

## ETHICS CASE

### Ethical Questions about Platelet Transfusions at the End of Life

Commentary by John P. Sherbeck, MD, and Renee D. Boss, MD

#### Abstract

This case of platelet transfusion in palliative care illustrates a common dilemma in transfusion medicine: approval of the use of a scarce, yet potentially life-saving, resource. As in this case, these decisions often involve seriously ill patients with acute needs and evolving goals of care. The use of resources to treat the patient at hand must be balanced against maintaining adequate resources to treat future patients. In this setting, the ethical principles of beneficence and social justice are in conflict.

#### Case

Dr. J, a second-year resident on the palliative care service, has become quite close to his patient, Emma, a 5-year-old girl with acute lymphoblastic leukemia. Two years ago, Emma completed successful chemotherapy and achieved remission, but a recent bone marrow biopsy showed lymphoblastic infiltration. She was started on a rescue therapy program with little response and underwent a bone marrow transplant. During this relapse, she has been hospitalized on multiple occasions for infections and bleeding, which required blood and platelet transfusions, and is now receiving palliative care for tumor lysis syndrome. It is Emma's medical team's opinion that there is no more that can be done to cure her leukemia, which prompted her transfer to the palliative care service. Shortly after transfer, Emma developed bright red blood per rectum, and Dr. J requested human leukocyte antigen (HLA)-matched platelet transfusion for her to help stop the bleeding.

Dr. S, a third-year pathology resident, received Dr. J's request for HLA-matched platelets. Typically, pathologists oversee platelet distribution, since they are the physicians responsible for administering transfusion services in a hospital—maintaining an adequate blood supply, monitoring blood donor and patient-recipient safety, ensuring appropriate blood utilization, and directing the preparation and safe use of blood components according to a hospital's platelet distribution protocol. Since Dr. S oversees a busy transfusion service with many sick patients requiring blood and platelets, one of her duties is to carefully assess each request for these limited resources. She contacts Dr. J and asks for more information about his request. Dr. S explains that HLA-matched

platelets are in short supply and most often used for patients who are still being aggressively treated to try to cure their illness.

Dr. J responds, "Hmmm. . . . Why would the fact that a patient is no longer receiving aggressive acute care prompt us to reconsider her use of this resource? We still have an obligation to treat her, even when the goal is palliative rather than curative." Both physicians wonder about how to proceed.

## Commentary

### Platelet Transfusion Basics

Like most products under the umbrella of transfusion medicine, platelet transfusions are derived from human donors. Platelets can be derived from a single donor (apheresis unit) or from multiple whole blood donors (pooled unit). In all cases of matched or directed donations, the product is an apheresis unit.

*Clinical indications for platelet transfusion.* Patients with indications for platelet transfusion generally fall into two categories: those with thrombocytopenia with active bleeding or nonbleeding patients at imminent risk of bleeding, for whom transfusion is used prophylactically. The latter include nonbleeding patients with severe thrombocytopenia (i.e., less than 10,000 platelets per microliter of blood) and patients with ongoing bone marrow suppression due to active chemotherapy or infection, for example. Thresholds for prophylactic platelet transfusion have been well studied [1]. One important consideration is the duration of the treatment effect; unlike red cell transfusion, in which a nonbleeding patient can experience benefit for weeks, the short life cycle of a platelet *in vivo* limits the therapeutic benefit to hours or days. Therefore, a single chronically thrombocytopenic patient, like Emma, might require an extraordinary number of transfusions over time.

*Alloimmunization.* If the transfused platelets harbor antigens that the recipient's immune system views as foreign, immune sensitization (alloimmunization) can occur. Human leukocyte antigen (HLA) class I antigens are by far the most common cause of platelet alloimmunization [2]. Subsequent transfusions harboring that antigen can result in antibody-mediated destruction of the donor platelets, a phenomenon known as premature clearance. Failure of the transfusion to raise platelet counts due to premature clearance of the platelets is clinically referred to as *refractoriness*. (It is worth noting, however, that not all cases of platelet refractoriness are immune mediated.) Platelet refractoriness is typically defined as three consecutive transfusions with less than expected (based on platelet dose and estimated body surface area) rise in platelet counts at one-hour post transfusion [3]. Not surprisingly, the theoretical risk of alloimmunization rises with the number of transfusions (both packed red cells and

platelets). However, even with repeated exposure, alloimmunization—and resulting refractoriness—occurs in a minority of patients [2, 4, 5].

*Compatibility and scarcity of donors for HLA platelets.* As alluded to in the case, and as mentioned above, platelets harbor HLA class I antigens, which are a common target for immune sensitization. To combat immune refractoriness, patients can receive platelets from specific donors with HLA-compatible antigens (“HLA platelets”). Testing for compatibility is performed *in vitro* and evaluates both the patient’s own HLA antigens and the reactivity of the patient’s plasma against other class I antigens found in the general population. Blood products are either HLA-compatible (i.e., the recipient plasma does not harbor HLA antibodies that react to the HLA antigens on the donor platelets) or HLA-identical (i.e., the recipient and donor HLA antigens are identical) [3]. In patients for whom it is difficult to find HLA-compatible platelets, cross-matched platelets—those that do not react *in vitro* with the recipient’s serum irrespective of antigen or antibody status—can be a suitable alternative.

