Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia

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Supplemental figure 1: CONSORT diagram of patient inclusion

Number of registered ALL patients in the Netherlands (1997-2004) (n = 957) [Veerman et al. 2009]

Excluded ALL9 protocol
- Not in ALL9 trial or Not eligible for ALL9 (n=75)
- Not in ALL9 trial or Not eligible for ALL9 (only BMD cohort) (n=29)
- Not a participating center (n=102)

Treated in the participating centers according to the DCOG-ALL9 protocol [Veerman et al. 2009] (n = 751)

Excluded for the BMD-ON study
- Pre-existing (genetic) disease affecting loco-motor system (n = 35)
  - 23 Down syndrome
  - 1 Noonan syndrome
  - 1 Goldenhar syndrome
  - 2 Osteogenesis imperfecta
  - 2 Legg-Calve-Perthes
  - 2 Spina bifida
  - Retardation of mental and motor development:
    - 1 meningitis, 1 microcephaly, 1 unsecified etiology
    - 1 periventricular leukomalacia with spastic bulbar palsy
- No follow-up data (moved to other country) (n = 20)
- Other Reasons
  - 1 Fancolny anemia
  - 1 Ganglioneuroblastoma
  - 1 Osteonecrosis after trauma

Excluded for DXA measurements
- Too young (< 4 years of age) (n = 118)

Eligible for the BMD-ON analyses (n = 575)

Eligible for BMD-ON analyses
- Lost to Follow-up / refusal parents (n = 109)

Included for BMD-ON analysis (n = 466)

Number of available scans per time point

<table>
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<th>DXA</th>
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<th>T1</th>
<th>T2</th>
<th>T3</th>
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<td>n = 328</td>
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<td>n = 82</td>
<td>n = 72</td>
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Abbreviations: ALL = acute lymphoblastic leukemia; DCOG = Dutch Childhood Oncology Group;
FU = follow-up; HR = high risk; SCT = stem-cell transplantation; yr. = year; BMI = Body Mass Index;
DXA = Dual X-Ray Absorptiometry; TB = total body; LS = lumber spine; ON = osteonecrosis ; n = number.
Supplemental figure 2: Comparison of $\Delta \text{BMD}_{\text{SDS}}$ change in pediatric ALL patients (4-18 years of age) with and without ON adjusted for age at diagnosis and risk group.

BMD change of the lumbar spine (2A) and total body (2B) in pediatric ALL patients (4-18 years of age) with and without ON. The dots represent the estimated mean from the mixed linear model and the whiskers represent the standard error of the mean BMD.

Abbreviations: T0 = at diagnosis; T1 = start maintenance therapy (32 weeks); T2 = at cessation therapy (109 weeks); T3 = 1 year after cessation of therapy (161 weeks); BMD$_{LB}$ = bone mineral density of the lumber spine; BMD$_{TB}$ = bone mineral density of total body; $\Delta_{T3-T0}$ = “interaction group time * ON”; $p =$ p-value ; * difference $p<0.05$. 

Supplemental Material - Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia
**Supplemental figure 3: Comparison of BMD SDS change in pediatric ALL patients (10-18 years of age) with and without ON.**

BMD change of the lumbar spine (3A) and total body (3B) in pediatric ALL patients (10-18 years of age) with and without ON. The dots represent the estimated mean from the mixed linear model and the whiskers represent the standard error of the mean BMD.

Abbreviations: T0 = at diagnosis; T1 = start maintenance therapy (32 weeks); T2 = at cessation therapy (109 weeks); T3 = 1 year after cessation of therapy (161 weeks); BMDLS = bone mineral density of the lumbar spine; BMDTB = bone mineral density of total body; $\Delta_{T3-T0}$ = “interaction group time * ON” ; $p =$ p-value ; * difference $p<0.05$. 

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**Supplemental Material - Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia**
Supplemental figure 4: Comparison of BMD$_{SDS}$ change in pediatric ALL patients (4-18 years of age) with and without ON stratified according to risk protocol.

BMD change of the lumbar spine (4A/C) and total body (4B/D) stratified according to risk protocol in pediatric ALL patients (4-18 years of age) with and without ON. The dots represent the estimated mean from the mixed linear model and the whiskers represent the standard error of the mean BMD.

Abbreviations: T0 = at diagnosis; T1 = start maintenance therapy (32 weeks); T2 = at cessation therapy (109 weeks); T3 = 1 year after cessation of therapy (161 weeks); BMD$_{LB}$ = bone mineral density of the lumber spine; BMD$_{TB}$ = bone mineral density of total body; $\Delta_{T3-T0}$ = “interaction group time * ON”; $p$ = p-value; * difference $p<0.05$. 

Supplemental Material - Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia