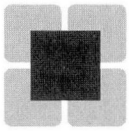

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Platelet transfusion therapy for medical and surgical patients

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SUMMARY Platelet transfusions have become more common as more patients undergo bone marrow transplantation and aggressive chemotherapy for malignant diseases. This paper reviews the indications for platelet transfusions and the factors that can decrease their effectiveness.

KEY POINTS Drug- or radiation-induced megakaryocytic hypoplasia is the primary indication for platelet transfusion.

Thrombotic thrombocytopenia purpura, pre-eclampsia, and other platelet-mediated microangiopathies are contraindications to platelet transfusion. Because amphotericin B can decrease platelet recovery and survival, doses of amphotericin B and platelet transfusions should be separated in time.

Alloimmunization should be suspected when a platelet transfusion fails to result in a corrected count increment ≥ 7500 per μL in a patient who has no clinical factors that would otherwise affect the results of platelet transfusion.

Febrile, nonhemolytic reactions are more frequent in platelet than in red cell transfusions, as are bacterial infections.

A stringent platelet transfusion policy is needed; recommended thresholds for platelet transfusion have ranged from 5000 per μL in stable amegakaryocytic patients to 100 000 per μL in patients undergoing neurologic or ophthalmologic surgery.

INDEX TERMS: BLOOD TRANSFUSION; PLATELET TRANSFUSION; CANCER CHEMOTHERAPY CLEVE CLIN J MED 1996; 63:245–250

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PLATELET TRANSFUSIONS have become more common as more patients undergo bone marrow transplantation and aggressive chemotherapy for malignant diseases. However, platelet transfusion therapy involves more than simply measuring the platelet count. The platelet count is important in deciding when to order a transfusion, but even more important are the patient's diagnosis and clinical condition. Although a number of factors can cause thrombocytopenia (*Table 1*), bone marrow transplantation and chemotherapy for neoplastic diseases have made drug- or radiation-induced megakaryocytic hypoplasia the primary reason for platelet transfusion.[1] This paper reviews the use of platelet transfusions in patients with malignant diseases, emphasizing the indications for transfusions and factors that decrease their effectiveness.

PLATELET KINETICS

The overall rate of platelet production in normal humans ranges from 35 000 to 44 000 platelets per μL per day,[2,3] and the normal platelet

TABLE 1
CAUSES OF THROMBOCYTOPENIA

Diminished platelet production
Megakaryocytic hypoplasia due to radiation or drugs
Marrow replacement (infiltration by carcinoma or leukemia)
Bone marrow failure (aplastic anemia)
Vitamin B_{12} or folic acid deficiency
Defects in thrombopoietic control
Hereditary disorders
Sex-linked (Wiskott-Aldrich syndrome)
Autosomal dominant (May-Hegglin anomaly)
Autosomal recessive (Bernard-Soulier syndrome)
Increased platelet consumption
Immune causes
Idiopathic thrombocytopenic purpura
Alloimmune thrombocytopenia
Secondary immune thrombocytopenia
Systemic lupus erythematosus
Lymphoproliferative disorders
Septicemia
Drugs (quinidine, heparin)
Nonimmune causes
Disseminated intravascular coagulopathy
Thrombotic microangiopathy
Thrombotic thrombocytopenia purpura
Hemolytic uremic syndrome
Platelet loss during hemorrhage
Extracorporeal perfusion
Hypersplenism
Hypothermia

life-span is 9.5 ± 0.6 days.[2] Approximately two thirds of the platelets are in the general circulation, and the remainder are reversibly sequestered, primarily in the spleen. The splenic pool accounts for about 30% of the whole-body platelet mass[2,4,5]—increasing to up to 90% in patients with splenomegaly.[5] Studies using radioactively labeled platelets indicate that about 10% of the platelets are found in the liver.[3,4] A normal platelet count ranges from 150 000 to 400 000 per μL.

RECOVERY AND SURVIVAL OF TRANSFUSED PLATELETS

Because different factors can affect platelet recovery and survival after transfusion, it is misleading to assume that each random-donor unit will increase the patient's platelet count by 5000 to 10 000 per μL. ("Platelet recovery" refers to the platelets that escape sequestration and damage by the reticuloendothelial system 10 minutes to 1 hour after platelet transfusion; "platelet survival" refers to the proportion of transfused platelets that remain in the circulation 18 to 24 hours later.)

