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

Prognosis of pediatric acute myeloid leukemia (AML) has improved significantly over the past two decades with survival rates now approaching 70%.[1] Therapy consists of a limited number of intensive chemotherapy courses mainly based on cytarabine and anthracycline.[2,3] Many pediatric late anthracycline cardiotoxicity studies have concerned heterogeneous diagnostic groups. Moreover, single childhood cancer studies were mainly conducted in acute lymphoblastic leukemia, whereas the highest doses of anthracycline are given in children with AML.[4-6] We report here a prospective multi-centric study of late cardiotoxicity in 185 patients surviving childhood AML. All were treated after 1989 in French clinical trials using intensive chemotherapy alone or chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT).

L.E.A. (Leucémie Enfant & Adolescent) is a French prospective long-term follow-up program involving all childhood acute leukemia survivors treated in the participating centers since 1980. Details of the programm are provided elsewhere.[7] As of 31 December 2011, 282 childhood AML survivors fulfilled the L.E.A. inclusion criteria and 218 (77.3%) of them agreed to participate. Among these 218, 185 were treated according to one of the 6 multicenter trial protocols ongoing in France after January 1989. All 185 had serial echocardiographic examination as part of their L.E.A. program, and all were included in the present study. All provided written informed consent. Cardiotoxicity was defined by either clinical symptoms of congestive heart failure or by an abnormal echocardiographic left ventricular function. Left ventricular function was considered abnormal when the shortening fraction (SF) was less than 28% or when the left ventricular ejection fraction (LVEF) was less than 55% on 2D echocardiography.[8-10] Cardiotoxicity was classified as late when it started or persisted beyond one year after the completion of first-line treatment.[9] Cumulative anthracycline doses used in each trial are described in the *Online Supplementary Table S1*, as well as the doxorubicin-equivalent doses using conversion factors of 0.83, 4.0 and 5.0 for daunorubicin, mitoxantrone and idarubicin, respectively.[10,11] Assessment of health status, long-term late effects on health-related quality of life (QoL), and statistical analysis are described in the *Online Supplementary Appendix*.

Characteristics of the study cohort are summarized in Table 1. Median age at the time of AML diagnosis and median follow-up duration to last cardiac evaluation were 6.53 and 9.5 years, respectively. Thirty-seven patients had a history of relapse. Median cumulative anthracycline dose was 372 mg/m² (*Online Supplementary Figure S1*). Ninety-nine patients were treated by chemotherapy alone, whereas the other 86 patients also received HSCT (57 in first remission, 25 in second remission, and 4 in more advanced disease). Thirty children received total body irradiation (TBI), but only 10 among the 57 transplanted in first remission did so.

Median number of echographic evaluations was 3 per patient. Subclinical cardiotoxicity (SCC) was observed in 23 of 185 patients (12.4%) at least once during their follow-up program. Median time from AML diagnosis to SCC detection was 4.40 years. In these 23 patients, the median value of the worst SF was 27% and the median value of the worst LVEF was 52. Only 3 of 23 patients had a worse SF value of less than 25% (2 had 20%; 1 had 24%). Six of 23 received anti-congestive therapy and none had cardiac transplantation. Five of those receiving anti-congestive therapy were still being treated at time of last evaluation, and 4 had more than 28% SF and more than 55% LVEF. Seventeen patients never received treatment: 11 had spontaneous improvement with more than 28% SF and more than 55% LVEF at last evaluation. Finally, at last cardiac evaluation, only 8 patients had an abnormal left ventricular function. Cumulative incidence (CI) of cardiotoxicity, estimated by the Kaplan-Meier method was 16% and 27% at 10 and 15 years, respectively (Figure 1A). CI of anti-congestive treatment at the same follow-up times was 5% and 7%.

The risk of developing cardiotoxicity depended on a previous history of relapse and on the cumulative anthracycline dose. At ten years from diagnosis, CI was 35% *versus* 11% in patients with or without history of relapse (P=0.02) (Figure 1B). Among 148 patients without any history of relapse, 10-year CI of cardiotoxicity was 14% in 97 patients treated with chemotherapy alone *versus* 8% in 51 patients who underwent HSCT in first remission (NS, Figure 1C). In transplanted children, the risk was not modified by either a grade 2-4 acute or an extensive chronic graft-*versus*-host disease. The CI of anti-congestive treatment in these 148 patients who never experienced relapse was 3% at ten and

Table 1. Patients characteristics.

