Thrombocytopenia in solid tumors: Prognostic significance

Majid Ghanavat,[1] Mina Ebrahimi,[2] Hassan Rafieemehr,[3] Mahmood Maniati,[2] Masumeh Maleki Behzad,[2] Saeid Shahrabi[4]

[1]Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan; [2]Thalassemia and Hemoglobinopathy Research Center, Research Institute of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz; [3]Department of Medical Laboratory Sciences, School of Paramedicine, Hamadan University of Medical Sciences, Hamadan; [4]Department of Biochemistry and Hematology, Faculty of Medicine, Semnan University Of Medical Sciences, Semnan, Iran

Abstract

Solid tumors are a heterogeneous group of malignancies that result from out-of-control proliferation of cells. Thrombocytopenia is a common complication among patients with solid tumors that predispose them to bleeding disorders. The aim of this review article is to investigate the underlying mechanisms of the risk and incidence of thrombocytopenia in solid tumors. It can be argued that thrombocytopenia is a poor prognostic factor in solid tumors that can result from several factors such as polymorphism and mutation in some transcription factors and cytokines involved in megakaryocytic maturation or from the adverse effects of treatment. Therefore, an understanding of the exact mechanism of thrombocytopenia pathogenesis in each stage of solid tumors can help in developing therapeutic strategies to decrease bleeding complications in these malignancies.

Correspondence: Saeid Shahrabi, Department of Biochemistry and Hematology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran.
E-mail: sshahrabi45@yahoo.com

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Introduction

Solid tumors are a heterogeneous group of malignancies that originate from abnormal growth of different cells.[1] Thrombocytopenia is a common complication in solid tumors that have a direct relationship with platelet count level.[2] It is evident that the incidence of thrombocytopenia in solid tumors depends not only on the platelet count, but also other aspects of underlying disease such as infiltration of megakaryocytes (MKs) in bone marrow (BM) niche by malignant cells,[3] a consequence of chemotherapy or radiation therapy, diffuse intravascular coagulation (DIC), and immune conditions including paraneoplastic syndrome (PNS) can be associated with incidence of thrombocytopenia in these malignancies.[4] Two major causes of thrombocytopenia in solid tumors are mutation and single nucleotide polymorphisms (SNPs) in genes such as cytokines and transcription factors (TFs) that are involved in platelet maturation and production. Thrombocytopenia has been correlated with poor prognosis in a variety of solid tumor types including cancers of the breast, lung, ovaries, as well as colorectal cancer. In fact, these cancers patients have been reported to be a greater risk of hemorrhagic complication than healthy individual or patients without thrombocytopenia. While infusion of platelet-rich plasma reverses this effect,[5] management and reduction of thrombocytopenia complication vary considerably depending on the etiology, severity and duration of thrombocytopenia. It seems, identifying the exact underlying mechanism of thrombocytopenia is essential for the timely prevention of serious bleeding complication in solid tumors. Therefore, in the following, we discuss the most common underlying mechanisms of thrombocytopenia and their possible role in prognosis of solid tumors.

Cytokine polymorphism-induced thrombocytopenia in solid tumors

Cytokines are important biological agents secreted in response to a wide range of cellular changes such as inflammation and damage from malignant tumors. Studies have shown that genetic alteration such as SNPs can alter cytokine secretion and function, which can lead to side effects such as thrombocytopenia.[6] For example, SNPs in some inflammatory cytokines may be associated with thrombocytopenia in immune thrombocytopenic purpura (ITP) and leukemia.[7,8] In this regard, we enumerate some of the most common cytokine SNPs that can be associated with thrombocytopenia in solid tumors.

Interleukin-1

IL-1 is an important inflammatory cytokine produced by macrophages, epithelial cells and monocytes and plays an important role in the regulation of megakaryopoiesis and autoantibody production.[9] This cytokine has three members, namely IL-1α, IL-1β and interleukin-1 receptor antagonist (IL-1Ra), the first two of which are expressed in inflammatory conditions and the latter has an anti-inflammatory role.[9] Recently, Yadav *et al*. showed that -31T>C SNP is associated with increased expression of IL-β gene and thus severe thrombocytopenia in ITP.[10] Also, it has been shown that by increasing the expression of IL-β -31T>C SNP is associated with incidence of thrombocytopenia in a wide range of solid tumors such as breast, lung, prostate cancer and colorectal neoplasia (Table 1).[11-14] The IL-1β is a potent pro-inflammatory cytokine which causes disturbance in the T helper (Th) cells imbalance leading to overproduction of inflammatory cytokine.[15] Although the exact mechanism of association between IL-1β SNPs and thrombocytopenia incidence in solid tumors has not been clearly identified, it may be, by increasing IL-1β expression as well as platelet clearance activation of macrophages and T cells, -31T>C SNP increased susceptibility to thrombocytopenia incidence in these malignancies. Interestingly, previous studies reported that some cases of IL-1β SNPs in ITP were associated with helicobacter pylori (*H. pylori*) infection.[16] On the other hand, IL-1β -31T>C SNP combined with H. pylori is associated with gastric cancer susceptibility.[17,18] It seems gastric cancer patients bearing this polymorphism are most likely to have hemorrhagic complications. However, this hypothesis should be confirmed in future studies. Overall, IL-1β -31T>C SNP appears to be involved in the incidence of thrombocytopenia by affecting the mechanisms involved in inflammatory condition as well as platelets destruction that can be associated with poor prognosis in solid tumors.

