Review Article

Incidence and management of non-immune platelet transfusion refractoriness: a narrative review

Takeshi Hagino[1#], Tomohiko Sato[2#], Nelson Hirokazu Tsuno[3], Tetsunori Tasaki[2]

[1]Department of Hematology, Tama-Hokubu Medical Center, Tokyo Metropolitan Health and Medical Treatment Corporation, Tokyo, Japan; [2]Division of Transfusion Medicine and Cell Therapy, The Jikei University Hospital, Tokyo, Japan; [3]Japanese Red Cross Kanto-Koshinetsu Block Blood Center, Tokyo, Japan

Contributions: (I) Conception and design: T Hagino, T Sato, NH Tsuno; (II) Administrative support: T Hagino, NH Tsuno, T Tasaki; (III) Provision of study materials or patients: NH Tsuno; (IV) Collection and assembly of data: T Hagino, T Sato, NH Tsuno; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Takeshi Hagino, MD. Department of Hematology, Tama-Hokubu Medical Center, Tokyo Metropolitan Health and Medical Treatment Corporation, 1-7-1 Aobachou, Higashimurayama-shi, Tokyo 189-8511, Japan. Email: hagip.homa@gmail.com.

Objective: This article aimed to describe incidence and management of non-immune platelet transfusion refractoriness (PTR) by referring to existing related literature and our clinical experience.

Background: Platelet transfusions are indicated to either stop serious bleeding in trauma and surgical patients (therapeutic administration) or prevent bleeding in patients with thrombocytopenia or platelet dysfunction (prophylactic administration). The effectiveness of platelet transfusion is evaluated by measurement of platelet count and post-transfusion corrected count increment (CCI). When the post-transfusion platelet count is lower than expected, PTR is suspected, which is an important issue especially in patients requiring frequent platelet transfusions such as hematological patients.

Methods: The medical literature of published observational/investigational studies, randomized controlled trials or systematic reviews and meta-analyses regarding non-immune and immune PTR were searched in November 2020 and analyzed.

Conclusions: PTR occurs in 30–70% of patients receiving transfusion due to various conditions of thrombocytopenia, with or without bleeding. The etiology of PTR can be separated into non-immune and immune. Non-immune PTR is more frequent than immune PTR, accounting for about two-thirds of refractory cases. If non-immune PTR is not appropriately diagnosed and managed, the subsequent platelet transfusions can elevate the risk of alloantibody production, leading to immune PTR. When PTR is suspected in patients receiving multiple platelet transfusions, potential causes of non-immune PTR should be promptly investigated prior to assessing alloimmunization profiles including anti-human leukocyte antigen (HLA) antibodies and platelet-specific alloantibodies. Appropriate management of non-immune PTR can consist of four steps: (I) Consider appropriate indication of platelet transfusion to avoid adverse events and alloimmunization, (II) investigate the causes of PTR, (III) select the best treatment plan according to the etiology of PTR, (IV) consider the coexistence of non-immune and immune causes.

Keywords: Platelet transfusion; platelet count; refractoriness; corrected count increment; non-immune cause

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Introduction: Incidence of non-immune platelet transfusion refractoriness

Platelet transfusions are indicated therapeutically for trauma and surgical patients, or prophylactically for patients with thrombocytopenia or platelet dysfunction. Although bleeding is a concern in patients with severe thrombocytopenia, the correlation between platelet count and bleeding risk is unclear. Hence, bleeding risk should be clinically assessed by underlying diseases, prior bleeding episodes, presence of purpura and so on (1). In invasive procedures such as surgery, prophylactic transfusion is used to maintain a platelet count of above 50×10^9/L until hemostasis is ensured (2,3). For spinal fluid testing, the British Committee for Standards in Haematology recommends a platelet count of above 50×10^9/L (4) and the American Society of Clinical Oncology recommends a platelet count of above 20×10^9/L (5). These thresholds should be used as guides, and it is important to prioritize clinical judgment based on individual patient and disease factors.

As platelet concentrate (PC) products are stored at room temperature, they have a shorter shelf-life and a higher risk of bacterial contamination compared to other products such as red blood cells and plasma (6,7). Native plasma, in which supplied PCs are suspended, can increase the risk of non-hemolytic transfusion reactions such as febrile and allergic reactions (8,9). Moreover, 30% to 40% of cases with platelet transfusions can show inadequate platelet count increment due to various causes (10,11).

