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Review

Thrombocytopenia in leukemia: Pathogenesis and prognosis

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Summary. Leukemias, a heterogeneous group of hematological disorders, are characterized by ineffective hematopoiesis and morphologic abnormalities of hematopoietic cells. Thrombocytopenia is a common problem among leukemia types that can lead to hemorrhagic complications in patients. The purpose of this review article is to identify the conditions associated with the incidence of thrombocytopenia in leukemias. It can be stated that although translocations have been considered responsible for this complication in many studies, other factors such as bone marrow failure, genes polymorphism, a mutation in some transcription factors, and the adverse effects of treatment could be associated with pathogenesis and poor prognosis of thrombocytopenia in leukemias. Considering the importance of thrombocytopenia in leukemias, it is hoped that the recognition of risk factors increasing the incidence of this complication in leukemic patients would be useful for prevention and treatment of this disorder.

Key words: Leukemia, Thrombocytopenia, Polymorphism, Mutation

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Introduction

Leukemias are a group of hematological malignancies characterized by an increase in immature or abnormal white blood cells in bone marrow (BM) and peripheral blood (PB). This group of malignancies is divided into acute and chronic as well as lymphocytic and myelocytic types according to clinical manifestations and the lineage involved, respectively (Tefferi and Vardiman, 2008; Appelbaum and Meshinchi, 2017). Patients with leukemia show symptoms such as anemia, neutropenia, and thrombocytopenia due to ineffective hematopoiesis and related complications, which include fatigue, weakness, infection, and bleeding (Loughran et al., 1985; Alter, 2007; Visco et al., 2008).

Thrombocytopenia is a bleeding disorder detected by platelet counts $<100\times10^9$/L, which is observed in a large number of patients with leukemia (Visco et al., 2008) and may be due to several causes such as ineffective hematopoiesis, suppression of megakaryocyte progenitor cells in BM by the malignant cells clone (Alter, 2007), gene mutations (Songdej and Rao, 2017), destruction of platelets in PB, and adverse effects of treatment (Leach et al., 2000; Druker et al., 2006). Given the essential role of thrombocytopenia in the occurrence of bleeding complications in leukemic patients, identification of the factors causing and aggravating this disorder can contribute to prognosis and thus selection of appropriate treatment protocols to prevent these complications. In this review, we attempt to identify the mechanisms of thrombocytopenia in leukemias and their probable role in prognosis.

Polymorphisms associated with thrombocytopenia in leukemia

Single nucleotide polymorphisms (SNPs) are genetic changes in the human genome that can affect various aspects of diseases, such as development, progression, clinical symptoms, and even response to treatment. For example, a number of these polymorphisms are responsible for the development of thrombocytopenia in immune thrombocytopenic purpura (ITP) (Rezaeeyan et al., 2017). Similar to ITP, the presence of polymorphisms in patients with leukemia and myelodysplastic syndrome (MDS) can lead to thrombocytopenia (Suwalska et al., 2008; Francis et al., 2015; Bestach et al., 2017). Herewith, we mention some of the polymorphisms and their impacts on the incidence of thrombocytopenia in leukemias.

Enzyme polymorphisms

Cytarabine is a chemotherapy drug that is widely used to treat patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) (Gabor et al., 2015; Megias-Vericat et al., 2017). Deoxycytidine kinase (DCK) is an enzyme involved in the metabolic pathway of cytarabine, and polymorphisms in various alleles of this enzyme affect the incidence of clinical findings such as survival rate, toxicity for skin, liver, lung, and death. DCK rs12648166 and DCK rs4694362 polymorphisms are associated with an increased risk of grade 3 and 4 thrombocytopenia in adults and children with AML and ALL, respectively, since they decrease the function of this enzyme and lead to the defective metabolism of cytarabine (Gabor et al., 2015; Megias-Vericat, 2017). Furthermore, gene analysis of other enzymes involved in cytarabine metabolism, including solute carrier family 28 member A 1 (SLC28A1), solute carrier family 28 member A 3 (SLC28A3), solute carrier family 29 member A 1 (SLC29A1), and cytidine deaminase (CDA) can also lead to varying degrees of thrombocytopenia in patients with AML and ALL (Table 1) (Gabor et al., 2015; Hyo Kim et al., 2015).

Methotrexate (MTX) is a chemotherapy drug commonly used to treat children with ALL. However, the defective metabolism of this drug can lead to problems in the treatment process and even death of the patients. Gamma glutamyl hydrolase (GGH) and 5,10-methylenetetrahydrofolate reductase (MTHFR) are two enzymes of the MTX metabolism pathway, and various SNPs can reduce their function. This genetic change can lead to incomplete metabolism and the resulting increase in the concentration of MTX in patient's serum, the toxic effects of which manifest in the form of thrombocytopenia in children with ALL (Kantar et al., 2009; Koomdee et al., 2012). Interestingly, different MTHFR genotypes are associated with varying degrees of MTX toxicity. Compared with other genotypes, the T677T genotype is associated with higher rates of thrombocytopenia and anemia, as well as increased relapse rates in children with ALL (El-Khodary et al., 2012). On the other hand, the polymorphism in ATP binding cassette subfamily C member 2 (ABCC2), an anion transporter contributing to the elimination of toxic effects of MTX, exacerbates the complications of MTX toxicity by decreasing the activity of this enzyme in children with ALL (Liu et al., 2014). Therefore, it is concluded that the coexistence of MTHFR and ABCC2 polymorphisms can be associated with an increased risk of thrombocytopenia and thus a poor prognosis in acute leukemia. It has also been observed that the toxic effects of MTX in malnourished children with ALL who receive this drug (as maintenance chemotherapy) can cause thrombocytopenia in over 50% of patients through the development of folate defect during treatment (Roy Moulik et al., 2017). Therefore, these findings suggest that the incidence of thrombocytopenia in children with ALL can be affected by drug doses, metabolic pathway defects, and perhaps nutritional status.

