The prevention of transfusion-associated graft-versus-host disease (TA-GVHD) is critical for the reduction of transfusion-related risks. Because this complication of transfusion is difficult to treat and, consequently, has a high mortality rate, the optimal approach to management of TA-GVHD is prevention. TA-GVHD is associated with the transfusion of cellular blood products (blood components that contain cells that retain the capability to engraft in a transfusion recipient), and prevention is most commonly achieved through gamma irradiation. Because prevention is critical, it is of the utmost importance to identify at-risk patients accurately. Although irradiation is quite effective at preventing TA-GVHD, there are suboptimal effects of irradiation on the red blood cell (RBC) membranes and increased costs that must be balanced. These factors lead to the adoption of selective protocols with only particular patients receiving irradiated blood products. We advocate less selective protocols and we highlight here our age-related policy for prevention of TA-GVHD in children with undiagnosed congenital immunodeficiency.

OVERVIEW OF TA-GVHD

GVHD was first recognized in experimental animal models of transplantation. It is now seen most often in association with progenitor cell transplantation. The disease has an acute and chronic form, presenting weeks to months after transplantation. It is characterized by fever, erythematous skin rash, signs of liver dysfunction, and gastrointestinal symptoms. GVHD is caused by donor T lymphocytes recognizing the host tissues as foreign and initiating an immunologic reaction against the host tissues. Treatment is difficult and usually involves immunosuppressive therapies or extracorporeal photopheresis.

TA-GVHD is a rare, but devastating complication of transfusion. It was first recognized in neonates who received intrauterine transfusions and in transfused children with congenital immunodeficiency syndromes, like Wiskott-Aldridge syndrome. TA-GVHD can develop between 3 and 30 days of the transfusion event, but it often presents in 8 to 10 days after transfusion. The patients generally develop an initial fever and cutaneous rash. At this point, the diagnosis may be overlooked because the skin lesions bear similarities to a drug reaction and the combination of fever and rash may be confused with a viral syndrome. Patients subsequently develop hepatitis, enterocolitis with diarrhea, and pancytopenia. The pathogenesis of the disease involves immunocompetent T lymphocytes present in cellular blood components that are capable of engrafting, proliferating, and mounting an immune response against the recipient in the setting of a recipient who is immunologically incapable of destroying the transfused T lymphocytes. TA-GVHD may also occur in immunocompetent recipients who do not recognize the transfused T cells as foreign. A number of reports also demonstrate that the risk of TA-GVHD is increased when fresh blood components (<3 days) are transfused.

TA-GVHD is similar to the GVHD that is seen in the setting of progenitor cell transplantation, but there is a distinct difference that must be emphasized. In TA-GVHD, patients develop pancytopenia because their hematopoietic cells are of host origin. It is this pancytopenia, specifically neutropenia, with associated life-threatening infections, which results in a very high mortality rate of 90% to 100%. In GVHD associated with progenitor cell transplantation, the recipient’s hematopoietic cells are of graft origin and are protected. In contrast to TA-GVHD, the mortality seen in GVHD associated with progenitor cell transplantation is much lower.
In general, there is no effective treatment for TA-GVHD. There are only rare case reports in the literature documenting successful treatment with progenitor cell transplantation.7,8 Because of this lack of effective treatment and the associated mortality rate approaching 100%, prevention is the only effective method of managing this transfusion-related complication. Gamma irradiation of cellular blood components is an effective method of preventing this complication; blood products that are not cellular (lacking white blood cells [WBCs] capable of engraftment) do not pose a risk for TA-GVHD and, consequently, do not require irradiation. Other means of inactivating WBCs and preventing engraftment such as X-rays can also be used to prevent TA-GVHD and may become more important as a means to avoid security concerns with the large amounts of radioactive materials contained in blood irradiators. Per AABB Standards, irradiation for the prevention of TA-GVHD is accomplished by delivering a minimum dose of 25 Gy (2500 cGy) to the central portion of the irradiation container with at least 15 Gy (1500 cGy) to all areas.9 Although leukoreduction has been considered by some to reduce or eliminate the risk of TA-GVHD, most experts believe that it is an inadequate approach for patients at risk. Pathogen reduction technologies inactivate WBCs and have been used in place of gamma irradiation for TA-GVHD prevention with pathogen-reduced platelets (PLTs) in other countries, but pathogen reduction technologies are not available in the United States.

