Late cardiomyopathy in childhood acute myeloid leukemia survivors: a study from the L.E.A. program

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Online Supplementary material

SUPPLEMENTAL METHODS

Study cohort

As detailed elsewhere, all participants in LEA cohort are summoned to the follow-up clinic at predefined dates, starting one year after HSCT or after completion of chemotherapy [1]. These visits repeat every 2 years until the age of 20 and at least 10 years of complete remission (CR), and every 4 years thereafter. An echographic evaluation of cardiac function is planned at each evaluation for all patients who have received anthracycline therapy. All 185 patients with AML had at least one echocardiographic examination as part of their L.E.A. follow-up program and all were included in the present study. Children with Down's syndrome and AML were not included in this study population.

The French multicentre AML trials

The details of these trials have been described elsewere[2-5]. Briefly, children treated in the LAME 89/91 study were scheduled to receive 3 courses of chemotherapy including an induction phase with mitoxantrone and cytarabine and two consolidation courses, one containing timed-sequential high-dose cytarabine, asparaginase and amsacrine[6]. In ELAM02 study, children received the same induction and 3 courses of consolidation chemotherapy, two of them including high-dose cytarabine. The European Organization of Research and Treatment of Cancer (EORTC) has performed two AML trials in France: EORTC 58872 evaluated a BFM-derived treatment regimen in which mitoxantrone was substituted to daunorubicin. The next EORTC 58921 trial compared idarubicin and mitoxantrone in induction course. Acute promyelocytic leukemia (APL) was treated with chemotherapy and All-trans-retinoic acid according to APL93 and APL2000 trials[4,7]. Children in the LAME91 and ELAM02 protocols also received amsacrine 450 mg/m^2 and 300 mg/m^2, respectively. In these two protocols, infants less than 1-year-old received a decreased anthracycline dose (2/3 for 0-6 months and 3/4 for 6-12 months). Cumulative doses of anthracycline used in each trial are described in table S1, as well as the doxorubicin-equivalent cumulative doses using conversion factors of 0.83, 4.0 and 5.0 for daunorubicin, mitoxantrone and idarubicin respectively[8-10]. The distribution of Cumulative anthracycline dose per patient is shown in figure S1.

The use of allogeneic hematopoietic stem cell transplantations (HSCT) for children with AML in first CR has varied during the two decades study period. At the beginning of the

years 1990, all children in complete remission were allocated to the HSCT arm if they had an HLA-identical sibling donor and very few were transplanted with an unrelated donor. This schedule was further modified and patients in CR1 were classified into 3 prognostic groups. Children in the favorable group did not receive any transplant in CR1. On the other hand, those in the high-risk group were transplanted with either a sibling or an unrelated transplant whereas only HLA-identical sibling donors were allowed in the intermediate group.

The relapse treatments were quite heterogeneous, but most of the patients received a fludarabine- and high-dose cytarabine- based re-induction with or without liposomal daunorubicin. All patients in 2nd CR were considered eligible for allogeneic bone marrow transplantation.

Assessment of health status and long-term late effects

As described previously[11], non-cardiac late effects in the L.E.A. program were categorized as follow: height growth failure, overweight, low weight, metabolic syndrome, gonadal dysfunction, thyroid dysfunction, second tumors, iron overload, cataract, alopecia, osteonecrosis, diabetes, CNS complications and "others".

Assessment of health-related quality of Life (HRQoL)

Adult patients were asked to complete a SF-36 questionnaire[12], a reliable instrument in assessing self-perceived health status in adult survivors of childhood cancer[13]. The SF-36 is comprised of 36 items describing 8 dimensions and two summary composite scores: the physical composite score (PCS) and the mental composite score (MCS).