Platelet transfusion refractoriness (PTR) is defined as a response significantly lower than expected to at least two consecutive platelet transfusions (12). Typically, PTR can develop in patients with hematological cancers, who usually require repeated platelet transfusions (13-17). The exact incidence of PTR is unknown, but it has been reported to occur in 30–70% of multi-transfused patients (13,14,17-20). PTR is often multifactorial and it can be due to non-immune and immune causes. About two-thirds of refractory cases are classified as non-immune PTR, in which platelet survival is shortened by various underlying conditions such as fever/sepsis, splenomegaly, hematopoietic stem cell transplantation (HSCT), disseminated intravascular coagulation (DIC), graft-versus-host disease (GVHD), vaso-occlusive diseases (VOD), drug-induced thrombocytopenia and hemorrhage (10,11,12,17). The remaining cases are classified as immune PTR. Among them, anti-human leukocyte antigen (HLA) antibodies are detected in 80–90% of cases, and antibodies to platelet-specific antigens including human platelet antigens (HPAs) and CD36 isoantigen or isoagglutinin to ABO antigens are the causative in the remaining cases. Alloimmunization to these antigens can be through previous transfusion, pregnancy or transplantation (11,17,21). Patients with immune PTR require transfusions of compatible platelets reflecting their alloimmunization profiles (12). (See the review article on immune PTR in this issue of *Annals of Blood*.) Appropriate assessment of PTR is critical, since poor response to platelet transfusion is associated with poor clinical outcomes such as inferior survival, longer hospitalization and higher hospitalization costs (22-24). When PTR is suspected, non-immune causes should be carefully assessed prior to investigating immune causes.

In this article, we describe the practical approaches for the diagnosis and the management of non-immune PTR, by referring to existing related literature and our clinical experience. We present this article in accordance with the narrative review reporting checklist (available at http://dx.doi.org/10.21037/aob-20-93).

Literature search strategy

The medical literature of published observational/investigational studies, randomized controlled trials or systematic reviews and meta-analyses regarding non-immune and immune PTR were analyzed. The PubMed/Medline electronic database and Google Scholar were searched in November 2020 using the primary phrases such as “platelet transfusion”, “platelet transfusion refractoriness”, “non-immune platelet transfusion refractoriness”, “immune platelet transfusion refractoriness”, “corrected count increment”, “incidence”, “management”. A hand search of ISBT Science Series and Annals of Blood was also added. Peer-reviewed articles in English or Japanese were considered and no constraints on publication type or date were imposed. Titles/abstracts of retrieved articles were checked for relevance, and other relevant papers were identified by manual searching of reference lists and the authors’ personal literature collections. When similar findings were reported in multiple articles, priority was given to those most recently published.

