Late thyroid complications in survivors of childhood acute leukemia. An L.E.A. study

Claire Oudin,[1,2] Pascal Auquier,[2] Yves Bertrand,[3] Philippe Chastagner,[4] Justyna Kanold,[5] Maryline Poirée,[6] Sandrine Thouvenin,[7] Stephane Ducassou,[8] Dominique Plantaz,[9] Marie-Dominique Tabone,[10] Jean-Hugues Dalle,[11] Virginie Gandemer,[12] Patrick Lutz,[13] Anne Sirvent,[14] Virginie Villes,[2] Vincent Barlogis,[1,2] André Baruchel,[11] Guy Leverger,[10] Julie Berbis,[2] and Gérard Michel[1,2]

[1]Department of Pediatric Hematology and Oncology, Timone Enfants Hospital and Aix-Marseille University; [2]Research Unit EA 3279 and Department of Public Health, Aix-Marseille University and Timone Hospital Marseille; [3]Department of Pediatric Hematology and Oncology, University Hospital of Lyon; [4]Department of Pediatric Onco-Haematology, Children's Hospital of Brabois, Vandoeuvre Les Nancy; [5]Department of Pediatric Hematology and Oncology, CIC Inserm 501, University Hospital of Clermont-Ferrand; [6]Pediatric Hematology and Oncology Department, University Hospital L'Archet, Nice; [7]Pediatric Hematology, University Hospital, Saint Etienne; [8]Department of Pediatric Hematology and Oncology, University Hospital of Bordeaux; [9]Department of Pediatric Hematology-Oncology, University Hospital of Grenoble; [10]Pediatric Hematology Department, Trousseau Hospital, Paris; [11]Pediatric Hematology Department, Robert Debré Hospital, Paris; [12]Department of Pediatric Hematology and Oncology, University Hospital of Rennes; [13]Department of Pediatric Hematology-Oncology, University Hospital, Strasbourg; and [14]Pediatric Hematology and Oncology Department, University Hospital, Montpellier, France
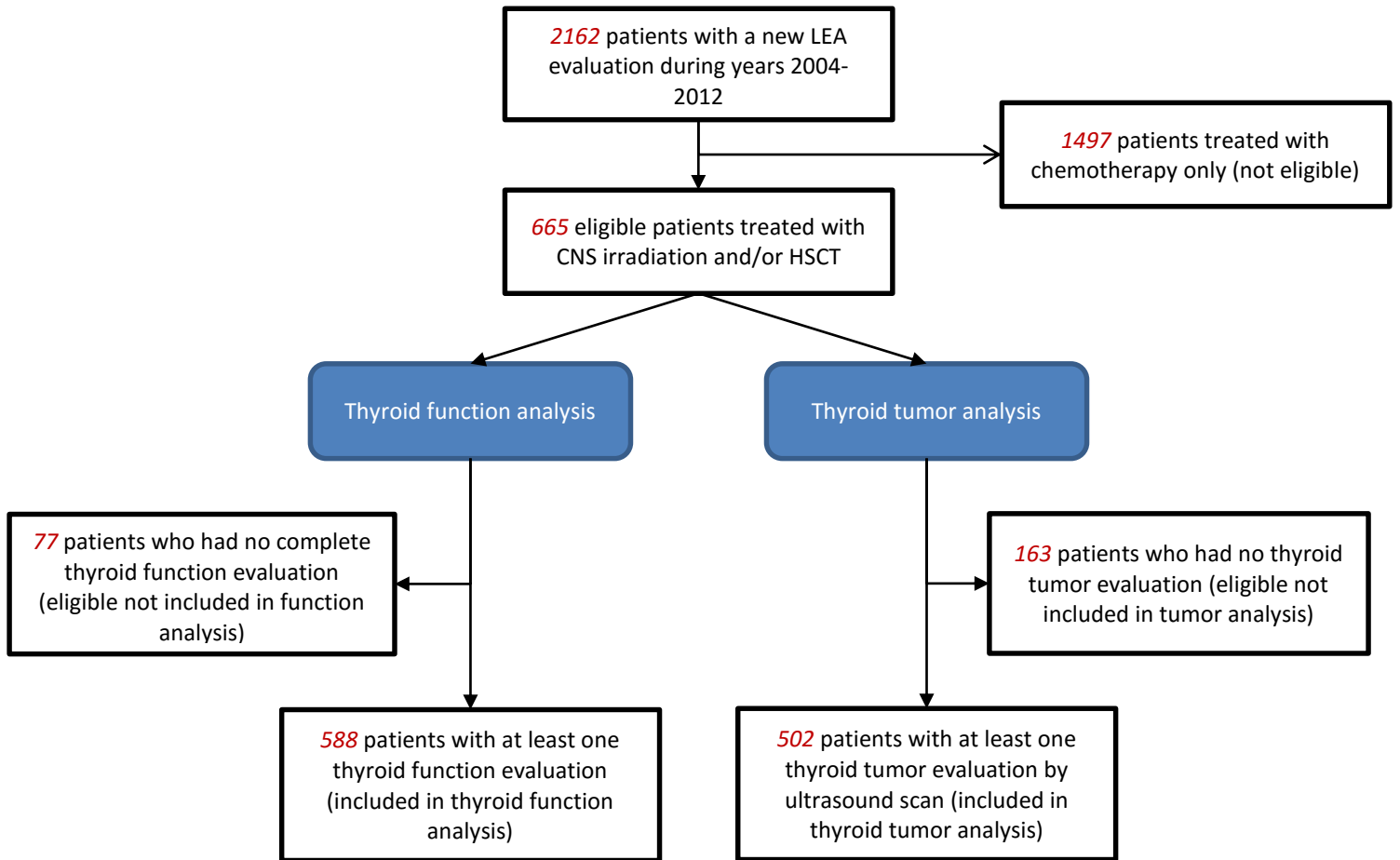
Supplemental data

