Effect of post-consolidation regimen on symptomatic osteonecrosis in three DCOG acute lymphoblastic leukemia protocols

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Supplementary methods

Patients

Children with ALL below 1 year of age were treated according to the Interfant protocol and patients with presence of the t(9;22) translocation (Philadelphia chromosome) or the corresponding fusion gene BCR/ABL in the leukemic cells were treated according to the DCOG EsPhALL protocol from December 2005 onwards and therefore not included in this study. Patients treated according to the ALL-10 and ALL-11 standard risk and high risk groups were not included because the treatment for these groups did not contain post-consolidation dexamethasone pulses. Exclusion criteria were Down syndrome and administration of the majority of treatment abroad.

Data collection

The high cumulative dose of dexamethasone that would be administered in DCOG ALL-9 led to the realization that bone toxicity might be an important side-effect of this protocol. Therefore, integration of prospective bone toxicity data collection (including osteonecrosis) was pursued within this protocol, and taken forward into ALL-10/11 (medical ethical committee number 187.154/1999/212 [ALL-9], 2004-203 [ALL-10] and 2012-287 [ALL-11]). Presence of clinical symptoms of osteonecrosis were evaluated using a standardized form at diagnosis, after 32 weeks of treatment, at treatment cessation and one year after treatment cessation in ALL-9 and at the start of each consecutive treatment block until one year after treatment cessation in ALL-10/11.[1] In addition, we retrospectively assessed detailed clinical information of these children from medical records. Characteristics of patients with osteonecrosis treated according to the

ALL-9 protocol have been previously described.[2] Data from the ALL-10 and ALL-11 protocols were combined for all analyses because treatment factors known to be associated with osteonecrosis did not substantially differ between these protocols.

Definition of osteonecrosis and severe osteonecrosis

All MRI scans were interpreted by musculoskeletal radiologists in one of the seven pediatric oncology centers in the Netherlands. Because osteonecrosis was a relatively unknown condition during the ALL-9 period, the MRI scans of patients diagnosed with osteonecrosis were reviewed by a single experienced pediatric musculoskeletal radiologist (ML) to confirm the diagnosis. In 10 patients, diagnosis of osteonecrosis was based on symptoms and classic abnormalities on X-rays through review by the same pediatric radiologist.

Risk factors

Potential risk factors for osteonecrosis included type of post-consolidation regimen (ALL-10/11 MRG versus ALL-9), sex (male versus female), age (years) and BMI (standard deviation score [SDS]) at ALL diagnosis. BMI SDS was calculated with the LMS method by Cole & Green using Dutch BMI reference values.[3] Less than 0.5% of patients had missing BMI SDS values. The method of analysis was intention-to-treat. Analyses were performed using IBM SPSS Statistics version 25. Mstate package[4] in the R-15 software environment was used to estimate the CION.[5,6]

Supplementary results

Affected sites

At first presentation of osteonecrosis, 15 patients (19%) experienced symptoms at a single site, whereas 81% had multifocal symptoms. Weight-bearing joints were affected in all patients (knee 61%; hip 53%; ankle/foot; 18%). Symptoms in upper extremities were additionally reported and radiologically confirmed in 7 patients (9%).

Management of osteonecrosis

When osteonecrosis occurred during therapy, anti-cancer treatment was modified in 54 patients (68%). Treatment with dexamethasone was permanently discontinued in 45 patients (57%), decreased in six patients (8%), and changed to prednisone in three patients (4%). Asparaginase treatment was not modified because of osteonecrosis in any of the patients, however, treatment of one teenager (1%) was switched from the ALL-10 MRG to the high risk protocol (without stem cell transplantation) after osteonecrosis occurrence, by which this patient would 1) no longer receive dexamethasone and 2) receive a lower cumulative dose of asparaginase. Patients were conservatively treated with physical therapy (57 patients, 72%), weight-bearing restrictions (43 patients, 54%), and/or bisphosphonates (15 patients, 19%). Symptoms of osteonecrosis completely resolved with conservative treatment in 31 patients (39%) at 0.1-9.0 years (median 4.5 years) of follow-up after diagnosis of osteonecrosis. Surgical interventions such as drilling, excision and grafting of the osteonecrosis and/or osteotomy were performed in 11 patients (14%). Ultimately, a joint replacement was performed in 12 patients (15%); four of these patients had previously had another type

of surgical intervention. Of the 15 patients with severe osteonecrosis, 10 (67%) required joint replacement, three (20%) reported chronic pain and two (13%) had no symptoms at follow-up.

