distal femoral metaphysis.

According to these MRI's characteristics, 2 types of lesions were described: bone marrow necrosis (long bone diaphysis and vertebral anterior body) and strictly speaking ON (epiphysis next to an articular cartilage).

Two classifications were used to assess osteonecrosis characteristics: the ARCO (Association Research Circulation Osseous) classification and the Niinimäki classification (51,52).

ARCO's classification defined 5 stages (0 to 4) for hip osteonecrosis and depended on radiological findings and the type of radiological exam this finding was found (Figure 3)

Figure 3: ARCO's international classification for hip osteonecrosis.

STAGE	0	1	2	3	4
FINDINGS	All present techniques normal or non-diagnostic	X-ray and CT are normal at least ONE of the below mentioned is positive	NO CRESCENT SIGN! X-RAY ABNORMAL: sclerosis, osteolysis, focal porosis	CRESCENT SIGN! on the X-ray and/or flattening of articular surface of femoral head	OSTEOARTHRITIS! joint space narrowing, acetabular changes, joint destruction
TECHNIQUES	X-ray, CT Scintigraph MRI	Scintigraph MRI *QUANTITATE on MRI	X-ray, CT Scintigraph MRI *QUANTITATE MRI & X-ray	X-ray, CT ONLY * QUANTITATE on X-ray	X-ray ONLY
SUBCLASSIFICATION	NO	<b>LOCATION</b> 			NO
QUANTITATION	NO	<b>QUANTITATION</b> % AREA INVOLVEMENT minimal A < 15 % moderate B 15 % - 30 % extensive C > 30 %	LENGTH of CRESCENT A < 15 % B 15 % - 30 % C > 30 %	% SURFACE COLLAPSE & DOME DEPRESSION  A < 15 % < 2 mm B 15 % - 30 % 2 mm - 4 mm C > 30 % > 4 mm	NO

The 2<sup>nd</sup> classification, established by Niinimäki et al., assessed osteonecrosis and bone marrow necrosis of all remaining bone areas (52). This system classified ON lesion in 6 stages (0 to 5), depending on the location and the extent of the lesions (Figure 4). In addition, the classification also defined the location on the skeleton and if it is a weight-bearing bone or not.

Figure 4: Niinimäki classification for ON and bone marrow necrosis concerning long bones and short bones either weight-bearing or not.

Location of osteonecrosis				
Weight-bearing bone*		Non-weight-bearing bone		
Long Bone	Short Bone	Long Bone	Short Bone	
Grade				
0	No osteonecrosis	No osteonecrosis	No osteonecrosis	No osteonecrosis
I	—	—	Diaphysis or metaphysis (0%)	Vertebral Body (0%)
II	Diaphysis or metaphysis (0%)	Vertebral Body (0%)	Epiphysis (<30%)	Bone Surface (<30%)
III	Epiphysis (<30%)	Bone Surface (<30%)	Epiphysis (≥30%)	Bone Surface (≥30%)
IV	Epiphysis (≥30%)	Bone Surface (≥30%)	—	—
V	Joint Deformation**			

The area of articular surface involvement (in percentage) is presented in parentheses.  
 \*Weight-bearing bones comprise the lower extremities, the pelvis and lumbar vertebrae.  
 \*\*Includes any deformation of the bone from sub-chondral local collapse to total destruction of the joint.

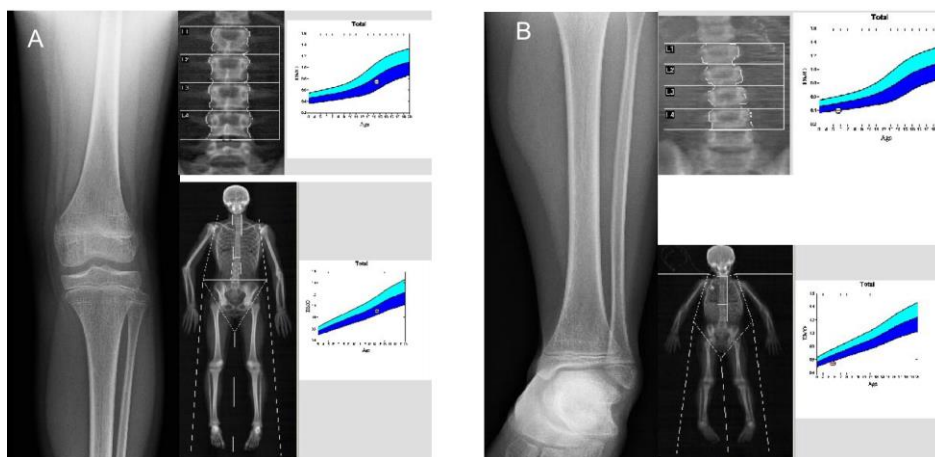
If there is multiple separate osteonecrotic lesions around a single joint, the overall grading is based on the grading assigned to the most severe lesion.

Definition of the location of osteonecrosis:  
 In long bone *diaphysis* or *metaphysis*, the location of osteonecrosis is named by the affected bone.  
 In long bone *epiphysis*, the location of osteonecrosis is named by the closest joint.  
 In *short bone*, the location of osteonecrosis is named by the affected extremity, except for *vertebrae*. *which* is classified as "spine".

### II.2.4 Osteopenia-osteoporosis (Z-score <2.5 SD)

Clinical manifestations of osteopenia were diffuse bone pain (lower-limb and/or spine associated to a diffuse demineralization on standard X-rays (Figure 5).

Figure 5: Illustration of bone demineralization



A: 5-y-o boy with osteoporosis (total body Z-score = -2.8 SD)

B: 15-y-o boy with osteopenia (total body Z-score = -1.6 SD)

To differentiate osteopenia from osteoporosis, an osteodensitometry was performed. Indications for this exam were fractures at initial diagnosis of ALL, multistage vertebral fractures, extended treatment by corticoids and patients with bone marrow grafts. A Z-score between [-2.5; -1] defined osteopenia and a Z-score < -2.5 defined osteoporosis. Three areas were analyzed: spine, proximal femur and full body. On these Z-scores depend the necessity for specific treatment or not (vitamin D and calcium supplementation, bisphosphonates).

### ***II.2.5    Management of orthopaedic complications***

All patients were treated symptomatically by painkillers, physiotherapy and weight-bearing discharge. Non-displaced long bone fractures and vertebral fractures were treated by cast or brace immobilization. A thoraco-lumbar brace was introduced for patients with symptomatic vertebral compression fractures, multistage and/or lumbar fractures. If required, a surgical treatment was performed including joint arthroplasty for severe osteonecrosis (ARCO stage 4 and Niinimäki stage 5) and osteosynthesis for displaced fracture.

### ***II.2.6    Statistical analysis***

Statistical analyses were performed using SPSS statistics 23.0 (SPSS Inc., Armonk, NY, USA). Continuous numeric data was expressed as Mean  $\pm$  Standard Error of the Mean and ranges [min-max]. Descriptive qualitative data was expressed as rates (%). To identify risk factors for orthopaedic morbidities, a logistical regression test was performed. A *p-value* <0.1 was considered significant.

## **II.3    RESULTS**

A total of 1293 children were treated for an ALL between 2007 and 2017 in 3 institutions. Mean age at the moment of ALL diagnosis was 6.8  $\pm$  0.1-year-old, (y.o), and orthopedic complications were found in 129 children (10 %) at the mean delay of 14.5  $\pm$  2.4 months, range from [0-70] months after treatment initiation.

### II.3.1 Patient ALL treatments

Over the study period, 114 patients received the FRALLE 2000 protocol, 12 the CAALL F01 and 2 the INTERFANT 06 (Table 2).

Table 2: Patients ALL treatments

		ALL patients	Osteonecrosis	Osteopenia
Total number of patients (n)		1293	70	59
	Age < 10 years	1018	31	35
	Age > 10 years	275	39	23
Age (years: y.o)	Mean $\pm$ SEM	6,8 $\pm$ 0.1	10 $\pm$ 0.6	11.7 $\pm$ 0.6
	[min-max]	[0.08-20.5]	[0.1-18.8] y.o	[0.4-13.7] y.o
Delay for orthopaedic complications	Mean $\pm$ SEM	14.5 $\pm$ 2.4	20.8 $\pm$ 3.4	5.67 $\pm$ 1.77
	[min-max]	[0-70] m	[1-70] m	[0-28] m
Follow-up	Mean $\pm$ SEM	4.32 $\pm$ 0.34	4.5 $\pm$ 0.61	4.1 $\pm$ 0.4
	[min-max]	[0.75-11.2]	[0.83-11.2]	[0.75-10.1]
Sex (number of patients)		726	42	38
	Male	(55%)		
		567	28	20
	Female	(44%)		
Immunophenotyping		996	54	49
	B	(77%)		
		197	16	9
	T			
Treatment protocols (number of patients and %)	FRALLE 2000	1114 (86%)	67	47
	CAALL F01	136 (10.5%)	3	9
	INTERFANT 06	44(3.5%)	0	2
Number of corticoid resistance (%)		131 (10.1%)	9	11
Number of death (%)		115 (8.9%)	8	2
Number of relapses (%)		126 (9.7%)	15	9
Number of bone marrow grafts (%)		62 (4.8%)	12	8

Regarding the mean dose of steroids, asparaginase and methotrexate received in each protocol, 2 groups were analyzed: the high-dose group (HDG = FRALLE 2000) and the low-dose group (LDG = CAALL F01 and INTERFANT 06). Eight patients were corticoid resistant (>1000/mm<sup>3</sup> leukemic cells at D8 of treatments). A bone marrow graft was performed in 20 patients meaning that a complementary conditioning treatment was necessary (fludarabine, busulfan and anti-thymocyte globulin) associated to immunosuppressive therapies

(cyclosporine, mycophenolic acid). Finally, 24 patients relapsed, requiring a specific new line of treatment including chemotherapies as previously mentioned, associated to cyclophosphamide and cytarabine.

