

CD markers polymorphisms as prognostic biomarkers in hematological malignancies

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Abstract

The clusters of differentiation (CD) are surface molecules used for immunophenotyping of cells. The expression of CD markers is widely used to classify hematological malignancies, including leukemia and lymphoma. Single nucleotide polymorphisms (SNPs) are crucial genetic changes that can be associated with abnormal expression and function of CD markers. In this paper, we assess the prognostic effect of CD markers' SNPs in hematological malignancies. Materials and methods and relevant literature was identified by a PubMed search (2001-2019) of

English language papers using the following terms: 'polymorphism', 'CD marker', 'leukemia', 'lymphoma', 'prognosis', 'CD marker', and 'polymorphism'. Many studies have demonstrated the effects of CD markers' polymorphisms on risk of hematological malignancies. Also, SNPs of CD markers can be related with clinicopathological features, invasiveness, and response to therapy of these disorders. Considering the importance of SNPs in the expressions of CD markers, these genetic changes could be used as potential prognostic biomarkers in hematological malignancies. It is hoped that the evaluation of SNPs in CD markers will enable early diagnosis, prognosis, and detection of response to treatment. However, better understanding of SNPs in CD markers that are involved in hematological malignancies requires further studies on different populations of the worldwide.

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Introduction

The cluster of differentiation (CD) markers are the key to distinguish and differentiate between cells. Surface CD markers have specific functions depending on the cell type and can be differentially expressed in response to environmental conditions and intracellular genetic changes.¹ Therefore, the detection of CD markers can be a useful approach to identify abnormal cells in disorders such as leukemia. Leukemia and lymphoma are a group of hematological malignancies originating from bone marrow (BM), which are related with high production and proliferation but non-differentiation of hematopoietic stem cells (HSCs). Accumulation of blast cells in BM, peripheral blood (PB), and lymph nodes leads to clinical manifestations among patients.² Abnormal expression of CD markers in BM and PB of patients is one of the first diagnostic features of leukemia. Therefore, the evaluation of CD markers' expressions is used as the first diagnostic strategy that is followed by an appropriate approach to monitoring the clinical course of leukemia.³ Despite the fact that specific immunophenotypic patterns have been defined for the diagnosis of leukemia and lymphoma, results of studies in recent years indicate the heterogeneous expressions of CD markers in these malignancies. Numerous environmental and genetic factors like single nucleotide polymorphisms (SNPs) can alter the expression patterns of these surface markers. Although cytogenetic alterations have been identified as an underlying cause of leukemia progression, SNPs can change the expression and function of CD markers and affect various aspects in the progression of these disorders, including the clinical course and response to treatment in patients.⁴ Therefore, detection of the primary mechanisms of

changes in CD markers' expressions in leukemia may contribute to the prognosis of these disorders.

Recent developments in molecular biology and the discovery of the association between SNPs of different genes with leukemia/lymphoma progression have highlighted the critical role of this genetic changes in the prognosis of these malignancies. Therefore, in this paper we discuss the most common SNPs in CD markers and their possible mechanisms for leukemia/lymphoma prognosis.

Effect of CD markers' polymorphisms on the clinical outcome of hematological malignancies

CD33

The presence of cytogenetic aberrations at the time of diagnosis is a major prognostic factor for acute myeloid leukemia (AML). However, studies have indicated that SNPs are among the genetic changes that can be associated with the prognosis of this malignancy by altering the expression and function of CD markers in AML blasts. CD33 is a well-known marker on the surface of AML blasts, which is targeted by chemotherapeutic agents such as gemtuzumab ozagamicin (GO) as a routine treatment of AML.⁵ Mortland *et al.* in their study showed that rs2455069, rs1803254, and rs12459419 SNPs were associated with decreased CD33 expression on the surface of blasts in children with AML.⁴ Although the primary role of CD33 has not been elucidated, it seems to be involved in both proliferation and survival of AML blasts.⁶ Hence, it is inferred that SNPs related to decreasing CD33 expression are associated with good prognosis in children with AML. In addition, decreased expression of CD33 reduces the need for GO therapy and its accompanying complications for patients, including shivering, fever, nausea, and vomiting.⁷ Furthermore, researchers showed that the TT genotype derived from rs12459419 SNP that involves exon 2 of CD33 gene, as well as carrying at least one C allele of

rs1803254 SNP leads to better overall survival (Table 1).⁴ Nevertheless, patients harboring AA or AG alleles caused by rs35112940 have a higher risk of recurrence and show decreased survival.⁴ In fact, CD33 SNPs appear to be a prognostic factor for assessing clinical course and response to treatment in AML patients through influencing clinical features.