Supplemental methods

Data regarding disease type, treatment modalities, irradiation modalities, and transplantation procedure were collected from the medical records. The chemotherapy protocol and the conditioning regimen depended on the protocols used at the time of transplantation, the underlying disease, disease status, and history of central nervous system irradiation involvement. The central nervous system irradiation dose (18 or 24 grays), field (cranial or cranio-spinal) and indication depended on the protocol used at the time of treatment.

	Hypothyroidism evaluation			Thyroid cancer evaluation		
	Participants group (n=588)	Non participants group (n=77)	p-value	Participants group (n=502)	Non participants group (n=163)	p-value
Gender						
Male *n (%)*	340 (57.8)	38 (49.3)	0.16	284 (56.6)	94 (57.7)	0.81
Female *n (%)*	248 (42.2)	39 (50.7)		218 (43.4)	69 (42.3)	
Leukemia type						
Acute myeloid leukemia *n (%)*	146 (24.8)	15 (19.5)	0.30	118 (23.5)	43 (26.4)	0.46
Acute lymphoid leukemia *n (%)*	442 (75.2)	62 (80.5)		384 (76.5)	120 (73.6)	
Relapse						
Yes	237 (40.3)	13 (16.9)	**$<10^{-3}$**	207 (41.2)	43 (26.4)	**0.001**
No	351 (59.7)	64 (83.1)		295 (58.5)	120 (73.6)	
Age at leukemia diagnosis (years) *Median (min-max)*	6.5 (3.4-11.2)	6.3 (3.4-11.7)	0.81	7.4 ± 0.2	7.2 ± 0.4	0.72
Treatment modality						
CNS irradiation, no HSCT *n (%)*	143 (24.3)	51 (66.2)	**$<10^{-3}$**	119 (23.7)	75 (46)	**$<10^{-3}$**
HSCT with TBI, with previous CNS irradiation *n (%)*	21 (3.6)	2 (2.6)		19 (3.8)	4 (2.5)	
HSCT with TBI, without previous CNS irradiation *n (%)*	289 (49.1)	8 (10.4)		255 (30.9)	42 (25.8)	
HSCT without TBI, with previous CNS irradiation *n (%)*	15 (2.6)	1 (1.3)		10 (2)	6 (3.7)	
HSCT without TBI, without previous CNS irradiation *n (%)*	120 (20.4)	15 (19.5)		99 (19.7)	36 (22.1)	
Age at transplantation/irradiation						
< 10 years *n (%)*	361 (61.4)	50 (64.9)	0.55	306 (61)	105 (64.4)	0.43
≥ 10 years *n (%)*	227 (38.6)	27 (35.1)		196 (39)	58 (35.6)	
Hematopoietic stem cell transplantation (HSCT) type						
Autologous *n(% of transplanted patients)*	91 (20.4)	1 (3.8)	**0.04**	70 (18.3)	22 (25)	0.15
Allogeneic *n(% of transplanted patients)*	354 (79.6)	25 (96.2)		313 (81.7)	66 (75)	
Age at transplantation (years)	8.8 ± 0.2	7.8 ± 1.0	0.32	8.9 ± 0.3	8.2 ± 0.5	0.26
Conditioning regimen before HSCT						
TBI-based *n(% of transplanted patients)*	310 (69.7)	10 (38.5)	**0.001**	274 (71.5)	46 (52.3)	**$<10^{-3}$**
Non-TBI based *n(% of transplanted patients)*	135 (30.3)	16 (61.5)		109 (28.5)	42 (47.7)	
Central nervous system (CNS) irradiation						
Yes *n (%)*	179 (30.4)	54 (70.1)	**$<10^{-3}$**	148 (29.5)	85 (52.1)	**$<10^{-3}$**
No *n (%)*	409 (69.6)	23 (29.9)		354 (70.5)	78 (47.9)	
Age at CNS irradiation (years)	8.5 ± 0.3	8.6 ± 0.7	0.84	8.6 ± 0.4	8.4 ± 0.5	0.70
CNS irradiation type						
Cranial irradiation *n(% of CNS irradiation recipients)*	122 (68.2)	41 (75.9)	0.25	106 (71.6)	57 (67)	0.48
Cerebro spinal irradiation *n(% of CNS irradiation recipients)*	53 (29.6)	12 (22.2)		39 (26.4)	26 (30.6)	
Unknown *n(% of CNS irradiation recipients)*	4 (2.2)	1 (1.9)		3 (2)	2 (2.4)	
CNS irradiation dose						
18 grays *n(% of CNS irradiation recipients)*	134 (74.9)	39 (72.2)	0.10	114 (77)	59 (69.4)	0.32
24 grays *n(% of CNS irradiation recipients)*	36 (20.1)	7 (13)		23 (15.5)	20 (23.5)	