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Supplementary Table 1. Overview of chemotherapeutic agents, previously reported to be associated with osteonecrosis, in DCOG ALL-9, ALL-10 and ALL-11.

ALL-9[7] *(1997—2004)*		
Inclusion criteria	- Newly diagnosed patients with T-lineage or precursor-B lineage ALL - Diagnosis ALL confirmed by DCOG laboratory - Age between ≥1 and <19 years - No treatment with systemic corticosteroids and/or cytostatics in a 4-week interval prior to diagnosis	
	NHR	HR
Stratification criteria	- WBC <50x10^9/L at dx - No CNS involvement or testis involvement or mediastinal enlargement at dx - No presence of the t(4;11)(q11;q23) or t(9;22) translocation or the corresponding fusion genes MLL/AF4 or BCR/ABL in the leukemia cells at dx - No T-lineage ALL	- All other patients
Induction/consolidation		
DEXA	6 mg/m^2/day for 28 days (3x5 day taper)	6 mg/m^2/day for 28 days (induction; 3x5 day taper) 6 mg/m^2/day for 7 days every 3 wks (intensification I)
L-ASP	4x6,000 IU/m^2 (2x/week from week 4 to 6)	4x6,000 IU/m^2 (2x/week from week 4 to 6) 9x10,000 IU/m^2 (1x/week from week 15 to 24)
Post-consolidation		
DEXA	6 mg/m^2/day for 14 days every 7 wks; 98 wks	6 mg/m^2/day for 14 days every 7 wks; 77 wks
L-ASP	None	None
No. DEXA pulses + ASP	0	0
Cumulative dose		
DEXA	1,370 mg/m^2	1,244 mg/m^2
L-ASP	24,000 IU/m^2	114,000 IU/m^2
ALL-10[8] *(2004—2012)*		
Inclusion criteria	- According to ALL-9 inclusion criteria - From December 2005 onwards: no presence of Ph-positive ALL (documented presence of t(9;22)(q34;q11) and/or of the BCR/ABL fusion transcript)	
	MR	
Stratification criteria	- Cytomorphological CR at day 33 - MRD-positivity at day 33 (TP1) and/or at day 79 (TP2), but MRD level at day 79 <10^{-3} - No presence of the t(4;11)(q11;q23) translocation or the corresponding fusion gene MLL/AF4 in the leukemia cells at dx (From July 2012 onwards: In case of IKZF1 deletion 1 year of additional maintenance therapy)	
Induction/consolidation		
PRED	60 mg/m^2/day for 28 days (3x3 day taper)	
L-ASP	8x5,000 IU/m^2 (every 3 days from day 12 to 36)	
Post-consolidation		

DEXA	6 mg/m^2/day for 5 days every 3 wks; 84 wks
PEG-ASP	15x2,500 IU/m^2 (every 2 weeks from week 1 to 31)
No. DEXA pulses + ASP	10
Cumulative dose	
GCs[1]	1,115 mg/m^2
ASP	40,000 IU/m^2 L-ASP 37,500 IU/m^2 PEG-ASP
ALL-11 *(2012—onwards)*	
Inclusion criteria	According to ALL-10
	MR
Stratification criteria	According to ALL-10
Induction/consolidation	
PRED	60 mg/m^2/day for 28 days (3x3 day taper)
PEG-ASP	3x1,500 IU/m^2 (every two weeks at day 12, 26 and 40) *If MRD+ at TP1, eligible for randomization: A=standard PEG-ASP (14x individualized dose during intensification) and B=experimental, early PEG-ASP (14x individualized dose during protocol 1B/M and intensification)*
Post-consolidation	
DEXA	6 mg/m^2/day for 5 days every 3 wks; 84 wks
PEG-ASP	14x individualized dose (no randomization or randomization A, every 2 weeks from week 1 to 29) or 8x individualized dose (randomization B, every 2 weeks from week 1 to 17)
No. DEXA pulses + ASP	10 (no randomization or randomization A) or 6 (randomization B)
Cumulative dose	
GCs[1]	1,115 mg/m^2
PEG-ASP	NA (individualized dose)

ALL=acute lymphoblastic leukemia; ASP=asparaginase; CR=complete remission; DCOG=Dutch Childhood Oncology Group; DEXA=dexamethasone; dx=diagnosis; CNS=central nervous system; GCs=glucocorticoids; HR=high risk; MR=medium risk; MRD=minimal residual disease; NA=not available; NHR=non-high risk; PRED=Prednisone; TP=time point; WBC=white blood cell count

[1]Dexamethasone equivalent

Supplementary Table 2. Grading of osteonecrosis associated with treatment of childhood acute lymphoblastic leukemia according to the Ponte di Legno toxicity working group.