### ***II.3.2 Characteristics of orthopaedic complications***

The total rate of orthopaedic complications was of 10.8% (n=129), followed during a mean time of  $4.32 \pm 0.34$  years, range from [0.75-11.2] after the end of treatments. A total of 70 patients developed an osteonecrosis during treatment (5.4%) (Table 2). A total of 109 lesions were described on MRIs, meaning that 39 patients (55.7%) had at least 2 lesions (Table 3). Most of the bone marrow necrosis were located at the spine (35.7%) and at lower-limb (38.6%), while epiphyseal osteonecrosis, were mainly located at lower-limb joints in 44.3% (knee>hip>ankle) followed by upper-limb in 4.3% (shoulder > elbow).

Table 3: Osteonecrosis lesions characteristics confirmed by MRI (number of radiological lesions n = 109)

		Epiphyseal osteonecrosis	Bone marrow necrosis
Number of location per patient (n)	Single	17	38
	Multiple	14	10
	2	12	7
	3	2	1
	4	0	2
Number of radiological lesions		47	62
Lower-limb	Hip	15	
	Knee	23	
	Pelvis		3
	Ankle		
	Foot	5	3
	Femur		17
	Tibia		14
Upper-limb	Shoulder	3	
	Elbow	1	
Spine			25
ARCO (Hip osteonecrosis n= 12)			
	Stage 1	2	
	Stage 2	8	
	Stage 3	2	
	Stage 4	3	
Niinimäki classification (remaining bones)			
	Stage 1	0	0
	Stage 2	9	56
	Stage 3	18	6
	Stage 4	5	0
	Stage 5	0	0

A total of 59 patients had osteopenia or osteoporosis and 51 children had a fracture indicating severe osteopenia/osteoporosis (4.8%): long bone fractures in 11 cases (2 children cumulated 3 fractures) and 40 compression vertebral fractures (Table 4).



Table 4: Osteopenia/osteoporosis patients' characteristics

		Osteopenia n=38	Osteoporosis n= 21		
Age (years)		10.4 ± 0.2 [0.4 -13.7]	12.7 ± 0.4 [3.3-16.5]		
X-rays (n = 74)	Number of exams	17	22		
	Bone demineralization	Location	5	2	
Osteodensitometry (n=124)	Number of exams	30	12		
	Z-score	-1.7 ± 0.1 [-1; -1.9]	-2.8 ± 0.1 [-2.5; -3.5]		
Fractures (n = 51)	Number of fractures	Single	33	16	
		Multiple	0	2	
	Location	Spine	26	14	
		Lower-limb	Tibia	3	2
			Femoral neck		1
			Foot		1
		Upper-limb	Clavicle	1	
Scapula			1		
	Wrist	2			
Specific treatment	Vitamin D and calcium supplementation	34	18		
	Bisphosphonates	3	8		

Most of long bone fractures were located at lower-limb. In the other cases, osteopenia was discovered on radiographies performed for diffuse osseous pain, showing bone demineralization. An osteodensitometry was performed in 124 patients, including 68 patients without any orthopaedic complications that had normal total body Z-score (mean score  $-0.5 \pm 0.1$ ), with significant difference compared to patients with orthopedic complications ( $p=0.027$ ).

### ***II.3.3 Management of orthopaedic complications***

Regarding osteonecrosis, different types of pain medication were used, depending on the intensity of pain: NSAIDS, Level 1 to 3 painkillers associated with weight-bearing discharge in case of mechanical pain. Physiotherapy consisted on joint soft active and passive mobilizations, muscular reinforcement and balneotherapy. One patient aged 17, received a knee stem cell infiltration in order to delay surgery, which would have consisted on knee replacement arthroplasty. Surgical treatment was performed in 4 children (3 ON, 1 osteopenia), that all received the FRALLE protocol and did not have recurrence of the disease, resistance to

corticoids or a bone marrow graft (Table 5). The patient with bilateral hip arthroplasty also had a shoulder arthrotomy for removing intra articular fragments secondary to ON.

Table 5: Characteristics of the patients with surgical treatment

	Age at surgery (years)	Type of ALL	Osteonecrosis		Osteopenia		
			ARCO stage	Surgery	Osteodensitometry	Bisphosphonates	Surgery
Patient 1	18	Pre-B	IV	THA			
Patient 2	13	Early Pre-B	IV	THA			
Patient 3	17	Early Pre-B	IV	Shoulder arthotomy			
	18			Bilateral THA			
Patient 4		B			No	No	Fracture osteosynthesis

THA: total hip arthroplasty

Regarding osteopenia, all patients received oral Vitamin D and calcium supplementation and intravenous bisphosphonates cures (mean number of 4 cures) was performed in 11 patients with diagnosed osteoporosis. All fractures, excepted one, consecutive to osteopenia, were treated by cast immobilization or brace, depending on the location of the fracture. One patient with a tibia shaft fracture required surgery to stabilize the fracture by an osteosynthesis.

### ***II.3.4 Risk factors for orthopaedic complications***

Regarding osteonecrosis, the analysis showed that patents treated by the FRALLE 2000 protocol were more likely to develop osteonecrosis (high dose group), as well as patients with relapses and bone marrow graft (Table 6). Nevertheless, corticoid resistance and age > 10 years were not contributive factors for osteonecrosis.

Regarding osteopenia, relapse and bone marrow graft were the 2 identified risk factors.

Type of leukemia, treatment protocol, corticoid resistance and age > 10 years, were not contributive factors for osteopenia.

Table 6: Risk-factors analysis for orthopaedic complications in ALL children

Risk factors		Osteonecrosis		Osteopenia	
		Odd ratio (90% CI)	<i>p-value</i>	Odd ratio (90% CI)	<i>p-value</i>
Type of leukemia	T	-0.32 (-0.39, 2.44)	0.13	-0.30 (-0.30, 2.58)	0.61
Protocol	FRALLE 2000	-0.35 (-0.35, 2.76)	<b>0.08*</b>	-0.30 (0.30, 2.76)	0.22
Corticoid resistance		-0.33 (-0.40, 2.43)	0.20	-0.29 (-0.29, 2.54)	0.93
Age > 10 years		0.04 (-3.72, 0.04)	0.99	0.04 (-3.72, 0.04)	0.99
Relapse		-0.31 (-0.52, 2.47)	<b>0.0003*</b>	-0.26 (-0.49, 2.60)	<b>&lt;10<sup>-5</sup>*</b>
Bone marrow graft		-0.33 (-0.49, 2.43)	<b>0.06*</b>	-0.27 (-0.57, 2.57)	<b>0.0002*</b>

\* significant  $p < 0.1$

## II.4 DISCUSSION

The global incidence of treatment-related orthopaedic morbidities in children with ALL was of nearly of 11% with 2 skeletal complications: osteonecrosis (54.3%) and osteopenia (45.7%). Management of osteonecrosis is far more challenging in the long-term, since irreversible articular cartilage damages can occur (3.1%) leading to joint replacement surgeries, only feasible at the end of growth and inevitably conducting to further surgeries in adulthood that will certainly impaired quality of life. On the other hand, osteopenia or osteoporosis have specific treatments that allowed good evolution suggesting poor impact on life quality in the adulthood.

### II.4.1 Characteristics of orthopaedic complications

Incidence of skeletal complications during ALL treatment were lower in the current study compared to prior literature (31,49,53,54). In the study by *Strauss et al.* cumulative incidence was up to 30%, with a systematic 5-years clinical and radiological evaluation, even though patients were not symptomatic, which had probably increase their rates (55). However, in the present study, regular follow-up was performed on a regular basis of once a year after the

treatment stopped and radiological exams were exclusively performed when skeletal complaints were addressed by.

The overall incidence of osteonecrosis was low in the current study (5.4%) but incidences widely differ in the literature, range from 0.7 to 72% (31,49,53,54,56,57). The review by *Mostoufi et al.*, indicated the influence of several factors such as the characteristics of the study population (type of leukemia, corticoid resistance and chemotherapy resistance), the study design and protocols for osteonecrosis detection (22). However, 3 studies reporting on symptomatic patients, found an incidence closed by 9%, quite similar to the current one, regardless the severity of the leukemia (46,54,55).

Regarding osteopenia, the overall incidence of fractures was 4% (long bones and vertebral fractures), which still are in the lowest rates of the literature (range from 14% to 30%) (46,58,59). These results might have been influenced by the highest number of patients followed in the current study, decreasing the total amount of complications. Finally, orthopaedic complications are also influenced by the treatment protocols as reported by *Elmantaser et al.* that compared 3 versions of one protocol (UKALL), one version corresponding to the FRALLE, except for the dexamethasone total dose, that was twice-lower for FRALLE (46).