Similar to MTX, 6-mercaptopurine (6-MP) is a chemotherapy drug used for the treatment of ALL patients. Various polymorphisms in the enzymes of its metabolic pathway, including thiopurine methyl-transferase (TPMT) and inosine triphosphatase (ITP), increase the adverse effects of this drug (Hawwa et al., 2008). The two alleles of TPMT*3C and TPMT*3A are the phenotypes of this enzyme with a decreased function relative to TPMT*1 (wild type). In addition to reducing the efficacy of 6-MP in patients due to the defective metabolism, these alleles can potentiate the adverse effects associated with increased concentrations of 6-MP, including thrombocytopenia in children with ALL (Table 1) (Peregud-Pogorzelski et al., 2011). Regarding the above, it is understood that polymorphisms in the enzymes of drug metabolism pathways are a commoner cause of thrombocytopenia in children with ALL than adults with AML. Therefore, our hypothesis here is that in addition to dosage, the patient's genetic background can induce the toxicity and side effects of chemotherapeutic agents such as thrombocytopenia in children with ALL.

Imatinib mesylate (IM) is the first line treatment for patients with chronic myeloid leukemia (CML). Despite the high efficacy of this drug in the treatment of patients, its side effects appear in the form of cytopenia (especially thrombocytopenia), and the resulting hemorrhagic risks can cause interruption of treatment in advanced stages of the disease (Ponte et al., 2017). In addition, study of the effect of polymorphisms on the occurrence of this complication showed that SNPs in carrier proteins of this drug, including ATP binding cassette superfamily B member 1 (ABCB1), ATP binding cassette superfamily G member 2 (ABCG2), and organic cation/carnitine transporter1 (OCT1), play a major role in increasing risk of thrombocytopenia after IM treatment in patients with CML during the chronic phase (Francis et al., 2015). These polymorphisms lead to the accumulation of this drug in patients' sera by decreasing the function of enzymes and the ensuing

Table 1. Some common gene polymorphisms associated with thrombocytopenia in leukemia.

Gene	Chro.	Rs number	Polymorphisms	Genotyping method	Leukemia	Effect of polymorphism	Ref.
Enzyme polymorphisms							
DCK	4q13.3	rs4694362	-201T>C	PCR	AML, ALL	Associated with grade 3 and 4 thrombocytopenia and delayed time of thrombocytopenia recovery	Gabor et al., 2015; Megias-Vericat et al., 2017
		rs12648166	208G>A	PCR			
MTHFR	1p36.3	rs1801131	A1298C	Real-time PCR	ALL	Associated with increased MTX toxicities that lead to thrombocytopenia	Kantar et al., 2009; El-Khodary et al., 2012; Koomdee et al., 2012
			C677T				
			T677T				
GGH	8q12.3	Not mentioned	-401C>T	PCR	ALL	Associated with defective MTX metabolism that leads to increased adverse effects of MTX accumulation including thrombocytopenia	Koomdee et al., 2012
TPMT	6p22.3	Not mentioned	TPMT* 3A (G460A and A719G)	PCR	ALL	Associated with increased adverse effect of 6-MP including thrombocytopenia	Peregud-Pogorzelski et al., 2011
		Not mentioned	TPMT *3C (A719G)				
ITP	20p13	Not mentioned	IVS2+21A□C	PCR	ALL	Associated with a higher concentration of 6-MP that leads to revealing its adverse effect including thrombocytopenia	Hawwa et al., 2008
ABCC2	10q24	rs717620	-24C>T	PCR	B and T-cell ALL	Can lead to higher MTX plasma concentrations associated with higher risk of thrombocytopenia	Liu et al., 2014
CDA	1p36.2	rs1048977	C>T	PCR	ALL,AML	Associated with increased adverse cytarabine reactions such as different grades of thrombocytopenia	Gabor et al., 2015; Hyo Kim et al., 2015
SLC28A3	9q21.3	rs7853758	GT haplotype				
		rs7867504	GT haplotype				
SLC29A1	6p21.1	rs324148	TC haplotype				
		rs9394992	CC haplotype				
ABCB1	7q21.12	rs1045642	3435C>T	Real-Time PCR	CML	Associated with increased IM concentration that leads to thrombocytopenia	Francis et al., 2015
		rs2032582	2677G>T/A				
ABCG2	4q22.1	rs22311442	421C>A				
OCT1	6q25.3	rs2282143	1022C>T				
		rs628031	1222A>G				
		rs622342	1386C>A				
Immune gene polymorphisms							
CTLA-4	2q23	rs231775	A>G49	PCR	B-CLL	Associated with dysregulation of immune responses and increased risk of thrombocytopenia	Pavkovic et al., 2003; Suwalska et al., 2008
		rs5742909	319C>T				
		rs3087243	642A>T				
CD28	2q33.2	rs3116496	17+3T>C				
ICOS	2q33.2	Not mentioned	1554+4G>T	PCR	B-CLL	Maybe associated with thrombocytopenia via increased B and T cells interaction	Suwalska et al., 2008
		rs10932029	ISV1+173T>C	TaqMan SNP Genotyping Assay	B-CLL	Maybe associated with thrombocytopenia via increased B- and T-cells interaction that leads to increased autoantibody production	Karabon et al., 2011
		rs10932037	1624C>T				
		rs4675379	2373G>C				
		rs10183087	602A>C				
Cytokines polymorphisms							
TNF	6p21.33	rs1800629	-308G/A	PCR	MDS,CMML, CLL, HCL,CML	Associated with inhibition of hematopoiesis that leads to cytopenias in MDS and autoimmune complication in CLL and HCL in advanced stage	Demeter et al., 1997a,b; Amirzargar et al., 2005; Bestach et al., 2017
IL-6	7p15.3	rs1800795	-174G/C		MDS,CML	Associated with inhibition of hematopoiesis that leads to cytopenia	Amirzargar et al., 2005; Bestach et al., 2017
LT-α	6p21.33	Not mentioned	TNFB*2 allele	PCR	CLL, HCL	Associated with cytopenia in advanced stage of this disease	Demeter et al., 1997a,b
TGF-β	19q13.2	Not mentioned	T^{29}-C	PCR	MDS	Associated with enhanced severe cytopenia in advanced stage	Gyulai et al., 2005
		Not mentioned	915G>C	PCR	CML	Maybe associated with thrombocytopenia in the accelerated phase of CML	Amirzargar et al., 2005
IFN-γ	12q15	Not mentioned	-33TT	PCR	CML	Maybe associated with thrombocytopenia in the accelerated phase of CMLvia activated Macrophages to clear platelets	Amirzargar et al., 2005
IL-10	1q32.1	Not mentioned	-1082G/A	PCR	CML	Maybe associated with thrombocytopenia in the accelerated phase of CML via a defect in tolerance and subsequently activated autoreactive B and T function	Amirzargar et al., 2005
			-819C/T				
IL-1A	2q14.1	rs1800587	-889C/T	PCR	CLL	Associated with development of thrombocytopenia	Sirotina et al., 2014
IL-1Ra	2q14.1	rs1800587	-889C/T				