CD44

CD44, which plays an important roles in cellular adhesion and migration, is a surface receptor on a large number of cells (including HSCs) that interacts with various ligands such as hyaluronic acid.⁸ Therefore, increasing CD44 expression could account for homing of normal HSCs or malignant cells in BM niches. Research has shown that CD44 rs13347 TT +CT genotypes are associated with increasing expression of CD44 in AML, which has been identified as a poor prognostic factor for this disease (Table 1).⁹ Although the molecular mechanism of association between CD44 rs13347 SNP and AML is unclear, increasing expression of CD44 can result in increased adhesion of HSCs to BM matrix that impairs normal differentiation and accumulation of immature blasts in BM niches. The results of a study by Loeffler-Ragg *et al.* can be mentioned in support of this hypothesis, which indicated that CD44 expression levels were higher in patients with myelodysplastic syndrome (MDS) progressing to AML relative to healthy controls.¹⁰ These findings suggest that the use of new therapeutic protocols for targeting CD44 can be useful in the improvement of AML patients. Since the induction of HSCs departure from BM to PB is the most common method to collect these stem cells for hematopoietic stem cell transplantation (HSCT), changing CD44 expression can be of high importance in stem cell mobilization. In this regard, investigations have shown that the TT genotype induced by CD44 rs13347 SNP is associated with increased expression of this marker, resulting in weak mobility of HSCs in response to granulocyte-colony stimulating factor (G-CSF) among patients with lymphoma and AML.¹¹ Martin-Antonio *et al.* indicated that healthy donors carrying the C allele of CD44 (CD44-2392 C) had lower expression of CD44 and increasing HSCs mobiliza-

Table 1. Genetic polymorphisms involved in clinicopathological characteristics of leukemia/lymphoma.

CD markers	Chr.	Biologic role	SNP	Region/ Allele	Disease	Population	Method	Effect	Ref.
CD33	19q13.4	Sialic acid-binding receptor	rs12459419	Exon 2	AML	American	PCR	Higher OS and decreased expression of CD33	4
			rs1803254	C>T; Ala14Val					
			rs2455069	3'-UTR	AML			Higher relapse risk and low OS	
			rs35112940	G>C (A>G); Arg69Gly					
CD44	11p13	Involved in cell-cell interactions, cell adhesion and migration	rs13347	promoter	AML	Chinese	Western Blot	May be a genetic modifier for developing AML	9
					HL, NHL, AML	Poland	PCR	Associated with poor mobilization of HSCs	11
CD185	11q23.3	Involved in B-cell migration into B-cell follicles of spleen and Peyer's patches	rs6421571	Intron	NHL	Chinese	PCR-RFLP	Increased susceptibility to NHL and development of disease toward high Ann Arbor stage (III + IV) stage	14
			rs80202369				Associated with increased susceptibility to NHL		
			rs1790192	Intron	NHL, FL, DLBCL, PTCL	Iowa	PCR	Associated with increased risk of malignancies and better event-free survival of FL patients.	15

AML, acute myeloid leukemia; OS, overall survival; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; HSC, hematopoietic stem cells; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

tion from BM to PB.¹² Obviously, reaching a sufficient quantity of HSCs is an essential prerequisite for a successful transplantation; nevertheless, factors such as TT genotypes of CD44 rs13347 SNP that have been relatively ignored may be a factor of not achieving sufficient levels of HSCs in PB of patients or donors in both autologous or allogeneic transplants. Although quantitative evaluation of CD34⁺ HSCs by flow cytometry is the most frequent method to assess the sufficient number of HSCs, assessment of CD44 SNPs seems to be effective in predicting the efficacy of hemapheresis and reducing its episodes. Moreover, this approach may be helpful in decreasing the dose of G-CSF and its complications in both patients and healthy donors.

CD185

CXCR5 or CD185 is a surface marker of circulating B-cells and follicular T-helper cells and plays an essential role in directing these cells toward secondary lymph nodes. The expression of CD185 has been reported in a number of malignancies, including non-Hodgkin lymphoma (NHL), which may indicate the involvement of this surface receptor in the development of these malignancies.¹³ In addition, genetic studies have indicated the association between several polymorphisms of CD185 gene with NHL incidence (Table 1).^{14,15} The results of these investigations show that the percentage of CD185 rs6421571 CT, TT, and rs80202369 AA genotypes is higher in NHL patients than in healthy subjects. Those who carry the rs6421571 TT genotype show increasing tumor mass (≥ 5 cm vs. > 5 cm) and progression to higher clinical stages of the disease.¹⁴ Interestingly, genetic research on the Iowa population has indicated that rs1790192 SNP of CD185 is related to an increased risk of follicular lymphoma (FL), while such patients have better survival than those without this SNP.¹⁵ This genetic change may account for transient and spontaneous improvement of FL patients that is seen in 25% of patients. Nevertheless, the hypothesis proposed by researchers for the association between CD185 SNPs and the incidence of NHL involves the impairment of activation and improper infiltration of lymphocyte lineages in lymph nodes as well as inhibition of tumor cell apoptosis.¹⁴ Given that extranodal tissues (including abdominal tissue) are of particular importance in lymphomas, CD185 SNPs may be an underlying cause of increasing extension and infiltration of tumor masses into these areas. Furthermore, disrupted function and migration of lymphocytes could reduce the resistance of patients to viral and bacterial infections, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), and *Helicobacter pylori* (*H. pylori*), which are the most common factors of infection in patients with lymphoma.^{16,17}

