Evaluation and management of platelet transfusion refractoriness

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Abstract

Platelet transfusion refractoriness (PTR), in which platelet counts do not increase after transfusion, occurs in many patients receiving platelet transfusions. PTR is a clinical condition that can harm patients. The causes of PTR can be divided into two types: immune and non-immune. Most cases of PTR are non-immune. Among immune causes, the most common is human leukocyte antigen (HLA) class I molecules. PTR caused by anti-HLA antibodies is usually managed by transfusing HLA-matched platelets. Therefore, it is important, especially for hemato-oncologists who frequently perform transfusion, to accurately diagnose whether the cause of platelet transfusion failure is alloimmune or non-immunological when determining the treatment direction for the patient. In this review, we discuss the definitions, causes, countermeasures, and prevention methods of PTR.

Key Words Platelet transfusion refractoriness, Platelet transfusion, Human leukocyte antigen, HLA-matched, Platelet count

INTRODUCTION

For decades, platelet (PLT) transfusions have been used to prevent or treat life-threatening bleeding. In particular, platelet transfusion plays an important role in reducing thrombocytopenia-induced hemorrhagic events during the early stages of chemotherapy [1-3]. Owing to these advances, the incidence of bleeding caused by acute leukemia has decreased [4]. According to the Korean Red Cross Blood Services statistics, the domestic platelet supply in 2020 was 1,727,115 units (28.7%), which, along with red blood cells, are the two most used blood components in Korea [5].

However, many patients receiving PLT transfusions suffer from PLT transfusion refractoriness (PTR), a phenomenon in which the PLT count does not increase to the desired level after transfusion. This phenomenon is caused by PLT consumption or destruction owing to immunological/non-immunological causes, which may lead to serious problems in the clinical treatment of patients. Therefore, in this review, we focus on the causes, diagnosis, and management of PTR.

INDICATIONS AND THRESHOLDS OF PLATELET TRANSFUSION

Suppose PLT transfusion is performed to prevent future bleeding or to treat bleeding that is currently occurring. In that case, the indication also depends on the possibility of future bleeding or the current bleeding situation. The national transfusion guidelines published by the Korea Centers for Disease Control and Prevention and Korean Society for Blood Transfusion set the principles for PLT product transfusions as follows: 1) PLT count is maintained at 10,000–20,000/μL in a stable state without bleeding; 2) PLT count is maintained at 20,000–50,000/μL in an unstable state without bleeding; and 3) for active bleeding or invasive treatment, PLT count is maintained at 50,000–100,000/μL [6].

Considering the specific situation, it is recommended to maintain a PLT count of >50,000/μL in cases of active bleeding and >100,000/μL in severe cases such as central nervous system bleeding, retinal hemorrhage, or multiple traumas. For prophylactic purposes in leukemia or aplastic anemia, it is recommended to maintain 10,000–20,000/μL in a stable state and >20,000/μL in an unstable state. In disseminated intravascular coagulation (DIC), the PLT count should be maintained at >50,000/μL and up to 100,000/μL in newborns [6]. Various other clinical situations and prophylactic PLT transfusions during invasive treatment can be easily identified by referring to the transfusion guidelines.

In addition, apart from the laboratory value, PLT transfusion is necessary even when the clinician judges that PLT transfusion is necessary, such as in cases with abnormal PLT

function or a continuous decrease in PLT count, or in case of continuous bleeding even after transfusion.

DEFINITION AND EVALUATION OF PLATELET TRANSFUSION REFRACTORINESS

PTR is defined as a condition in which the increase in PLT count after PLT transfusion is less than expected [7]. In general, the increase in the PLT count after transfusion depends on the number of PLTs in the transfused components and the distribution of transfused PLTs in the body. Although the number of PLTs in blood components is highly variable due to the inherent nature of donated blood, 1 unit of PLT concentrate is thought to contain 6.3 (from 320 mL whole blood) or 7.7 (from 400 mL whole blood)$\times 10^{10}$ PLTs, and 1 unit of apheresis PLT (AP) is thought to contain 3.0×10^{11} PLTs [6].

Several equations have been used to assess responses to PLT transfusion, and corrected count increments (CCIs) are widely used to determine PTR (Table 1) [7]. Therefore, the first step when PTR is suspected is to compute the CCIs 1 and 24 h after PLT transfusion. CCI can be calculated using the following formula [7-10]:

$$CCI = \frac{(Absolute\ count\ increment,\ /\mu L) \times (Body\ surface\ area,\ m^2)}{(Number\ of\ platelets\ transfused,\ \times 10^{11})}$$

These values may help discriminate between immunologic and non-immunologic causes of post-transfusion purpura (PTP). When the immunologic antibody-mediated clearance of transfused PLTs causes PTP, the PLT count begins to drop rapidly after the completion of transfusion.