Fever, infection, hypersplenism, disseminated intravascular coagulopathy (DIC), and prolonged storage can all decrease platelet recovery.[6] In addition, bone marrow transplantation, a palpable spleen, HLA antibody grade, and previous administration of amphotericin B all affect transfused platelet recovery and survival.

The corrected count increment (CCI) is a reasonable method to empirically quantify platelet transfusion responsiveness, as it accounts for the actual platelet count after transfusion, the number of platelets transfused, and the patient's size. The CCI is defined as the platelet count increment (per μL) × body surface area (in m^2) / number of platelets transfused ($\times 10^{11}$). (The platelet count increment is the difference between the platelet count 10 minutes or 1 hour after transfusion and the pretransfusion level.)

Amphotericin B

Because amphotericin B can decrease recovery and survival of transfused platelets, doses of amphotericin B and platelet transfusions should be separated in time. In a prospective study in clinically stable patients, we found that amphotericin B did not decrease platelet recovery or survival if given at least 2 hours after or before the transfusion.[7]

Splenomegaly

Splenomegaly is generally believed to reduce platelet survival and recovery. However, in a recent study, 45% of platelet transfusions in stable splenomegalic patients produced adequate increases in platelet counts.[8]

Alloimmunization

Alloimmunization to HLA or platelet-specific antigen should be suspected when a platelet transfusion fails to result in a CCI of 7500 or greater in a patient who has no clinical factors that would otherwise affect the results of platelet transfusion. In practice, at least two trials of random-donor platelets should be considered before declaring refractoriness, since stable patients occasionally have no response to an individual transfusion but have adequate responses to subsequent transfusions. Whenever possible, alloimmunization should be confirmed by testing for lymphocytotoxic antibodies in the recipient's serum.[9]

Patients who become alloimmunized usually do so within 4 to 6 weeks after the initial platelet transfusion. Patients who do not produce lymphocytotoxic

antibodies by this time usually remain responsive to random-donor platelet transfusions throughout their entire subsequent clinical course.[10]

Although most patients who become alloimmunized remain permanently unresponsive to random-donor platelets, 30% subsequently have significant decreases in their antibody levels, and approximately 10% regain responsiveness to random-donor platelets.[11] Thus, serial measurements of lymphocytotoxic antibody can help in deciding the type of platelets required at different times in a patient's clinical course.

In the presence of HLA antibodies, HLA-matched platelets can produce good therapeutic responses in many patients.[12] Unfortunately, the profound polymorphism of the HLA antigen system and the markedly different frequencies of particular antigens often make it difficult to find an HLA-compatible donor.[13] Even perfectly HLA-matched platelets fail to produce a response in 40% to 60% of alloimmunized patients; this failure may be related to ABO incompatibility, platelet-specific antibody, antibodies against vancomycin, or incompatibilities in the Bw4-Bw6 system, a biallelic system closely associated with the HLA-B locus.[14–16]

In one study, 76% of patients who received transfusions from mismatched donors who had certain antigens that are poorly expressed on platelets, such as HLA-B12 (or its splits B44 and B45), received at least one satisfactory transfusion.[17]

Another option when perfect matches are not available is to use platelets from donors with cross-reactive HLA antigens.[18] In a recent study, one-antigen mismatch transfusions were effective in 58% to 73% of recipients. An inverse relationship between the CCI and lymphocytotoxic antibody level exists, ie, the lower the lymphocytotoxic antibody level, the more likely the patient will have a favorable response to the transfusion.[19] Another alternative to obtaining HLA-matched units is to use crossmatching to obtain compatible units.[20,21] In severely alloimmunized patients, for whom many donor units have to be screened by crossmatching, and for whom there are no HLA-matched donors, perfusion through a protein A column (Prosorba A, Imré Corp, Seattle, WA) appears well tolerated and effective.[22,23]

Prolonged storage

Prolonged storage causes a small but significant decrease in platelet recovery.[24] Fresh and stored platelets might be expected to survive similarly in clinically stable patients; however, in a study in unstable patients with bacterial infections, graft-vs-host disease, splenomegaly, or veno-occlusive disease or who were treated with amphotericin B, significantly more patients needed another transfusion within 24 hours if given stored rather than fresh platelets.[6]

RISKS OF PLATELET TRANSFUSION

Platelet transfusions pose the same risks of infection as other blood components. However, the following differences exist.

