Leukemia Research 86 (2019) 106228

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

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Impact of *DARC*, *GSDMA* and *CXCL2* polymorphisms on induction toxicity in children with acute lymphoblastic leukemia: A complementary study

Nowadays, children with acute lymphoblastic leukemia (ALL) have a 5-year survival rate approaching 90% [1] but can still experience severe toxicities while on treatment, especially during remission induction. Among these toxicities, infection is a major cause of treatment related mortality [2,3]. Furthermore, infections may cause treatment delay, compromising disease control and survival. One of the main risk factors for infection is profound and prolonged neutropenia [2]. While it occurs in all children during the induction treatment, the duration of severe neutropenia varies greatly between patients [4]. Indeed, the onset of neutropenia depends, among other factors, on patient's ability to metabolize drugs, as well as on host genetic predisposition to develop leucopenia and neutropenia. Several genes have been associated with lower white blood cell (WBC) counts, such as Duffy antigen receptor for chemokine (*DARC)*, Chemokine ligand 2 (*CXLX2)* and Gasdermin A (*GSDMA)* genes [5–9]. We previously reported that particular polymorphisms in these genes correlated with the onset of chemotherapy complications during consolidation and maintenance treatment in childhood patients with ALL [10]. Here we aimed to explore if a similar association between significantly associated polymorphisms in *DARC*, *CXCL2* and *GSDMA* might determine the complications occurring during remission induction including duration of low absolute phagocyte count (APC), proven infections and delay between induction and consolidation phase.

The study population was composed of 236 children consecutively diagnosed with ALL at the Sainte-Justine University Health Center, (SJUHC) at Montreal, between July 1995 and July 2005. Children were treated with the Dana-Farber Cancer Institute (DFCI) ALL Consortium protocols DFCI95-01 or 00-01, which have comparable induction treatment [11,12]. The study was approved by SJUHC Institutional Review Board.

Only SNPs that were significantly associated in previous study were analyzed [10]. Previously obtained genotypes using DNA extracted from buccal swabs or blood samples at remission, for *DARC* rs3027012 and rs12075, as well as for *CXCL2* rs1680408 and *GSDMA* rs3859192 [10], were used for testing the association with treatment complications during induction phase. Data were collected retrospectively from medical charts and included duration of APC lower than 0.5×10^9/L, febrile episodes due to documented infections, and delay of post-induction treatment due to infection or hypocellular bone marrow. The APC corresponded to the sum of neutrophil and absolute monocyte counts. Febrile episodes were defined as fever > 38 °C for ≥1 day. Delay between induction and consolidation was defined by more than 2 days of delay compared to the date planned by the treatment protocol.

Post-induction delay and febrile episodes due to infection (more than one episode) were analyzed in relation to genotypes as binary variables by chi-square or Fisher test, as applicable. Duration of APC < 0.5×10^9/L was analyzed as continuous variables using *t*-test or ANOVA. To estimate the risk associated with the genotypes, duration of APC was also dichotomized below and above median. The analyses were performed according to the appropriate genetic model (dominant or recessive) expressed relative to the minor allele of each polymorphism. A flow chart of analyses is presented in Supplemental Fig. 1. False discovery rate [13] (FDR) was calculated to account for multiple testing, taking into account all SNPs and all analyzed outcomes. For associated genotypes, logistic regression analyses were also performed and included in all cases beside genotypes, assignment of the patients to the prognostic risk group, neutrophil count at diagnosis, leukemia cell phenotype, central nervous system (CNS) status, as well as age and sex. Positively associated genotypes were additionally analyzed through exploratory analysis with end-induction minimal residual disease [14] (MRD) that was available for 85 patients. MRD was dichotomize as detectable (> 0.01% of leukemic cells), vs undetectable levels; detectable levels were also analyzed as continuous variable when normalized through logarithmic transformation. Statistical analyses were performed using SPSS version 20.0 (Chicago, IL, USA).