PTWG grade 1	Asymptomatic with findings only by MRI.
PTWG grade 2	Symptomatic, not limiting or only slightly limiting self-care activity of daily living. Lesions only outside joint lines in non-weight-bearing bones.
PTWG grade 3	Symptomatic, not limiting or only slightly limiting self-care activity of daily living. Lesions in weight-bearing bones or affecting joint lines in non-weight-bearing bones.
PTWG grade 4	Symptomatic with deformation by imaging of one or more joints and/or substantially limiting self-care activity of daily living.

MRI=magnetic resonance imaging; PTWG=Ponte di Legno toxicity working group

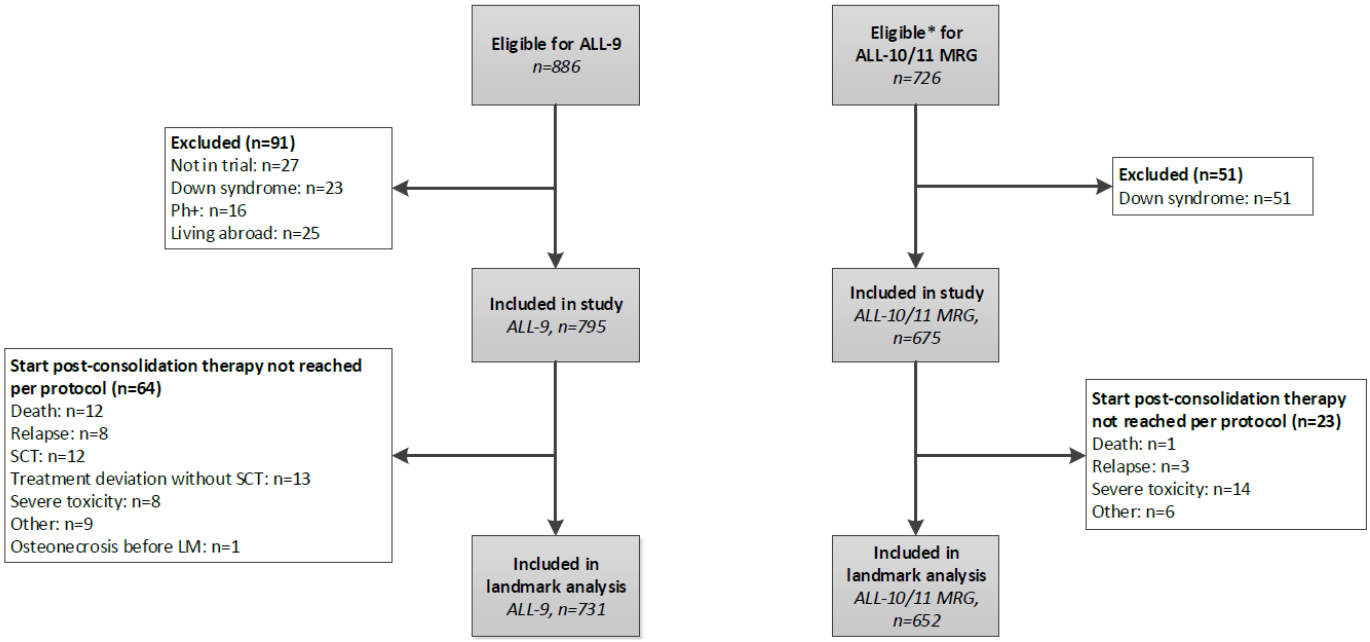
Supplementary Table 3. Baseline characteristics of patients treated with long pulses dexamethasone (ALL-9) and patients treated with short pulses dexamethasone (asparaginase intensified ALL-10/11 MRG) during post-consolidation therapy.