CD95/CD178

CD95 (Fas) induces apoptosis in cells following its binding to CD178 (Fas ligand) and the association between the presence of SNPs in the gene of this CD marker and clinical findings of AML patients has been demonstrated.¹⁸ CD95 -1377 G>A polymorphism, often expressed as heterozygote (GA) and homozygote (AA) variants, is a known SNP among AML patients. This SNP has been shown to affect the binding site of CD95 with stimulatory protein 1 (SP1) transcription factor. Indeed, CD95 -1377 G>A SNP generates a variant of CD95 gene that reduces the expression of this surface marker due to low binding affinity to SP1.¹⁸ Since CD95/CD178 interaction has a potential role in apoptosis, the induction of resistance to apoptosis of AML blast cells by these variants is a hypothesis supported by most researchers for the link between CD95 -1377 G>A SNP and AML prognosis. -670 CD95 SNP is another polymorphism affecting CD95 binding to signal transducer and activator of transcription 1 (STAT1). Remarkably,

allelic analysis of these SNPs showed that co-expression of -1377A/-670A haplotype increased the risk of AML up to six-fold relative to those having -1377G/1377G haplotype.¹⁸ However; evidence suggests that the effects of CD95/CD178 SNPs are not similar in all populations. For example, no correlation has been reported between CD95/CD178 SNPs and AML incidence in Korean and Chinese populations.^{19,20} In fact, it is inferred that CD95/CD178 may have different functions in various populations depending on the inherited allele. Furthermore, SNPs could modulate protective or resistance mechanisms of AML blast cells against apoptosis by altering the function of downstream genes of CD95/CD178 promoter. Although no association has been reported between CD95 -1377 SNP and chronic myeloid leukemia (CML), research has shown that -670 GG and CD178 -844 TC SNPs are associated with increasing risk of CML and disease progression to accelerated and blast phases.²¹ Unlike what observed in AML and CML, Tong *et al.* demonstrated that children carrying CD95 (-1377A, -670G) and CD178 (-844C) polymorphisms had reduced risk of acute lymphoblastic leukemia (ALL).²² Nonetheless, investigation of the association between these SNPs with ALL prognosis has shown that CD95 -670 GG genotypes are directly related to liver tissue involvement in patients.²³ Notably, Faree *et al.* in their study showed that CD95 -670 AA genotype was associated with increased risk of incidence, more clinical findings, and decreased survival in patients with adult T-cell leukemia (ATL).²⁴ In effect, these findings suggest that the association between CD95 SNPs is not limited to a specific genotype and that the effect of CD95 -670 SNP on clinical findings of hematological malignancies appears to be greater than CD95 -1377 SNP.

A notable point in the association between CD95/CD178 SNPs for prognosis of hematological malignancies is the difference in the effect of these genetic changes among diverse populations (Table 2).^{25,26} These contradictory results suggest that different effects of CD95/CD178 SNPs on the incidence and prognosis of hematological malignancies in various populations can be due to the influence of several factors, including environmental factors, race of population under survey, environmental-genetic interactions, frequency of alleles at these gene locations and the relationship between different genotypes derived from them. It seems that the biological roles of CD95/CD178 SNPs and their fixation in the genetic pool of individuals are of prognostic value. Hence, a general overview of the status of these polymorphisms and determining their relationship with the incidence and prognosis of hematological malignancies require extensive investigations in different populations of the world as well as comparison of results.

CD38

CD38 is a diagnostic marker of chronic lymphoblastic leukemia (CLL) that plays a vital role in activating intracellular signaling pathways following the stimulation of malignant B-cells receptors. CD38 expression is typically associated with increasing proliferation and survival of malignant B-cells and has been recognized as a poor prognostic marker in CLL.^{27,28} In addition, evidence has shown that CD38 is a prognostic marker that it increased expression is associated with B-CLL pathogenesis.²⁹ rs6449182 SNP is a well-known polymorphism in CD38 gene and several studies have suggested its relationship with increased expression of CD38 and the risk of CLL in different populations (Table 3).^{30,31} Investigations on this polymorphism indicate that patients carrying the rs6449182 GG genotype have a higher expression level of CD38 and progression to higher clinical stages relative to patients lacking this genetic change.³⁰⁻³² Although determining disease stage is the most common method for detecting CLL prognosis, clinical factors and laboratory findings such as age, sex, tumor

mass, serum lactate dehydrogenase (LDH), and genetic background of patients are also of importance in assessment of disease progress. In this regard, Aydin *et al.* in a study on an Italian population showed that male CLL patients bearing the CD38 rs6449182 G allele had more aggressive disease than female patients.³² Although the overall risk of CLL is higher in older men than in women, the reason why men with CD38 rs6449182 G allele exhibit more aggressive disease has not been determined; this event may

be related to decreasing production of sex hormones in older ages or the influence of environmental factors such as smoking that is an unfavorable environmental risk factor in men. Moreover, researchers found that the serum level of LDH as an indicator of tumor mass and disease progression to Richter syndrome (RS) was higher in patients with this genotype.³² Although the survival of CLL patients not having poor prognostic factors is approximately equal to normal individuals of similar age range, multiple genetic

Table 2. Summary of CD95/CD178 polymorphisms in hematological malignancies.