#### ***II.4.2 Risk factors for orthopaedic complications***

Causes of orthopedic complications are multifactorial (47,60). High dose of corticoids such as dexamethasone, are particularly well-known risk factors, as well as asparaginase, that decreases dexamethasone clearance and potentiates the risk of ON induced by glucocorticoids (34,55,61). Our results showed that the patients treated by FRALLE 2000 protocol have a higher risk of osteonecrosis development than the other, since this protocol combined high-doses of steroids and asparaginase as demonstrated by *Burger et al.* (53). Furthermore, it has also been reported

by *Jastaniah et al.*, that the type of asparaginase (L-asparaginase vs. pegylated-asparaginase) also influenced the rate of osteonecrosis (62,63).

In addition, patients with a type T of ALL were more likely to develop osteonecrosis, even though results were closed to significance, but similarly, these patients received higher doses than patients with type B ALL. Therefore, further improvements in ALL therapeutics is required to decrease the rate of ON, which remains the less reversible orthopaedic complication in the long-term, especially when it involves epiphysis.

Regarding osteopenia, only relapsing and bone marrow graft were significant risk factors, conversely to treatment protocols. This result surprisingly differed from literature findings, but might be explain by the fact that other therapeutics were used with higher doses of steroids (mean dose of dexamethasone (mg/m<sup>2</sup>) 480-850 > 232-457) (61).

The fact that relapses and bone marrow graft were risk-factors either for ON or osteopenia was not surprising. As a matter of fact, a relapse implied an additional line of treatment superimposed to the total doses already accumulated as well as bone marrow graft, since additional medication is required (22,64).

Finally, recent literature reported age > 10 years as a major risk of ON (mean 14.2% ± 1.3%), which is attributed to the fact that adolescent maturing bone might be more susceptible to the development of bone marrow necrosis. Indeed, since corticosteroids induced fat-cell hypertrophy resulting in elevated intraosseous pressure and reduced intramedullary blood flow, the ultimate result is ischemia and necrosis of the bone marrow (22,31). Conversely, immature bones are predominantly affected by epiphyseal osteonecrosis, due to the presence of fertile growth plate that might be damaged (22,54). However, the present study did not report this risk-factor as significant since less than 20% of the patients were > 10-year-old.

### ***II.4.3      Management of the orthopaedic complications***

Since pain medications, weight-bearing discharge and physiotherapy were required for the management of acute skeletal complications, these could not last in the long-term and preventing solutions should be found to assure an almost normal quality of life during adulthood. Regarding osteopenia, vitamin D and calcium deficiency, and poor outdoor recreational activities have been proved to decrease bone mineral density. Therefore, systematic vitamin D and calcium supplementation was performed and practitioners did also encouraged outdoor activities as preventing measures (22,60,61). Bisphosphonates had the same indication as in adult osteoporosis (Z-score < -2.5 SD and/or multiple fractures) (65). However, the efficiency of bisphosphonates to prevent from osteonecrosis, is still debated, since it contributes to sooth bone pain and improve function by anti-osteoclastic effects but does not prevent from bone and joint destruction (22,32). Interesting results have been reported with the hyperbaric oxygen therapy (HBO) in early ON stages, resulting from the following mechanisms: HBO increases the neo-vascularization of ischemic tissues, induces osteoblastic proliferation and decreases rates of free radicals in the ischemic bone (32,66). Surgical management by articular cartilage drilling has been also described for early stages, but the efficiency is still uncertain (32). However, in advanced stages (3 in the present study), neither of prior mentioned therapeutics could have been beneficial since joints were already destroyed and joint replacement surgery was inevitable (Table 5). *Bidecci et al.* reported that joint replacement surgeries are frequently performed within 3-years after 1<sup>st</sup> symptoms of ON (32). Rates of surgery have been reported up to 16.5% of prior series and predominantly at the hip (67). However, in the present study, most children were still underage to have joint replacement surgery. Furthermore, only 5 patients were classified ARCO > 3 and 6 Niinimäki > 4, which is a possible explanation for the low-incidence of surgeries performed. *Henneghan et al.* recorded 44.4% of hip arthroscopy and 17% of THA, but the severity of initial lesions was not reported

(67). Regarding fractures secondary to osteopenia, they all consolidated in similar delay to healthy children, without any complications.

#### ***II.4.4 Limitations***

The main limitation of this study was its retrospective nature that did not ensure a complete data recovering. However, the current series is the largest one ever performed.

The majority of the patient were treated by the FRALLE protocol that belong to an older protocol initiates in the 2000s with high doses of steroids and L-asparaginase. However, total rate of skeletal complications was in the lowest range of the literature (10%), and recent improvements in treatment protocols (lower doses of steroids and introduction of pelygated-asparaginase) might lower these rates. (33,34). Nonetheless, further investigation and prospective studies are required.

Finally, the lack of quality of life assessment in also a limitation, since orthopaedic morbidities might affect daily activities. However, osteopenia was curable by supplementation medication and pain due to bone marrow necrosis, progressively resolved. Still remains the management of epiphyseal necrosis that depended on the severity of the ON.

In conclusion, orthopedic complications (osteonecrosis and osteopenia) were present in 10% of the patients and mutual identified risk factors were relapses and bone marrow graft. Treatment protocol (FRALLE) with high-dose of steroids and asparaginase were only identified as a risk-factor for osteonecrosis. At last follow-up, only 0.2% of the patients required surgery and only for epiphyseal osteonecrosis. This requires further investigation to prevent children from articular deformities and destruction. Finally, the detection of orthopaedic complications and prescription of complementary exams should be based on clinical evaluation.

### **III PART 3:**

## **Management and prognosis of vertebral fractures in children with acute lymphoblastic leukemia**

### **III.1 INTRODUCTION**

Acute lymphoblastic leukemia (ALL) is the most common neoplasia in children, whose survival has steadily increased over the last decades, so that expected cure rate is now greater than 90% (1). Therefore, current goals are moving beyond cure and aims to return to a normal life. However, several long-term morbidities, might occur during treatment and affect the quality of life especially during adulthood (5). Two orthopaedic complications have been reported in the literature: osteonecrosis and osteopenia (11,22). However, solely osteopenia has been demonstrated to be involved with spinal morbidities by causing spontaneous vertebral compression fractures due to (1) proliferation of the clonal cells in the vertebral bone marrow and (2) biomechanical properties of trabecular bone, which vertebral anterior bodies are essentially composed of (68). Thus, vertebral bone mineral density (BMD) is lower than long bones, which have a higher density of cortical bone, trabecular bones have a higher metabolic rate and consequently variations of BMD are occurring earlier in spine than in the rest of the body, which explains why vertebral compressions fracture are particularly found in leukemic patients (68) Two revealing conditions have been reported for vertebral compression fractures: disease-related fractures diagnosed at initial diagnosis and treatment-related fractures occurring after the treatment started. Three treatment-related risk factors have been described: age < 5 years, spine Z-score < -2 (low BMD) and corticoid treatment (5,22,69) .

Since children spine is growing — growth peak occurring at pre-puberty — bone remodeling after vertebral fractures remains possible, especially in young children. Vertebral growth leans on mostly 2 types of ossifications. First, the enchondral ossification of anterior vertebral bodies



with growth plates adjacent to intervertebral discs that allow growth in high. Second, the growth of the posterior arch depending on the neurocentral cartilage, which determines pedicles' length and diameter of the medullar canal (70). Because of these characteristics, spinal curves progressively evolve during childhood, until the final sagittal alignment is obtained. Consequently, after a spinal fracture, children are capable of spontaneous correction. In ALL, vertebral compression fractures usually occurred on multiple adjacent or non-adjacent vertebrae. But, the exact amount of bone remodeling remains uncertain as well as the risk of epiphysiodesis, that might occur after a fracture. As a matter of fact, an anterior epiphysiodesis will impaired natural evolution of sagittal curves, by creating a localized hyper kyphosis which is a well-known risk factor for impaired quality of life in the long term (37,38,71). The aim of the study was to investigate occurrence and evolution of vertebral compression fractures in children with ALL.

## **III.2 MATERIAL AND METHODS**

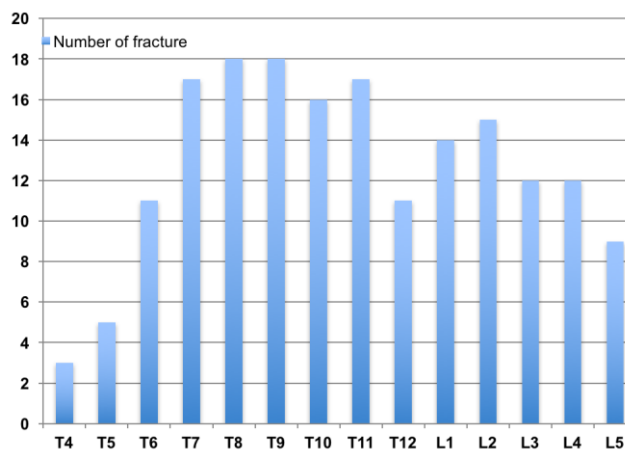
### ***III.2.1 Study design***

A multicentric (3 different pediatric university hospitals) and retrospective study was conducted between 2007 and 2017 including all children treated for an ALL in these institutions. All data was collected after approval by local ethic committees. Inclusion criteria were: (1) patients <18 years-old with ALL, (2) vertebral compression fractures, (3) full-spine standing radiographs (antero-posterior and lateral side views) at initial symptoms and (4) a minimum of 1-year follow-up (FU). The immunophenotypic classification was used to characterized the patients' type of disease (9). Patients suffering from another type of leukemia were excluded (myeloblastic leukemia, Burkitt lymphoma and biphenotypic leukemia) as well as ALL secondary to a syndrome (Down syndrome, Fanconi anemia).