	Long pulses DEXA (ALL-9) *N=795*		**Short pulses DEXA + ASP** (ALL-10/11 MRG) *N=675*		
	Number	%	Number	%	P-value[1]
Sex					0.097
Male	485	61.0	383	56.7	
Female	310	39.0	292	43.3	
Age (yrs)					0.239
Median	4		5		
IQR	6		7		
Range	1—17		1—18		
Height (cm)					0.107
Median	112		116		
IQR	39		46		
Range	72—195		72—196		
Weight (kg)					0.063
Median	19.8		21.0		
IQR	15.8		21.6		
Range	8.9—103.0		6.8—94.8		
BMI (SDS)					0.102
Median	-0.32		-0.24		
IQR	1.4		1.3		
Range	-4.2—7.6		-4.8—3.3		

ASP=asparaginase; BMI=body mass index; DEXA=dexamethasone; GCs=glucocorticoids; HR= high risk; IQR=interquartile range; MR=medium risk; NA=not available; NHR= non-high risk

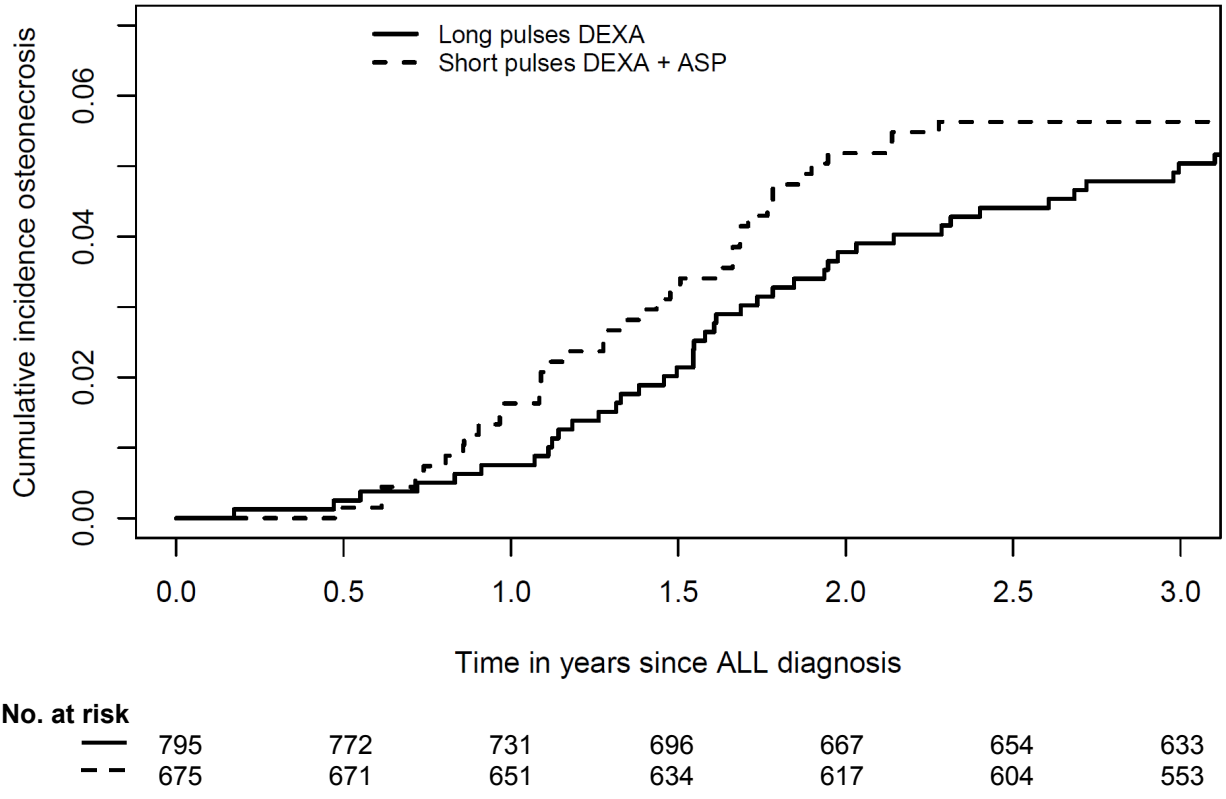
[1]Chi-square p-value for categorical variables, student T-test p-value for normally distributed continuous variables and Mood's median test p-values for non-normally distributed continuous variables.

Supplementary Figure 1. Flow diagram of study participants.



ALL=acute lymphoblastic leukemia; LM=landmark; MRG=medium risk group; Ph+= Philadelphia chromosome positive; SCT=stem cell transplantation. *Patients not in trial, Ph+ patients and patients living abroad were not eligible for these protocols.

Supplementary Figure 2. Cumulative incidence of symptomatic osteonecrosis for patients treated with long pulses dexamethasone (n=795) and patients treated with short pulses dexamethasone plus asparaginase (n=675) since ALL diagnosis.



ALL=acute lymphoblastic leukemia; ASP=asparaginase; DEXA=dexamethasone