Type of malignancy	Country	Evaluated SNPs			Number of Case/Control	Method	Results	Ref.
		CD95 rs2234767 (-1377G>A)	rs1800682 (-670T>C)	CD178 rs763110 (-844T>C)				
AML	United Kingdom	✓	✓	-	454/934	PCR-RFLP	- CD95 -1377AA has twice AML development risk. - 1377A/-670A haplotype of CD95 promoter SNP had highest risk of AML development.	18
	Korea	✓	✓	✓	592/858	PCR	- Not associated with AML risk in the Korean population	19
	China	-	✓	-	98/2014	Meta-Analysis	- Was not associated with AML developing.	20
Childhood <i>de novo</i> AML	Multi-Ethnicity	✓	-	-	440/ Not mentioned	PCR	- Reduction in CD95 enriches the expression of apoptosis resistant clones in AML blast cells.	25
Childhood ALL	China	✓	✓	✓	361/519	PCR-RFLP	- Combination of some protection variant forms is associated with decreased risk of childhood ALL	22
ALL	Iran	✓	✓	-	142/117	PCR-RFLP	- -670 GG genotype is associated with liver involvement.	23
CML	India	✓	✓	-	386/386	PCR-RFLP	- CD95 -670 GG and CD178 -844 TC SNPs are associated with reduced event-free survival and development of CML - CD95-670 AG associated with accelerated phase - CD178 -844TC SNP associated with development of blast phase	21
ATL	Brazil	-	✓	-	31/33	PCR-RFLP	- Associated with susceptibility, clinical manifestation and survival.	24
FL	Spain	-	-	✓	Cohort, 126	PCR	- The C allele in this site is associated with a better response to rituximab therapy	26

AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia; CML, Chronic myeloid leukemia; ATL, adult T leukemia; FL, follicular lymphoma; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Table 3. Association of CD38 polymorphisms and prognosis of CLL.

First author, year of study	Country	Case/Control	Method	Evaluated SNPs	Results	Refs
Jamroziak, 2009	Polish Caucasian	460/503	RFLP-PCR, ARMS-PCR, Flow cytometry	rs6449182 rs1800561	- rs6449182 G and rs1800561 T alleles are associated with high expression of CD38 as well as increased risk of B-CLL.	30
Aydin, 2008	Italy	248/232	PCR, FACS, FISH	rs6449182	- In combination analysis, the patient with rs6449182 G allele harboring high level of ZAP70 expression has unfavorable prognostic marker. - rs6449182 G allele was associated with clinical and laboratory markers including increased LDH level, higher lymph node involvement and splenomegaly. - rs6449182 G allele may represent an independent risk factor for RS development.	32
Abramenko, 2012	Ukrainian	328/271	RFLP-PCR	rs6449182	- GG genotype is associated with dyslipidemia such as increase in LDL which is an antigenic stimulus for B-cells prior to or after neoplastic transformation.	31

PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; FACS, fluorescence-activated cell sorter; FISH, fluorescence in situ hybridization; LDL, low density lipoprotein; LDH, lactate dehydrogenase; CLL, chronic lymphocytic leukemia; RS, Richter syndrome.

and environmental factors such as aging and the incidence of SNPs can alter disease progression conditions.³³ For instance, elderly patients with CLL have been shown to bear increased risk of high cholesterol levels and atherosclerosis than younger patients.³⁴ Interestingly, the results of Abramenko *et al.* research on a Ukrainian population have indicated that CD38 rs6449182 SNP is associated with increasing levels of total cholesterol (TC), triglycerides (TG), and low-density lipoproteins (LDL) in patients with CLL.³¹ Since the increase in LDL levels has been recognized as a trigger for neoplastic transformation of B-cells,³⁵ CD38 rs6449182 SNP seems to be a poor prognostic factor increasing the risk of CLL in patients. In support of this hypothesis, there is evidence showing that LDL and HDL levels are elevated in the early stages of newly diagnosed CLL patients.³⁴

Although CD38 expression is an essential factor in the prediction of CLL prognosis, evaluation of the impact of genetic changes on the expression of this marker and its relationship with clinical findings and response to treatment in patients has been relatively neglected. In brief, the detection of CD38 SNPs in the early phase of disease can provide valuable information on CLL prognosis and even the choice of appropriate treatment protocols independent of cytogenetic changes and clinical findings such as adenopathy and splenomegaly.