AABB Standards explicitly require that irradiated cellular blood products should be given to: 1) any patient at risk for TA-GVHD, 2) patients receiving components donated by a blood relative, and 3) patients receiving products that have been selected on the basis of HLA compatibility either by HLA typing or crossmatching. Patients at risk of developing TA-GVHD reported in the literature include fetuses receiving intrauterine transfusion, premature infants, neonates who require RBC exchange including those with erythroblastosis fetalis, patients with hematologic malignancies and certain solid tumors, recipients of intensive chemotherapy and/or progenitor cell transplantation, patients receiving purine antimetabolites such as fludarabine, granulocyte recipients, and patients with congenital immunodeficiency syndromes such as severe combined immunodeficiency syndrome (SCIDS).10,11 At our institution, we provide irradiated cellular blood products for all patients who have any of the above-mentioned clinical conditions and risk factors for developing TA-GVHD. There are many published guidelines and reviews that vary in their recommendations from general guidance to explicit indications that can be used by individual institutions to determine who should receive irradiated blood components.

Hospitals and transfusion services must develop their own guidelines or protocols that list patients considered at risk for TA-GVHD and provide irradiated blood products for these patients by physician order or upon receipt of information that the patient meets the criteria for receiving irradiated blood components. To determine a policy on irradiation for prevention of TA-GVHD, each institution must assess the advantages and disadvantages of irradiated blood products as related to the risks of TA-GVHD for their patient population. Although irradiation does not affect PLT products, irradiated RBCs have a decreased shelf life with increased membrane permeability leading to hemolysis and potassium leakage. The costs of irradiation include the requirement for an irradiator, irradiation indicator stickers and staff time to perform the irradiation, the option of purchasing irradiated products from one’s blood supplier, and the cost of decreased shelf life of irradiated RBCs. Consequently, the determination of a policy for irradiation is complex and multifactorial. Indeed, surveys have shown that there is variability in TA-GVHD prevention policies across institutions.12,13 Unfortunately, these selective protocols can miss some patients at risk for TA-GVHD as shown by our experience, suggesting that protocols that would offer universal irradiation are more prudent.

**OUR EXPERIENCE**

**Case presentation**

In October 1991, a 4-month-old child was admitted via our emergency room with the diagnosis of respiratory distress. This condition progressed over the next several days and the child was transferred to the intensive care unit. The patient was anemic and hypoxic. To optimize oxygen delivery to the tissues, RBC transfusions were performed. At the time of these transfusions, we had no protocols in place to provide leukoreduced or fresh blood components to this patient. Due to a lack of clinical improvement, the patient underwent bronchoscopy. Studies taken from the bronchoscopy procedure revealed that the child had *Pneumocystis carinii* pneumonia. Since our hospital is located in an inner-city area where human immunodeficiency virus (HIV) is common, it was assumed that the patient was suffering from AIDS and that irradiated blood was not required for transfusion therapy.1 A subsequent immunologic workup revealed SCIDS, and HIV antibody testing was negative. The patient’s respiratory status improved and he was transferred to the routine floor. A skin rash developed that was proven on biopsy to be TA-GVHD. Despite the recent clinical improvement, the child worsened with thrombocytopenia, disseminated intravascular coagulopathy, and hypotension. Cardiac arrhythmias ensued, leading to cardiac arrest. The child could not be resuscitated and was pronounced dead. Thus, although the child recovered from *Pneumocystis* pneumonia, he ultimately died due to TA-GVHD related to...
Implementation of age-related policy

After the identification of this case, we reassessed our indications for irradiating blood products. Multiple discussions were held to assess the risk management implications of these events. We found that the policy regarding blood irradiation at the time was based on the patient having a risk-defining diagnosis or being on a particular therapy, but there was no consideration for TA-GVHD prevention in the at-risk patient before diagnosis. Our pediatric division suggested that we implement a universal irradiation policy for all children receiving transfusions. The transfusion service questioned this recommendation for several reasons: 1) we noted that a universal practice of irradiation for all children probably to age 18 would require irradiated blood for many services such as obstetrics, 2) we expressed concerns about hemolysis in units of RBCs with longer storage dates, and 3) we were concerned that our policy should be evidence based since our international stature as an academic leader could force similar practices at other hospitals where irradiation was not easily accessible. It was felt by our pediatric clinical immunologists (two faculty experts were consulted privately and independently) that diagnostic, disease-defining infections due to SCIDS would reliably occur by the time a child reached 6 years of age. Consequently, to prevent similar cases, we implemented a policy of irradiating all cellular blood products for children before their sixth birthday. This policy has been in effect since January 1992. At our institution, patients at risk for TA-GVHD are identified through several methods. Patients may be placed on an irradiated protocol based on their location or clinical service. For example, all patients on the inpatient leukemia unit are placed on an irradiated protocol. Physicians may contact transfusion medicine or note on the patient’s requisition that the patient has a risk factor for TA-GVHD, such as having the diagnosis of SCIDS. Additionally, we irradiate all directed donation cellular blood products and all PLT products at the time the products are entered into inventory. With the implementation of our age-related policy, the technologist receiving the patient’s sample in transfusion medicine notes the patient’s date of birth and age; if the patient is under 6 years of age, the patient is placed on an “irradiated child” protocol.