Febrile, nonhemolytic reactions are more frequent in platelet than in red cell transfusions. Aye et al[25] demonstrated that unfiltered platelet concentrates accumulate high levels of cytokines, which singly or in combination can produce the signs and symptoms of a febrile transfusion reaction. In addition, filtering out white blood cells from platelet concentrates before storage can prevent this cytokine release without inducing significant platelet activation or granule release. The use of acetaminophen 650 mg orally 15 to 20 minutes before platelet transfusions, especially for random-donor platelet concentrates, reduces the frequency and severity of platelet transfusion reactions.[26]

Bacterial infections are also more frequent with platelet transfusions than with red blood cell transfusions. The contaminating organisms are often skin saprophytes (similar to organisms isolated in catheter sepsis). Severe symptoms may not appear until several hours after a transfusion, by which time one might overlook that the patient received platelets.[27] Therefore, septic events or deaths due to platelet contamination may be underreported and mistakenly attributed to catheter sepsis.[28] Cases of bacterial sepsis from platelets have increased, likely because of increased storage time and the increasing use of platelets.[28]

INDICATIONS FOR PLATELET TRANSFUSION

The goals of platelet transfusion in patients undergoing aggressive chemotherapy are to prevent bleeding and to treat active bleeding due to thrombocytopenia. Over the past 3 decades, physicians have struggled to define the precise indications for platelet transfusions. A stringent, rational policy is necessary to minimize the risks of blood product transfusions and to avoid overusing already-strained resources. *Table 2* summarizes the findings and recommendations from various reports.

TABLE 2
PLATELET COUNTS AND CLINICAL PICTURE AS INDICATIONS FOR PLATELET TRANSFUSION

Condition	Threshold platelet count (per μL)	Investigators
Amegakaryocytic thrombocytopenia		
Stable inpatients	10 000	Hussein and Hoeltge (present review)
With fever or mild coagulation disorders	20 000	
With active bleeding and decreasing hemoglobin	50 000	
With acute progranulocytic leukemia and active disseminated intravascular coagulopathy, or nonneurologic or nonophthalmologic surgical procedure	50 000	
Neurologic or ophthalmologic surgical procedures	100 000	
Thrombocytopenia due to peripheral destruction		
Surgical patients (except neurologic or ophthalmologic)	20 000*	Bishop et al[35]
Neurologic or ophthalmologic surgery	100 000	American College of Pathologists[36]
After cardiopulmonary bypass surgery	100 000*	Simon et al[37]

*Or with excessive microvascular bleeding

Thresholds in nonsurgical amegakaryocytic thrombocytopenic patients

In 1962, Gaydos et al[29] reported that the frequency of hemorrhage increased with progressively lower platelet counts in patients with acute leukemia. A threshold platelet level above which significant hemorrhage did not occur could not be identified, but gross hemorrhage occurred on fewer than 1% of days when the platelet count was more than 20 000 per μL. On the basis of this report, a platelet count of 20 000 per μL has been generally adopted as a target level for prophylactic platelet transfusion.[30,31]

However, several studies failed to show that patients with acute leukemia who received prophylactic platelet transfusions had a lower incidence of bleeding, needed fewer units of packed red blood cells, or survived longer than did those who received transfusions for specific indications only (such as clinically significant bleeding or a platelet count less than 20 000 per μL preceded by a decline of at least 50% in the preceding 24 hours).[32,33] Because of the lack of agreement about the need for prophylactic platelet transfusions and at what platelet count they should be given, a transfusion strategy based on both the platelet count and on clinical factors appears most rational.[30]

Gmür et al[34] found that a safe threshold for prophylactic transfusions is 5000 per μL in patients who have no fever or bleeding manifestations, and 10 000 per μL in patients with such signs. In patients with coagulation disorders or anatomical lesions or receiving anticoagulation therapy the threshold should be at least 20 000 per μL.

For actively treated amegakaryocytic thrombocytopenic patients who have no other complications, we give platelets if serial platelet counts suggest the next day's count will be less than 10 000 per μL. If it is difficult to predict the platelet count in 24 hours, we usually repeat a complete blood count in 8 to 12 hours and make a decision on the basis of this count. In patients with active bleeding causing a decrease in hemoglobin concentration, we keep the platelet count between 40 000 and 50 000 per μL until the active bleeding is under control for 48 to 72 hours, then maintain it at more than 20 000 per μL for 2 to 5 days. In patients with acute progranulocytic leukemia and active DIC, the platelet count is kept between 40 000 and 50 000 per μL at all times until the DIC has resolved. A target of approximately 20 000 per μL appears reasonable for patients with fever or coexisting mild coagulation disorders. In patients who need a lumbar puncture, a platelet count of 30 000 is acceptable if the prothrombin and partial thromboplastin times and fibrinogen level are normal.

