Review Article

Research progress on the immunological platelet transfusion refractoriness in patients with acute leukemia: a narrative review

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Abstract: Acute leukemia (AL) is a malignant clonal disease of hematopoietic stem cells, many patients have achieved remission, long-term survival, and even cured. Thrombocytopenia is one of the main clinical manifestations of AL. With the development of blood transfusion medicine, platelet transfusion has become an important measure for the treatment of AL. However, platelet transfusion refractoriness (PTR) increases the risk of bleeding in patients and intensifies the demand for platelet transfusion, the occurrence of PTR is still a huge challenge for clinicians. This article reviews the research on the mechanism, prevention and treatment of immunological PTR in AL. PTR includes immune and non-immune factors, immune factors are an important reason for PTR. Some patients are prone to PTR, while others are not. The specific mechanism is currently unclear. Among the immune factors, humoral immunity is currently considered to be the main reason, including HLA antigen incompatibility, antibodies produced by platelet-specific antigens (HPA), and ABO blood group incompatibility, it has been discovered that anti-CD36-mediated alloimmune responses can produce platelet immune abnormalities. There is still a lack of effective methods to completely prevent and treat immunological PTR, we still need to conduct more in-depth research on the mechanism of immunological PTR in AL. Only by further clarifying the mechanism of immunological PTR can be possible to find more effective prevention and treatment methods.

Keywords: Platelet transfusion refractoriness (PTR); acute leukemia (AL); alloimmunity

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Platelet transfusion refractoriness (PTR) in acute leukemia (AL) is a major clinical problem at present

AL is a malignant clonal disease of hematopoietic stem cells. Abnormal blasts and immature cells (leukemia cells) in the bone marrow proliferate in large numbers, accumulate in the bone marrow and inhibit normal hematopoiesis, and extensively infiltrate the liver, spleen, lymph nodes and other extramedullary organs. It is manifested by signs of anemia, bleeding, infection and infiltration. After modern treatment, many patients have achieved remission, long-term survival, and even cured. Thrombocytopenia is one of the main clinical manifestations of AL. It will appear at the onset and during the bone marrow suppression period after chemotherapy. In severe cases, it can lead to life-threatening bleeding. Platelet transfusion is an important supportive treatment measure for AL (1). Stanworth *et al.* showed that preventive platelet transfusion in hematological malignancies including AL is effective and very important in reducing the risk of bleeding (2). This article is presented in accordance with the narrative review reporting checklist

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PTR means that the patient's platelet count has not been effectively increased after platelet transfusion, and the clinical bleeding symptoms have not been improved (3). The effect of platelet transfusion was evaluated using the corrected increase in platelet count index [corrected count increment (CCI)] or the percentage of platelet recovery [percent platelet recovery (PPR)] after transfusion. Clinically, after platelet transfusion, 1-h CCI <7.5, 24-h CCI <4.5 or 1-h PPR <60%, 24-h PPR <40% are judged to be refractory to platelet transfusion. The first use of platelet transfusion therapy in 1959 greatly reduced the rate of death of leukemia patients from bleeding (4). PTR includes immune and non-immune factors, immune destruction is an important cause of PTR, and its mechanism is mainly the production of antibodies corresponding to the antigens of platelets in the body, which are commonly HLA and HPA antibodies (5,6).

However, PTR often occurs in patients with AL, which increases the risk of bleeding. PTR further increases the demand for platelets and aggravates the limited availability of the platelet supply. Patients in the department of hematology account for about 80% of platelet use in our hospital, many of which are used for infusion of AL PTR patients. Some researchers believe that the incidence of PTR is the highest in patients with AL (7). The current conventional prevention and treatment methods for AL immune PTR are generally not effective, and the mechanism of immune PTR is still unclear. Therefore, the mechanism of immune PTR in AL patients is studied, and intervention measures are taken according to its characteristics to improve the immunity of AL patients. The prevention and treatment effects of immune PTR are of great significance for reducing the bleeding risk of AL patients and saving platelets.

Anti-HLA antibodies are the main reason in the mechanism of immunological PTR

PTR includes immune and non-immune factors. Non-immune factors include fever, severe infection, splenomegaly, disseminated intravascular coagulation (DIC), and the use of antibiotics. Among the immune factors, humoral immunity is currently considered to be the main reason, including ABO blood group incompatibility, HLA antigen incompatibility and antibodies produced by platelet-specific antigens (HPA). When the patient has allogeneic immunity due to pregnancy or history of blood transfusion, the corresponding antibody to the antigen of platelets is produced. Because human platelets have HLA-class I antigens and HPA, repeated platelet transfusions can cause HPA and HLA-class I antigens to stimulate the patient's body to produce an allo-immune response, leading to the destruction of exogenous platelets, shortening the lifespan of incompatible platelets. The greater the number of transfusions, the higher the possibility of platelet antibody production, which can lead to an ineffective platelet transfusion. About 80% of immunological PTR is mainly caused by HLA antibodies, followed by HPA antibodies (8), and a small number of patients have both antibodies (6). Saris A and other studies have shown that platelets appearing to undergo apoptosis during storage are more likely to cause PTR after transfusion (9).