CD markers SNPs and defective of immune responses

Neutropenia is one of the most important side effects of persistent chemotherapy in hematological malignancies, which predisposes to bacterial and fungal infections. CD284 or toll-like receptor 4 (TLR4) is a surface marker of neutrophils interacting with lipopolysaccharides and activating the nuclear factor κB (NF-κβ) signaling pathway, which plays a crucial role in combating pathogens and inhibiting apoptosis of neutrophils. Nonetheless, genetic investigations have shown that SNPs can cause neutropenia and recurrent infections in patients with hematological malignancies by impairing CD284 function. For example, three SNPs including rs11536889, rs1927911, and rs6478317 in CD284 gene, have been reported as a contributing factor to neutropenia and increased mortality in children with ALL.³⁶ Considering the fact that drug intoxication is a complication of repeated chemotherapy in AML, the expression of CD284 SNPs can be associated with more serious consequences in these patients. In this regard, studies show that patients with AML who carry CD284 rs4986791 and rs4986790 SNPs as well as CD282 (TLR2) rs5743708 SNP are faced with exacerbated side effects of chemotherapy such as prolonged periods of fever and increased risk of pneumonia, invasive fungal disease, and sepsis.^{37,38} On the other hand, since HSCT is the most effective approach to achieve long-term remission in patients with AML, the incidence of CD284 SNPs might be a barrier to successful transplantation and a cause of relapse. Therefore, it seems that monitoring of these genetic changes in AML patients offers new approaches to the choice of supportive treatments after chemotherapy and HSCT in these patients. Studies indicate that decreased expression of CD284 is associated with lower resistance to lipopolysaccharides of pathogens, which increases susceptibility to *H. pylori* infection in individuals. Mucosa-associated lymphoid tissue (MALT) lymphoma is a type of lymphoma that originates from gastric tissue and is associated with *H. pylori* infection. Moreover, genetic studies on a German population have revealed that individuals carrying at least one G allele caused by rs4986790 SNP CD284 are more susceptible to *H. pylori* infection and progression of MALT lymphoma than others.^{39,40} Although no such association has been reported in the Greek population, evidence

suggests a correlation between CD14 -159C/T SNP and the incidence of MALT lymphoma in this population.⁴¹ Because CD284 acts as a transmembrane co-receptor for CD14 in response to microbial lipopolysaccharides, this type of SNP may be associated with impaired CD284/CD14 interaction. On the other hand, overexpression of CD14 has been recognized as a factor of body's susceptibility to *H. pylori* and the initiation of inflammatory processes.⁴² Given that autoimmune and inflammatory disorders such as Sjögren syndrome, Hashimoto's thyroiditis, and ocular inflammation are common in some patients with MALT lymphoma,⁴³ CD284 and CD14 SNPs might be involved in progression to these disorders. Besides, the importance of CD14 SNPs in the development and progression of MALT lymphoma could be related to the effect of these genetic changes on the function of B-cells as the main cells involved in this malignancy. As reported by Yu *et al.*, CD14 -260 TT genotypes are strongly associated with B-ALL expression, although such association has not been observed in T-ALL.⁴⁴

Inappropriate activation of TLRs has been reported as another underlying mechanism for the incidence of lymphoma. For instance, overexpression of CD289 (TLR9) is one of the most well-known abnormal expression patterns of TLRs in a wide range of lymphomas, including mantle cell, B-cell small lymphocytic, follicular, and diffuse large B-cell. In addition, the role of CD289 in binding unmethylated CpG DNA motifs of B-cells has been recognized to activate these cells against fungal, viral, and bacterial infections. CD289 can also be involved in the recognition of self nucleic acids and thus it is believed that increasing expression of CD289 is involved in the pathogenesis of autoimmune diseases.⁴⁵ rs5743836 SNP is one of the most prevalent genetic alterations of CD289 that has been shown to increase susceptibility to HL and Crohn's disease.⁴⁶⁻⁴⁸ Since rs5743836 SNP is associated with increased expression of CD289, genetic investigations have reported higher B-cell proliferation and subsequent enhancement of immune stimulation as a basic mechanism of this polymorphism in HL and NHL pathogenesis.^{47,49} However, the effect of this genetic variation is different across populations, so that rs5743836 SNP is related with increased NHL risk in the population of Portugal and Italy but no such association has been reported in the United States.⁴⁹ Noack *et al.* recently showed that rs5743836 SNP can be effective in response to CD289 agonists, which is a therapeutic strategy inducing the death of Burkitt's lymphoma (BL) cells (Table 4). Indeed, this finding suggests that CD289 rs5743836 SNP can be considered as a prognostic factor of response to treatment.⁵⁰ The importance of CD289 SNPs is not limited to the incidence and prognosis of lymphomas and the inheritance of different variants of CD289 can also affect different aspects of leukemia. Research has shown that patients with AML bearing CC genotype of rs5743836 have a higher overall survival after HSCT than those having TC/TT genotype.⁵¹ The CC allele of rs5743836 SNP appears to decrease CD289 expression, which is in turn associated with reduced activation of T helper and cytotoxic T-cells as well as decreasing graft *versus* host disease (GVHD),⁵¹ while rs352140 C variant allele is related with increasing incidence of viral infections in children with ALL who are in the remission phase after chemotherapy.⁵² It seems that polymorphisms in TLRs, as the first factors in detecting pathogens, play an essential role in determining susceptibility to infections and the occurrence of hematological malignancies. However, altered function of immune cells (including T-cells) is not dependent only on the expression and function of TLRs. Effective activation of T-cells requires a balance between stimulatory receptors such as CD28 and inducible co-stimulator (ICOS) or CD278 with inhibitory receptors like cytotoxic T-lymphocyte associated protein-4 (CTLA-4) or CD152. Impaired

