Background: Platelet transfusion is a critical and often necessary aspect of managing cancer. Low platelet counts frequently lead to bleeding complications; however, the drugs used to combat malignancy commonly lead to decreased production and destruction of the very cell whose function is essential to stop bleeding. The transfusion of allogeneic platelet products helps to promote hemostasis, but alloimmunization may make it difficult to manage other complications associated with cancer.

Methods: The literature relating to platelet transfusion in patients with cancer was reviewed.

Results: Platelet storage, dosing, transfusion indications, and transfusion response are essential topics for health care professionals to understand because many patients with cancer will require platelet transfusions during the course of treatment. The workup and differentiation of non–immune-mediated compared with immune-mediated platelet refractoriness are vital because platelet management is different between types of refractoriness.

Conclusions: A combination of appropriate utilization of platelet inventory and laboratory testing coupled with communication between those caring for patients with cancer and those providing blood products is essential for effective patient care.

Introduction

Platelets are discoid anucleate cells that measure 3 to 5 µm at their greatest diameter. They are derived from megakaryocytes in the bone marrow and contain ABO antigens on their surface. Platelets are an essential component of hemostasis because they are responsible for forming a platelet plug, providing a framework for the formation of fibrin clots, and secreting cytokines and growth factors. Platelets express A and B red blood cell antigens, class I human leukocyte antigen (HLA), and platelet-specific antigens (eg, human platelet antigen [HPA]) on their surface.

Platelets are available from 2 sources based on the method in which they are collected: apheresis platelets and whole blood–derived platelets. Apheresis platelets are obtained via an apheresis collection device from a single donor. Oftentimes, 2 or 3 apheresis platelet units can be acquired during this single collection event; each of these units is considered 1 adult dose. Whole blood–derived platelets are acquired from the platelet concentrate portion of a whole blood donation. Routinely, 4 to 6 platelet concentrates are pooled together to obtain a typical dose.
Both apheresis platelet and pooled whole blood-derived platelet units must contain a minimum of $3 \times 10^{11}$ platelets per bag. These 2 products have similar clinical effects and can be interchangeably used.$^{2,5}$

The leukoreduction of platelets provides several benefits, including the reduction of (1) the platelet alloimmunization rate, (2) cytomegalovirus transmission due to transfusion, and (3) febrile nonhemolytic transfusion reactions.$^{2}$

Storage and Dosing
Platelets are stored in the blood bank at room temperature ($68°–75°F$ [$20°–24°C$]) on a platelet rotator to facilitate the exchange of oxygen. Primarily due to their risk of bacterial contamination (approximate risk: 1 per 1,000 units), platelets have a shelf life of 5 days; the day of collection is considered day 0.$^6$ Volunteers who donate blood are tested for HIV, hepatitis B and C, and West Nile virus infections, and blood collection facilities must also screen all platelet products for bacteria,$^7,8$ either via bacterial cultures or assessing bacterial growth by oxygen consumption measurement.$^3$

One dose of platelets should increase the platelet count of an average-sized adult by 35,000 to 40,000/µL,$^7$ and this increment can be measured with a post-transfusion platelet count or complete blood count. In adult patients, platelets are dosed in units. Dosing of platelets for pediatric patients may be done based on body weight (typical pediatric platelet dose, 5–10 mL/kg).$^5$

Indications for Transfusion
A platelet transfusion may be indicated for either a quantitative defect (thrombocytopenia) or a qualitative defect (dysfunctional platelets). The normal range for a platelet count is approximately 150,000 to 450,000/µL; however, the platelet count is but one aspect in determining a patient’s risk for bleeding.

Many etiologies of thrombocytopenia exist in patients with cancer. The patient’s disease may directly cause thrombocytopenia via tumor involvement of the bone marrow, spleen, or both. Although myeloablative chemotherapeutic regimens may cause prolonged thrombocytopenias, nonmyeloablative chemotherapies produces variable degrees of thrombocytopenia based on drug selection, drug dosage, and number of cycles administered. Patients with cancer can develop microangiopathic conditions that may lead to platelet destruction, including disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and vasculitis. Immune thrombocytopenia has been associated with patients with lymphoproliferative malignancies.$^{10}$ Commonly used antibiotics, such as penicillins and cephalosporins, may also cause thrombocytopenia via an immune-mediated, drug-induced mechanism known as hapten-dependent antibody formation.$^{11}$