DCK: Deoxycytidine kinase, MTHFR: methylenetetrahydrofolate reductase, GGH: gamma glutamyl hydrolase, TPMT: thiopurinemethyltransferase, ITP: inosine triphosphatase, 6-MP: 6-mercaptopurine, ABCC2: ATP binding cassette subfamily C member 2,MTX: methotrexate, CDA: cytidine deaminase, SLC28A3: solute carrier family 28 member A3, SLC29A1: solute carrier family 29 member A1, ABCB1: ATP binding cassette subfamily B member 1, ABCG2: ATP binding cassette subfamily G member 2, IM: imatinib mesylate, OCT1: organic cation/carnitine transporter1,CTLA-4: cytotoxic T-lymphocyte antigen4, ICOS: inducible co-stimulator, TNF: tumor necrosis factor-alpha, IL-6: interleukin-6, LT-α: lymphotoxin α, TNFB: tumor necrosis factor-b, TGF-β: growth factor-beta, IFN-γ: interferon-gamma, IL-10:interleukin 10, IL-1A:interleukin-1a, IL-1Ra: interleukin-1 receptor antagonist, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, CLL: chronic lymphoblastic leukemia, MDS: myelodysplastic syndrome, CMML: chronic myelomonocytic leukemia, HCL: hairy cell leukemia, PCR: polymerase chain reaction.

incomplete metabolism of IM. Therefore, cytotoxic effects of increased IM concentrations appear in the form of grade 2-4 thrombocytopenia in CML patients (Table 1) (Francis et al., 2015). It is concluded that the patients receiving an inappropriate dose of IM or those who have one or more of these polymorphisms can be at increased risk of developing thrombocytopenia and thus have a poor prognosis. Therefore, recognition of these risk factors in patients can be helpful in the prevention of this complication.

Immune system related gene polymorphisms

Evidence shows that the altered function of the immune system can lead to several types of autoimmune diseases and hematological malignancies. For instance, the immune system may be responsible for platelet destruction in autoimmune bleeding disorders such as ITP, as well as fetal and neonatal alloimmune thrombocytopenia (FNAIT) (Curtis, 2015; Chen et al., 2017; Zufferey et al., 2017). ITP may be diagnosed as primary (without a specific reason) and secondary (often following viral and bacterial infections, autoimmune diseases, and lymphoproliferative neoplasms such as CLL) forms (Jang et al., 2017). The incidence of secondary ITP in adults increases with age, and its prevalence in women is higher than males (Stasi et al., 2008). In contrast, the incidence of secondary ITP in children is also relatively high and it often occurs due to immune deficiency and infections (Jang et al., 2017). Regarding the association between immune deficiency and infections with thrombocytopenia, leukemic patients undergoing bone marrow transplantation (BMT) with compromised immune systems are likely to experience secondary ITP due to viral and bacterial infections. Moreover, autoimmune cytopenia (anemia, neutropenia, and thrombocytopenia) is a clinical outcome detected in the advanced stages of chronic lymphoblastic leukemia (CLL), which is associated with a poor prognosis in both Rai and Binet classifications (Rai et al., 1975; Binet et al., 1981). Although the pathophysiology of autoimmune cytopenia has not been elucidated in these diseases, it has been shown that in addition to BM failure, the defects in regulatory mechanisms of the immune system can play a role in these complications (Suwalska et al., 2008). The costimulatory molecules of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and inducible co-stimulator (ICOS) are two known inhibitory receptors of the CD28 family that are highly expressed on functional T-cells and play a role in regulating the function of these cells (Walunas et al., 1994). Studies of the genomes of patients with B-cell chronic lymphocytic leukemia (B-CLL) revealed the association of polymorphisms in the genes of these receptors with an increased risk of disease, autoimmune complications, and incidence of thrombocytopenia (Pavkovic et al., 2003; Suwalska et al., 2008). However, Suwalska et al. indicated that the CD28, CTLA-4, and ICOS gene polymorphisms were not associated with gender or age at diagnosis (Suwalska et al., 2008). Meanwhile, ICOS polymorphisms, which are associated with the defective expression of this receptor, have a direct correlation with B-CLL progression to advanced stages of the disease (Karabon et al., 2011). Since ICOS is necessary for the interaction of B and T lymphocytes, as well as normal antibody responses to T-cell-dependent antigens, the incidence of thrombocytopenia in advanced stages of CLL (stage IV of the Ria Classification or stage C of Binet Classification) may be a function of these polymorphisms, which enhance autoantibody production against platelets by increasing the interaction between B and T lymphocytes.