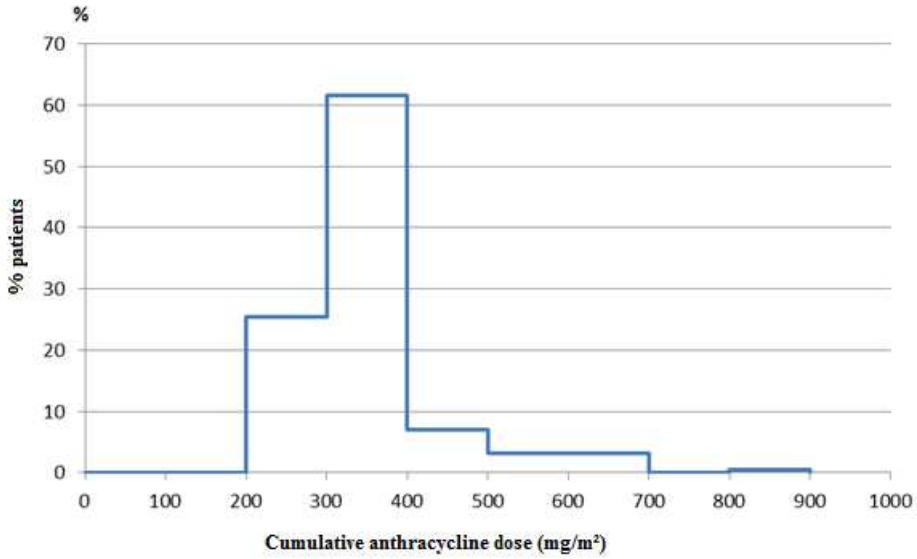
Statistical analysis:

Categorical variables were summarized using counts and percentages and continuous variables with means and standard error of means (SEM) or medians and Inter quartile range (IQR). Roc curves were used in an attempt to define a threshold of cumulative anthracycline dose which might be predictive of cardiotoxicity. Prevalence rates of cardiotoxicity were expressed as percentage of affected patients in a given population. Cumulative incidences of cardiotoxicity over time were estimated using the Kaplan–Meier method and displayed with their 95% confidence interval (95% CI). Differences between groups were tested using the Renyi test when curves were crossing whereas the log rank test was used when they were not. A Cox regression model was employed to evaluate the predictors of cardiotoxicity. Hazard ratios (HRs) were estimated with their 95% CI. As the HRs for each risk factor did not change over time, it was allowed to use the HRs as the relative risk. Comparisons of adults' QoL scores between groups were made with t-test. To help interpret the clinical significance of

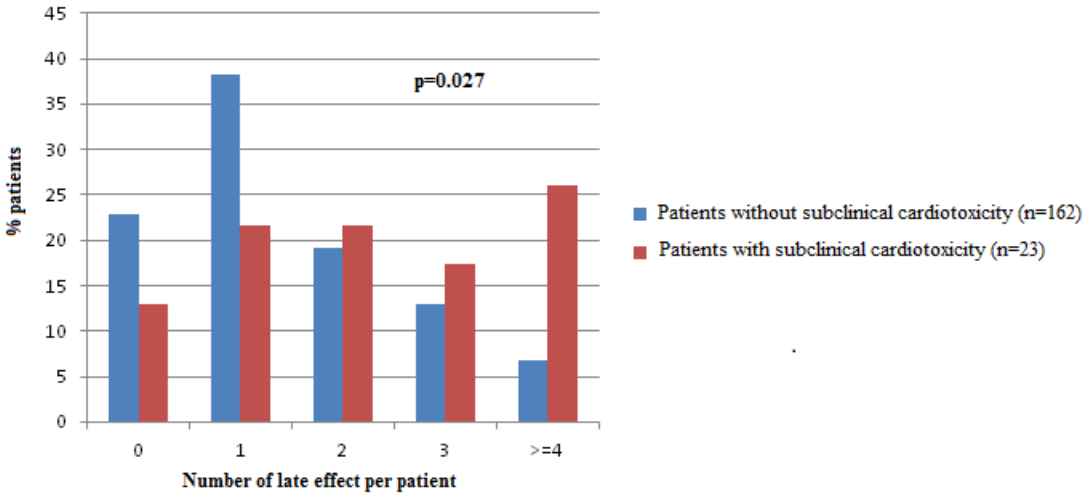
differences in means scores of QoL dimensions, effect sizes were calculated. We considered an effect size of 0.2-0.49 as “small”, 0.5-0.79 as “medium” and 0.8 or higher as “large”[14]. Multiple linear regression models were constructed to identify the potential link between occurrence of cardiotoxicity and the patient’s QoL scores.