### **Ethically and Clinically Relevant Considerations for Platelet Allocation in Transfusion Medicine**

*Finding donors.* While HLA platelets have potential to support chronically transfused, refractory patients, finding suitable donors can be a monumental task. Blood suppliers, including the American Red Cross, maintain national databases of known platelet donors and their HLA type and facilitate testing and identification [6]. Once a suitable donor is found, a number of time-sensitive criteria must be met. First and foremost, donors must be currently eligible to donate (according to Red Cross or other eligibility requirements). Second, the donated platelets must be expeditiously collected, processed, and shipped to the transfusion center, since platelet lifespan is typically five days after collection. The issue of cost is also paramount; blood products, in general, are one of the largest costs within a laboratory. The additional work to process HLA platelets drives the cost of an apheresis unit significantly higher than a random platelet unit [7]. Because of these criteria and cost considerations, random platelets should be transfused in the event of acute, life-threatening bleeding, even in patients who have historically received HLA platelets. In other words, in an urgent situation, the risk of immune refractoriness is tolerated, from an ethical and clinical standpoint, to respond robustly to the acuity of a patient’s condition.

*Palliative care transfusions considerations.* The World Health Organization (WHO) defines [palliative care](#) as “improving the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering” [8]. There is very little literature addressing practical or ethical considerations that arise in cases of bleeding due to thrombocytopenia in nontrauma patients near the end of life, however [9, 10]. Bleeding can create suffering for all involved; platelet transfusion would be a palliative intervention. During active bleeding,

the use of random platelets is warranted. If the patient is already immune refractory, pooled platelets may be superior to apheresis platelets, as there is a greater chance that at least one of the donors is compatible with the patient [11]. In general, transfusion practices for patients at the end of life are similar to those for the general population. Yet platelet transfusion in the seriously ill, which is common, is often an acute approach to a chronic problem. And because chronically transfused patients are at increasing risk of becoming alloimmunized, they can pose a large burden to the HLA platelet supply.

Regardless of the underlying pathology, transfusion is not a curative therapy but an acute treatment for a symptom of the underlying process. Therefore, patients without a goal of cure remain eligible for transfusion as a part of symptom management. Yet, unique questions arise when considering the use of the scarce resource of HLA platelets for patients near the end of life. The key benefit of HLA platelets is for refractory patients who need ongoing, long-term transfusion. It is reasonable to consider reserving HLA platelets for those patients with longer life expectancies. Diverting HLA platelets to a patient who will not receive the long-term benefit is potentially diverting them away from a patient who will. Alternative strategies do exist for bleeding patients like Emma, including the use of random platelets, local hemorrhage control, and so on. The preemptive use of HLA platelets as a prophylactic against alloimmunization should not be attempted; it creates an undue burden on the population and causes a delay in platelet delivery and associated symptom relief [12, 13].

*HLA platelet distribution policies.* While caring for the individual patient is the goal at the bedside, organizations must balance individual goals of care with the capacity to care for *all* patients. This is the essence of the ethical conflict between beneficence and social justice. The use of scarce HLA platelets is a prime example of the difficulty in balancing the needs of the individual with the needs of the population. While there is no substitute for clinical decision making, organizations must establish policies that ensure rational and [just use of limited resources](#). A platelet distribution protocol is an example of an organizational policy to reduce unnecessary variability in transfusion practices and, in so doing, increase availability of blood products for all patients [14, 15]. It is important to note that platelet distribution protocols generally target objective platelet levels or degree of hemostasis without consideration of subjective patient comfort or distress. The protocols can thus create a bias in favor of acute over palliative goals of care. In situations in which patient or family requests for transfusion conflict with clinician recommendations, ethics consultations should be considered.

When facing decisions about more critical resource shortages, like HLA platelets, organizations often require involvement of expert consultants or gatekeepers, like Dr. S in this case. Typically, these are blood bank medical directors or pathology residents or fellows acting in their stead. The purpose of the consultant is to act as a liaison between the laboratory and the wards and act as a careful steward of resources. The pathologist

performs a laboratory evaluation to address a series of clinical and empirical questions: Is the patient platelet refractory? If so, what is the likelihood the patient is alloimmunized? Once these questions are answered, appropriate transfusion recommendations can be made. The pathologist's role is, first and foremost, to ensure that patients who need blood products have access to them. But appropriate use is a moving target. Releasing a platelet unit for a patient with a count of less than 50 platelets per microliter of blood prior to a diagnostic lumbar puncture is appropriate when there is plenty of product. If the same request is made at a trauma center with a severe platelet shortage, it would be reasonable to deny the request until inventory has improved. To return to Emma's case, because she is actively bleeding, she should receive random platelets and be monitored for evidence of refractoriness.

*Communication between pathologists and clinicians.* Throughout this consultative process it is imperative that lines of communication remain open. A pathologist is typically unable to assess the patient at the bedside and thus relies on clinical colleagues to paint a timely and accurate picture of the patient's condition, vulnerabilities, and needs. Likewise, it is imperative that the blood bank or the pathologist communicates to clinicians about inventory and product selection relevant to the patient. This communication allows for appropriate triaging and use of products, such as HLA platelets, in times of shortage. Although usage of the word "gatekeeper" might imply an adversarial relationship for some, a common goal of both the bedside clinician and the pathologist is to appropriately manage the patient.

### **Application to the Case**

For Emma, whose active bleeding is likely due in some part to thrombocytopenia, it is appropriate to initiate a platelet transfusion now to limit her distress and increase her comfort. Given the inherent time delay for HLA platelets, together with the lack of evidence that she is immune refractory, she should be transfused with random platelets. Additional methods to control hemorrhage, including localized pressure, should be used as well. Once Emma is transfused, her platelet counts should be closely monitored, and if her thrombocytopenia remains refractory to platelet transfusion, she should be further evaluated for possible alloimmunization. Early discussions with Emma's physicians, her family, and both blood bank and ethics consultants could assist with coordinating goals of care if HLA platelets are indicated to improve Emma's comfort.

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