The AABB (formerly American Association of Blood Banks) recommends the following prophylactic platelet transfusion triggers: less than 10,000/µL in adult inpatients with therapy-induced hypoproliferative thrombocytopenia, less than 20,000/µL for central venous catheter placement, and less than 50,000/µL for either diagnostic lumbar puncture or major elective non-neuroaxial surgery.$^{12}$ Other common platelet transfusion triggers include less than 10,000/µL for stable, nonbleeding patients and less than 20,000/µL for febrile patients. A trigger of 100,000/µL is often used for neurosurgical patients or those patients experiencing ophthalmological bleeding.$^{2,9}$ Despite these AABB recommendations, debate continues about the rationale, efficacy, and threshold of prophylactic platelet transfusions in patients with cancer. For example, Stanworth et al$^{13}$ suggested that the effectiveness of prophylactic platelet transfusions may vary between specific groups of patients with cancer. When comparing chemotherapy and allogeneic hematopoietic stem cell transplantation among patients receiving prophylactic platelet transfusion versus not receiving prophylactic dosing, they reported decreased bleeding events in the prophylactic platelet transfusion group. However, when comparing patients who received autologous hematopoietic stem cell transplantation, the researchers saw no difference in bleeding events between the prophylactic and nonprophylactic platelet transfusion groups.$^{13}$ Moreover, Schiffer$^{14}$ emphasized the need for studies to evaluate platelet prophylaxis in patients with acute leukemia and protracted thrombocytopenia due to induction chemotherapy.

Platelet Dysfunction
Platelets become dysfunctional for many causes, including medication and herbal supplement use, renal failure (uremia), and genetic abnormalities (eg, Glanzmann thrombasthenia, Bernard–Soulier syndrome). In addition, the membranes used in cardiopulmonary bypass circuits and extracorporeal membrane oxygenation circuits can also cause platelet dysfunction.$^{15}$

The most common medication to cause platelet dysfunction is aspirin, which irreversibly inhibits the enzyme cyclooxygenase I.$^{15}$ A myriad of other medications inhibit platelet function, including nonspecific nonsteroidal anti-inflammatory drugs, adenosine diphosphate receptor inhibitors, adenosine reuptake inhibitors, glycoprotein IIB/IIIa inhibitors, thromboxane inhibitors, and β-lactam antibiotics.$^{15}$

Response to Platelet Transfusion
Several aspects of the platelet product can affect a patient’s response to transfusion, including dose of platelets received, type of product (apheresis or whole
Platelet refractoriness can be defined as the failure to achieve a 1-hour post-transfusion platelet increment of 11,000/µL on 2 consecutive transfusions.17 Because transfusing ABO-incompatible platelets may also negatively impact the post-transfusion platelet increment, many institutions require this failure to be with ABO-identical or ABO-compatible platelets.

Platelet refractoriness can be broken down into 2 broad categories: non–immune-mediated and immune-mediated. Non–immune-mediated platelet refractoriness can be due to splenomegaly, sepsis, fever, medications, and active bleeding. Two-thirds of cases of platelet refractoriness are estimated to be nonimmune in nature and another one-fifth comprise both nonimmune and immune causes.20 Immune-mediated platelet refractoriness is due to alloantibody formation against the HLA system, the HPA system, or both. Risk factors for alloimmunization to these systems include prior transfusion, pregnancy, and transplantation.20

The 1-hour post-transfusion platelet increment helps to identify patients with platelet refractoriness, and it is also a key differentiating factor between the majority of nonimmune and immune causes. Although patients with nonimmune causes of refractoriness will typically show some platelet increment within 1 hour following the transfusion (likely a minimum increment of < 35,000/µL seen in nonrefractory patients), patients with immune-mediated refractoriness often do not demonstrate such an increment. One caveat to this differentiating factor is in patients with splenomegaly; in these patients, up to 90% of the total body platelet mass may be sequestered by the spleen.21 Nevertheless, an appropriate platelet transfusion strategy can still be pursued. For a nonimmune refractory patient, the underlying disease processes should be treated and more platelets should be transfused; by contrast, in an immune refractory patient, more appropriate platelets should be obtained.

### HLA-Matched and Crossmatched Platelets

Transfusing patients who are refractory to platelets with anti-HLA or anti-HPA antibodies centers on identifying the antibody specificity and procuring antigen-negative platelets. If a screening test for anti-HLA antibodies is positive, then the first step in providing HLA-matched platelets is to determine the HLA type of the patient. The specificity of the anti-HLA antibodies may also be determined at this stage in the evaluation. The blood bank will then communicate with the blood supplier to obtain HLA-matched platelets (matching the HLA class I antigens, specifically the A and B loci). Some blood suppliers have databases of the HLA class I antigen types of apheresis platelet donors to facilitate the identification of potential donor–patient matches.22

Two strategies exist for the procurement of HLA-matched platelets. The first method involves identifying donors who are a high-grade match (grade A or B) with the HLA type of the patient. The second method, known as antibody specificity prediction, utilizes the antibody specificity to ob-
taining HLA antigen-negative platelets. These 2 strategies are specific to each blood supplier and, thus, vary by region. The process to obtain HLA-matched platelets may take several days or even weeks based on the HLA type of the patient, the specificity of antibodies, and donor availability.