Diagnosis of platelet transfusion refractoriness

Following a platelet transfusion, platelet count can rise with

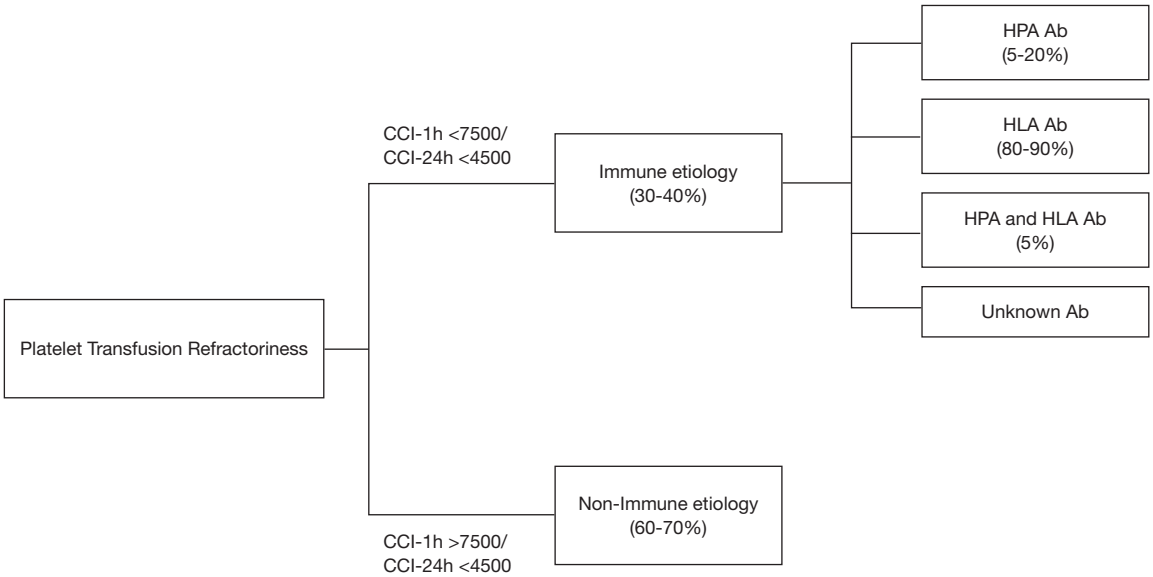

Figure 1 Identification of the etiology of platelet transfusions refractoriness (32). CCI, corrected count increment; HPA, human platelet antigen; HLA, human leukocyte antigen.

a peak at 10 minutes to one hour and show a gradual decline over 72 hours. Typical dosing of platelet transfusion for an adult is a pool of 6 whole blood derived platelets or one apheresis platelet, by which the platelet count increment 24-hour post-transfusion in a 70 kg patient is clinically expected to be 30×10^9/L to 60×10^9/L. Prior to platelet transfusion, "predicted platelet increase" can be calculated by the following formula:

Predicted platelet increase ($\times10^6$/L) = [number of platelets transfused/circulatory blood flow (mL) $\times10^3$] $\times2/3$, where circulatory blood flow (mL) = Body weight (kg) $\times70$

(Multiplication by 2/3 reflects the accumulation of 1/3 of transfused platelets in the spleen)

In Japan, all PCs transfused are leukoreduced single-donor apheresis-derived, and supplied by the Japanese Red Cross Society (JRCS). In the clinical practice, a 10-unit PC bag (volume of about 200 mL), containing about 2.0×10^{11} platelets, is commonly used, which gives a predicted platelet count increase of about 30×10^9/L in a patient with a body weight of 70 kg (25,26).

If suboptimal platelet increases are suspected, corrected count increment (CCI) is helpful in assessing the effectiveness of PC transfusion based on the amount of platelets transfused compared to the body surface area (26). The formula of CCI is as follows:

Corrected count increment ($\times10^6$/L/m^2) = [(post-transfusion count) – (pre-transfusion count)] ($\times10^6$/L) × [body surface area] (m^2)/[number of platelets transfused $\times10^{11}$].

For assessing suspected PTR cases, measurement of CCI 1-hour post-transfusion (CCI-1h) as well as CCI 24-hour post-transfusion (CCI-24h) is encouraged, since CCI-1h can help differentiate immune PTR from non-immune PTR (27). CCI-24h higher than 4,500 indicates normal platelet survival *in vivo*, while CCI-1h higher than 7,500 indicates normal platelet recovery *in vivo* (5,11,17,27-29). The previous guidelines from Western countries recommended CCI-1h measurement with an interval of one hour or more after the transfusion, which was a hurdle for clinicians and patients, especially those receiving transfusion at an outpatient setting. In the revised guidelines, including the Japanese one, the interval for the measurement of CCI-1h was changed to "10 minutes to one hour" after transfusion (30,31). Presently, CCI-1h measurement can be performed between 10-min and 1-hour post-transfusion, and CCI-24h between 16 and 24 hours post-transfusion. *Figure 1* shows the differentiation between immune and non-immune PTR, according to CCI-24h and CCI-1h (32). Typically, non-immune PTR cases present with CCI-1h above 7,500 and CCI-24h below 4,500, reflecting normal platelet recovery and reduced platelet survival. On the other hand, typical immune PTR cases present with CCI-1h below 7,500 and the CCI-24h below 4,500, reflecting reduced platelet recovery almost immediately after transfusion (within

one hour). According to the report by Legler *et al.*, among 145 consecutive patients receiving platelet transfusions, 28% (40/145) developed PTR, with non-immune PTR (predominantly due to fever and sepsis) accounting for the majority (63%), and immune-alone PTR accounted for only 18% (10).