expression of these surface markers is related with the incidence of B-CLL.^{53,54} Besides, genetic research shows that CD152g.319C>T, CD28c.17+3T>C, and CD278c.1554+4GT SNPs play a role in the incidence of B-CLL in the Polish population. In addition, carriers of CD152g.319C,>T,[T] and CD28c.17+3T>C SNPs are more likely to progress to higher stages of the disease.⁵⁵ Progression of disease toward higher clinical stages in patients with CD278 (rs10932029) ISV1 + 173T>C [TT], (rs10183087) 602A>C [AA], (rs10932037) 1624C>T[CC], and (rs4675379 2373G>C [GG] has been reported to be lower than in other individuals.⁵⁶ It is concluded that these genetic alterations change the expression status of T-cells by affecting the expressions of these CD markers (*i.e.* increasing expression of CD28, CD272, and CD278) in a way that sends stimulatory messages to B-cells and increases their proliferation. The precise mechanism of SNPs role in stimulatory and inhibitory T-cell receptors for the development and progression of hematological malignancies remains to be elucidated and needs further studies.

Effect of CD marker polymorphisms on targeted therapy

Although cytogenetic changes at the time of leukemia diagnosis (especially AML) are important prognostic factors, abnormal expression of genes due to mutation or SNPs can affect clinical findings and response to therapy. Perhaps homozygous inheritance of TT genotype of CD33 rs12459419 SNP is a molecular abnormality involved in response of AML patients to GO treatment. The carriers of this allele have a poor response to GO and show increasing minimal residual disease (MRD) levels.^{57,58} whereas those harboring the CC genotype of this polymorphism have higher disease-free survival and reduced relapse risk following GO therapy;⁵⁹ however, this prognostic pattern is not the same in all patients. Mortland *et al.* revealed that the TT genotype of rs12459419 was associated with a favorable-risk disease and good response to GO therapy, while patients carrying variant allele (AA+ AG) for CD33 rs35112940 have reduced overall and disease-free survival as well

Table 4. Polymorphisms of immune-related CD markers and prognostic effects in hematological malignancies.

CD markers	Chr.	Annotation name	Function	SNP	Location	Malignancy	Method	Effect	Ref.
CD284	9q33.1	TLR4	Plays a fundamental role in pathogen recognition and activation of innate immunity	rs11536889	3'-UTR	ALL	PCR	Association with the risk of developing neutropenia and infectious complications	36
				rs1927911	Intron	AML	PCR	Associated with long-lasting fever and increased risk of sepsis and pneumonia after chemotherapy	37
				rs6478317	Promoter				
				rs4986790	Exon 5				
CD282	4q31.3	TLR2	Plays a role in pathogen recognition and activation of innate immunity	rs5743708	Promoter	AML	PCR	Associated with development of Sepsis, pneumonia, and invasive fungal disease in AML patients who undergo induction chemotherapy.	37,38
CD14	5q31.3	CD14 molecule	Mediates the innate immune response to bacterial lipopolysaccharides	-159C/T	Promoter	MALT lymphoma	RFLP-PCR	Enhances CD14 expression that might contribute to the development of <i>H. pylori</i> associated malignancy	41
				rs2569190	Promoter	ALL	PCR	Associated with developing risk of B-ALL	44
CD289	3p21.2	TLR9	Plays a fundamental role in pathogen recognition and activation of innate immunity.	rs5743836	Promoter	HL	PCR	May increase the susceptibility to HL	48
						NHL	PCR	Enhanced CD289 function that increases B-cell proliferation upon CpG stimulation as well as NLH risk	49
						BL	qRT-PCR	C allele results in enhanced NF-kB activation following TLR9 triggering that leads to induced apoptosis in BL cells	50
						AML	PCR	C allele is associated with reduced CD289 gene expression and slower reconstitution of Th and cytotoxic T cells after transplantation	51
				rs352140	Promoter	ALL	PCR	C variant allele is associated with increased risk of infection during the remission induction period of treatment	52
CD28	2q33.2	CD28 molecule	Is essential for T-cell proliferation, activation, and survival	17+3T>C	Promoter	B-CLL	PCR	CD28 and CD278 may be associated with dysregulation of immune response and increased proliferation of B-cells that leads to increased risk of B-CLL	55
CD278	2q33.2	ICOS	Plays an important role in regulation of immune responses	1554+4GT	Promoter				
CD152	2q33.2	CTLA-4	Transmits an inhibitory signal to T cells	g319C>T +49A/G	Promoter	NHL	PCR	May have a role in genetic susceptibility to NHL	57