Patient ABO antibodies can also cause immunological PTR, but rarely unless the ABO antibodies are very high titer due to the much lower ABO antigen expression on platelets compared to RBCs. This might be less of an issue in China if most of the patients and donors are blood group O, but this might not be the case for some blood donors who are A or B when given to group O recipients, but again this is a very uncommon cause of PTR compared to HLA antibodies.

In recent years, it has been discovered that anti-CD36-mediated alloimmune responses can produce platelet immune abnormalities (5,10,11). CD36 antigen, also called platelet glycoprotein 4 (GPIV), is mainly expressed on platelets and monocytes. This antigen often disappears on some cells due to mutations in the expressed gene. There are two types of CD36 deficiency. Among them, it disappears on platelets and monocytes as CD36 type I deletion, and type II deletion is only undetectable on platelets, so only type I patients will produce CD36 antibodies (12). The exposure of type I patients to CD36 antigen, such as multiple blood transfusions, pregnancy, will result in an alloimmune response to develop CD36 antibodies (13). Xu *et al.* found that CD36 type I deletion and type II deletion are rare in the South China population, with an incidence of about 0.5% and 1.3%, respectively (14). Xia *et al.* reported two cases of PTR patients (AL and myelodysplastic syndrome), the test found that compared with healthy controls, the expression of CD36 in platelets and monocytes of two patients was lower, indicating that both patients had CD36 type I deletion (15). It shows that immunological PTR in patients with blood diseases can also be mediated by anti-CD36.

The process of HLA and HPA antibodies production is

first obtained by antigen presenting cells (APCs) to obtain HLA and HPA and then transfer the antigens information to $CD4^+$ helper T cells, causing T cell activation, and T cells further activate B cells to produce humoral immunity (5,16). In recent years, studies have also shown that $CD8^+$ cytotoxic T cells also play a role in the immune destruction of platelets (17). At present, while the mechanism by which patients can develop HLA or HPA antibodies, the reasons for why some patients develop these antibodies and others do not is still unclear.

Some patients with AL are particularly prone to immunological PTR, while others are not. The mechanism is still unclear

Dutcher JP reported that some AL patients are prone to immunological PTR. In acute myeloid leukemia (AML) patients with multiple platelet transfusions, some patients never develop immunological PTR, while some patients are prone to allogeneic immunity and lead to PTR, there was no difference in age and gender of patients between these two groups (18). In our clinical work, we also found that some patients are prone to occur, while others are not. In our study, the incidence of immune PTR in AL was 25%, which was near to N. Agarwal's reports of Indians and higher than C.A. Schiffer reports of American. Killick, S.B reported that PTR occurred in 15–25% of patients with thrombocytopenia in British. Differences in the probability of occurrence may be due to ethnic differences and diseases types, AL may have higher incidence of PTR (19). We think there are differences in the immune function of AL patients. Therefore, studying the immune characteristics of these patients will help to clarify the mechanism of immunological PTR.

Comont *et al.* observed 897 patients with AML and found that PTR is more likely to occur in patients with a history of pregnancy, extramedullary infiltration, low white blood cell count, infection, and hemophagocytic syndrome. The early and late mortality due to severe bleeding was significantly higher in patients with PTR than in patients without PTR. The average time from diagnosis of AML or chemotherapy to diagnosis of PTR is 17 days (9–25 days) and 9 days (5–15 days), respectively. No obvious chromosomal karyotypes and gene mutations were found to be related to PTR, however, the incidence rate of FLT3-ITD mutant in the PTR group was 9.7%, and the non-PTR group was 22.8%, it seems that the FLT3-ITD mutation with poor prognosis is not prone to PTR (20). Solves *et al.* reported that the incidence of PTR in allogeneic hematopoietic stem cell transplantation in patients with blood diseases including AML is high and the condition is serious. Among them, the incidence of PTR in cord blood stem cell transplantation is higher than that in peripheral blood hematopoietic stem cell transplantation (21). In short, AL patients have a high incidence of immunological PTR, a high risk of bleeding, and there are still many unclear mechanisms. Whether the occurrence of PTR is related to prognostic stratification is unclear.

Hu *et al.* retrospectively analyzed the potential causes and clinical features of PTR in 560 patients with *de novo* AML, and found that patients with core binding factor AML (CBF-AML) had higher risk to develop HLA-class I antibodies and PTR (22).