### ***III.2.2 Vertebral compression fractures data***

Age at diagnosis and the delay with onset of the disease were recorded, as well as the number and precise location of the vertebrae involved in the compression fractures (Figure 1).

Figure 1: Level of injured vertebrae



In order to analyze growth residual potential, Risser index and stage of puberty were also recorded.

Fractures were treated two ways, depending on the severity of the deformity, the extent and location of the fractures and the age at diagnosis. First, a symptomatic treatment, that consisted on painkiller administration if necessary and a simple clinical and radiological follow-up for patients with no major pain and incidental diagnosis. Patient with spinal symptoms, were treated with a thoraco-lumbar brace in addition to prior symptomatic treatments.

An osteodensitometry was performed in cases of numerous and multiple stage vertebral fracture to calculate total-body and spine Z-score in order to evaluate the need for bisphosphonates.

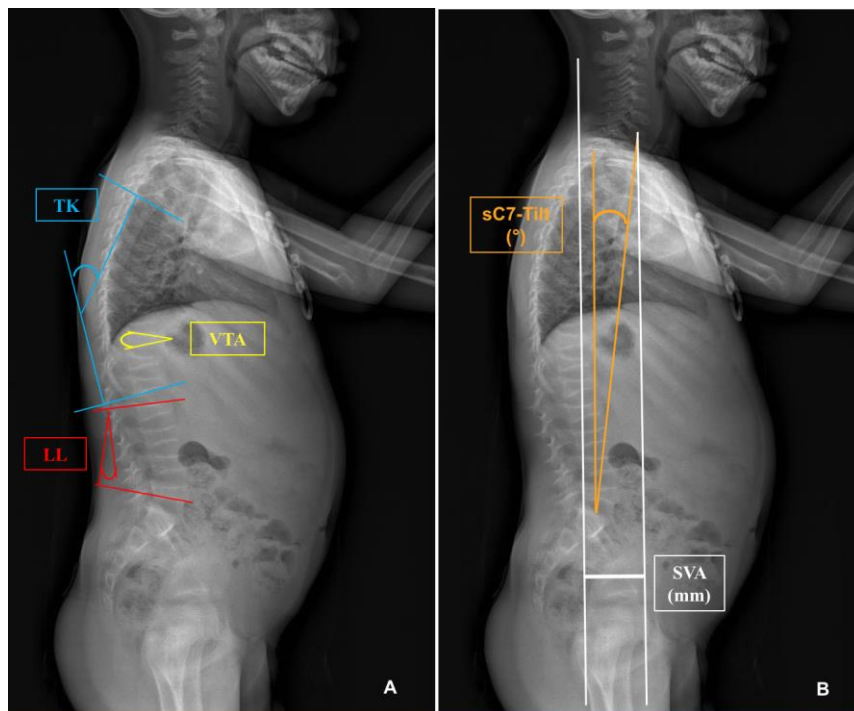
### ***III.2.3 Radiological measurements***

Full-spine biplanar radiographs in standing position were used for measurements. All data were measured on X-rays at initial diagnosis and at latest FU ( $\geq 1$  year) by a single experienced and

independent operator, using the Carestream software (Kodak Carestream, Rochester, NY, USA).

Since no coronal plane misalignment was noted, only sagittal parameters were measured in this study. Local parameters included T4-T12 thoracic kyphosis (TK), L1-L5 lumbar lordosis (LL), vertebral traumatic angle (VTA) (Figure 2).

Figure 2: Radiographic measurements performed



A: Local sagittal measures (TK, LL and VTA)

B: global sagittal measures (SVA and sC7-tilt).

VTA measures the vertebrae deformity at fracture's level and corresponds to the angle between the lower and the upper end plate of the fracture. Two types of vertebral compression fractures were identified: anterior compression fractures (only the anterior wall of the vertebral body was impaired) and circumferential compression fractures both anterior and posterior wall of the vertebral body were impaired). A percentage of compression (CP) was measured in order to evaluate the importance of the compression. This percentage was measured differently

according to the type of fracture. First the ratio between heights (mm) of the anterior (AW) and posterior (PW) walls of the fractured vertebra was measured for anterior compression fractures (ACF) and the ratio between heights of the anterior wall of the fractured vertebra and the posterior wall of the adjacent normal vertebra was measured for circumferential compression fractures (CCF), since posterior wall heights do not vary much from one adjacent vertebra to the other (Figure 3) (72–74). Thereafter, fractured vertebrae were classified as slightly ( $CP \leq 25\%$ ), moderately ( $25\% < CP < 50\%$ ), highly ( $50\% < CP < 75\%$ ) or very highly ( $CP \geq 75\%$ ) compressed.

Figure 3: Illustration of the 2 types of compression fractures and measurement of the percentage of compression (CP)



A: circumferential compression fracture (CCF)

B: anterior compression fracture (ACF)

C: percentage of compression ( $CP = 1 - AW/PW$ ).

Global sagittal parameters measured the sagittal vertical axis (SVA) and the sagittal C7-tilt (sC7-Tilt) (Figure 2). SVA corresponded to the distance between the C7 plumbline and the postero-superior corner of 1<sup>st</sup> sacral vertebral body (75). The measurement was considered

positive if directed  $> 2$  cm forwards and negative if directed  $< 2$  cm backwards, sC7-Tilt was defined by the angle between the line joining the center of C7 and the middle of the sacral endplate and the vertical reference axis in the sagittal plane (76,77). Sagittal misalignment was defined by a sC7-tilt  $> 6^\circ$  anteriorly or posteriorly (77). Pelvic parameters included pelvic incidence (PI), pelvic tilt (PT) and sacral slope (SS) (78).

#### ***III.2.4 Statistical analysis***

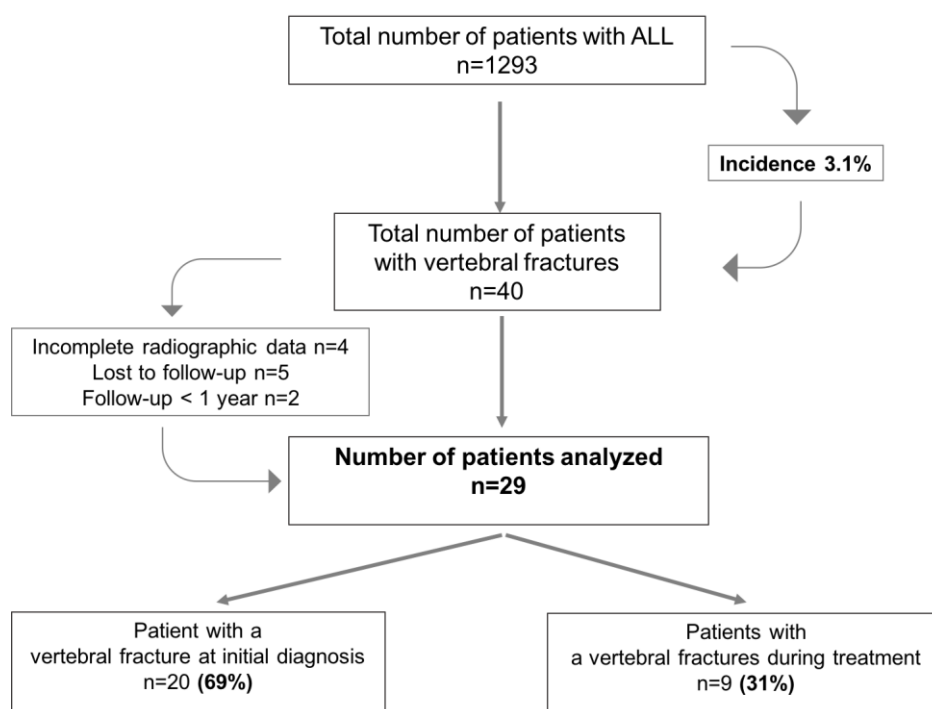
Statistical analyses were performed using SPSS statistics 23.0 (SPSS Inc., Armonk, NY, USA). Continuous numeric data was expressed as Mean  $\pm$  Standard Error of the Mean (SEM) and ranges [min-max]. Descriptive qualitative data was expressed as percentage rates. A Shapiro-Wilk test was performed to assess data distribution. A Student T-test was performed for data with normal distribution. A Mann-Whitney test was performed to compare data with non-parametric distribution. A *p-value*  $< 0.05$  was considered significant.

### **III.3 RESULTS**

#### ***III.3.1 Patients characteristics and fracture localization***

A total of 1293 children were treated for an ALL between 2007 and 2017 in 3 institutions with a global incidence of 3% for vertebral fractures (n=40) (Figure 4).