Major causes of non-immune PTR

Non-immune PTR accounts for about two-thirds of all refractory cases, and the reported causes consist of the patient's underlying disorders (33), as well as factors related to PC products such as platelet counts in the transfused products, the period of storage, and others (34). Major causes of non-immune PTR are described below.

Fever/infection/sepsis

Fever is the most frequently reported cause of non-immune PTR (12,35). Since fever can be secondary to various conditions, such as infection/sepsis, DIC, drug allergy, and HSCT, it is still unclear whether fever is an independent cause of poor response to platelet transfusion (12,36). Freireich *et al.* showed that the percentage platelet recovery (PPR) after transfusion is worse in patients with higher body temperature, and the worst in the presence of sepsis (37). In an observational study of HLA-alloimmunized patients who received transfusions of random donor PC, most febrile patients had significantly reduced PPRs, while sufficient PPRs were achieved in those receiving HLA-matched platelets (38). Among the various infections implicated in thrombocytopenia and PTR (39,40), mycoplasma pneumoniae infection has been reported to be associated with idiopathic thrombocytopenic purpura (ITP) (41) and thrombotic microangiopathy (TMA) (42). Sepsis, which can cause secondary thrombocytopenia through the production of platelet-associated IgG and the immune destruction of platelets (43,44), has been reported to negatively affect the post-transfusion platelet count increment, and to be related with an unfavorable prognosis in severely ill patients (45,46). Kelton *et al.* identified increased platelet-associated IgG in septicemic patients with thrombocytopenia, providing some insights for the immune destruction of platelets. In septicemic patients, it has been hypothesized that bacteria in the bloodstream can trigger platelet destruction and shortened lifespan through induction of vascular damage, which leads to platelet consumption (47-49).

In patients with hematological malignancies, the combination of fever, infection and antibiotic therapy has been reported to be the most common cause of PTR (11), but the precise mechanism of this interaction is still unclear (33). In our experience of 224 platelet transfusions in 13 hematological patients with non-immune PTR, the CCI-1h of those who developed post-transfusion fever was comparable to that of patients without fever pre- and post-transfusion, which also suggests uncertain relevance of transfusion-related fever to platelet recovery (31).

DIC

DIC is characterized by systemic activation of blood coagulation and increased platelet consumption, which results in life-threatening hemorrhage (50). Despite lack of evidence, platelet transfusion is indicated in DIC patients with serious bleeding or those with a platelet count below 50×10^9/L who need urgent/emergent surgery (51). These patients can be refractory to platelet transfusion mainly due to the increased platelet consumption (11,29,33,52-55). The bleeding tendency is more severe or apparent in patients with leukemia, solid cancer, obstetric disease or severe infection (56). Of note, aggressive DIC can result in low CCI-1h, resembling immune PTR. Since treatment of the underlying cause is the major principle in DIC management, it is anticipated that proper DIC management can alleviate the related platelet consumption and PTR.

Splenomegaly

The spleen is the most important organ affecting the platelet count increment after transfusion (17,57,58), with about one-third of transfused platelets being retained in the spleen. In patients with splenomegaly, higher amounts of platelets accumulate in the enlarged spleen, reducing the platelet count in the peripheral blood. Studies using radiolabeled platelets have indicated that when platelets are transfused into patients with splenomegaly, large amounts of platelets are pooled into the spleen, thus not exerting their hemostatic function in the periphery (59). Therefore, the evaluation on the required amount of PC to be transfused as well as the indication for transfusion should be carefully considered. In fact, in patients with splenomegaly, up to 85% of transfused platelets, compared to 61% in normal patients, are destroyed; the recovery of peripheral platelet count immediately after transfusion was 26% in patients with splenomegaly,

Table 1 Causative agents implicated in drug-induced thrombocytopenia. *Table 1* was prepared based on references (64-69)

