Evaluation of endothelial function in childhood standard risk acute lymphoblastic leukemia survivors: Role of subclinical markers and identification of preventable factors.

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Introduction

Results of the Childhood Cancer Survivor Study (SSCC) show that within 30 years after antineoplastic treatment, the risk of cardio-vascular disease (CVD)-related death in childhood malignancy survivors is 8 times higher than in the general population (1). Up to now, there are only few data published on the effects of chemotherapy on peripheral vasculature. Onset and progression of the decline of vascular function in young acute lymphoblastic leukemia (ALL) survivors are not completely understood (2,3).

Aim

To assess subclinical markers of inflammation and endothelial dysfunction in young survivors from ALL treated with chemotherapy without cranial irradiation (AIEOP 2000 and 2009 standard risk protocols).

Methods

We determined	
What?	▪ Auxological data (height SDS, BMI SDS, waist circumference (WC), hip circumference (HC), WC/H and WC/HC ratio) ▪ BP assessment [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] ▪ Glucose and lipid profile, serum CV markers [**Interleukin 6 (IL-6), Vascular Cell Adhesion Molecule (VCAM), Intercellular Adhesion Molecule (ICAM), Tumor Necrosis Factor-alfa (TNF-α), Endogenous secretory Receptor for Advanced Glycation End products (Es-RAGE)**] ▪ **Ultrasound parameters of endothelial function (carotid intima–media thickness, c-IMT)**
Who?	In **28 ALL survivors** (71% male, 18% prepubertal, **aged 15.98±4.41 years**) at least two years after the end of chemotherapy (**mean follow-up 8.57±3.14 years**) and in **22 sex- and age-matched controls** (64% male, aged 16.59±5.60 years). Exclusion criteria were: (a) endocrine and/or metabolic disorders before ALL diagnosis; (b) cardiovascular disorders before ALL diagnosis; (c) genetic syndromes; (d) smoking habits; (e) family history of precocious CVD.

Results

(A) Clinical and biochemical characteristics of ALL survivors.

Parameters	Mean value ± SDS (range)
BMI SDS at diagnosis ALL	-0.34 ± 1.42 (-3.35 - +2.80)
BMI SDS off-therapy	0.55 ± 1.30 (-1.25 - +3.13)
WC/H ratio off-therapy	0.48 ± 0.08 (0.39 – 0.71)
WC/HC ratio off-therapy	0.91 ± 0.07 (0.73 – 1.06)
Fasting Glucose/Insulin ratio	13.03 ± 6.71 (2.23 – 28.51)
HOMA index	1.96 ± 1.54 (0.5 – 8.47)
Insulin-resistance (n,%)	**4 (14%)**
Total Cholesterol (mg/dl)	155.41 ±24.84 (99-193)
Low-density Lipoprotein Cholesterol (LDL-C)(mg/dl)	90.28 ± 21.76 (47-134)
Triglycerides (TG) (mg/dl)	70.77 ± 39.74 (32 – 189)
Dyslipidemia (n,%)	**7 (25%)**
Hypertension (n/%)	**5 (17.8%)**
Metabolic syndrome (Weiss' definition) (n,%)	**1 (3.5%)**

(B) Serum endothelial biomarkers in ALL survivors and controls (mean value ± SDS).

Parameters	ALL Survivors	Controls	p- value
IL-6 (pg/ml)	1.39 ± 0.74	1.70 ± 1.24	0.67
VCAM (pg/ml)	1488.92 ± 534.53	1614.31 ± 725.11	0.65
ICAM (pg/ml)	109.96 ± 55.3	104.30 ± 55.63	0.46
TNF-α (pg/ml)	8.15 ± 7.39	7.78 ± 5.15	0.75
Es-RAGE (ng/ml)	**0.18 ± 0.07**	**0.27 ± 0.08**	**< 0.001**

(C) In ALL survivors, mean c-IMT was documented within the normal range for age (0.55 ± 0.14 mm, range 0.4 – 0.85 mm).

(D) In ALL survivors, multiple regression analysis (model: R^2 0.94, $p < 0.001$) identified Total Cholesterol (SE 0.15, p 0.003) and WC/HC ratio (SE 0.25, p 0.001) as independent significant predictors for c-IMT value.

(E) Correlation analysis (R^2) between cardiovascular risk markers and clinical and biochemical parameters in ALL survivors (*p<0.05).

Parameters	Es-Rage	IL-6	TNF-α	c-IMT
BMI-SDS off-therapy	**-0.42***	+0.32	+0.02	+0.40
WC/H	**-0.41***	**+0.41***	+0.12	+0.36
WC/HC	**-0.38***	**+0.51***	+0.20	-0.03
LDL-C (mg/dl)	**-0.43***	+0.08	-0.21	**+0.56***
TG (mg/dl)	-0.33	**+0.40***	+0.04	+0.39
SBP (mmHg)	-0.16	-0.02	+0.04	**+0.56***
DBP (mmHg)	+0.13	+0.11	**+0.50***	**+0.66***

Conclusions

- **To our knowledge, this is the first study on Es-RAGE levels in an homogeneous cohort of young ALL survivors.**
- **The detection of low levels of Es-RAGE in ALL survivors could be due to their consumption in a chronic endothelial inflammatory condition that seems to be only partially reversible after chemotherapy.**
- **In ALL survivors, as in general population, all the investigated CV markers correlate with modifiable clinical and biochemical parameters. Therefore, a healthy lifestyle should be encouraged soon after chemotherapy.**

References: (1) Armstrong GT, et al. J Clin Oncol 2009; 27(14):2328-38. **(2)** Giordano P, et al. Int J Cardiol 2017;228:621-627.
(3) Dengel DR, et al.Pediatr Blood Cancer 2014; 61: 532-537.