In this case, the PLT count decreased rapidly from 1 h after PLT transfusion, and anti-HLA and anti-human PLT antigen (HPA) antibodies were the primary causative agents [10].

PTR of non-immunological causes refers to a state in which PLTs are decreased due to a non-immunological cause, such as a patient's underlying condition, pathological condition, or drug use. In this case, the PLT count recovers immediately after PLT transfusion, but the PLT count decreases again after 24 h. Non-immunological causes account for approx-

imately 70% of total PTR [10, 11]. Usually, if the 24 h CCI is <5,000/μL, PTR is suspected; in such cases, the 1 h CCI is additionally calculated. If the 1 h CCI is ≤7,500/μL, an immunological cause of PTR is suspected, whereas if it is >7,500/μL, a non-immunological cause of PTR is suspected [10].

MANAGEMENT OF PLATELET TRANSFUSION REFRACTORINESS

Non-immune

PTR due to non-immunological causes accounts for the majority of the total PTR, and its causes may include sepsis, splenomegaly, DIC, and fever (Table 2) [7, 12, 13]. In addition, various drugs such as penicillin, cephalosporin, quinine, non-steroidal anti-inflammatory drugs, heparin, and L-dopa contribute to non-immunological causes [7, 14, 15]. Correcting and removing non-immunological causes of PTR is a fundamental solution [7].

Immune

In cases of PTR caused by immunological factors (Table 2), an increase in the PLT count can be expected when PLTs that do not react to the patient's antibody is transfused. This is the same principle as that of red blood cell transfusion, in which a patient with an unexpected antibody is transfused to avoid the antibody. There are three main ways to avoid these antibodies: 1) selection of an HLA crossmatch-compatible PLT unit, 2) if the HLA antibody is identified, select the antigen-negative PLT units, and 3) select the same HLA-matched PLT units as the patient. HLA crossmatching is method used to check whether there is a reaction between the patient's serum and the PLTs to be transfused. If it is compatible with a crossmatch, it is expected that an immune reaction will not occur when blood components are transfused. This method does not require the identification of anti-HLA antibodies and has the advantage of being applicable to antibodies other than anti-HLA antibodies, particularly anti-HPA antibodies. However, it may be difficult to identify a crossmatch-compatible PLT agent in highly sensitized patients, and additional sensitization may occur after transfusion. In addition, crossmatching can only be

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Table 1. Various formula to assess platelet transfusion refractoriness (modified from Rebulla,1993).

Post-transfusion platelet increment (PPI)=(post-transfusion platelet count)-(pre-transfusion platelet count)

$$Corrected\ count\ increment\ (CCI) = \frac{PPL\ (/\mu L) \times BSA\ (m^2)}{Number\ of\ platelets\ transfused\ (10^{11})}$$

$$Percentage\ platelet\ recovery\ (PPR) = \frac{PPL\ (/\mu L) \times TBV \times 100\%}{Number\ of\ platelets\ transfused\ (10^{11})}$$

Percentage platelet increment (PPI)=PPR/0.67 (0.67 accounts for splenic pooling)

Abbreviations: BSA, body surface area; TBV, total blood volume.

Table 2. Etiology of platelet transfusion refractoriness.

Immune factors (<20%)	Non-immune factors (>80%)
Antibodies to HLA class I (80–90%)	Accerlerated platelet consumption (MAHA, DIC)
Antibodies to HPA (10–20%)	Active bleeding
ABO-mismatched platelets	Medications (Infectious disease agents; ampicillin, amoxicillin, cephalosporins, penicillin, piperacillin/tazobactam, rifampin, sulfonamides and vancomycinHistamin-receptor antagonists: cimetidine, famotidine etc., Analgesic; acetaminophen, fentanyl, ibuprofen, and naproxen chemotherpeutics and immunosuppressants: rituximab, and cyclosporin antithrombotics; heparin and GPIIb/IIIa antagonists)
Antibodies to drug-platelet glycoprotein complex	Graft-versus-host disease
Autoimmune (unknown)	Splenic sequestration
	Poor platelet quality

Abbreviations: DIC, diffuse intravascular coagulation; GPIIb/IIIa, glycoproteinIIb/IIIa; HLA, human leukocyte antigen; HPA, human platelet antigen; MAHA, microangiopathic hemolytic anemia.

attempted when there is a sufficient stock of PLTs in medical institutions. However, there are two different methods in which the HLA type of the blood donor is identified in advance, and PLT components prepared with matched HLA type are selected for transfusion. In Korea, when a relevant HLA antibody is identified, the method of choice is to transfuse HLA-matched PLT components. This is possible through the HLA-matched PLT donor registration system, operated by the Korean Red Cross. The basic work order is as follows. Suppose immunological PTR caused by HLA antibodies is suspected in a medical institution. In that case, the HLA-A and-B types of the patient are typed, and HLA-matched PLT preparation is requested from the Korean Red Cross. The Korean Red Cross requests AP blood donors from registered blood donors who meet the HLA criteria and supply the blood to the requesting institution to transfuse the components to patients. Currently, 4,080 HLA-compliant PLT donors are registered in the Korean Red Cross [16]. Blood from these HLA-compliant PLT donors is valuable and should be used only when necessary.