Interleukin-6

IL-6 is a glycoprotein that plays a role in various physiologic and pathophysiologic processes such as inflammation, infection and carcinogenesis. The -174 G/C polymorphism increases the expression of IL-6 levels, which is also confirmed in the ITP pathogenesis.[19] This polymorphism has been reported in many malignancies including adenocarcinoma and hepatocellular carcinoma, along with colorectal, lung, gastric, and ovarian cancers.[11,20-25] The possible role of IL-6 -174 G/C SNP in the incidence of thrombocytopenia, especially GG genotype, could be related to the induction of antibody production against platelets. This finding suggests that this type of polymorphism is likely to enhance poor clinicopathological outcomes such as bleeding in solid tumors. In addition, IL-6 is one of the most important pro-infammatory cytokines involved in the pathogenesis of cancers such as hepatocellular carcinoma. On the other hand, spontaneous bleeding due to rupture of hepatocellular carcinoma is often a life-threatening complication and a poor prognostic factor in this disease.[26] Because of the association between IL-6 -174 G/C SNP and the increased risk of thrombocytopenia, this genetic variant probably contributes to the incidence of thrombocytopenia in solid tumors by inducing circulating IL-6 level and thus inflammatory processes which are associated with platelet destruction.

Tumor necrosis factor-α

Tumor necrosis factor-α (TNF-α) is one of the most important inflammatory cytokines that and several studies have demonstrated the association of G/A polymorphism in -308 loci of its gene with ITP pathogenesis.[27-29] In addition, the presence of this SNP has been reported in many solid tumors including breast, lung, gastric, hepatocellular, prostate, colorectal, and ovarian cancers (Table 1).[30-35] Breast and ovarian are the most malignant tumors among women that can be associated with poor clinical outcome such as menorrhagia and serious problems including loss of fertility. Since TNF-α -308 G/A SNP is associated with the incidence of thrombocytopenia, women with solid tumors at reproductive age who carry this SNP are at a greater risk of serious bleeding complication compared with men. It follows that identification of predictive/prognostic risk factors in women with solid tumors may improve clinical management. In addition, given the importance of the presence of bleeding complication in gastric and colorectal cancers, especially in young and elderly male patients,[36] clinicians must pay more attention to patients' genetic background in order to have an appropriate management of tumor bleeding.

The effect of TFs expression on the incidence of thrombocytopenia in solid tumors

TFs regulate the expression of their target genes by binding to the DNA. Given that a number of TFs play an important role in MKs maturation and platelet production, we will enumerate some of the alteration in TFs expression and their possible underlying mechanism that can be associated with the incidence of thrombocytopenia in solid tumors.

GATA3. The GATA family is a group of zinc finger DNA-binding protein TFs that control differentiation of the hematopoietic stem cells (HSCs) into different cell types and has six members from GATA1 to 6.[37] GATA3 plays a role in T cell development by inducing Th2 development and Th1 suppression.[38] Yao *et al*. have shown that by downregulation of T-bet, a Th1-specific TF, GATA-3 plays a critical role in imbalance of Th1/Th2 ratio as well as ITP pathogenesis.[39] Recently, it has been shown that overexpression of GATA3 is associated with an unfavorable prognosis in breast cancer patients. Since Th2 cells are involved in B cell activation and antibody production in ITP,[40,41] mutations associated with GATA3 overexpression can be considered as a potent stimulator of platelets destruction as well as poor prognosis for thrombocytopenia incidence in breast cancer.[42]

Table 1. Common cytokines polymorphisms and mutation, which are associated with thrombocytopenia in solid tumors.