Indeed, there is not a large amount of literature that shows that the incidence of PTR is different in the subtypes of leukemia. However, most patients who need platelet transfusion are AL in clinical, our study mainly focuses on AL. We retrospectively analyzed the clinical characteristics of immunological PTR in 890 AL patients in our hospital over the past 10 years and the clinical factors affecting immunological PTR, and analyzed the relationship between immunological PTR and age, gender, type of leukemia, number of blood product transfusions, cytogenetics and molecular biology, as well as the treatment effect of conventional methods, we found that in AML, patients with a moderate prognosis are more likely to develop immunological PTR than patients with a poor prognosis. NPM1 mutations are related to immunological PTR. In ALL, the incidence of immunological PTR in the good prognosis group is lower than that in the poor prognosis group. We believe that the occurrence of immunological PTR is related to the clinical characteristics of AL itself, and the prognostic stratification of AL may affect the occurrence of immunological PTR (19).

Prevention and treatment of immunological PTR

At present, the main methods to prevent immunological PTR are as follows: infusion of leukocyte-filtered blood products, this removal of more than 99.9% of white blood cells, and can delay or prevent the onset of ineffective platelet transfusion caused by the development of HLA antibodies. In our hospital, all AL patients were mostly infused of leukocyte-filtered blood products. Due to the presence of HLA-class I antigens on the surface of platelets, leukocyte filtration cannot completely prevent

the development of HLA antibodies; the establishment of HLA donor pools; the use of platelets matching platelets (23,24). In addition to HLA-class I antibodies, there are HPA antibodies that cause platelet transfusions to be ineffective (25), but the infusion of compatible platelets can only ensure that the blood transfusion is effective, and cannot completely prevent the platelets from stimulating the body to produce antibodies. This could be due to the fact that the compatible platelets are not always fully HLA matched, and might be only partially matched. Moreover, it is difficult to find HLA-matched platelets. Comont *et al.* reported that the average time from the diagnosis of immunological PTR to the infusion of HLA-matched platelets is 12.5 days, and thrombopoietin receptor agonists cannot shorten the thrombocytopenia time and the risk of bleeding (20). Schmidt *et al.* reported that for HLA antigen-mediated PTR, selecting donors with negative population reactive antibodies can overcome PTR (26), but this method has a narrow application range. In addition, Cid explored autologous frozen platelets to prevent PTR, but it is difficult to implement for patients with malignant hematological disease (27). Meinke *et al.* confirmed that platelet antigens can be evaded from immune platelet destruction by weakening platelet antigens by acid treatment but this is not routinely performed outside of experimental settings (28). There is still a way to evade PTR by suppressing the costimulatory molecular signal pathway of T19 cells through immunomodulation, but it is not feasible for patients with immunocompromised blood diseases (29).

Cid *et al.* treated PTR patients with platelet transfusion immediately after with rituximab treatment. The 24-CCI index and the improvement of bleeding symptoms were evaluated. The results showed that the effect of platelet transfusion was significantly improved. After 4 weeks of administration of rituximab, the patient was weakly positive for HLA antibodies (30). It is consistent with the results of Yu *et al.* (31). Most studies have shown that for patients with hematological diseases, injection of high-dose gamma globulin, plasma exchange and rituximab therapy can improve PTR to a certain extent, and HLA antibodies are significantly lower than before immunotherapy (30). The occurrence of PTR in AL patients can occur during the first infusion or after multiple infusions (32). For patients with PTR in CD36 type I deletion AML, Saw *et al.* found that platelet counts were significantly increased after transfusion of platelets with CD36 type I deletion from blood donors (33). However, in some areas, the treatment of PTR due to the loss of CD36 type I in patients with AML is not optimistic, because of the extremely low platelet level after chemotherapy, the matching type cannot be found quickly for platelets, the treatment of patients shifted to less invasive and less bone marrow suppression chemotherapy regimens (13). Khatri *et al.* reported that PTR occurred in patients with aplastic anemia due to CD36 type I deletion after the use of immunosuppressive agents such as gamma globulin/rituximab, the effect of platelet transfusion in patients was also significantly improved (34).

In general, there is still a lack of effective methods to completely prevent and treat immunological PTR, and the occurrence of PTR is still a huge challenge for clinicians. Although the current application of platelet antibody detection and platelet matching has improved the effect of platelet transfusion, due to individual differences and scarcity of blood resources, platelet matching is still greatly restricted. Glucocorticoids, high-dose gamma globulin, rituximab and other methods have improved the infusion effect to a certain extent, but it may be limited to the patient's condition, and the efficacy is uncertain. Up to now, there is still less literature of the application of glucocorticoids, high-dose gamma globulin, rituximab and other methods in treatment and management of PTR. Therefore, we still need to conduct more in-depth research on the mechanism of immunological PTR in AL. Only by further clarifying the mechanism of immunological PTR can be possible to find more effective prevention and treatment methods.

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