Although CTLA-4 and ICOS polymorphisms are among the causes of relapse following primary chemotherapy in AML patients, as well as increased incidence of graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation (HSCT) in patients with AML, ALL and CML (Perez-Garcia et al., 2009; Wu et al., 2009), little information is available on the association of polymorphism in these immune-related genes and thrombocytopenia in these malignancies than what is known on CLL. More genetic studies are likely to reveal the possible relationship between these polymorphisms and clinical findings, including thrombocytopenia in hematological malignancies.

Cytokine polymorphisms

Cytokines are key elements in the interaction of malignant clone cells with BM microenvironment and can affect several clinical manifestations of malignancies. Interleukine-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are inflammatory cytokines that can plays a role in the pathogenesis of autoimmune and hematological malignancies such as MDS (Braun and Fenaux 2013; Bestach et al., 2017). Although malignant clone cells in BM can be effective in the production of these cytokines, different polymorphisms in their genes may also be associated with changing serum levels of these cytokines. Rs1800629 (TNF-α-308G>A) is a polymorphism that increases the serum concentrations of TNF-α and has a well-known role in ITP disease. This change can be associated with thrombocytopenia through increased platelet destruction by T-cytotoxic ($TCD8^+$) cells (Rezaeeyan et al., 2017). Leukemic cells in hematological malignancies such as CLL and hairy cell leukemia (HCL) play a recognized role in the production of TNF-α and lymphotoxin α (LT-α), which can lead to the proliferation and increased activity of neoplastic B-cells in advanced stages of the disease. On the other hand, studies on the genome of these patients have indicated the polymorphisms associated with an increased expression of these cytokines, which can have a direct correlation with clinical findings (especially pancytopenia) in the advanced stages of these malignancies (Table 1) (Demeter et al., 1997a,b). Additionally, interleukin-1 (IL-1) and interleukin-1

receptor antagonist (IL-1Ra) poly-morphisms in CLL patients are associated with an increased risk of disease progression and the incidence of thrombocytopenia in these patients (Sirotina et al., 2014). Similarly, analysis of MDS patients' samples has raised a clear correlation between TNF-α and IL-6 polymorphisms with the occurrence of thrombo-cytopenia in these patients (Belli et al., 2011; Bestach et al., 2017). Furthermore, the polymorphisms in transforming growth factor-beta (TGF-β), which acts as a negative regulator of hematopoietic stem and progenitor cells, are associated with increased concentrations of this cytokine that can enhance cytopenia in MDS patients (Gyulai et al., 2005).

Polymorphisms in type 1 and type 2 cytokines, which are respectively produced by T helper 1 (Th1) and T helper 2 (Th2) cells, appear to be responsible for thrombocytopenia in leukemia. For example, the release of several of these cytokines in CML patients is affected by these polymorphisms (Table 1) (Amirzargar et al., 2005). Interferon-gamma (IFN-γ) is a cytokine of Th1 cells that enhances the function of macrophages, which, in turn, increase the function of Th1 cells. It has been observed that some SNPs increase the production of this cytokine in CML patients. On the other hand, polymorphisms in a number of Th2 cytokines such as interleukin-4 (IL-4) and interleukin-10 (IL-10), which are respectively involved in the modulation of Th1 responses and maintenance of tolerance, are associated with a reduced production of these cytokines in CML (Amirzargar et al., 2005). Since IFN-γ enhances the function of macrophages in clearance of platelets in ITP and as IL-10 is also required to regulate the function of autoreactive B- and T-cells in ITP (Hua et al., 2014), perhaps SNPs that cause the ectopic production of these cytokines in CML patients are related to the incidence of thrombocytopenia in the accelerated phase. Taken together, polymorphisms in various cytokines can be associated with the incidence of thrombocytopenia in chronic leukemia and MDS. However, there is little information about the association between cytokine SNPs with the incidence of thrombocytopenia in acute leukemias. Therefore, further studies are needed to confirm the relationship between cytokine polymorphisms with clinical findings, especially thrombocytopenia, in acute leukemias. The detection of these genetic changes in acute and chronic leukemias can help prevent their complications and consequently contribute to disease management.

Mutations inducing thrombocytopenia in leukemias

Chromosomal translocations and mutations in a number of genes play a key role in the development and progression of leukemias and can be effective in the pathogenesis and prognosis of these malignancies. In this regard, it has been shown that some transcription factor (TF) mutations can affect various aspects of megakaryocyte (MKs) growth, platelet production as well as function in MDS and leukemias (Songdej et al., 2017). In the following, we mention some of the most common TFs mutations in leukemias that can be associated with thrombocytopenia in these malignancies.