Drug Category	Drugs
Antithrombotics	Heparin, Clopidogrel/ticlopidine, GPIIb/IIIa antagonists
Infectious disease agents	Ampicillin, Amoxicillin, Cephalosporins, Ciprofloxacin/levofloxacin, Linezolid, Metronidazole, Nafcillin, Penicillin, Piperacillin/tazobactam, Rifampin, Sulfonamides, Vancomycin, Amphotericin
Histamine-receptor antagonists	Cimetidine, Famotidine, Ranitidine
Analgesic agents	Acetaminophen, Diclofenac, Fentanyl, Ibuprofen, Naproxen, Salicylates
Chemotherapeutic and immunosuppressant agents	Bleomycin, Cyclosporine, Oxaliplatin, Fludarabine, Rituximab
Cinchona alkaloids	Quinine, Quinidine
Platelet inhibitors	Abciximab, Eptifibatide, Tirofiban
Antirheumatic agents	Gold salts, D-penicillamine
Sedatives and anticonvulsant agents	Carbamazepine, Phenytoin, Valproic acid, Diazepam
Diuretic agents	Chlorothiazide, Hydrochlorothiazide

compared to 59% in normal patients, and 97–98% in asplenic patients; transfused platelets were found in the spleen in 80% of splenomegaly patients 30 minutes after transfusion, but only 40% of normal patients (60). A case report showed that splenectomy reduced the frequency of platelet transfusions and improved CCI in a patient with myelodysplastic syndrome (MDS) developing PTR due to splenomegaly (61). It should be noted that hypersplenism can also result in low CCI-1h, resembling immune PTR.

Bleeding

Clinical bleeding is often listed as a non-immune cause of PTR (62,63), but it is thought that bleeding itself is a consequence rather than a cause of reduced survival of platelets (22). Actually, in patients who were refractory to pooled random-donor platelet transfusions, fever and splenomegaly, but not bleeding, were found to correlate with the reduced CCI-1h after HLA-matched platelet transfusion (29). Severely active bleeding can also result in low CCI-1h, resembling immune PTR. Therefore, it is important for clinicians to recognize PTR as a sensitive clinical marker for the occurrence of bleeding and impaired patient survival (22).

Drugs

Drug-induced thrombocytopenia is a clinical condition that affects a small percentage of patients taking certain drugs. Causative agents are listed in *Table 1*. Patients with a typical history of drug-induced thrombocytopenia may have negative antibody tests (70,71) because metabolites produced *in vivo* can be sensitizing agents (72,73). Drug-induced thrombocytopenia is usually considered to be immune-mediated (74), and clinically, drug-induced platelet-specific autoimmunity resembles acute ITP (75). Thus, drug-induced thrombocytopenia should be suspected in patients with PTR.

Drug-induced thrombocytopenia does not require specific treatment other than the discontinuation of the sensitizing agent. Patients with drug-induced thrombocytopenia are often treated with corticosteroids, intravenous immunoglobulin (64) and plasma exchange (76), however, the benefit of such treatments is unknown.

HSCT

HSCT has been shown to be associated with an impaired response to platelet transfusion (19,52,77-79). Complications such as fever, infection, acute GVHD, and sepsis have been shown as factors affecting platelet transfusion in patients undergoing HSCT (80,81). GVHD-associated TMA (82) may lead to increased production of anti-platelet autoantibodies and accelerated platelet destruction (83). In one series by Rio *et al.*, 100% (13/13) of patients with sinusoidal obstruction syndrome (SOS) developed PTR as early as 6±2 days after transplantation (84).

Factors related to PC products

The period of PC storage, the ABO compatibility of the transfused PC and the irradiation of PC may also affect the CCI. Recently, pathogen-reduction/inactivation (PI) treatment of PC has also been shown to affect CCI (85).

In hematological patients, longer storage period (up to 5 to 7 days) of PC is associated with a lower CCI compared to shorter storage period (less than 3 days) (86,87). Platelet count recovery of patients receiving ABO-incompatible platelets is reported to be as low as one-third of those receiving ABO-identical platelets (88,89). In the previous studies investigating the effects of ABO incompatibility in thrombocytopenic patients who were refractory to platelet transfusion due to HLA antibodies, ABO-incompatible HLA-matched platelet transfusions were inferior to ABO-identical HLA-matched platelet transfusions in terms of platelet recovery and CCI (88,90,91). Our experience with multiple transfusions of HLA-matched PC to a single MDS patient with multiple specificity HLA antibodies also confirmed the lower effectiveness of ABO-incompatible PCs compared to the compatible ones (92).