	N=185
Age at diagnosis (median, IQR)	6.53 (2.53 - 11.87)
0 - 2.53	46 (24.9%)
2.53 - 0.6.53	47 (25.4%)
6.53 - 11.87	46 (24.9%)
≥11.87	46 (24.9%)
Sex	
Male	91 (50.8%)
Female	94 (49.2%)
First-line therapy	
LAM 89/91	54 (29.2%)
ELAM02	98 (52.9%)
EORTC 58872 - 58921	24 (13.0%)
APL 2000 + 1993	9 (4.9%)
Cumulative anthracycline dose (mg/m²)	
≤460 mg/m²	170 (91.9%)
>460 mg/m²	15 (8.1%)
History of relapse	
Yes	37 (20%)
no	148 (80%)
Allogeneic HSCT	
All patients	86 (46.5%)
HSCT in CR1	57 (30.8%)
Conditioning with total body irradiation	30 (34.9%)
Children who received more than one HSCT [n (%)]	7 (3.7%)
Type of graft	
HLA-identical sibling donor	46 (54.1%)
HLA-haploidentical related donor	5 (5.9%)
Unrelated donor	20 (22.4%)
Unrelated cord blood	15 (17.6%)
Median follow-up duration from diagnosis to last echocardiogram (years, IQR)	9.50 (5.12 - 14.42)
Median number of echocardiogramm (IQR)	3 (2 - 5)

IRQ: interquartile; HSCT: allogeneic hematopoietic stem cell transplantation.

15 years. The value of 460 mg/m² was identified as a threshold of cumulative dose of anthracycline with receiver operating characteristics (ROC) curve, with a sensitivity of 26.09%, a specificity of 94.44%, and an accuracy of 85.95%. The 10-year SCC estimated risk was 37% in patients treated with more than 460 mg/m² and 15% in patients with less (*P*=0.02). History of relapse and a higher cumulative anthracycline dose were the only risk factors that proved significant in the univariate analysis (*Online Supplementary Table S2*). Both factors remained significant in the multivariate Cox regression analysis after including the following potential confounding variables: sex, age at AML diagnosis, HSCT in first complete remission and TBI (Tables 2 and 3). When distributing patients according to the cumulative number of long-term late effects, patients with SCC were significantly more severely impaired: 43.5% of them developed more than 2 other sequelae *versus* 13.8% of patients without SCC (*Online Supplementary Figure S2*). The mean number of late effects, excluding cardiac dysfunction, was 2.22+-0.29 in the first group *versus* 1.43+-0.09 in the second group (*P*=0.004). Among 73 patients who had reached adulthood at time of evaluation, 15 had subclinical cardiotoxicity and 58 did not. We did not detect any difference in the self-reported QoL between the

Table 2. Risk factors for the occurrence of subclinical cardiotoxicity. Multivariate Cox model including history of relapse.

	Hazard ratio HR (IC 95%)	*P*
Sex		
Females	Reference values	
Males	0.60 (0.24 - 1.5)	0.282
Age at diagnosis (distribution by quartile)		
0 - 2.53	ref	
2.53 - 6.53	1.24 (0.40 - 3.75)	0.709
6.53 - 11.83	1.01 (0.29 - 3.44)	0.991
≥11.83	1.01 (0.27 - 3.79)	0.983
Relapse		
No	Reference values	
Yes	4.26 (1.42 - 12.79)	0.010
HSCT in 1st CR		
No		
Yes	1.54 (0.55 - 4.31)	0.412
TBI		
No	Reference values	
Yes	0.90 (0.28 - 2.84)	0.856

Table 3. Risk factors for the occurrence of subclinical cardiotoxicity. Cox model including cumulative anthracycline dose.

	Hazard Ratio HR (IC 95%)	*P*
Sex		
Females	Reference values	
Males	0.72 (0.28 - 1.80)	0.475
Age at diagnosis (distribution by quartile)		
0 - 2.53	Reference values	
2.53 - 6.53	1.22 (0.40 - 3.72)	0.733
6.53 - 11.83	0.79 (0.23 - 2.69)	0.704
≥11.83	0.88 (0.24 - 3.22)	0.843
Cumulative anthracycline dose (mg/m² equ doxo)		
<460	Reference values	
≥460	3.42 (1.10 - 10.72)	0.035
HSCT in 1st CR		
No		
Yes	1.03 (0.38 - 2.80)	0.950
TBI		
No	Reference values	
Yes	1.39 (0.45 - 4.26)	0.57

TBI: total body irradiation; HSCT: allogeneic hematopoietic stem cell transplantation; CR: complete response.