Impact of policy

In November 1995, a 7-month-old was admitted to our hospital and received a RBC transfusion. The product was irradiated solely due to this age-based protocol. He subsequently was diagnosed with P. carinii pneumonia in the setting of SCIDS. Shortly after receipt of the transfusion, we were called by a pediatrician expressing concern for this patient. She was very relieved when we reminded her that our routine age-based irradiation policy was in place without requiring a specific physician request, which had not been made in this case.

We previously estimated that the incidence of undiagnosed SCIDS in our hospital population under the age of 6 years is 1 in 1052. We transfuse approximately 263 patients per year on this age-based protocol for the prevention of TA-GVHD. Annually, a mean of 213 additional patients in this age group require irradiated blood components for other indications, including intensive chemotherapy, neonatal status, and bone marrow transplantation. We acknowledge that the costs of irradiation may be of greater significance for those institutions that do not have in-house irradiation capability and obtain irradiated products from their blood supplier. The increased cost associated with the additional irradiation is minimal when compared with the costs of other patient safety and transfusion safety initiatives.

CONCLUSIONS

The incidence of SCIDS is estimated to be between 1 in 50,000 and 1 in 100,000 births. Children with SCIDS present with life-threatening infections and they may require a blood transfusion before they are diagnosed as having SCIDS, placing them at risk for TA-GVHD due to transfusion of nonirradiated blood products. In many cases these patients are originally seen by general pediatricians or emergency room physicians who might order blood components without recognizing the possibility of SCIDS and the requirement for blood irradiation for these children.

Before adopting this age-based protocol to prevent TA-GVHD in undiagnosed SCIDS, our irradiation protocol was selective for at-risk patients. We irradiated for specific patients at the request of their physician. This procedure required that the patient’s physician recognize the potential risk, contact the transfusion medicine service, and specifically request irradiation. Other guidelines to identify at-risk patients and prevent them from being missed by selective protocols include providing irradiated blood for patients admitted to specific services or hospital locations, previous identification in hospital information systems as requiring irradiation, reliance on blood bank staff to recognize high-risk patients, or other mechanisms that may lessen similar events but will never eliminate them entirely.

Our age-based protocol encompasses all children under the age of 6 years. With this broad protocol, some patients who are not at risk for TA-GVHD receive irradiated products. The risks associated with receiving irradiated blood products are minimal. The increased
costs of irradiation compare favorably with the costs of other interventions to prevent transfusion-related complications.

Selective transfusion protocols are prone to errors, relying upon individual physicians, their knowledge base, and their understanding of the patient’s clinical condition. In an effort to achieve universal transfusion safety, we strongly oppose selective transfusion protocols and we are in favor of more universal protocols. Universal irradiation of cellular blood products has been previously proposed, but not embraced by the transfusion community possibly due to issues of cost. In Japan, the risk of developing TA-GVHD has been shown to be higher (1:874) compared to white persons in the United States (1:7174); this increased risk is generally attributed to homogeneity of HLA haplotypes due to decreased genetic diversity in the Japanese population. Of note, the Japanese Red Cross does provide universal irradiation of blood components and there has not been a confirmed case of TA-GVHD in Japan since 2000. If pathogen-reduced components become available, irradiation will become redundant, offering an additional advantage to pathogen reduction beyond reducing the risks of infectious disease transmission.

The current risk of TA-GVHD is unknown and may vary based on the use of leukoreduction or fresh blood components, pathogen reduction, and different therapies that suppress the immune system of transfusion recipients around the world. Hemovigilance systems have not recorded many cases but the true incidence may still be obscured by misdiagnosis and underreporting.

Although we feel that universal irradiation is the best current solution to preventing TA-GVHD, we know that our age-based protocol prevented TA-GVHD in at least one patient. We do not know how many other patients have been protected by implementation of our procedure. We feel that our protocol has been successful and has contributed to the safety of blood transfusion at our institution; we have not had any cases of TA-GVHD at our institution since 1991.

Even though SCIDS is uncommon and reports of TA-GVHD are rare, we recommend irradiated blood products for all children under the age of 6 years, since there are minimal risks to this protocol, prevention of frequently lethal cases of TA-GVHD is important, and the true costs are small in our environment. Other institutions should determine whether the costs of providing irradiated blood components to all children under 6 years can be justified in their institutions.

REFERENCES