Figure 4: Study's flow-chart



Among these 40 patients, 11 patients were excluded (Figure 3) leaving a total of 29 patients to analyze mean age  $8.1 \pm 0.5$  years, range from [0.4 to 15.5] years (Table 1).

Table 1: Patient's demographics

		Number of patients	%
Age	< 8 y.o	13	0.45
	$\geq$ 8 y.o	16	0.55
Sex	Female	12	0.41
	Male	17	0.59
Puberty stage	Immature	22	0.76
	Mature	7	0.24
Type of ALL (immunophenotyping)	B	7	0.24
	Pre-B	11	0.38
	Early pre-B	8	0.28
	T	3	0.1
Death		1	0.04
Relapses		6	0.21

y.o: year-old; ALL: acute lymphoblastic leukemia

Mean number of fracture per patients was  $6.2 \pm 0.6$  vertebra (total of 178 fractures: 116 thoracic and 62 lumbar), with a mean of  $4.2 \pm 0.6$  consecutive levels affected, range from 2 to 12 consecutive levels (Table 2, Figure 1) and a mean CP (%) of  $0.26 \pm 0.02$ , range [0.07;0.64].

Table 2: Fracture's' characteristics

	Number of patients	%
Number of fractured levels	1 fracture	4 0.14
	2 to 3 fractures	2 0.07
	4 to 5 fractures	6 0.21
	6 to 9 fractures	14 0.48
	10 to 13	3 0.1
Levels of fracture	Upper thoracic (T4-T5)	5 0.17
	Mid thoracic (T6-T8)	20 0.69
	Low-thoracic (T9-T10)	13 0.45
	Thoraco-lumbar (T11-L2)	18 0.62
	Lumbar (L3-L5)	18 0.62
Adjacent fractures region	Thoracic	23 0.79
	Lumbar	17 0.59
Number of adjacent segments affected	0	4 0.14
	1	16 0.55
	2	8 0.27
	3	1 0.04
Stages of compression	Slightly	14 0.48
	Moderately	14 0.48
	Highly	1 0.04
	Very highly	0
Risser index	< 2	24 0.83
	$\geq 2$	5 0.17

An osteodensitometry was performed in 11 patients with a mean spinal Z-score of  $-1.4 \pm 0.6$  (range from -3.4 to 0.4) and a mean total body Z score  $-0.5 \pm 0.3$  (range from -1.8 to 0.6).

### ***III.3.2 Patients' treatments for ALL***

Three protocols were used during the study period: 20 patients received the protocol FRALLE 2000, 8 in the protocol CAALL and 1 in the protocol INTERFANT 06 (Table 3).

Table 3: Treatment protocols used for the patients with vertebral fractures (n=29)

Protocol	Number of patients	Mean dose of PDN (mg/m <sup>2</sup> )	Mean dose of DXM (mg/m <sup>2</sup> )
FRALLE 2000 A	3		
FRALLE 2000 B	16	4316	456
FRALLE T	1		
CAALL	8	1374	418
INTERFANT06	1	420	177

PDN: prednisolone, DXM: dexamethasone

Regarding the mean dose of corticoids received in the different protocols, 2 groups were analyzed: the high-dose group (HDG = FRALLE 2000) and the low-dose group (LDG = CAAL and INTERFANT06).

### ***III.3.3 Vertebral fractures treatments***

A total of 85 ACF (48%) and 93 CCF (52%) were found and 22 patients had the association of both types of fractures. At mean FU of  $3 \pm 1.9$  years [range from 1 to 10 years], no patient required surgical management. All fractures were treated conservatively, by brace (n=16, 55.1%) or without brace (n= 13, 44.9%). Mean duration of bracing was  $6 \pm 2.8$  months (range from 3 to 48 months) and only one patient had poor observance. At last FU, 4 patients remained painful (1 with brace, 3 with symptomatic treatment) and were limited in their recreational activities particularly while standing.

### ***III.3.4 Sagittal parameters analysis***

The global analysis comparing initial and last follow-up sagittal alignment found almost no significant differences, except for LL that significantly increased (p=0.02). However, patients had a correct global alignment (SVA and sC7-Tilt close to standard values) at final FU and the traumatic angle (VTA) showed an almost significant improvement meaning that some bone remodeling occurred (Table 4).



Table 4: Evolution of sagittal parameters between initial and last follow-up. Data is expressed as Mean  $\pm$  SEM and their ranges [min-max].

Sagittal measurements		Initial	FU	<i>p-value</i>
Global parameters	SVA (mm)	8.6 $\pm$ 24.6 [-35;50]	11.2 $\pm$ 4.8 [-28;59]	0.70
	sC7-Tilt (°)	3.4 $\pm$ 0.4 [ 0;9]	4.2 $\pm$ 0.6 [0;14]	0.43
Local parameters	Thoracic kyphosis (°)	29.9 $\pm$ 2.0 [9 ; 62]	33.4° $\pm$ 2.0 [10 ; 60]	0.37
	Lumbar lordosis	25.1 $\pm$ 3.5 [-37 ; 49]	31.2 $\pm$ 3.9 [-40 ;52]	<b>0.02*</b>
	VTA (°)	8.1 $\pm$ 0.7 [2 ; 20]	6.2 $\pm$ 0.7 [0.8;14]	0.05
	CP (%)	0.23 $\pm$ 0.01 [0.09;0.64]	0.19 $\pm$ 0.01 [ 0.03;0.41]	0.13
Pelvic parameters	Pelvic incidence (°)	47.1 $\pm$ 1.2 [37;65]	49.7 $\pm$ 2.2 [22;86]	0.33
	Pelvic tilt (°)	15.2 $\pm$ 2.2 [ -30; 35]	15.7 $\pm$ 1.7 [-9;30]	0.9
	Sacral slope (°)	30.3° $\pm$ 1.4 [10;42]	34 $\pm$ 2.1 [18;80]	0.24

SVA: sagittal vertical axis; sC7-tilt: sagittal tilt of C7; VTA: vertebral traumatic angle; CP: percentage of compression

Regarding the impact of brace, there was no significant improvement in the brace group compared to the non-brace group. However, patients with brace, recovered their lumbar lordosis better than patients without brace and global sagittal alignment was maintained.

Table 5: Sub-group analysis comparing effect of bracing at last follow-up. Data is expressed as means  $\pm$  SEM and their ranges [min-max].

		Initial			FU		
		Brace (n=16)	No brace (n=13)	<i>p-value</i>	Brace (n=16)	No brace (n=13)	<i>p-value</i>
Global parameters	SVA (mm)	10.5 $\pm$ 6.0 [-32;50]	6.2 $\pm$ 7.2 [-35;45]	0.7	16.6 $\pm$ 5.9 [-25;50]	4.5 $\pm$ 7.7 [-28;59]	0.18
	sC7-Tilt (°)	1.5 $\pm$ 1 [-6;7]	0.3 $\pm$ 1.2 [-5;9]	0.46	2.4 $\pm$ 5.9 [-5;14]	0.3 $\pm$ 1.4 [-5;12]	0.25
Local parameters	Thoracic kyphosis (°)	30.6 $\pm$ 3.4 [9;62]	29.2 $\pm$ 2.1 [14;40]	0.72	33.4 $\pm$ 2.7 [10;50]	28.8 $\pm$ 5.7 [-29;60]	0.6
	Lumbar lordosis	-18.6 $\pm$ 6.1 [-42;49]	26.6 $\pm$ 6.0 [-37;49]	0.27	36.8 $\pm$ 3.94 [12;50]	31.5 $\pm$ 4.8 [-27;51]	0.72
	VTA (°)	8.4 $\pm$ 0.8 [2.6;13.3]	7.7 $\pm$ 1.2 [2;20]	0.36	6.0 $\pm$ 0.7 [1;13]	6.4 $\pm$ 1.5 [0.75;14]	0.63
	CP (%)	0.25 $\pm$ 0.03 [0.07;0.64]	0.28 $\pm$ 0.03 [0.09;0.49]	0.61	0.19 $\pm$ 0.03 [0.03;0.41]	0.25 $\pm$ 0.04 [0.1;0.45]	0.19
Pelvic parameters	Pelvic incidence (°)	45.5 $\pm$ 2.2 [20;60]	47.1 $\pm$ 2.0 [37;65]	0.77	48.2 $\pm$ 2.3 [28;63]	51.5 $\pm$ 4.2 [22;86]	0.55
	Pelvic tilt (°)	15.4 $\pm$ 2.8 [-10;35]	16.5 $\pm$ 2.3 [-4;26]	0.74	16.8 $\pm$ 1.9 [3;30]	14.4 $\pm$ 3.0 [-9;28]	0.51
	Sacral slope (°)	30.1 $\pm$ 1.9 [10;42]	30.6 $\pm$ 2.1 [16;42]	0.79	31.4 $\pm$ 1.6 [19;42]	37.1 $\pm$ 3.9 [18;80]	0.17

Regarding the influence of treatment (high-doses vs. low-doses), patients with low-doses had increased anterior tilt, with decrease LL and more vertebral compression according to the percentage of compression (Table 6).