Runt-related transcription factor 1

RUNX1 is a transcription factor that plays an important role in regulating the expression of certain genes in the process of hematopoiesis (de Bruijn and Dzierzak, 2017). Moreover, this factor has a recognized role in the oncogenesis and progression of AML. Common translocations of RUNX1 play a role in the development of leukemias, including t(8;21)(q22;q22) or t(3;21)(q26.2;q22) in AML and t(12;21)(p13;q22) in ALL (Lutterbach and Hiebert, 2000). RUNX1 gene rearrangements affect the function of RUNX1, leading to clinical complications (including thrombocytopenia) in ALL and AML patients. For example, in a case report of a child with AML having t(8; 21), macrothrombo-cytopenia was one of the side effects of this fusion. However, this type of thrombocytopenia did not result in significant hemorrhagic complications and was associated with a favorable response to treatment (Rheingold, 2007). In contrast, (q13; q22) t(5;21), which is a rare translocation in hematological malignancies such as chronic myelomonocytic leukemia (CMML), is associated with thrombocytopenia and severe hemorrhagic complications that can lead to the death of patients whose genes harbor this fusion (Liu et al., 2004). Interestingly, Jerome Hadjadj et al. in a recent study have shown that ITP is a rare complication in CMML, especially in the elderly having cytogenetic abnormalities with no bleeding complications but a high response to standard first-line therapies (Hadjadj et al., 2014). Although in this study, cytogenetic abnormalities in patients have not been detected, cytogenetic abnormalities other than t(5;21) may be responsible for this type of thrombocytopenia. On the other hand, several studies have reported the association between different mutations of this factor with thrombocytopenia in familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML), which causes significant defects in the differentiation of MKs and increases the tendency of these abnormalities toward myeloid malignancies (Table 2) (Buijs et al., 2001; Michaud et al., 2002; Walker et al., 2002; Kirito et al., 2008).

RUNX1 mutations are the most common mutations in hematological malignancies, which have been detected in 15-37% of CMML (Kuo et al., 2009; Kohlmann et al., 2010), 5-20% of AML (Schnittger et al., 2011), and 10-15% of MDS cases (Chen et al., 2007; Dicker et al., 2010). These mutations are frequently seen in older patients with normal karyotype AML FAB (French-American-British) M0 morphology (Rose et al., 2017). Interestingly, RUNX1 domain mutations are associated with high-risk thrombocytopenia and a poor prognosis in AML and MDS patients (Owen et al., 2008). These mutations can reduce MKs maturation by disrupting the reduced expression of non-muscle myosin

Table 2. Common mutations associated with thrombocytopenia in hematological malignancies.

Annotated gene	Function	Chro.	Annotation	Mutation type	Malignancies	Outcome	Ref.
RUNX1	Binds to the core element of many enhancers and promoters and involved in the development of normal hematopoiesis	21q22.1	G→C1887	Missense	AML M2, FPD/AML	Associated with increased immature megakaryocytes in BM that leads to severe thrombocytopenia	Walker et al., 2002
			198G→T	Missense	FPD/AML,AML M1	Associated with thrombocytopenia and abnormal platelet function	Buijs et al., 2001
			102G→C	Frameshift	FPD/AML	Associated with lack of a functional C-terminal of RUNX1with increased risk of FPD/AML	Kirito et al., 2008
			G336fsX563 (C terminal)	Frameshift	T-ALL, MDS	Associated with thrombocytopenia with no bleeding	Owen et al., 2008
			A28fsX109 (N terminal)	Frameshift	AML with monosomy 5, AML with normal karyotype	Associated with thrombocytopenia, easy bruising and epistaxis	Owen et al., 2008
			D96H(N terminal)	Missense	MDS-RARS with normal karyotype, MDS-RA MLD with trisomy 8	Associated with thrombocytopenia, easy bruising but no postsurgical bleeding	Owen et al., 2008
			R292X(C terminal)	Nonsense	MDS	Associated with thrombocytopenia, with bleeding history	Owen et al., 2008
ETV6	Involved in protein-protein interactions with itself and other proteins by N- and C-terminal domain and has a role in hematopoiesis and megakaryocyte maturation	12p13.2	641C>T	Missense	ALL, Mixed-phenotype acute leukemia	Decreased megakaryocyte maturation, thrombocytopenia with nosebleeds and menorrhagia	Noetzli et al., 2015
			1252A>G	Frameshift	ALL	Decreased megakaryocyte maturation that leads to thrombocytopenia	Noetzli et al., 2015
			L394P	Missense	ALL	Associated with thrombocytopenia and tendency to bleeding	Topka et al., 2015
			N385fs	Frameshift	ALL,AML,MDS	Associated with thrombocytopenia and increased risk of ALL in MDS patients	Topka et al., 2015
			1195C>T	Frameshift	Pre-B cell ALL, MDS	Associated with thrombocytopenia with easy bruising in ALL patients and predisposition to acute leukemia in MDS patients	Noetzli et al, 2015; Zhang et al., 2015
EVI1	Involved in hematopoiesis, apoptosis, cell differentiation and proliferation	3q26.2	2266A>G	Missense	Radioulnar synostosis with amegakaryocytic thrombocytopenia, acute megakaryoblastic leukemia with trisomy 21?	Associated with development of Mendelian disorder and induced myeloid malignancies	Niihori et al., 2015
			2248C>T	Missense			
			2252A>G	Missense			
HOXA11	This transcription factor regulates morphogenesis, differentiation of megakaryocytes and involved in the regulation of uterine development	7p15.2	HOXA11-ΔH3	Deletion	Amegakaryocytic thrombocytopenia with radio-ulnar synostosis, CML?	Can lead to a loss of DNA binding, thus disrupting normal megakaryocytic differentiation	Lawrence et al., 1996; Horvat-Switzer et al., 2006
GATA1	Playing an integral role in the development of several hematopoietic cell lines, including the erythroid, megakaryocyte eosinophil, and mast cell lineages	Xp11.23	Lacks the N-terminal	Missense	AML-M7	Associated with poorer maturation of megakaryocytes that do not generate platelets	Wechsler et al., 2002; Ono et al., 2015
ANKRD26	This protein functions in protein-protein interactions and has a role in lymphocyte and megakaryocyte differentiation	10p12.1	-125T→G	A single nucleotide substitution	AML	Associated with dysmegakaryopoiesis that leads to decrease of platelet release and subsequently bleeding tendency	Noris et al., 2011
			-127A→T	A single nucleotide substitution	AML,CLL	Associated with reduction in megakaryocytes maturation that leads to decreases in platelet count in peripheral blood and subsequently bleeding tendency	Noris et al., 2011
			-134G→A	A single nucleotide substitution	AML,CML	Associated with dysmegakaryopoiesis that leads to decreases of platelet release and subsequently bleeding tendency	Noris et al., 2011