Previously, Button *et al.* showed that the gamma-irradiation of PC at a dose of 5,000 cGy prior to transfusion was required to negatively affect platelet recovery (93), while Read *et al.* showed that up to 3,000 cGy had no effect on *in vivo* recovery or survival of irradiated platelets (94). Slichter *et al.* has shown that lower doses of 2,500 to 3,000 cGy can reduce CCI-1h, but not CCI-24h (17). Thus, the impact of gamma irradiation of platelets is still controversial (95).

PI treatment of donor platelets can negatively affect platelet recovery of recipients. Patients transfused with PI-platelets can have lower CCI-1h and CCI-24h than those with standard platelets, with a relative risk of platelet refractoriness of about 2.7 (96). Therefore, patients receiving PI-platelets require more frequent platelet transfusions than those with standard platelets. Despite the potential benefit of PI treatment in preventing post-transfusion GVHD, it has been recently reported that PI-platelets have no impact on preventing HLA alloimmunization (97).

Others

Repeated platelet transfusions in hematological patients lead to PTR (17), and this can be observed even in cases in which alloantibodies are not produced. It is possibly triggered by the vascular endothelial damage caused by the chemotherapy agents. It has been reported that hemophagocytic syndrome (HPS) is associated with PTR. A case report showed that treatment of relapsed acute leukemia with etoposide effectively relieved the HPS as well as the PTR (98).

Studies have shown that pooled whole blood-derived PC (WB-PC) and single-donor apheresis PC have similar rates of alloimmunization (20), but that single-donor apheresis PC shows significantly higher CCI-1h to CCI-24h compared to WB-PC (99).

Volume-reduced washed platelets may be beneficial for PTR cases because equal volumes can increase platelet count more efficiently than standard platelets (100). Despite the other advantages of shortened transfusion times and reduced volume loads (101), volume reduction can lead to spontaneous activation and aggregability of platelets (100,102).

Management of non-immune PTR

When PTR develops in patients receiving PC transfusion, the implementation of the appropriate management is essential. We propose below a multi-step approach for the management of PTR, especially focusing on non-immune-mediated PTR, based on the reported literature and our experience. By following these steps, clinicians can avoid unnecessary transfusions that may cause adverse transfusion reactions as well as immune-mediated PTR, consequently contributing for the improvement of healthcare economics.

Consider appropriate indication of platelet transfusion to avoid adverse events and alloimmunization

Suspected PTR patients should be carefully evaluated for various factors such as the current platelet count, the changes of platelet count over time, the presence/absence of bleeding symptoms, the primary disease and underlying conditions including the degree of organ damage, and the history of transplantation. Although a platelet count of 7×10^9/L is required to maintain the strength of the vessel wall (103), the majority of patients in a stable condition do not experience bleeding even when the count is below 5×10^9/L (104).

In 1962, Gaydos *et al.* performed a retrospective analysis of acute leukemia and suggested that a platelet count of 20×10^9/L should be considered as a transfusion trigger because severe bleeding was rare in patients with platelet

counts above 20×10^9/L (105). The result might have been affected by aspirin, an inhibitor of the platelet function, since it was frequently used as an antipyretic agent in those days. Thereafter, lowering this platelet transfusion trigger to 10×10^9/L for patients without comorbidities has been shown to have no impact on the frequency of bleeding and result in a 20–30% reduction in platelet use (106-109). Other reports suggest that a trigger value of 5×10^9/L is acceptable for uncomplicated patients (110), whereas a target of 20×10^9/L is recommended for patients with acute promyelocytic leukemia due to the strong bleeding tendency associated with DIC (4). Ethical issues make it difficult to design a comparative study with trigger values below 10×10^9/L, and it is still unclear how far the threshold can be safely lowered. The clinical trigger of prophylactic platelet transfusion is currently thought to be 10×10^9/L to 20×10^9/L, and some reports suggest that 10×10^9/L may be acceptable in patients after HSCT (5,81,109,111). Chronic thrombocytopenia due to aplastic anemia and MDS can be managed according to the above criteria of platelet transfusion, however, for cases requiring iterative transfusions, a platelet count of 5×10^9/L should be the trigger value (112).

Patients with consumptive thrombocytopenia such as ITP, thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT), are not usually eligible for prophylactic platelet transfusion. But platelet transfusion should be considered when bleeding is severe, or an invasive treatment is needed, or it remains difficult to stop bleeding even with other treatments. A large-scale retrospective study by Goel *et al*. showed that platelet transfusions are associated with higher odds of arterial thrombosis and mortality among patients with TTP and HIT (113). Therefore, clinicians should keep in mind that platelet transfusion has been identified as a potential exacerbator of TTP and HIT.