Table 6: Sub-group analysis comparing the effect of corticoids doses on sagittal parameters at last follow-up. Data is expressed as means  $\pm$  SEM and their ranges [min-max]

		Initial			FU		
		HDG (n=20)	LDG (n=9)	<i>p-value</i>	HDG (n=20)	LDG (n=9)	<i>p-value</i>
Global parameters	SVA (mm)	2.5 $\pm$ 5.1 [-32;42]	22.1 $\pm$ 8.3 [-35;50]	<b>0.04*</b>	8.7 $\pm$ 5.6 [-28;50]	16.8 $\pm$ 2.2 [-25;59]	0.42
	sC7-Tilt (°)	-0.1 $\pm$ 0.9 [-6;7]	3.5 $\pm$ 1.2 [-4;9]	0.05	0.35 $\pm$ 0.91 [-5;9]	4.0 $\pm$ 2.2 [-5;14]	0.14
Local parameters	Thoracic kyphosis (°)	31.5 $\pm$ 2.5 [12;62]	26.4 $\pm$ 3.7 [9;40]	0.33	28.2 $\pm$ 3.5 [-29;51]	38.6 $\pm$ 3.8 [24;60]	0.57
	Lumbar lordosis	28.4 $\pm$ 4.1 [-37;46]	8.3 $\pm$ 9.5 [-42;49]	<b>0.03*</b>	33.3 $\pm$ 4.4 [-40;52]	26.8 $\pm$ 8.3 [-27;51]	0.08
	VTA (°)	7.4 $\pm$ 1.1 [3.6;13]	8.44 $\pm$ 0.9 [2;20]	0.59	5.8 $\pm$ 0.9 [0.8;14]	7.2 $\pm$ 0.9 [4.3;11.6]	0.28
	PC (%)	0.25 $\pm$ 0.02 [0.09;0.64]	0.29 $\pm$ 0.04 [0.07;0.49]	0.27	0.19 $\pm$ 0.03 [0.03;0.45]	0.26 $\pm$ 0.04 [0.12;0.41]	<b>0.04*</b>
Pelvic parameters	Pelvic incidence (°)	47.5 $\pm$ 1.64 [37-65]	43.2 $\pm$ 3.14 [20-54]	0.25	49.0 $\pm$ 3.0 [22;86]	51.4 $\pm$ 2.5 [42;63]	0.4
	Pelvic tilt (°)	15.5 $\pm$ 1.7 [-4;28]	16.6 $\pm$ 4.5 [-10;35]	0.6	13.7 $\pm$ 2.0 [-9;27]	20.1 $\pm$ 2.6 [7;30]	0.11
	Sacral slope (°)	32 $\pm$ 1.4 [18;42]	26.7 $\pm$ 3.1 [10;42]	0.08	35.2 $\pm$ 2.7 [19;80]	31.3 $\pm$ 2.5 [18;42]	0.52

Most compression vertebral fractures were a direct consequence of the disease (n=20), since only 9 patients developed fractures during treatment. Regarding the comparison between these 2 groups, results showed significant improvement of LL at last follow-up as well as pelvic parameters in the group of patients with vertebral fractures at initial diagnosis, probably corresponding to the remodeling effect during growth and sagittal parameters changes occurring during growth (Table 7).

Table 7: Sub-group analysis comparing the evolution of sagittal parameters at last follow-up between patients with vertebral fractures at diagnosis (n=20) and patients with treatment-related fractures (n=9). Data is expressed as means  $\pm$  SEM and their ranges [min-max]

		Initial			FU		
		At diagnosis n=20	During treatment n=9	<i>p-value</i>	At diagnosis n=20	During treatment n=9	<i>p-value</i>
Global parameters	SVA (mm)	10.5 $\pm$ 5.6 [-35;50]	5.3 $\pm$ 8.4 [-32;35]	0.74	11.7 $\pm$ 6.1 [0-59]	10.1 $\pm$ 7.9 [-24;40]	1
	sC7-Tilt (°)	1.2 $\pm$ 0.9 [-5;9]	0.38 $\pm$ 1.5 [-6;6]	0.7	2.1 $\pm$ 1.3 [-5;14]	0.1 $\pm$ 1.1 [-5;5]	0.45
Local parameters	Thoracic kyphosis (°)	28.7 $\pm$ 2.1 [9;45]	32.7 $\pm$ 4.7 [14;62]	0.42	33.8 $\pm$ 2.5 [10;60]	33.8 $\pm$ 2.96 [23;50]	0.52
	Lumbar lordosis	15.1 $\pm$ 5.4 [-42;39]	37.8 $\pm$ 2.73 [26;49]	<b>0.03*</b>	28.3 $\pm$ 5.5 [-40;52]	26 $\pm$ 7.7 [-29;50]	0.56
	VTA (°)	8.11 $\pm$ 0.8 [3;20]	8.1 $\pm$ 1.5 [2;13.3]	0.9	6.3 $\pm$ 0.8 [1;14]	6.0 $\pm$ 1.4 [0.8;13]	0.7
	PC (%)	0.28 $\pm$ 0.03 [0.07;0.64]	0.23 $\pm$ 0.03 [0.1;0.33]	0.48	0.23 $\pm$ 0.03 [0.03;0.41]	0.17 $\pm$ 0.02 [0.1;0.25]	0.36
Pelvic parameters	Pelvic incidence (°)	47.2 $\pm$ 2.0 [20;65]	44 $\pm$ 2.0 [37;55]	0.14	50.6 $\pm$ 2.3 [39-86]	47.7 $\pm$ 5.2 [22;63]	1
	Pelvic tilt (°)	19.2 $\pm$ 2.1 [-10;35]	8.7 $\pm$ 2.2 [-4;17]	<b>0.01*</b>	16.2 $\pm$ 1.9 [3;30]	14.6 $\pm$ 3.6 [-9;27]	0.91
	Sacral slope (°)	28.1 $\pm$ 1.6 [10;40]	35.3 $\pm$ 2.0 [26;42]	<b>0.03*</b>	34.4 $\pm$ 2.7 [18;80]	33.1 $\pm$ 2.41 [19;42]	0.65

\*  $p < 0.05$ : significant difference

### III.4 DISCUSSION

The incidence of symptomatic vertebral compression fractures was low (3.1%) in the current study and no surgery was required at last follow-up with a correct correction of global sagittal alignment at final follow-up (min 1-year).

### ***III.4.1 Incidence of vertebral compression fracture in ALL***

Previous literature had reported rates varying from 2% to 26.4%. *Hogler et al.* and *Winkel et al.*, had similar values with respectively 3.6 and 2% of the patients with symptomatic vertebral fractures (61,69).

*Cummings et al.* have reported a prevalence of 26.4% of vertebral fractures in children newly diagnosed, but systematic full-spine radiographs were performed at initial diagnosis even though the patients did not complained about any back pain (79). As reported in the present study, vertebral fractures were indeed, frequently present at initial diagnosis (n=20). However, leukemia caused diffuse bone pain and vertebral fractures have been frequently reported to be asymptomatic or masked by other pain location (80). Nonetheless, pain rapidly disappears when the treatment is initiate and therefore, exposing these children to systematic radiation exposure might not be indicated.

### ***III.4.2 Characteristics of vertebral fractures***

Most of the fractures were multistage, essentially at the mid-thoracic level and at the thoraco-lumbar junction. The prevalence of mid-thoracic fracture (69%) probably resulted from the biomechanical stress-forces applied at these levels due to natural thoracic kyphosis, that increased flexion moments when a vertebra is injured (72,81). Regarding thoraco-lumbar junction, this level was involved in 62% of the patients, since it is a transitional area between more rigid vertebrae fixed to ribs and a more flexible area with lumbar vertebrae, that increased compression forces (81).

### ***III.4.3 Evolution of vertebral compression fractures***

The present study, showed no difference in global sagittal parameters (SVA, s-C7tilt) measurements between diagnosis and last follow-up, confirming children growth remodeling potential after vertebral compression fractures and with local parameters within standard values at FU, also suggesting no evidence for epiphysiodesis. Indeed, more than half of the patients were < 8-year-old and high percentage of compression was only found in 1 patient (initial CP 55% to 41% at FU).

However, the lack of significant improvement of local parameters except for lumbar lordosis might be explained by possible spinal compensatory mechanisms involving other structures than bone, as mentioned by *Mody et al.* and *Schlösser et al.*, that highlighted the importance of intervertebral discs in adolescent idiopathic scoliosis deformity (69,82,83). However, in the present study, no tridimensional deformities were found, but the role of intervertebral discs might have been to absorb flexion and compression moments, resulting in correct global sagittal alignment at FU, with a remodeling at lumbar level.

### ***III.4.4 Influence of therapeutics in compression fractures evolution***

Surprisingly, current results found no significant effect of brace on local and global parameters, whereas bracing is the gold-standard pediatric vertebral fractures treatment (Table 5) (82). Nonetheless, these results suggest that bracing might be effective on pain management, but might not need to be maintained over 6-months, when fractures are already healed. Furthermore, overall patients had a slight or moderate compression, that did not greatly affect measurements, but further surveillance is required and long-term results need to be evaluate.