RUNX1: runt-related transcription factor 1, ETV6: ETS variant 6, EVI1: ectopic virus integration site 1, HOXA11: Homeobox A 11, ANKRD26: ankyrin repeat domain 26, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia, CLL: chronic lymphoblastic leukemia, MDS: myelodysplastic syndrome, FPD/AML: familial platelet disorder with predisposition to acute myeloid leukemia, BM: bone marrow

IIA (MYH9) and IIB (MYH10) (Bluteau et al., 2012; Lordier et al., 2012). Since RUNX1 regulates the expression of some genes and pathways in MKs and platelets, RUNX1 mutations have been shown to be highly related to defective platelet production and function in leukemias and the subsequent incidence of thrombocytopenia (Michaud et al., 2008). Thus, with respect to the association of RUNX1 mutations with thrombocytopenia, analysis of the RUNX1 mutation in patients with leukemia, especially AML and MDS, is likely to be helpful in managing the patients and choosing the appropriate treatment protocols to prevent this complication.

ETS variant 6

ETV6 is a known tumor suppressor from the EST family and an important factor in the final development of MKs (Hock et al., 2004; Kar and Gutierrez-Hartmann, 2013). The absence or reduction of this factor in animal models is associated with reduced colony formation of MKs and consequent thrombocytopenia (Wang et al., 1998). ETV6-RUNX1 translocation in ALL and AML patients with t (12,12) is often accompanied with somatic mutations in ETV6, which causes the loss of function of this factor (Romana et al., 1996; Barjesteh van Waalwijk van Doorn-Khosrovani et al., 2005). Moreover, these mutations have been reported in inherited thrombocytopenia, primarily B-cell ALL, and 1% of children with ALL (Moriyama et al., 2015; Noetzli et al., 2015; Zhang et al., 2015). Comparison of the samples of these patients with normal samples indicates an increase in immature MKs and a decrease of platelet counts in PB. Also, these patients exhibit variable degrees of thrombocytopenia and disrupted platelet function following ETV6 mutations (Zhang et al., 2015). These findings suggest that these mutations may influence ETV6 function, causing impaired MKs development and platelet production, which result in thrombocytopenia in these patients.

Ectopic virus integration site 1

EVI1 is a transcription factor that plays an important role in self-renewal and differentiation of hematopoietic stem cells (HSCs) following interaction with other TFs such as GATA1 and RUNX1 (Kataoka et al., 2011; Niihori et al., 2015). Defective MKs differentiation has been reported in animal models lacking EVI1, which indicates the involvement of this factor in MKs development (Buonamici et al., 2004). Furthermore, a mutation in this factor is associated with a significant decrease of MKs in BM, the incidence of thrombocytopenia, increased risk of myeloid leukemias in radio-ulnar synostosis and congenital amegakaryocytic thrombocytopenia (CAMT) (Niihori et al., 2015). On the other hand, RNA binding motif protein 15 (RBM15) and EVI1 translocation [t(1.21)/RBM15/EVI1] is a rare cytogenetic abnormality in children with acute megakaryoblastic leukemia with trisomy 21 (Shahjahani et al., 2015), a fusion that disrupts a number of signaling pathways in megakaryoblasts. Although the presence of EVI1 mutations has not been detected in acute megakaryoblastic leukemia, unknown EVI1 mutations may be associated with a risk of thrombocytopenia and a poor prognosis in these patients.

GATA1

GATA1 is a transcription factor that plays a crucial role in megakaryopoiesis and erythropoiesis by binding to the GATA motif of DNA (Shivdasani et al., 1997; Orkin et al., 1998). Inherited mutations that cause defective binding of GATA1 N-terminal to palindromic DNA binding sites are responsible for several congenital thrombocytopenias and dyserythropoietic anemias (Nichols et al., 2000; Freson et al., 2002). In addition, those with GATA1 mutation lacking this functional factor show rather reduced platelet aggregation in response to collagen and ristocetin (Hughan et al., 2005). Recently, the GATA1 mutation has been recognized as a reason for thrombocytopenia in X-linked thrombocytopenia and AML-M7 with acquired trisomy 21 (Wechsler et al., 2002; Ono et al., 2015). As GATA1 plays a major role in the growth and development of MKs, it seems that mutations causing the loss or decrease of this factor can contribute to thrombocytopenia in patients with hematological malignancies.