SUPPLEMENTAL FIGURES

Supplemental figure S1: distribution of Cumulative anthracycline dose (mg/m²)



Supplemental figure S2: Number of late effects per patients with or without subclinical cardiotoxicity



SUPPLEMENTAL TABLES

Supplemental Table S1: Anthracycline regimen in french AML trials (1989-2011)

	N	Drugs (mg/m²)	Doxorubicin-equivalent cumulative doses mg/m²
LAME91 (1989_1998)	**54**	Mitoxantrone (60*) Daunorubicin (160)	372
ELAM02 (1998-2011)	**98**	Mitoxantrone (60) Daunorubicin (160)	372
EORTC 58872 (1987-1992)	**8**	Mitoxantrone (150)	600
EORTC 58921 (1993-2000)	**16**	Mitoxantrone (60) - Daunorubicin (80) or** Idarubicin (60) - Daunorubicin (80)	306 / 366**
APL93 (1989-2000)	**2**	Daunorubicin (315)	411
APL2000 (2000-2011)	**7**	Daunorubicin (315)	411

Cumulative doses of anthracycline are described as the doxorubicin-equivalent cumulative doses using conversion factors of 0.83, 4 and 5 for daunorubicin, mitoxantrone and idarubicin respectively

**additional induction when blast>20% on bone marrow aspiration on day 20: +24mg/m²*
*** Randomized control trial Mitoxantrone or Idarubicin*

Supplemental Table S2: **Risk factors for the occurrence of subclinical cardiotoxicity**

(univariate analyses)

	n=185	**Subclinical cardiotoxicity n (%)**	**Risk at 10 years** *(95% CI)*	**Risk at 15 years** *(95% CI)*	**p-value**
Gender					
Females	*94*	13 (13.8)	0.22 (0.36 - 0.13)	0.22 (0.13 - 0.36)	
males	*91*	10 (11.0)	0.13 (0.06 - 0.26)	0.38 (0.17 - 0.71)	0.503
Age at diagnosis (distribution by quartile)					
[0 - 2.53 [	*46*	6 (13.0)	0.19 (0.09 - 0.39)	0.19 (0.09 - 0.39)	
[2.53 - 6.53 [	*47*	8 (17.0)	0.17 (0.07 - 0.38)	0.54 (0.25 - 0.87)	0.824
[6.53 - 11.83 [	*46*	5 (10.9)	0.18 (0.07 - 0.41)	0.18 (0.07 - 0.41)	
>=11.83	*46*	4 (8.7)	0.08 (0.03 - 0.23)	0.20 (0.06 - 0.54)	
Cumulative anthracycline dose (mg/m^2 equ doxo)					
<460	*168*	17 (10.1)	0.15 (0.09 - 0.24)	0.17 (0.10 - 0.26)	0.021
>=460	*15*	6 (35.3)	0.37 (0.15 - 0.74)	NA	
History of relapse					
No	*148*	13 (8.8)	0.11 (0.06 - 0.20)	0.13 (0.08 - 0.23)	0.003
yes	*37*	10 (27.0)	0.35 (0.17 - 0.62)	NA	
HSCT in 1st CR					
No	*128*	15 (11.7)	0.15 (0.09 - 0.26)	0.23 (0.13 - 0.38)	0.95
yes	*57*	8 (14.0)	0.17 (0.08 - 0.35)	0.35 (0.15 - 0.67)	
TBI					
No	*154*	15 (9.7)	0.13 (0.07 - 0.22)	0.19 (0.11 - 0.34)	0.129
yes	*30*	8 (25.8)	0.35 (0.17 - 0.61)	0.51 (0.24 - 0.84)	
Trials					
LAM 89/91	*54*	15 (27.8)	0.24 (0.15 - 0.39)	0.37 (0.23 - 0.57)	
ELAM 02	*98*	5 (5.1)	0.15 (0.05 - 0.43)	0.15 (0.05 - 0.43)	0.127
EORTC 58872 - 58921	*24*	3 (12.5)	0.09 (0.02 - 0.31)	0.15 (0.05 - 0.41)	
APL 1993 + 2000	*9*	0 (0.0)	NA	NA	