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-CLL, B-chronic lymphoblastic leukemia; MALT, mucosa-associated lymphoid tissue; HL, Hodgkin lymphoma; NHL, Non Hodgkin lymphoma; BL, Burkitt's lymphoma; *H. pylori*, *Helicobacter pylori*; NF-kB, nuclear factor kB; TLR, toll like receptor; Th, T helper; ICOS, inducible co-stimulator; CTLA-4, cytotoxic T-lymphocyte associated protein-4; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

as increased risk of relapse.⁶⁰ The remarkable variation in the effects of CD33 SNPs on clinical findings and response to treatment in AML patients may suggest that SNPs are an underlying factor of resistance to GO therapy in AML patients. Therefore, genetic sequencing of patients to detect the genetic changes is important from a biological point of view and can provide independent prognostic information on the identification of risk factors. Interestingly, the study of the effect of rs12459419 SNP on CD33 expression has yielded inconsistent results and has been shown to be associated with the decrease, increase, or lack of change in CD33 expression.^{58,59,61} These findings suggest that although CD33 is a unique prognostic marker in AML, SNPs might be more valuable than CD33 expression in the prognosis of disease progression and multidrug resistance (MDR). In other words, the diagnosis of this genetic disorder can be a differentiating factor in the prognosis of response to treatment among patients.

CD20 is the most important marker on 80% of malignant B-cell masses in disorders such as CLL and diffuse large B-cell lymphoma (DLBCL). The expression of this marker increases over the course of malignancy and is a potential therapeutic target for rituximab (RTX), a chimeric monoclonal antibody against CD20 on B-cells and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Rs2070770 is a common polymorphism in CD20 gene that has been reported to be associated with CLL.⁶² In addition, research has shown that SNPs can affect CD20 expression and response to RTX-containing drugs. For instance, Zang *et al.* revealed that patients with *de novo* DLBCL in a Chinese population carrying the T allele of CD20 rs2070770 SNP are associated with decreased CD20 expression, a favorable response to RTX-containing drugs, and increase in survival.⁶³ However, the results of another study in the same population indicated that the subjects who inherit C genotype of this SNP have a better response to treatment and a longer survival than those with at least one T allele.⁶⁴ While the precise mechanism of the influence of different alleles on response to RTX therapy has not been elucidated, the CD20 rs2070770 SNP could be a favorable prognostic factor in patients with DLBCL. However, there is evidence suggesting that it has no effect on DLBCL prognosis.⁶⁵ These findings indicated that the association between CD20 SNP and RTX-containing-drugs is a controversial topic and that determining the impact of these polymorphisms on disease prognosis requires further collaboration among researchers to obtain accurate information in this regard. The response to R-CHOP in DLBCL patients may not be related solely to genetic alterations of CD20 as the primary target of this therapeutic protocol but rather the transfer of drug components across the membrane (ABCG2) or CD338 ATP binding cassette could have been disrupted. ATP binding cassette subfamily G member 2 (ABCG2) or CD338 is a membrane pump that has been shown to increase the flow of drugs such as doxorubicin, vincristine, and prednisone from cytoplasm to the extracellular matrix.⁶⁶ Moreover, CD338 is a major cause of MDR in hematological malignancies,⁶⁷ so that targeting CD338 is widely used in DLBCL to overcome MDR.⁶⁸ Liu *et al.* in a recent study revealed that patients with DLBCL treated with R-CHOP carrying CD338 rs2231137 GG genotype had poorer progression-free survival (PFS) and event-free survival (EFS) than those bearing AA or GG genotypes.⁶⁹ It seems that the GG genotype could have produced a phenotype of CD338 that is unable to transport drug components across the membrane. There is also evidence suggesting that AA or GG genotypes are favorable factors reducing the risk of infection in patients with DLBCL treated with R-CHOP.⁷⁰ Indeed, these findings indicate that the genetic background of patients can also be effective on clinical presentations of a particular therapeutic protocol.

Discussion and future perspective

Hematological malignancies are neoplastic disorders, and cytogenetic abnormalities as well as clinical features are the most important factors in their classification. The phenotype of the involved cells, often characterized by the expression of surface CD markers, is another feature playing an essential role in the diagnosis and prognosis of hematological malignancies and solid tumors.^{3,71,72} Although flow cytometry is a practical technique to analyze the expression levels of CD markers, genetic alterations (including SNPs) affecting expression patterns of CD markers may cause significant limitations in the classification and precise prognosis of hematological malignancies.⁷³⁻⁷⁵ As an example, CD38 rs6449182 is a known polymorphism in CLL and it has been shown that patients carrying the GG genotype of this polymorphism have more aggressive disease.^{30,31} Although clinical symptoms such as BM, PB, and lymph node involvement are the most crucial prognostic factors in CLL, the CD38 rs6449182 SNP has been shown to be associated with biochemical abnormalities such as increased LDH and lipoproteins, which indicates the progression toward advanced clinical stages. Since the increase in lipoproteins such as HDL and LDL has been identified as a stimulus for increasing B-cell proliferation,³⁵ the evaluation of CD38 SNPs should provide new clues regarding the etiology and development of CLL. Similarly, research has shown that CD95 -670 G>A and CD178 -844 T>C SNPs are associated with the progression of CML toward accelerated and blast phases.²¹ Given that CD95/CD178 is involved in the apoptosis process, these genetic changes could influence blast cells' resistance to apoptosis by affecting the expression and alteration of intracellular mechanisms. Indeed, this finding suggests that CD95/CD178 SNPs as potential prognostic factors provide for different degrees of disease progression in CML patients and are important in defining high-risk groups.