Regarding treatment protocols, patients from the HDG had surprisingly better results and less severe compression fractures than the LDG (Table 6). As suggested by *Løvs et al.*, patients have variable sensitivity to corticoids that modify pharmacokinetics (84). Most of the patients had fractures prior to treatment, though these findings suggested better remodeling in the HDG group, especially since patients with fracture at initial diagnosis had more local parameters disorders (Table 7).

#### ***III.4.5 Limitations***

The main limitation of this study was its retrospective nature that did not ensure a complete data recovering, especially regarding radiographic exams. However, the current series is the largest one ever performed and overall incidence of non-documented vertebral fractures was 3.1%, that also leave a small sample size to analyze and might make our findings less significant. Further investigation is therefore required to also analyze other factors in the long-term (bone marrow graft, relapse treatment), since more than half of our patients were under 8-year-old and were still not mature at last FU. Finally, functional assessment was not performed to evaluate the accurate impact on life quality.

In conclusion, vertebral compression fractures in children with ALL evolved favorably, with no major impairment in global sagittal alignment. Initially, most of these fractures are due to the disease and are not induced by treatments, but with poor severity since almost all patients had a slight or moderate percentage of compression. Finally, remodeling predominantly occurred at lumbar level with a significant improvement of lumbar curves but intervertebral discs might also play a role.

## CONCLUSION

Dans la leucémie aiguë lymphoblastique, les signes cliniques évocateurs du diagnostic sont nombreux. Outre l'altération de l'état général associant pâleur et asthénie et adénopathies, les manifestations musculo-squelettiques représentent une part non négligeable des modes de révélation de la maladie. Notre étude consistait à réaliser une cartographie de ces manifestations dans une importante cohorte d'enfants atteints de LAL. Bien que l'incidence de leur survenue soit inférieure à celles retrouvées dans la littérature, nous avons montré que ces symptômes se manifestaient principalement de 3 manières : douleurs osseuses, arthrites ou fractures pathologiques. Les douleurs osseuses étaient les plus fréquentes, souvent diffuses ou localisées au niveau des membres inférieurs et du rachis. Il est donc important de garder à l'esprit que tout enfant présentant une altération de l'état général et des manifestations musculo-squelettiques doit être adressé rapidement à un hôpital pédiatrique de référence. Des examens complémentaires (numération formule sanguine, radiographies des zones symptomatiques) y seront pratiqués afin d'orienter plus précisément le diagnostic. Quatre lésions radiologiques ont été décrites : les bandes claires métaphysaires, les lésions ostéolytiques, les réactions périostées et une déminéralisation diffuse. Bien que non pathognomoniques, elles orientent fortement le diagnostic. Celles-ci étaient cependant peu fréquentes dans notre étude mais les radiographies étaient réalisées uniquement devant des symptômes cliniques à l'inverse de ce qui a été rapporté dans la littérature. Nous ne recommandons pas ces radiographies systématiques qui vont mettre en évidence certes des lésions radiologiques mais qui ne modifieront pas l'attitude thérapeutique et exposera ces enfants à des radiations inutiles, auxquelles ils auront de toute manière le loisir d'être exposés lors de leur suivi. Enfin, l'absence de lésion radiologique ne doit pas être rassurante.

Une fois le diagnostic confirmé, un protocole thérapeutique doit être rapidement initié, mais ceux-ci ne sont pas dénués d'effets secondaires aigus ou à long terme. Outre les effets inhérents aux différentes chimiothérapies (syndrome de lyse tumorale, aplasie, risque hémorragique), l'appareil musculo-squelettique n'est pas épargné par ces complications. Deux complications orthopédiques ont été décrites : l'ostéonécrose et l'ostéopénie. Les ostéonécroses concernent essentiellement les articulations du membre inférieur et le rachis. Leur risque de survenue est augmenté chez les patients traités dans le groupe FRALLE 2000 en raison d'un taux élevé de corticoïdes, d'asparagine et de méthotrexate, molécules qui sont ostéotoxiques. Cette étude montre également que la rechute de la maladie ainsi que la greffe de moelle osseuse sont



associées à un risque accru d'ostéonécrose. En effet, dans ces deux cas les protocoles thérapeutiques incluent de nouvelles doses de corticoïdes et de chimiothérapies. L'ostéopénie est fréquente chez les enfants leucémiques notamment en cas de greffe de moelle osseuse ou de rechute de l'hémopathie et provoquent dans la plupart des cas des tassements vertébraux.

Avec la diminution de la mortalité se pose la question de la qualité de vie de ces enfants à l'âge adulte. Ces complications orthopédiques peuvent être à l'origine de douleurs osseuses et d'une impotence fonctionnelle invalidante, qui doivent être prévenues dans la mesure du possible et prise en charge précocement. Une supplémentation en calcium et en vitamine D est fortement recommandée et un traitement par biphosphonates en cas d'ostéoporose avérée et/ou de fractures multiples, peut être proposé bien que leurs effets soient toujours débattus chez l'enfant. Jusqu'à ce jour aucun traitement n'existe pour prévenir ni ralentir la survenue d'une ostéonécrose. En cas de formes évoluées, les douleurs osseuses quotidiennes deviennent invalidantes. Une consultation dans un centre spécialisé de la douleur peut être proposé pour une prise en charge optimale alliant diverses thérapeutiques (antalgiques de pallier 1 à 3, physiothérapie, kinésithérapie, soutien psychologique). Au dernier recul, seulement 0.2% des enfants ont bénéficié d'une intervention chirurgicale, uniquement en cas d'ostéonécrose épiphysaire. Un suivi orthopédique et rhumatologique rapproché est fortement recommandé, afin de prévenir les déformations et destructions articulaires. Au cours du suivi, la détection de nouvelles complications orthopédiques peut être réaliser grâce à une ostéodensitométrie et/ou une IRM, orientée sur les observations de l'examen clinique.

Les tassements vertébraux sont du fait de l'hémopathie elle-même sur un os trabéculaire moins résistant aux contraintes car envahit et des traitements ostéotoxiques (corticoïdes et chimiothérapies : asparaginase et methotrexate). Deux types de fractures vertébrales ont été décrits : une compression antérieure et une compression globale avec un pourcentage moyen de tassement de 20 % dans notre série. La majorité des patients présentaient des tassements adjacents (4 vertèbres adjacentes en moyenne) qui auraient pu perturber la statique rachidienne. L'analyse radiologique comparative à 3 ans de recul montrait uniquement une rééquilibration dans le secteur lombaire, sachant que les mesures globales étaient peu perturbées au moment du diagnostic. C'est dans ce secteur que le remodelage osseux a dû se faire avec sans doute un rôle des disques inter-vertébraux qui reste à étudier. Les différentes analyses en sous-groupe ont montré peu de corrections dans les patients traités par corset, une meilleure évolution des patients traités par hautes doses de corticoïdes, ce qui est peu étonnant étant donné que la majorité des patients présentaient des tassements vertébraux au moment du diagnostic et non après traitement. Ces résultats sont mitigés mais probablement liés au fait que bien que les

fractures soient multiétagées et adjacentes, elles étaient « harmonieuses » avec un pourcentage de compression relativement faible, sans grand déséquilibre initial et survenant chez des enfants en bas âge n'ayant pas encore atteint le pic de croissance pubertaire. Un suivi en fin de croissance semble nécessaire afin de confirmer ou non nos résultats et le corset nous semble donc indiqué à visée antalgique et non correctrice.

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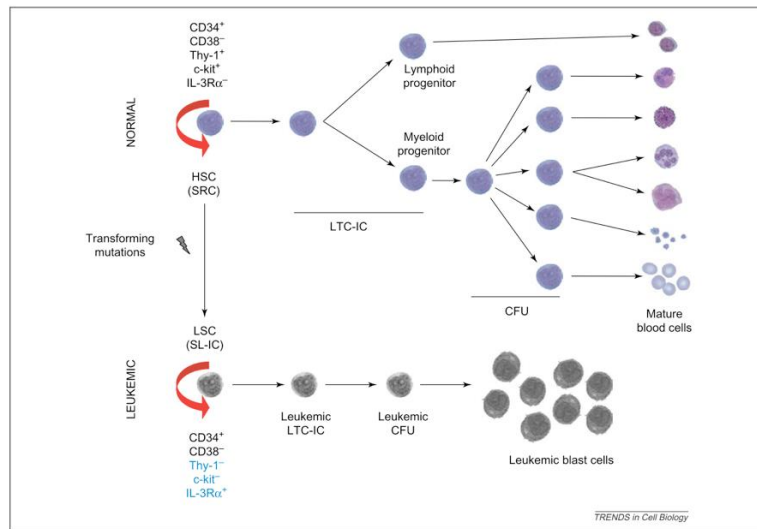
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# ANNEXES