CI : confidence interval

Supplemental Table S3: Effect of **Subclinical cardiotoxicity** (SCC) on QoL of adults: multivariate linear regression analyses

	Univariate analysis			**Multiple linear regression models**		
	without SCC n=58	with SCC n=15	P-value	β-coefficient	P-value	Effect size
	mean ± s.d	mean ± s.d.				
Physical functioning	92.16 ± 15.45	95.67 ± 7.76	0.398	0.13	0.369	0.247
Social functioning	79.09 ± 20.06	80.83 ± 21.06	0.768	-0.02	0.904	0.086
Role: physical	81.90 ± 32.03	86.67 ± 22.89	0.59	0.13	0.356	0.157
Role: emotional	64.37 ± 30.50	56.67 ± 29.41	0.383	-0.18	0.196	0.255
Mental health	68.28 ± 16.47	63.73 ± 17.24	0.349	-0.19	0.171	0.273
Vitality	63.10 ± 17.89	62.50 ± 19.84	0.91	-0.05	0.695	0.033
Bodily pain	79.83 ± 23.04	83.53 ± 18.38	0.566	0.08	0.594	0.168
General health	77.38 ± 20.26	67.20 ± 22.42	0.094	-0.19	0.17	0.485
Physical composite score	54.68 ± 7.81	56.00 ± 4.50	0.532	0.17	0.255	0.183
Mental composite score	44.68 ± 9.75	41.99 ± 8.67	0.333	-0.22	0.109	0.283

Co-variables: gender, age at diagnosis, SCC, HSCT in 1st CR, relapse, TBI. Bold values*: p* <0.05 was significant
Abbreviations: QoL, quality of life; s.d., standard deviation; β, standardised β-coefficients

Supplemental Table S4: **Overview of publications on prevalence of late cardiotoxicity in pediatric AML survivors**

	St Jude group (15)	**BFM group (16)**	**Teaming et al (17)**	**Our study**
Study design	retrospective	Prospective, multicenter	Retrospective single center	Prospective multicenter
Numbers	77	547	86	185
SCC Endpoint	SF≤25%	SF<30%	SF<28%	SF<28% and/or FE<55
Prevalence of late **cardiotoxicity**	8%	2.9% (16/547)	17.4%	12.4%
Median time follow-up (year)	16.7	5.3	7.28	9.5
Cumulative incidence all in first line treatment alone In 1st line + salvage therapy after relapse	Not related	5% ±1% at 11y	Not related	16% & 27% at 10 & 15y 11% at 10y 35% at 10y
Median cumulative anthracycline dose * (mg/m²)	335	**269-400**	**449-488**	372
Allogeneic SCT	15/77	unknown	19	86/185
Risk factors		1. early cardiotoxicity 2. secondary AML	1. early cardiotoxicity 2. history of relapse	1. cumulative anthracycline dose>460mg/m² 2. history of relapse

*described as doxorubicin-equivalent cumulative doses using conversion factors of 0.83, 4 and 5 for daunorubicin, mitoxantrone and idarubicin respectively

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