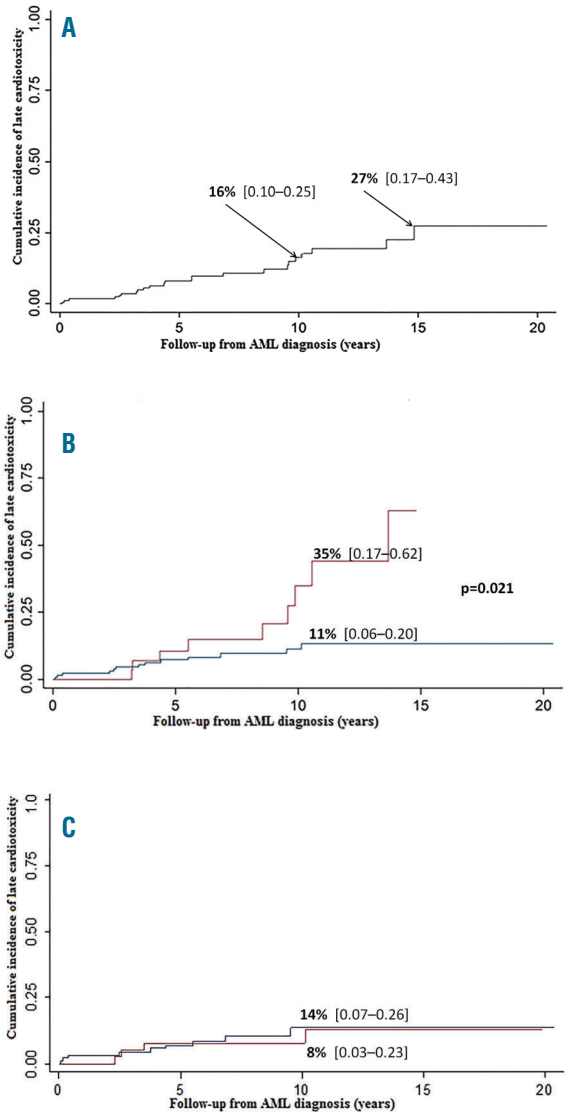

Figure 1. Cumulative incidence subclinical cardiotoxicity over time based on Kaplan-Meier estimates (A), for all patients (n=185); (B) for patients with (red line) or without (blue line) history of relapse (C) among 148 patients without history of relapse, cumulative incidence of SCC in 97 patients treated with chemotherapy alone (blue line) *versus* 51 patients with chemotherapy and HSCT (red line).

two groups (*Online Supplementary Table S3*).

Online Supplementary Table S4 provides details on the main late cardiotoxicity studies previously conducted in childhood AML survivors. In our study, overall prevalence of late cardiotoxicity was 12.4% resulting in a 16% 10-year CI. Furthermore, the risk was strongly dependent on the total amount of therapy: 10-year CI was 11% in patients who received first-line therapy alone compared to 35% in those who also required salvage therapy for relapsed disease. The same feature has already been published by Temming *et al.* who reported a 12% prevalence of late cardiotoxicity after first-line treatment only *versus* 37% after first-line treatment plus salvage therapy for relapse.[12] The German group also underlined a high risk of late cardiotoxicity in patients who had been treated twice with anthracycline because of secondary AML, which is consistent with our results.[13] In transplanted children, when our study was restricted to patients who never experienced leukemia relapse, we did not detect any difference in late cardiotoxicity between those who received HSCT during their first CR and those treated with chemotherapy only. Similar results have been published by Leung *et al*.[14] Most of the children transplanted for AML in France since 1989 received busulfan and cyclophosphamide as conditioning regimen.[15] Although a young age at diagnosis had been identified as a risk factor for cardiotoxicity in previous publications,[9] this was not observed in our study, perhaps partly because in French AML trials the anthracycline dose was deceased in infants under one year of age. We also acknowledge that the statistical power of a risk factor analysis is limited by the relatively low number and mild severity of cardiotoxic events.

Because L.E.A. is a prospective cohort with serial health status evaluations, we were able to provide follow-up data after diagnosis of cardiomyopathy. Interestingly, only 6 among 23 patients with late cardiotoxicity required anti-congestive therapy. Fifteen among these 23 (including 4 of 6 who received therapy) had improvement and, at last L.E.A. evaluation, no longer met our echographic criteria for cardiomyopathy. This feature of transient cardiomyopathy occurrence has already been reported in the German as well as in the UK experience of childhood AML survivors' late cardiotoxicity.[12,13] Although potentially reassuring, this concept of possible improvement must be interpreted with caution because long-term persistence of such an improvement cannot be predicted and will require longer follow up. In addition, we cannot exclude the possibility that some apparent improvements were, in fact, due to underestimation of cardiac function in a previous echocardiogram.

Impairment in several domains of QoL has been described in childhood cancer survivors, but to the best of our knowledge, our study is the first to focus on the impact of late cardiac dysfunction. It is worthy of note that we did not detect any difference in QoL domains when comparing patients with or without late cardiac toxicity. This could appear surprising, but we have to consider that the QoL questionnaire assesses patients' self-perceived health status. None of the patients with echocardiographic abnormality suffered from clinical heart failure and only a few required anti-congestive therapy. Moreover, more than half of patients detected with SCC had further improvement and normal cardiac function at last evaluation, which is when they filled in the QoL questionnaire.

Finally, the relatively low burden of cardiac complications described here should be interpreted in the context of a late complication whose prevalence and severity increase according to the length of post-therapy interval.[9] Thus, although the median follow-up time between diagnosis and last evaluation was 9.5 years in this L.E.A study, an even longer follow-up duration is required.

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