To suppress the immune reaction in PTR caused by immunological factors, intravenous immunoglobulin (IVIg) was administered. However, in one study, when IVIg was administered together with PLT components, the 1 h CCI improved, but the 24 h CCI did not show any difference. Therefore, this method has not yet been recommended owing to its failure to demonstrate clinical benefits [17].

FUTURE DIRECTIONS

Human leukocyte antigen-depleted platelet

Since anti-HLA antibodies account for the majority of immunological causes, efforts have been made to produce PLT preparations for transfusion using HLA-depleted PLT, in which HLA molecules have been removed from PLTs. There are two methods of manufacturing HLA-depleted PLTs. One is to produce PLT from stem cells, and the other is to modify PLTs chemically. The production method from

stem cells is that only HLA class I molecules are expressed on the PLT surface, and beta2-microglobulin is required for HLA class I molecule expression. In other words, when a beta2-microglobulin knockout stem cell is used to differentiate into PLTs, the PLTs obtained here cannot express HLA class I molecules [18, 19]. Such stem cell-derived PLTs are free from concerns about infectious diseases and have the advantage that they can be freely supplied at any time, as long as a proper PLT manufacturing process is established. However, they are still difficult to mass-produce and have economic problems [20]. Another method for preparing HLA-depleted PLTs is a chemical modification, which accidentally discovery that HLA class I molecules lose their antigenicity upon acid exposure [21]. Currently, HLA depletion using citric acid is in its established stage [22, 23]. The HLA depletion method using citric acid treatment is relatively inexpensive and suitable for mass production; however, HLA class I molecules cannot be completely eliminated. In addition, there are concerns about infectious diseases, such as existing blood transfusions. No method has yet been established for clinical use, and research is ongoing.

Slow and continuous infusion of platelet

In general, it is a principle to complete transfusion as soon as possible when there are no side effects on the patient. However, several researchers have attempted to slowly transfuse PLTs over a long period in patients with PLT transfusion intolerance and have shown promising results [24, 25]. This is based on the idea that, because the number of PLTs removed by immune clearance is proportional to the number of PLTs in the blood, it would be more beneficial for patients to maintain only the PLT count above the minimum concentration required for hemostasis than to rapidly increase the PLT count. This is similar to the goal of maintaining a concentration above the minimum inhibitory concentration (MIC) for a long time during antibiotic treatment in cases of bacterial infections (time above MIC) [26]. A clinical trial is also in progress, and if the results are published, it is expected that more information on the effects of slow infusion will

be obtained [27]. However, because of the characteristics of biological products, once converted to an open system, the possibility of bacterial growth cannot be excluded, as PLTs stored at room temperature are vulnerable to bacterial contamination [28]. Therefore, it is necessary to consider the balance between the benefits and risks obtained from a slow infusion.

Eculizumab

Recently, Vo *et al.* [29] published an interesting pilot study on PTR inhibition in HLA-sensitized patients using eculizumab, a monoclonal antibody that inhibits C5 complement. In this study, 1,200 mg of eculizumab was administered over 30–40 min, and PLTs were transfused within 48 h. In three or four patients, the random PLT count increased in PLT count equivalent to the HLA-matched PLT count after transfusion [29]. However, further studies involving larger patient groups are required.

PREVENTION OF PLATELET TRANSFUSION REFRACTORINESS

For PTR caused by non-immunological causes, there is no preventive method other than correcting the cause; however, for PTR caused by immunological causes, minimizing immunological exposure is effective. As a strategy to minimize immunological exposure, transfusions should be performed only when necessary to minimize the amount of transfusion. Theoretically, transfusion of AP, rather than PLT concentrates, is thought to cause less frequent HLA sensitization by reducing the chance of exposure to various allogeneic antigens. However, transfusion of AP did not reduce PTR incidence compared with transfusion of PLT concentrates [30]. Nonetheless, considering factors such as minimizing various side effects of transfusion and reducing workload in and PTR, AP transfusion is considered appropriate if possible. Among the PLTs supplied in Korea, AP accounts for approximately 12.9% of the total; therefore, it is necessary to prioritize which patients should be supplied with limited AP [31].

CONCLUSIONS

PTR is a challenging condition frequently encountered in clinical situations. In particular, hemato-oncologists who frequently perform blood transfusions should be familiar with the causes of PTR and its assessment and countermeasures. In addition, various methods to overcome PTR are being studied, and improved clinical outcomes can be expected in the future with the development of methods to manage patients with PTR.

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