HOXA11

Translocations involving chromosome 11q 23 are among the most common chromosomal abnormalities in human hematological malignancies (Borrow et al., 1996; Nakamura et al., 1999; Wong et al., 1999). Homeobox (HOX) proteins are a group of oncoproteins in HSCs that are encoded in this region, and their expression is reduced during maturation (Lawrence et al., 1996). A number of HOX gene mutations in the pre-leukemic precursors inhibit the differentiation of these cells, which is associated with a poor prognosis (Hess et al., 2006). HomeoboxA 11 (HOXA11) is a member of homeobox TFs family, which plays a role in MKs differentiation and bone morphogenesis (Magli et al., 1997). Karyotype analysis in leukemic cells of CML patients indicates the presence of t (7; 11) (p15; p15) chromosomal translocation in these patients, which causes nucleoporin 98 (NUP98) gene fusion with HOXA11 and disease progression to the blastic phase (Fujino et al., 2002). On the other hand, a direct correlation has been recently reported between the mutation of HOXA11 and the incidence of thrombocytopenia in patients with radio-ulnar synostosis and congenital amegakaryocytic thrombocytopenia (CAMT) (Thompson and Nguyen, 2000; Horvat-Switzer and Thompson, 2006). Considering the involvement of HOXA11 in MKs differentiation and the incidence of thrombocytopenia

following heterozygous mutations of HOXA11 gene, the prevalence of thrombocytopenia in CML patients in the accelerated phase may be attributed to the coexistence of t (7;11) (p15;p15) and HOXA11 gene mutations that could lead to this disorder in patients through the loss of normal function of HOXA11.

ANKRD26

Besides the role of TFs mutation in the development of thrombocytopenia, mutations in regulators of these factors can also be associated with thrombocytopenia. For example, ankyrin repeat domain 26 (ANKRD26) is a protein in the internal cell membrane that interacts with signal transduction proteins (Bluteau et al., 2014). It also plays an important role in MKs maturation as well as T- and B-cell differentiation. It has been shown that the deficiency of this factor can be associated with MKs maturation arrest and defective T- and B-lymphocyte development (Noris et al., 2011). Hereditary mutations in the 5'-untranslated region of ANKRD26 that result in the loss of function of this protein are responsible for thrombocytopenia in patients with inherent thrombocytopenia (Noris et al., 2011). It has also been shown that ANKRD26 mutations can lead to a similar phenotype with RUNX1 mutations in patients with CML, CLL, AML, and MDS, which is often associated with thrombocytopenia in these patients (Table 2) (Pippucci et al., 2011).

In general, mutations in some TFs can be associated with the disruption of MKs maturation as well as platelet production and function, which result in thrombocytopenia. Identification of these genetic changes in leukemic patients can open new perspectives on clinical outcomes and prognosis of these genetic abnormalities in patients.

Discussion

Thrombocytopenia is a clinical symptom in leukemias that is commonly associated with a poor prognosis due to hemorrhagic complications. In addition to BM replacement with leukemic cells, many other factors can be effective in the incidence of thrombocytopenia, including genetic abnormalities (polymorphisms and mutations), increased platelet destruction in PB, and chemotherapy. Therefore, several studies have been conducted to evaluate the cause of this disorder in leukemic patients, which have indicated that thrombocytopenia is a poor prognostic factor in these patients and requires a proper diagnosis of etiology for its management. Normally, BM microenvironment contains different hematopoietic progenitor cells, and there is a balance between the proliferation and differentiation of these cells. However, the imbalance between proliferation and differentiation of hematopoietic progenitors in the neoplastic niche in leukemia can play a crucial role in the pathophysiology of these malignancies (Saki et al., 2011; Azizidoost et al., 2014). In these conditions, an increased number of leukemic cells in BM can lead to defective megakaryopoiesis. In this regard, Jayanta Kumar Das et al. in their recent study have shown that decreased number of megakaryocytes, as well as dysplastic forms of these cells, can be associated with thrombocytopenia in leukemia, especially AML, ALL, and CML in blastic phase (Das et al., 2017). However, the exact mechanism of association between the increase in leukemic cells with dysmegakaryopoiesis in these malignancies has not been elucidated. Our hypothesis here is that the blast cells are likely to occupy the MKs niche in BM during blastic phases of acute leukemia and CML due to rapid leukocytosis and prevent the normal proliferation and differentiation of MKs. Furthermore, since MKs are derived from a precursor distinct from lymphoid and myeloid precursors, dysplastic forms of MKs can suggest the presence of genetic changes such as polymorphism and mutation in genes that are associated with their maturity. Although thrombocytopenia of leukemia is often a function of BM failure in patients, it may occur as an adverse effect of chemotherapy. In the latter case, increasing dosage of drugs or the occurrence of genetic changes such as polymorphism in their degrading enzymes can lead to this complication, which is associated with a poor prognosis (Kantar et al., 2009; Koomdee et al., 2012; Ponte et al., 2017). Moreover, certain therapeutic protocols may be responsible for thrombocytopenia in leukemia. For example, acute immune thrombocytopenia is a rare side effect of Fludarabine, which was first reported in CLL patients exposed to this drug in 1994 (Montillo et al., 1994). This complication is associated with symptoms such as epistaxis, skin petechiae, and poor prognosis in patients. Interestingly, BM biopsy and PB assessment in patients show normal MKs and the lack of antiplatelet antibodies (Fernandez et al., 2003). Although Cyclosporine and rituximab can be effective in the treatment of this type of thrombocytopenia, Fludarabine-associated immune thrombocytopenia is refractory to standard therapies for thrombocytopenia such as corticosteroids, eltrombopag, second-generation thrombopoietin receptor agonists, and IVIG (Hegde et al., 2002; Fernandez et al., 2003). In contrast, the use of rituximab to treat patients with HCL can lead to hemorrhagic thrombocytopenia in some patients (Thachil et al., 2006). Despite the fact that chemotherapy drugs can have a significant effect on the control and treatment of leukemia, thrombocytopenia after high-dose chemotherapy is a clinical problem in young girls and women with hematological malignancies (Meirow and Nugent, 2001). Meirow et al. demonstrated that thrombocytopenia was an adverse effect of luteinizing hormone-releasing hormone agonist and depo-medroxyprogesterone acetate (DMPA) in females exposed to a high dose of these chemotherapic agents (Meirow et al., 2006). In such conditions, menorrhagia can be a serious bleeding complication in women of reproductive age (Meirow et al., 2006). On the other hand, some chemotherapy drugs affect women's sex