Investigate the causes of PTR

The clinical evaluation of the possible non-immune causes is essential (114). Combined measurements of CCI-1h and CCI-24h values can help differentiation between immune and non-immune PTR (See Diagnosis section and *Figure 1*). A CCI-1h in the normal range accompanied with a low CCI-24h indicates a shortened platelet survival, which is typically seen in non-immune PTR.

Select the best treatment plan according to the etiology of PTR

For non-immune PTR cases, the best way to improve the transfusion response is appropriate treatment of the underlying diseases (29).

When PTR persists after the appropriate treatment of the non-immune causes, immune PTR, alone or in combination, should be suspected. Since about 80–90% of immune PTR cases are due to anti-HLA antibodies (11), screening for anti-HLA antibodies is indicated, concomitantly with testing for anti-HPA antibodies. Anti-CD36 isoantibodies, which are found in a higher frequency among Asian and African populations (115), may also cause PTR, so it should be considered when other antibodies are not identified. For immune PTR due to anti-HLA antibodies, transfusion of HLA-matched platelets is strongly recommended. Since HLA matching of platelets requires recruitment of compatible donors, testing of HLA/HPA antigens/antibodies and crossmatching, HLA-matched platelets are usually expensive and not always available in many countries. Thus, antibody specificity prediction method is applied in some countries as a reasonable way to find "HLA-compatible" platelets (38,65) (See the review article on immune PTR in this issue of *Annals of Blood*).

Tranexamic acid, a fibrinolytic inhibitor, has been shown to prevent bleeding and reduce the need of blood transfusion, including PC, in surgical patients, but its role as an alternative to platelet transfusion in PTR cases remains to be investigated (116). The TREATT trial is underway to assess the safety and efficacy of using prophylactic tranexamic acid during a period of intensive chemotherapy and associated thrombocytopenia in hematological patients (66).

Consider the coexistence of non-immune and immune causes

When managing PTR cases, it is important for clinicians to consider the coexistence of non-immune and immune causes. Actually, the combination of immune and non-immune factors is identified in a substantial proportion of PTR cases. In a prospective study of 266 PC transfusions in 26 patients with hematological malignancies, PTR developed in 44% (116/266). Among them, 67% (78/116) were due to non-immune, and 4% (5/116) due to immune factors alone, but the remaining 21% (24/116) was due to both non-immune and immune causes (11).

Limitations and future perspective

This article has several limitations. First, this article could not cover all literature regarding non-immune and immune PTR due to the nature of narrative review. Second, although we aimed to review the non-immune PTR, it is not feasible to describe non-immune PTR without mentioning to immune PTR, because of their close association. Third, dependent on the various etiologies, there are no consistent approaches for the diagnosis and management of the condition, mostly relying on the management of the underlying condition. There is a need to accumulate experience and data related to non-immune PTR and develop concise and consistent algorithms for the appropriate diagnosis and management of this condition.

Summary

When PTR is suspected, common and possible non-immune causes such as fever/sepsis, DIC and splenomegaly should be investigated in the early stage, because non-immune PTR is about twice as frequent as immune PTR. This step can prevent unnecessary platelet transfusions, preventing immune PTR. The combined evaluation of CCI-1h and CCI-24h may help differentiate PTR of immune and non-immune etiologies. Typically, in non-immune PTR, CCI-1h is within the normal range, but CCI-24h is usually low, reflecting shortened platelet survival. However, conditions such as aggressive DIC, hypersplenism, and severely active bleeding are known to be associated with low CCI-1h, so caution is needed. When the appropriate management of the non-immune causes does not improve the condition, the presence of immune PTR, alone or in combination, should be suspected. In case immune PTR is suspected, screening for anti-HLA antibodies is indicated, and if confirmed, transfusion of HLA-matched PC is indicated. Due to the multifactorial nature of the non-immune PTR, clinicians are recommended to follow the four steps described in this review for the appropriate diagnosis and management of the condition. Reducing unnecessary transfusions is pivotal in preventing not only the adverse events of transfusion but also alloimmunization and the subsequent immune PTR, consequently contributing for the improvement of the healthcare economics.

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