Gene	Chr.	Rs number	Polymorphism	Malignancies	Mechanism	Ref.
IL-1β	q14.12	rs1143627	-31T>C	BC, PC, LC, CN	Can be associated with platelet clearance by inducing pr-inflammatory cytokines	10-14
IL-1 RaII	2q12	NR	Allele II	GC	Decrease neutralization effect of IL-1	17
IL-6	7p15.3	rs1800795	-174G/C	BC, AD, HC, CC, LC, GC, OC	Associated with antibody production against platelets	11,20-25
TNF-α	p21.336	rs1800629	-308G/A	BC, LC, GC, HC, PC, CC, OC	Increased level of TNF- and destruction of platelets	14,27,30,35

IL-1, interlukin-1; IL-6, interlukin-6; TNF-α, tumor necrosis factor alpha; BC, breast cancer; PC, prostate cancer; LC, lung cancer; CN, colorectal neoplasia; AD, adenocarcinoma; HC, hepatocellular carcinoma; CC, colorectal carcinoma; OC, ovarian cancer; GC: gastric cancer; NR, not reported.

ETS variant 6

ETS variant 6 (ETV6) is a tumor suppressor of the ETS family that plays a role in the megakaryopoiesis through DNA binding domains.[43] It has been shown that gremlin mutations in ETV6 which is related to the absence or reduction of this factor in human and animal models are associated with decreased of MKs maturation and consequent thrombocytopenia.[44,45] In addition to mutations, translocations that result in loss of function of ETV6 have been reported as the causes of thrombocytopenia in different diseases. For example, the fusion of ETV6/ neurotrophic tyrosine receptor kinase3 (NTRK3), a transmembrane surface receptor on the surface of neuronal and non-neuronal cells, can lead to the loss of ETV6 function in radiation-associated thyroid and breast cancer (Table 2).[46,47] These findings suggest that ETV6/NTRK3 fusion may causing impaired MKs maturation, increased platelets production, and subsequently thrombocytopenia in solid tumors patients.

Ecotropic viral integration site-1

Ecotropic viral integration site-1 (EVI-1) is an oncogenic TF factor that play an important role in proliferation, differentiation and self-renewal of HSCs and MKs maturation.[48] It has been shown that the expression of transforming growth factor β1 (TGF-β1) and its receptors (TGF-βR) plays a vital role in the pathogenesis of the ITP.[49] On the other hand, due to overexpression of EVI-1 and inhibition of the TGF-β1 signaling pathway, EVI-1 plays a role in the pathogens of colorectal cancer.[50] Similarly, the presence of rs6774494 A> G polymorphism in EVI-1 can lead to an increase in the expression of this TF as well as increased susceptibility to breast cancer.[51] Although overexpression of EVI-1 is associated with increased risk of colorectal and breast cancer, it seems patients with high EVI-1 expression experience low thrombocytopenic complications due to TGF-β1 signaling pathway suppression.

Homeobox (HOX) genes

Homeobox (HOX) genes encode a group of binding proteins that play an important role in proliferation, self-renewal, and differentiation of HSCs and tumor suppressors.[52] Homeobox A 11 (HOXA11) is a member of the homeobox TFs family, which has a well-known role in MKs differentiation.[53] Studies have shown that HOXA11 mutation can be associated with thrombocytopenia in amegakaryocytic thrombocytopenia with radio-ulnar synostosis syndrome by inhibiting megakaryocytic differentiation.[54] Several studies have shown that hypermethylation in the HOXA11 promoter region results in low expression of the HOXA11 gene and is associated with increased risk and unfavorable prognosis of gastric, breast, and lung cancers.[55-57] Considering the involvement of HOXA11 in MKs differentiation and the incidence of thrombocytopenia following low HOXA11 expression, demethylation drugs may be useful as a therapeutic strategy to reduce thrombocytopenia and its adverse effects in solid tumor patients. In addition, mutation and decreased expression of non-muscle myosin IIA (MYH9), a TFs involved in MKs maturation, is associated with thrombocytopenia in familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML) and gastric carcinoma.[58,59] Thus, with regard to the association of MYH9 mutations with thrombocytopenia, analyzing its mutations in patients with solid tumors is likely to be helpful in managing thrombocytopenic events and choosing appropriate treatment protocols to prevent bleeding complication.

Discussion

The incidence of hemorrhagic complication is relatively commonplace in patients with solid tumors and has a direct relationship with platelet counts. Beside platelet counts, numerous factors have been suggested to increase the risk of thrombocytopenia in solid tumors including the effect of genetic abnormalities (polymorphisms and mutations), chemotherapeutic agents side effect, and imbalance of immune cells, which are involved in platelets destruction. Despite the administration of prophylactic platelet transfusions, patients with solid tumors remain at risk of clinically significant hemorrhages. Therefore, proper diagnosis of thrombocytopenia etiology in solid tumors is important for the management of its bleeding complication. Normally, MKs differentiates to mature platelets is under the influence of some TFs expression and cytokines secretion. It seems infiltration of the BM by tumor cells and incidence of mutations and SNPs in TFs and cytokines can lead to defective megakaryopoiesis. In addition, solid tumor patients can show refractory thrombocytopenia in response to chemotherapeutic agents. For example, tamoxifen, doxorubicin, paclitaxel, and cisplatin can induce thrombocytopenia due to

Table 2. Common alteration expression of genes that associated with thrombocytopenia in solid tumors.