hormones and can cause disruption of menstruation, which leads to uterine bleeding (Müller, 2003). Therefore, it is understood that the incidence of thrombocytopenia in females with leukemia can be associated with a poorer prognosis than in males. In addition, thrombocytopenia may follow immune dysregulation in leukemic patients (Mauro et al., 2000). In this case, a range of abnormalities in different cell populations, including decreased T regulatory (Treg) cells and ectopic production of cytokines, can be associated with the production of autoantibodies against platelets and thrombocytopenia in leukemia (Amirzargar et al., 2005; Hamblin, 2006). Moreover, polymorphisms in functional T-cell regulators such as CTLA-4 and ICOS are associated with an increased risk of autoimmune complications in B-CLL (Suwalska et al., 2008; Karabon et al., 2011). On the other hand, SNPs in a number of inflammatory cytokines such as TNF-α and IL-1 in malignant B-cells are associated with increased secretion of these cytokines, which can lead to immune thrombocytopenia in these patients (Demeter et al., 1997b; Sirotina et al., 2014). Fludarabine is also likely to play a major role in the incidence of this disorder by suppressing $TCD4^+$ cells and increasing the malignant B-cell function (Kipps and Carson, 1993). On the other hand, rituximab can inhibit the exacerbation of thrombocytopenia through interfering with platelets clearance by macrophages (Hegde et al., 2002).

Despite the positive effect of IM in the treatment of CML patients, the second generation of tyrosine kinase inhibitors (TKIs) such as dasatinib, nilotinib, and bosutinib can also be effective in the treatment of patients who do not respond to IM (Cortes et al., 2007; Hochhaus et al., 2007; Kantarjian et al., 2007; Awidi et al., 2017). Although these TKIs have a significant effect on the treatment of CML patients, some adverse effects of these drugs (like thrombocytopenia) may complicate the process of treatment. The importance of this issue is manifested when 10-15% of patients receiving IM (Druker et al., 2006) and over 50% of patients treated with second-generation TKIs show thrombocytopenia (Hochhaus et al., 2007; Kantarjian et al., 2007). Given the importance of thrombocytopenia in CML patients, genetic studies on the genome of these patients have shown that polymorphism in drug carrier enzymes such as ABCB1, ABCG2, and OCT1 is another major cause of this disorder in these patients (Francis et al., 2015). Similarly, polymorphism in enzymes such as TPMT, MTHFR, and GGH that are involved in the metabolism of drugs like MTX and 6-MP leads to incomplete metabolism and the resulting increase in the concentration of these drugs in AML and ALL patients (Kantar et al., 2009; El-Khodary et al., 2012; Koomdee et al., 2012). Consequently, this increased concentration leads to thrombocytopenia in these patients. In fact, these findings suggest that besides the drug dose, the genetic background of patients may also have an effective role in the appearance of clinical findings of a particular treatment protocol. On the other hand, many patients with leukemia need to receive platelets to prevent bleeding from thrombocytopenia, which is associated with an increased risk of viral and bacterial infections in patients (Wallace et al., 1995). Despite the effective role of antibiotics such as amphotericin B and vancomycin in preventing these infections, various degrees of thrombocytopenia have been reported in patients after receiving these antibiotics (Matthews and Yuen, 1992). Although the precise mechanism of thrombocytopenia induction by amphotericin B is not known, vancomycin-dependent antibodies are responsible for thrombocytopenia in patients taking this antibiotic (Christie et al., 1990). Although the differentiation of thrombocytopenia due to chemotherapy drugs from cytopenia because of BM failure is a difficult task, mutations in TFs such as RUNX1, ETV6, EVI1, GATA1, and ANKRD26, which are involved in MK differentiation and platelet production, can also play a major role in thrombocytopenia in leukemias. The mutations associated with these TFs can be related to the occurrence of thrombocytopenia in leukemias by affecting different aspects in the growth of MKs, as well as platelet production and function (Wechsler et al., 2002; Kuo et al., 2009; Noris et al., 2011; Noetzli et al., 2015).

Overall, we conclude that thrombocytopenia is a marker of poor prognosis in leukemias. Besides BM deficiency and underlying diseases, factors such as the treatment protocol, defective metabolism of chemotherapy drugs, ectopic production and expression of some immune system factors as well as genes involved in MKs differentiation and platelet production can play a role in the development of thrombocytopenia. It seems that the toxic effects of chemotherapeutic agents and mutation of TFs play a key role in the incidence of thrombocytopenia in ALL children and adults with AML, respectively. However, thrombocytopenia in chronic leukemia can often be related to SNPs in the immune mediators. Although there have been no studies to compare the prognosis of thrombocytopenia in acute and chronic leukemias, it seems that acute leukemias are associated with a poorer prognosis than chronic leukemias due to a rapid progression of the former. Also, due to the menstrual process, thrombocytopenia may be associated with a poorer prognosis in females than males. Therefore, the correct diagnosis of the underlying cause of thrombocytopenia at the onset of the disease, as well as timely decision-making and clinical management, can prevent the poor prognosis of this disorder and help improve the patient's conditions.

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Compliance with ethical standards

Conflict of Interest. The authors declare no conflict of interest.
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