The process to obtain HPA-matched platelets is similar to the process used to obtain HLA-matched platelets. If a screening test for anti-HPA antibodies is positive, then both the patient’s HPA type and the antibody specificity should be determined. The process to obtain HPA-matched platelets follows the same approach as obtaining HLA-matched platelets.

An alternative to obtaining either HLA- or HPA-matched platelets for alloimmunized patients involves the use of crossmatched platelets. Typically, platelet crossmatching is performed at blood centers via solid-phase red cell adherence assay to assess the compatibility between the serum of the patient and the platelets of the donor (Wendy Enting, LPN, oral communication, November 2014). Crossmatch-compatible platelets are presumed to lack the antigen(s) to which the patient has formed antibodies. Benefits to platelet crossmatching include rapid turnaround time (hours), simultaneous screening of multiple platelet units, and the ability to obtain platelets without having to perform HLA/HPA typing on the patient and donor. In a systematic literature review, Vassallo et al found that while platelet crossmatching did not greatly improve failure rates (typically 20%–30% using HLA-matched platelets) in alloimmunized refractory patients, platelet crossmatching did improve the availability of platelets for these patients. In an observational study of 114 patients who received 1,621 platelet transfusions, Petz et al concluded that all 3 methods for the selection of platelets for alloimmunized patients (HLA-matched, crossmatched, and antibody specificity prediction) were equally effective as measured by the PPR.

**Laboratory Assays**

Many different assays may be utilized to identify the presence and specificity of HLA and HPA antibodies. The various methodologies include lymphocytotoxicity testing, platelet immunofluorescence testing, lymphocyte immunofluorescence testing, enzyme-linked immunosorbent assays (ELISAs), antigen-capture ELISAs, monoclonal antibody-specific immobilization of platelet antigens, and flow cytometric assays. Each methodology has a unique set of benefits and drawbacks. In addition to variations in sensitivity and specificity rates, other factors that the health care professional must consider include assay complexity, turnaround time for obtaining results, the reproducibility of results, and concordance rates across different platforms. The nuances and selection of these assays are determined by blood suppliers, reference laboratories, or both.

**Mitigating Platelet Transfusions**

The prevention of alloimmunization plays an important role in improving patient care and reducing the number of platelets transfused. Both leukoreduction and ultraviolet B irradiation were demonstrated in the TRAP study to be equally effective in preventing antibody-mediated platelet refractoriness during chemotherapy for acute myeloid leukemia. A total of 17% of study volunteers who received leukoreduced platelets became alloimmunized compared with 45% of those who received nonleukoreduced platelets. All platelets for patients with cancer should be leukoreduced; currently, nearly all platelets collected today are leukoreduced by blood suppliers.

Many strategies have been proposed to mitigate the need for platelet transfusions, particularly in refractory patients. Medications such as antifibrinolytics (ε-aminocaproic acid), intravenous immunoglobulin, Rhesus immune globulin, and cyclosporine A have been used with varied success in small studies, as have other modalities such as plasma exchange, immunoadsorption, and massive platelet transfusion. Thrombopoietin receptor agonists (eg, eltrombopag, romiplostim) designed to increase platelet production have shown some effectiveness for the treatment of thrombocytopenia in patients with immune thrombocytopenia and chronic hepatitis C. Currently, clinical trials to expand these indications to treat thrombocytopenia in patients with cancer are ongoing (eltrombopag trials: NCT01656252, NCT02093325, NCT01147809, NCT01488565; romiplostim trials: NCT00299182, NCT02052882).

**Conclusions**

Platelet transfusion has a well-defined role in the treatment of patients with cancer. By understanding the requirements of storage, dosing, indications, and responses to platelet transfusion, health care professionals can provide the most appropriate care for their patients. Further knowledge of platelet refractoriness and how to care for refractory patients will enhance the proper utilization of laboratory testing and the allocation of scarce resources.

**References**


14. Schiffer CA. They took a mulligan and mostly got it right...the issue of prophylactic platelet transfusion for patients receiving autologous stem cell transplantation. Transfusion. 2014;54(10):2372-2374.