Chemotherapy-induced mucositis or emesis often causes hemorrhage in previously stable thrombocytopenic patients. Previously stable amegakaryocytic thrombocytopenic patients who become infected often have precipitous declines in platelet counts and are therefore at a markedly increased risk of bleeding and need aggressive prophylactic platelet support.[30]

Threshold in surgical patients with amegakaryocytic thrombocytopenia

Bishop and colleagues[35] reviewed the surgical experience of 167 thrombocytopenic patients with

leukemia who underwent surgery at the University of Maryland Cancer Center, where the standard practice is to target preoperative platelet levels at a minimum of 50 000 per μL and postoperative counts around 50 000 for 3 days after major surgical procedures. Patients with a median platelet count of 56 000 per μL had no increase in mortality at 1 month. Included in this series were 13 laparotomies, 9 craniotomies, and 4 thoracotomies. In only 7% of the procedures was perioperative blood loss greater than 500 mL and transfusion requirements greater than four units of red blood cells, and in only one case did there appear to be any significant thrombocytopenia-related bleeding (a hematoma). These findings support the recent guidelines from the College of American Pathologists, which recommend a perioperative platelet transfusion for patients with platelet counts less than 50 000.[36]

Thresholds in surgical patients with thrombocytopenia due to peripheral destruction

An easy and cost-effective method of evaluating thrombocytopenia is to obtain a detailed history, perform a good physical examination, and assess the peripheral blood smear. Increased numbers of large platelets in the absence of any dysplastic morphology in the white cells, red cells, or platelets suggest the bone marrow is intact and a consumptive or destructive process is the cause of the thrombocytopenia. In the absence of red cell fragments, schistocytes, or coagulopathy, idiopathic thrombocytopenic purpura can be diagnosed.

In patients in whom thrombocytopenia is the sole abnormality of the coagulation system, perioperative and postoperative platelet transfusions should be considered if the platelet count is less than 50 000 per μL or if there is evidence of microvascular bleeding.[36] For neurologic or ophthalmologic surgery, a platelet count near 100 000 per μL is recommended.[37] After a cardiopulmonary bypass procedure, platelet transfusion is indicated if the platelet count is less than 100 000 and accompanied by greater-than-expected microvascular bleeding (small-vessel bleeding in the surgical field as opposed to bleeding from larger, open vessels). After surgery, microvascular bleeding may be identified at the bedside as significant bleeding and ecchymosis distinct from the surgical wound.[36] After bypass surgery, mild thrombocytopenia (a platelet count as low as 58 000 per μL) and transient platelet dysfunction do not necessitate platelet concentrates, and prophylactic use of platelets in bypass surgery is not indicated.[37]

Platelet transfusion in immune thrombocytopenia

Transfusion in patients with immune thrombocytopenia is limited to those with active bleeding or to some who are at high risk and awaiting a response to other treatments. Approximately 40% of patients with idiopathic thrombocytopenic purpura respond to random-donor platelet transfusions, but this response may be short-lived.[38] Pretreatment or simultaneous treatment with intravenous immunoglobulin improves responsiveness to platelet transfusions.[39]

Platelet transfusion for patients with functional platelet defects

In congenital platelet disorders such as Glanzmann's thrombasthenia, Bernard-Soulier syndrome, or storage pool disorders, platelet transfusion is often effective in stopping bleeding episodes or as surgical prophylaxis.[40,41]

CONTRAINDICATIONS TO PLATELET TRANSFUSIONS

Thrombotic thrombocytopenia purpura, preeclampsia, and other platelet-mediated microangiopathies are contraindications to platelet transfusion.[42,43] Platelet transfusion should be considered in thrombotic thrombocytopenic purpura and related syndromes only as a desperate attempt to stop life-threatening thrombocytopenia-related bleeding until other treatments increase the platelet count.[44]

Platelet transfusion has also been implicated in precipitating thrombosis in heparin-associated thrombocytopenia. Heparin-associated in vitro platelet hyperaggregation provides a plausible explanation for this occurrence. As heparin-induced thrombocytopenia rarely results in life-threatening hemorrhage, platelet transfusion is usually not indicated and should be viewed as possibly dangerous.[44]

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