All SNPs were analyzed for an association with post-induction delay, febrile episodes due to infection, and APC reduction below 0.5×10^9/L, using the same genetic model as in previous study [10]. Two SNPs in the *DARC* gene were assessed, rs12075 according to the recessive model, and rs3027012 according to the dominant model. The homozygosity for the minor allele G of *DARC* rs12075 was associated with a lower risk of post-induction delay (p = 0.02, OR = 0.1, 95% CI 0.02–1.0, Table 1), less frequent febrile episodes (p = 0.04, OR = 0.3 95% CI = 0.09–1.0, Table 1) and on average, lower number of days with APC below 0.5×10^9/L (p = 0.008, Fig. 1A). The latter association was reflected in the protective effect of GG genotype when the duration of APC reduction was recoded as above and below the median (p = 0.009, OR = 0.3 95% CI = 0.1-0.8, Table 1). In contrast, the minor T allele of *DARC* rs3027012, was associated with longer duration of APC reduction (p = 0.01, Fig. 1B), reflected by the higher risk

Abbreviations: ALL, acute lymphoblastic leukemia; APC, absolute phagocyte count; SNPs, single nucleotide polymorphisms; DARC, Duffy antigen receptor for chemokine; CXCL2, Chemoline ligand 2; GSDMA, Gasdermin A; SJUHC, Sainte-Justine University Health Center; DFCI, Dana-Farber Cancer Institute; HRQOL, Health-related quality of life

https://doi.org/10.1016/j.leukres.2019.106228
Received 12 July 2019
Available online 29 September 2019

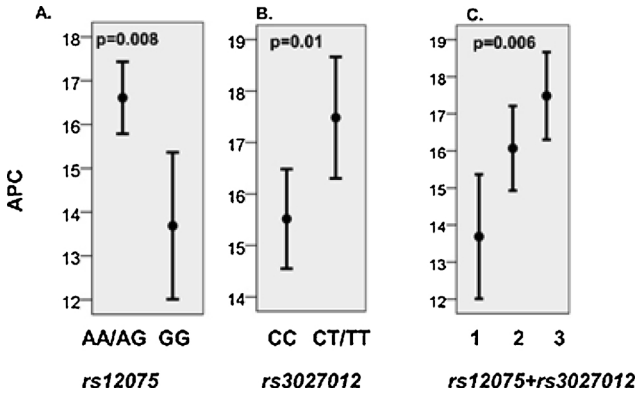

Fig. 1. *DARC* genotypes in relation to the duration of neutropenia.
Average number of days with absolute phagocyte count (APC) lower than $< 0.5 \times 10^9$/L with 95% CI are given for individuals with indicated genotypes, for rs12075 in A, rs3027012 in B and combination of two SNPs in C. In C, 1 is presence of protective GG genotype for rs12075, 3 is presence of risk allele T (TT and CT genotypes) for rs3027012, and 2 is absence of either protective or risk genotype at two *DARC* loci. P value for the difference between groups is indicated on the plots.

Table 1
Association of genetic polymorphisms in *DARC* and *CXCL2* with neutropenic and infectious complications during induction phase of childhood ALL treatment.

Phenotype	GENE	SNP	SUBST.	GEN.	Complications N(%)		OR (95% CI)	p
					+	–		
Induction delay	*DARC*	rs12075	A > G	AA/AG	37 (97.4)	137 (82.5)	1	0.02
				GG	1(2.6)	29 (17.5)	0.1 (0.02-1.0)	
Febrile episodes				AA/AG	52 (94.5)	149 (83.7)	1	0.04
				GG	3 (5.5)	29 (16.3)	0.3 (0.09-1.0)	
APC < 0.5 x10^9/L				AA/AG	100 (92.6)	101 (80.8)	1	0.009
				GG	8 (7.4)	24 (19.2)	0.3 (0.1-0.8)	
APC < 0.5 x10^9/L		rs3027012	C > T	CC	60 (55.0)	89 (70.1)	1	0.02
				CT/TT	49 (45.0)	38 (29.9)	1.9 (1.1-3.3)	
Induction delay/inf.	*CXCL2*	rs16850408	C > A	CC/CA	8 (61.5)	143 (86.1)	1	0.02
				AA	5 (38.5)	23 (13.9)	3.9 (1.2-12.9)	

OR is estimated for each SNP using appropriate genetic model expressed relative to the minor allele; All SNPs are presented as a substitution from major to minor allele. Frequencies of genotypes are calculated for each group, defined as presence (+) or absence (-) of indicated complication, each summing up to 100%. APC $< 0.5 \times 10^9$cells/L, number of days with absolute phagocyte count $< 0.5 \times 10^9$cells/L, categorized according to median; values above median are recoded as presence of complication. For febrile episodes, presence of complication corresponds to the presence of more than one episode. Induction delay/inf., induction delay due to infection; OR, odds ratio; CI, confidence interval; Subst., Substitution; Gen., genotype.

associated with CT and TT genotypes (p = 0.02 OR = 1.9 95% CI = 1.1–3.3, Table 1). Similar association with the number of days with APC below 0.5×10^9/L was noted when two DARC polymorphisms were analyzed together (p = 0.006, Fig. 1C).