Other *n(% of CNS irradiation recipients)*	8 (4.5)	6 (11.1)		9 (6.1)	5 (5.9)	
Time from diagnosis to last visit (years) *Median (min-max)*	12.6 [6.4-18.8]	13.9 [6.0-21.3]	0.49	12.5 [6.4-19.1]	13.9 [6.3-19.1]	0.45

Supplemental Table 1. Patients' characteristics. Comparison between participant and non participant patients. CNS: central nervous system; HSCT: hematopoietic stem cell transplantation; TBI: total body irradiation

Supplemental figure: flow chart. CNS: central nervous system, HSCT: hematopoietic stem cell transplantation

	Number (%)	p-value	10 years Cumulative incidence (%)	[95%CI]	20 years Cumulative incidence (%)	[95%CI]
Gender						
Male	49 (14.5)		15.0	[11.3-19.9]	18.4	[13.9-24.1]
Female	50 (20.4)	0.16	18.5	[13.7-24.9]	28.8	[22.0-37.3]
Leukemia type						
Acute myeloid leukemia	15 (10.3)		11.4	[6.9-18.7]	14.5	[8.2-24.9]
Acute lymphoid leukemia	84 (19.2)	0.09	18.0	[14.3-22.5]	25.3	[20.5-31.0]
Age at transplantation/irradiation						
< 10 years	71 (19.8)		18.6	[14.6-23.6]	26.2	[20.9-32.4]
≥ 10 years	28 (12.5)	0.13	13.2	[8.7-19.8]	16.9	[11.4-24.8]
Hematopoietic stem cell transplantation type						
Autologous	22 (25.3)		20.6	[13.3-31.1]	25.3	[17.0-36.6]
Allogeneic	71 (20.2)	0.46	22.8	[17.9-28.7]	32.5	[25.4-41.1]
Treatment modality						
HSCT without TBI. without previous CNS irradiation	9 (7.5)		7.0	[3.5-13.5]	12.1	[4.9-28.4]
CNS irradiation. no HSCT	6 (4.2)		1.0	[0.1-6.8]	5.0	[1.9-13.2]
HSCT with TBI. with previous CNS irradiation	6 (33.3)	$<10^{-3}$	23.0	[9.3-50.3]	30.0	[13.6-58.1]
HSCT with TBI. without previous CNS irradiation	72 (25.1)		28.4	[22.7-35.1]	34.7	[28.2-42.3]
HSCT without TBI. with previous CNS irradiation	6 (42.9)		14.9	[3.9-47.7]	39.8	[18.7-71.2]
CNS irradiation type						
Cranial irradiation	10 (8.4)		3.7	[1.4-9.5]	8.1	[3.8-16.6]
Cerebro spinal irradiation	7 (13.5)	0.37	4.8	[1.2-17.7]	17.6	[8.1-35.8]
CNS irradiation dose						
18 grays	7 (5.4)		2.8	[0.9-8.6]	7.0	[3.1-15.2]
24 grays	8 (22.2)		6.8	[1.7-25.0]	23.9	[11.4-46.0]
Other	3 (37.5)	0.01	25.0	[6.9-68.5]	25.0	[6.9-68.5]

Supplemental Table 2. Univariate analysis: risk factors for **primary** hypothyroidism (n=582). CNS: central nervous system; HSCT: hematopoietic stem cell transplantation; TBI: total body irradiation

Variables	N	%	aHR	95%CI	p-value
Age at transplantation/irradiation					
< 10 years	358	61.5	1		
≥ 10 years	224	38.5	**0.58**	**0.37-0.91**	**0.02**
Gender					
Male	337	57.9	1		
Female	245	42.1	1.46	0.97-2.17	0.07
Leukemia type					
Acute lymphoid leukemia	437	75.1	1		
Acute myeloid leukemia	145	24.9	0.60	0.31-1.13	0.12
Treatment modality					
HSCT without TBI, without previous CNS irradiation	120	20.6	1		
CNS irradiation, no HSCT	143	24.6	**0.26**	**0.09-0.80**	**0.02**
HSCT with TBI, with previous CNS irradiation	18	3.1	2.15	0.69-6.64	0.18
HSCT with TBI, without previous CNS irradiation	287	49.3	**2.69**	**1.22-5.91**	**0.01**
HSCT without TBI, with previous CNS irradiation	14	2.4	**3.04**	**1.05-8.78**	**0.04**

Supplemental Table 3. Risk factors for **primary** hypothyroidism: multivariate analysis (n=582). CNS: central nervous system; HSCT: hematopoietic stem cell transplantation; TBI: total body irradiation. In bold: significant values