Gene	Chr.	Function	Mutation/expression and translocation	Malignancy	Outcome	Ref.
GATA3	10p14	T cell development, kidneys, mammary gland, epithelial cells, central nervous system development	High expression of GATA3	BC	Imbalance T-bet/GATA3 ratio and promotes thrombocytopenia due to increase IFN-γ, IL-6 *etc.*	42
ETV6	12p13.2	Plays a role in megakaryopoiesis	ETV6-NTRK3 translocation t(12;15)	BC, TT	Associated with disruption of MKs maturation	46,47
EVI-1	3q26.2	Proliferation, differentiation and self-renewal of HSCs and MKs maturation	Over expression of EVI-1	CC	May be associated with low thrombocytopenic complications due to TGF-β1 signaling pathway suppression	50,51
			rs6774494 A > G polymorphism	BC		
HOXA11	7p15.2	Tumor suppressor, proliferation, differentiation and self-renewal HSCs	H3,ypermethylation in promoter region of HOXA11	GC, BC, OC, LC	Dysregulation of MKs maturation as well as platelets production	55-57

ETV6, ETS variant6; EVI-1, Ecotropic viral integration site-1; HOX, Homeobox (HOX) genes; HSCs, Hematopoietic stem cells; MKs, megakaryocytes; NTKR3, Neurotrophic tyrosine receptor kinase3; TGF-β, transforming growth factor beta 1; IFN-γ, Interferon gamma; MYH9, non-muscle myosin IIA; BC, breast cancer; TT, thyroid tumors; CC, colon cancer; GC, gastric cancer; OC, ovarian cancer; LC, lung cancer.

inducing IL-1β, IL-6 production in solid tumors.[60-64] It is likely chemotherapeutic agents deregulate MKs maturation and lead to thrombocytopenia as a side effect. In patients with solid tumors, few studies have been conducted to deal with the independent predictive role of imbalance Th cell subtypes in the risk of thrombocytopenia to provide estimates of their impact on the severity of bleeding. Many abnormal cellular immune modulations have been described in patients with ITP such as decreased regulatory T (Treg) cells and increased Th1 and Th17 levels and their cytokine secretion.[65] By secretion of IL-17 and interferon gamma (IFN-γ), as potential inflammatory cytokines, Th17 and Th1 play a crucial role in ITP pathogenesis.[66-68] Several studies have also shown that Th17 frequencies are elevated in patients with gastric, lung, and colorectal cancers and play a critical pathogenic role in these malignancies.[69-71] Considering the role of increased Th17 and Th1 as well as decreased Treg/Th17 ratio in ITP pathogenesis, it is suggested that these abnormalities could be associated with thrombocytopenia in solid tumors. Similar to Th17 cells, Th1 cells can be involved in thrombocytopenia incidence via production of IFN-γ and IL-2 that stimulate platelets clearance by macrophages.[65] Moreover, IFN-γ +874 A/T polymorphism increases the level of IFN-γ expression and plays an important role in susceptibility to autoimmune and solid tumor diseases.[64,72-74] Although the possible associations between this SNP with thrombocytopenia have not been systematically investigated, IFN-γ +874 A/T SNP can be associated with a decrease in platelet count and all severities of bleeding in solid tumors. Although platelet transfusion is usually recommended for adult and pediatric patients who undergo autologous and allogenic stem-cell transplantation and invasive procedures,[75] physicians are recommended to consider platelet transfusion in patients with solid tumor who have risk factors such as SNPs and mutations in genes that are involved in MKs maturation and side effect of chemotherapeutic protocols especially in females at fertility age. This strategy may be helpful in successful management of hemorrhage complication of patients.

Conclusions

Several factors such as polymorphism and mutation in some TFs and cytokines, and effects of treatment could be associated with the incidence of thrombocytopenia in solid tumors. In spite of the importance of serious bleeding complication in solid tumors, few studies have yet analyzed the exact mechanisms of the impact of SNPs and mutation in the incidence of thrombocytopenia in solid tumors. A careful evaluation of these genetic changes and a better understanding of their role in the incidence of thrombocytopenia can be helpful in choosing the most appropriate treatment protocols, even based on genetic backgrounds of patients to improve their clinical conditions.

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