We also observed an association with the *CXCL2* rs1680408 variant according to the recessive model; AA genotype was associated with a higher risk of post-induction delay due to infection (p = 0.02, OR = 3.9, 95% CI 1.2–12.9, Table 1).

All results were significant with FDR < 10% and all remained significant in multivariate models (*DARC* polymorphisms, p = 0.03, OR = 1.6 95% CI = 1.1–2.6 and *CXCL2*, p = 0.05, OR = 3.5 95% CI = 1.0–12.5, Supplementary Table S1).

No association of *GSDMA* rs3859192 with the studied phenotypes was found using previously reported dominant genetic model (shown in Supplementary Table S2 with all remaining non-significant associations).

Infection is one of the major complications of chemotherapy in children with ALL, especially during the induction phase. Its incidence depends mainly on pathogen virulence, but also on the susceptibility of the host [4]. Patients with profound and prolonged episodes of neutropenia have a greater potential for infection. Intensive treatment is equally associated with poor health-related quality of life [15]. A better risk stratification could contribute to less infections and a better treatment outcome.

We have shown that the duration of neutropenia and occurrence of infections during induction phase varied according to polymorphisms in genes determining leukocyte/neutrophil counts. The minor T allele of *DARC* rs3027012 was associated with longer duration of APC reduction, whereas the GG genotype of *DARC* rs12075 had a protective effect. The AA genotype of rs1680408 *CXCL2* conferred a higher risk of post-induction delay due to infection and the *DARC* rs12075 GG genotype was associated with less frequent febrile episodes due to infection.

Although limited to DFCI95-01 and 00-01 protocols, these results are in concordance with our previous study [10]. Indeed, a protective effect was seen in that study for *DARC* rs12075, whereby GG genotype was associated with lower risk of febrile neutropenia-related hospitalization, whereas the minor T allele of *DARC* rs3077012 conferred higher risk of treatment complications depicted by more frequent APC reduction and febrile neutropenia. The rs12075 leads to Gly42Asp replacement differentiating Duffy Fya and Fyb antigens [6]; the rs3027012 is located in the 5′UTR of *DARC* gene and is predicted to affect several transcription factors binding sites [10]. Concordance was also noted for *CXCL2* rs16850408, which correlated in the same

recessive model with higher frequency of infections during maintenance and consolidation. [10] The rs16850408 is predicted to alter the expression of *CXCL2* gene (The Genotype-Tissue Expression (GTEx) Portal) [16]. We also analyzed in exploratory fashion association of these polymorphisms with MRD. *DARC* rs12075 GG genotype was more frequent among patients with no detectable MRD ($p = 0.03$), whereas among patients with detectable levels (> 0.01% of leukemic cells), mean MRD tended to be higher in the carriers of *DARC* rs3077012 T allele (Supplemental Figure 2). This would suggest that SNP-related susceptibility to leukocyte kill from chemotherapy is not extending to the lymphoblast population but would rather reflect less or more frequent treatment complications associated with protective (rs12075) or risk (rs3077012) genotype, respectively; possibly affecting treatment course and its efficacy. It is also possible that patients with higher MRD might take more time to recover APC. The MRD analyses were conducted nevertheless in a limited number of patients and further analyses are needed to confirm these hypotheses. No association was noted between *GSDMA* rs3859192 and the studied outcomes, which might be due to the sample size limitation, or its less predictive role in comparison to other polymorphisms. Functional effect of associated polymorphism needs to be further elucidated, particularly that of *DARC* rs3077012 and *CXCL2* rs16850408, which are currently predicted to affect the expression of respective genes. It is also possible that the same polymorphisms can affect onset of treatment-related neutropenia or infection in other cancer types. No data are yet available in that regard.

In conclusion, this complementary study showed that variations in *DARC* and *CXCL2* genes influence the onset of chemotherapy complications in pediatric ALL, regardless of treatment phases. They could be used as pharmacogenomics markers to prevent infection and delays between chemotherapy phases, by identifying patients who may benefit the most from, or require more prolonged antibiotic prophylaxis. The relationship with antibiotic prophylaxis should be further evaluated, as well as applicability to other populations given that this study was conducted in patients of European descent.

Funding

Coast to Coast against Cancer Foundation, Leukemia Lymphoma Society of Canada, Cancer Research society, Canadian Institutes of Health Research and Charles Bruneau Foundation, supported this study.

Declaration of Competing Interest

The authors declare no conflicts of interest

Acknowledgement

We thank all patients and their parents who consented to participate in genetics studies related to leukemia.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.106228.

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