## Annexe 1: Illustration de l'hématopoïèse normale et pathologique de la leucémie aiguë



HSC: Hematopoietic Stem Cells

LSC; Leukemic Stem Cells

SRC: SCID (Severe Combine ImmunoDeficient) Repopulating Cell

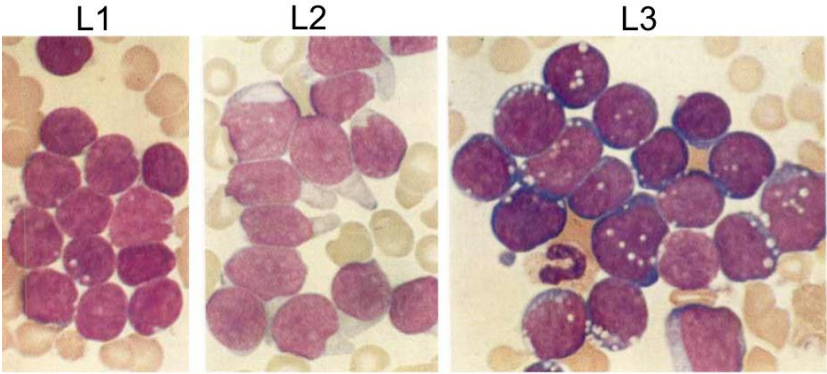
LTC-IC: Long Term Culture Initiating Cell

CFU: Colony Forming Unit

## Annexe 2: Classification Fanco-americano-britannique (FAB)

Caractéristiques cytologiques	L1	L2	L3
Taille cellulaire	Prédominance de petite	Large, hétérogène en taille	Large et homogène
Chromatine nucléolée	Homogène	Variable, hétérogène	Finement mouchetée et homogène
Formes du noyau	Régulier, quelques indentations	Variable, hétérogène	Régulier, ovale ou rond
Nucléole	Non visible, ou petit et à peine visible	Irrégulier : fentes et indentations fréquentes	Important, une ou plusieurs vésicules
Quantité de cytoplasme	Faible	Un ou plusieurs, souvent larges	Moyennement abondant
Basophilie du cytoplasme	Faible ou modérée, rarement intense	Variable, moyennement abondant	Très intense
Vacuoles cytoplasmiques	Variable	Variable	Souvent nombreuses

Annexe 3: Frottis médullaire de cellules leucémiques lymphoblastiques (x800)



Annexe 4: Classification immuno-phénotypique en fonction de la présence de certains marqueurs de surface.

Marqueurs de surface		HLA-DR	CD19	CD24	CD10	CD20	CD21	CD22	CD23	clg	slg
Lignée B	Pré pré-B	+	+	+	+	±	-	<b>Cyt</b>	-	-	-
	Pré-B	+	+	+	+	+	+	+	-	+	-
	B	+	+	+	-	+	+	+	+	-	+
		CD7	CD2	CD5	CD1	CD4	CD8	CD3			
Lignée T		+	+	+	-	+	+	+			

Cyt: Cytoplasm

CIg: Cytoplasmic Immunoglobulin

SIg: Surface Immunoglobulin

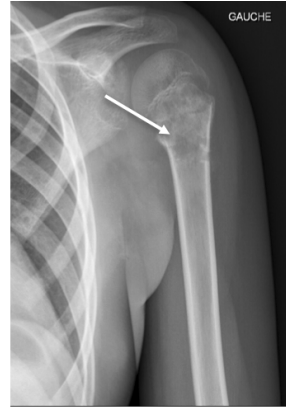
Annexe 5 : Manifestations osseuses radiologiques des leucémies aiguës



Bandes claires  
métaphysaires



Appositions  
périostées



Ostéolyse



Déminéralisation  
diffuse

## **RESUME** : Manifestations et complications orthopédiques dans la leucémie aiguë lymphoblastique de l'enfant : *étude épidémiologique et thérapeutique*

**Introduction** : La leucémie aiguë lymphoblastique (LAL) est le cancer le plus fréquent de l'enfant et peut être suspecté devant plusieurs symptômes dont des signes ostéo-articulaires. Les progrès thérapeutiques ont permis de rendre cette maladie curable mais non sans complications qui peuvent altérer la qualité de vie future. L'objectif de cette thèse était d'étudier ces manifestations orthopédiques au diagnostic, d'analyser les complications orthopédiques en cours de traitement et enfin d'étudier l'évolution et le retentissement de l'une d'entre elles : les tassements vertébraux.

**Matériels et méthodes** : Il s'agissait d'un travail rétrospectif incluant tous les patients atteints de LAL entre 2007 et 2017 dans 3 centres hospitaliers universitaires. Les patients atteints d'un autre type de leucémie ou dans le cadre d'un syndrome ont été exclus. Ont été recherchés tous les patients ayant présenté des manifestations orthopédiques au diagnostic et en cours de traitement. Tous leurs examens radiologiques ont été analysés. Plusieurs mesures ont été réalisées dans le plan sagittal sur les clichés de rachis entier debout pour les tassements vertébraux. Une analyse des paramètres a été réalisée au diagnostic et au dernier recul. Pour les différentes études, une recherche d'éventuels facteurs de risque a été réalisée.

**Résultats** : Un total de 1293 patients (âge moyen  $6,8 \pm 0,1$  ans), ont été traités pour une LAL : 10,7% des patients présentaient des manifestations orthopédiques au diagnostic (douleurs osseuses 76,7%, arthrites 6,6% et fractures pathologiques 16,7%) parmi lesquels 118 examens radiologiques qui ont mis en évidence des lésions radiologiques (bandes claires métaphysaires, lésions ostéolytiques, appositions périostées, déminéralisation diffuse). En cours de traitement, 10% des patients (n=129) ont présenté des complications au recul moyen de 4,3 ans (ostéonécrose 54,3% et ostéopénie 45,7%). Les patients ostéopéniques étaient traités par supplémentation calcique et vitamine D associés à des bisphosphonates en cas d'ostéoporose (n=11). Parmi les ostéonécroses, 2 types ont été identifiées : les ostéonécroses épiphysaires (n=31) et les infarctus osseux diaphysaires (n=39). Un traitement chirurgical a été nécessaire dans 3,1% des cas pour des nécroses ayant conduit à des destructions articulaires. Des facteurs de risque ont été identifiés : greffe de moelle osseuse, la récurrence de la maladie ainsi que les fortes doses de corticoïdes uniquement pour les ostéonécroses. Parmi la population totale, 2,2% des patients ont eu des tassements vertébraux (n=29). Tous les patients ont été traités de manière conservatrice dont 16 par un corset pour une durée moyenne de 6 mois. Au dernier recul, les patients ne présentaient pas de déséquilibre sagittal avec possibilité de rééquilibration dans le secteur lombaire. Aucun traitement ou facteur de risque n'a montré une incidence sur l'évolution naturelle.

**Conclusion** : Les manifestations orthopédiques sont fréquentes dans la LAL et tout enfant présentant ces symptômes associés à une altération de l'état général doit être adressé en urgence dans un centre de référence. Les complications orthopédiques en cours de traitements sont le plus souvent réversibles. Les tassements vertébraux évoluent favorablement sans causer de déséquilibre sagittal du fait de la possibilité de remodelage osseux. Devant l'apparition de ces complications patient et parents doivent donc être rassurés.

## **ABSTRACT**: Orthopaedic manifestations and complications in children with acute lymphoblastic leukemia: *epidemiologic and therapeutic study*

**Introduction**: Acute lymphoblastic leukemia (ALL) is the most frequent pediatric cancer, which can be revealed by different symptoms such as osteo-articular manifestations. ALL is a curable disease thanks to medical advances but several complications might occur, altering quality of life. The aim of this work was to provide an overview of musculo-skeletal manifestations at diagnosis, to report osteo-articular treatment-related complication and to investigate vertebral compression fractures treatment and evolution.

**Materials and methods**: A retrospective study was conducted between 2007 and 2017 including all children diagnosed with ALL in 3 pediatric university hospitals. Patients suffering from another type of leukemia were excluded as well as ALL secondary to a syndrome. All the patients with orthopaedic manifestations at initial diagnosis and during treatment were reported. Radiological exams were analyzed. Regarding compression vertebral fractures, sagittal measures on full-spine standing radiographs were performed.

**Results**: A total of 1293 children (mean age  $6.8 \pm 0.1$ -year-old) were diagnosed and treated for an ALL: 10.7% had orthopaedic manifestations at initial diagnosis (bone pain 76.7%, pathological fractures 16.7% and arthritis 6.6%). In 118 cases, radiological exams were performed showing radiolucent metaphyseal bands, osteolysis, periosteal reactions and diffuse bone demineralization. Orthopedic complications were found in 10% (n=129) with a mean follow-up of 4.3 years (osteonecrosis 54.3% and osteopenia 45.7%). Regarding osteopenia, patients received oral Vitamin D and calcium supplementation and intravenous bisphosphonates for 11 patients with confirmed osteoporosis. Surgical treatment was performed in 3.1% for epiphyseal necrosis with articular damages. Several risk factors were identified: relapses and bone marrow graft, as well as high dose of corticoids for osteonecrosis. Among the global population, 2.2% had vertebral compression fractures, treated conservatively (including 16 patients with brace). At last follow-up, patients had a correct global alignment and traumatic vertebral angle showed improvement due to remodeling effects.

**Conclusion**: Orthopaedic manifestations are frequent and the diagnosis of ALL should be raised in front of a child with loss of condition and musculo-skeletal symptoms. These patients should be urgently addressed for further management. Orthopaedic complications are reversible in most of the cases, except for epiphyseal necrosis. Vertebral compression fractures, even multistage have a good prognosis with no global misalignment at final follow-up, with or without treatment. Therefore, patients and parents should be reassured during treatment.