Although the expression pattern of CD markers is not widely used in differential diagnosis of lymphomas, CD markers' SNPs appear to be important in the prognosis of these disorders that are associated with extracellular infiltration of malignant cells. Conceivably, CD185 SNPs that are related with the infiltration of malignant lymphocytes into lymph nodes, increased tumor mass size, and progression to higher clinical stages in the NHL have been identified as a poor prognostic factor in this disorder.¹⁴ In fact, evaluation of SNPs in lymphomas can help determine the prognosis and the extent of tissue involvement. SNPs in CD markers, especially immune-related CD markers, have clinical implications and might lead to alleles of these functional surface markers that are not susceptible to infectious pathogens, paving the way for progression to malignancies. Similarly, several investigations have revealed that genetic variation from SNPs in immune-related CD markers such as CD284 and CD14 can provide conditions for *H. pylori* infection and the incidence of MALT lymphoma.^{39,41} It seems that CD284 and CD14 SNPs contribute to *H. pylori* survival in the acidic environment of the stomach and its confrontation with host's immune system and thus have serious clinical consequences. However, epidemiological studies have shown that the effect of these SNPs is not the same in all populations, so no association was reported between these polymorphisms and the incidence of MALT lymphoma in the Greek population.⁴¹ In fact, it seems that various factors such as ethnicity and geography are involved in the extent of adaptation to genetic variation resulting from polymorphisms as well as susceptibility to *H. pylori* and progression toward malignancies. Because immune-related CD markers play an essential role in regulating immune function, imbalances in their expressions have been identified as a factor of body's susceptibility to a

variety of diseases. CD152g.319C>T, CD28c.17+ 3T>C, and CD278c.1554+4GT SNPs that cause imbalanced expressions of inhibitory and stimulatory T-cell receptors have been recognized as poor prognostic factors in association with increased risk of B-CLL.^{55,56} It seems that these SNPs decrease the activity of inhibitory receptor promoters (CD152) and in contrast increase the activity of the stimulatory receptors (CD28 and CD278), which results in increased proliferation of B-cells and susceptibility to B-CLL.⁵⁵ However, the precise mechanism of these SNPs is unclear and needs further study.

One of the biggest challenges facing patients with hematological malignancies is the failure to respond favorably to treatment as well as disease relapse. The fact that many drugs have diverse effects on different individuals has been accepted, but there is evidence suggesting that patients often have different levels of resistance to drugs, some of them needing lower or higher doses to achieve the desired therapeutic effect and sometimes a medication may not have any therapeutic effect in patients. Although drug interactions can sometimes lead to poor response to therapy in patients using multiple drugs, many differences can be due to genetic variation. For instance, clinical results from genetic studies on AML and DLBCL patients have shown that different genotypes of CD20 rs2070770 SNP, as well as CD33 rs12459419 and rs35112940 SNPs, can be effective in the mode of patients' response to treatment.^{58-60,63,64} Researchers also believe that the expressions of SNPs in proteins involved in the transport of drugs, which are often expressed as CD markers at the cell surface, can influence the response of the patients to many drugs.⁶⁹ It is inferred that the genetic makeup of patients can be a main cause of variation in response to drugs. These findings point to the necessity of individual medical treatment, which simply means prescribing specific medications and treatments based on genetic makeup that works best for the patient and minimize failure of optimal response and risk of recurrence. Overall, the results of genetic investigations indicate that SNPs of CD markers are a main factor for altering and even determining the biological phenotype of hematological malignancies. However, SNPs by themselves cannot affect different aspects of these disorders, including incidence, progression, prognosis, and response to therapy by altering the expression and function of CD markers, but the interaction of these genetic changes with environmental factors determines the risk of disease in an individual, severity of the disease, and even how they respond to treatment. These findings suggest that the prognosis of SNPs in CD markers varies across populations and may even lead to different responses to therapeutic agents. In other words, some of these genetic changes can cause rapid progression of the disease and require a different type and dose of a particular drug in patients, while the same change could not have significant effect on individual or other populations. Although it is difficult to design genetic tests that can identify a particular SNP and predict its impact on a person's disease progression and response to a specific drug, it appears that the detection of genetic changes (including SNPs) in CD markers as significant diagnostic and prognostic factors in hematological malignancies can contribute to better understanding and predict the clinical course of these disorders. Moreover, physicians will be able to quickly prescribe optimal treatment with available drugs by analyzing the genetic history, maximizing the value of the treatment process by choosing a precise treatment protocol. It is hoped that the evaluation of SNPs of CD markers will enable early detection of these disorders, their prognosis and response to treatment besides assessing the potential for hematological malignancies in different populations around the world, thereby minimize side effects as well as the cost of medical care for patients by providing appropriate doses of drug.

Highlights

- Several CD marker-related SNPs can affect leukemia/lymphoma pathogenesis and prognosis.
- SNPs in multiple CD markers can be associated with drug resistance in leukemia/lymphoma.
- Different CD marker-related SNPs can be a new therapeutic target in leukemia/lymphoma.

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