Prevention of Transfusion-Associated Graft-Versus-Host Disease With Blood Product Irradiation

The Past, Present, and Future

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Transfusion-associated graft-versus-host disease (TA-GVHD) is a disease with a very high mortality rate. In this report, we discuss TA-GVHD from a historical perspective, highlight the pathogenesis of TA-GVHD, and emphasize the importance of blood product irradiation, which is a very effective means to prevent this disease. We summarize the current recommendations in different patient populations from different countries and review recent developments, such as alternatives for the use of radioactive materials. We also speculate on future directions.

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Clinical pathologists and blood bank personnel are consulted for advice on whether irradiated blood products are required for patients’ transfusion needs. Transfusion-associated graft-versus-host disease (TA-GVHD) is the sole indication for providing irradiated products. Although there are universal indications, the practice is mostly either based on expert recommendations from regulatory agencies or in light of the clinical picture. In this paper, we will provide a practical overview for consulting pathologists on the topic of blood product irradiation, including: (1) a review of the history and pathogenesis of TA-GVHD and the applications of product irradiation; (2) comments on the types of irradiation platforms available; (3) descriptions of the side effects and pitfalls of product irradiation; and (4) discussion of alternatives to irradiation for the prevention of TA-GVHD.

HISTORY OF GVHD

World War II led to numerous scientific discoveries and was also an open field laboratory for mankind. In August 1945, 2 atomic bombings destroyed Hiroshima and Nagasaki, killing tens of thousands of people and leaving many more injured. People who were in the hypocenter of the explosions were killed by the heat and the blast effect of the nuclear bombs. Individuals outside of the hypocenter were exposed to total-body irradiation (TBI) in various doses.1 These survivors who received high-dose TBI frequently developed neurovascular and gastrointestinal symptoms along with bone marrow (BM) aplasia, and the condition was named “acute radiation syndrome.”1,2

A team led by Vos et al3 and Van Bekkum4 conducted multiple experiments, primarily via mouse models, to evaluate the possible treatment of acute radiation syndrome with BM infusions. The team found that mice that received supralethal doses of TBI alone showed signs of acute radiation syndrome; mice that received the same doses of TBI with concomitant allogeneic BM transplant survived; and mice that received the same doses of TBI with concomitant allogeneic BM transplant died. The histologic examination of the last group showed the presence of BM regeneration, but it also showed multiorgan failure in the skin, gastrointestinal tract, liver, and lymphoid tissues. The condition was named “secondary syndrome.” In 1962, Barnes et al5 suggested that the term “graft-versus-host disease” be used instead of “secondary syndrome” because of immunologic reactions as the triggering mechanism.

In 1955, 1 year before the publication of Van Bekkum’s paper, a Japanese cardiac surgeon described 12 patients with postoperative erythroderma who received donor blood transfusions.6 In later years, a form of GVHD—(transfusion-associated GVHD, or TA-GVHD)—was recognized in immunocompromised patients following nonirradiated, non–related-donor blood product transfusions.7 In 1989, a group of Israeli cardiac surgeons observed postoperative erythroderma in 2 immunocompetent patients who received HLA homozygous whole-blood transfusions, but because the histology of the skin lesions was very similar to previously described GVHD histology, they stated that postoperative erythroderma is a skin manifestation of GVHD and that GVHD could also occur in immunocompetent patients who received transfusions of nonirradiated blood products from HLA-homozygous donors for 1 of the recipient’s haplotypes.8

PATHOGENESIS OF TA-GVHD

Transfused T lymphocytes are the cause of TA-GVHD, wherein it is believed that both CD4+ and CD8+ T
lymphocytes play critical roles. Current models indicate that the initial activation of helper CD4\(^+\) cells by foreign HLA antigens is followed by the activation of cytotoxic CD8\(^+\) cells, which then mediate much of the pathology of this disorder.\(^9,10\) In an immunocompetent recipient, when there is a class I and/or class II HLA-mismatched transfusion, the recipient’s immune system will attack the transfused T lymphocytes, preventing engraftment and proliferation. In contrast, if the recipient is immunocompromised and/or the transfused T lymphocytes are HLA homozgyous for 1 of the recipient’s haplotypes (even in an immunocompetent recipient), then the recipient’s immune system will consider these cells as self so that these T lymphocytes can engraft, proliferate, and attack the host (Figure).\(^8,11–14\) The minimum number of lymphocytes required for engraftment is 1 \(3\times10^7\) cells per kilogram, and various blood products contain different amounts of lymphocytes (Table 1).\(^9,15\) The risk of TA-GVHD depends on the degree of HLA homogeneity between donor and recipient; high degrees of homogeneity are found in certain countries, such as Japan and Israel, or in blood relatives in more diverse populations.\(^8\) TA-GVHD risks also depend on the nature and degree of immunosuppression of the transfusion recipient. If the blood product is from a nondirected donation, the estimated risk of TA-GVHD correlates closely with the common haplotype frequencies in the population and ranges between 1 in 17 700 and 1 in 39 000 in whites in the United States, between 1 in 6900 and 1 in 48 500 in Germans, and between 1 in 1600 and 1 in 7900 in Japanese groups.\(^16\) For directed donations from first-degree relatives, the risk increases 21-fold in whites in the United States, 18-fold in Germans, and 11-fold in Japanese populations.\(^16\)

In hematopoietic stem cell transplantation, circulating donor stem cells "home" to lymphoid tissues and BM by a complex mechanism which involves signaling, antigen activation, enzyme secretion, cytoskeleton rearrangement, adhesion, and anchoring.\(^17\) In TA-GVHD, by similar mechanisms, transfused T lymphocytes "home" to host lymphoid tissues, where they encounter host HLA antigens.\(^8\) The donor CD4\(^+\) and CD8\(^+\) lymphocytes react to the unshared class I and/or class II HLA antigens.\(^8\) Two days to 6 weeks later, the donor T lymphocytes traffic to nonlymphoid organs, such as skin, gut, and liver, and characteristic lesions begin developing in the patient.\(^19\) Although a detailed histologic description of TA-GVHD is beyond the scope of this article, Table 2 contains typical pathologic (as well as clinical) features of this entity. The symptoms could be mild and may be masked by the underlying disease that required the transfusion. The presence of skin lesions, decreasing blood cell counts, and elevated liver enzymes generally lead to skin, liver, and BM biopsies that suggest GVHD. Observing a different lymphocyte population in the patient’s circulation by serology-based HLA typing methods may be indicative of TA-GVHD, but it is not itself sufficient, because more than half of reported cases do not demonstrate unique lymphocyte populations by flow cytometry. The definitive diagnosis typically requires methods based on

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**Table 1. Number of Lymphocytes in Various Blood Products**

| Product                              | No. of Lymphocytes |
|--------------------------------------|--------------------|
| Whole blood and packed red cells     | \(1 \times 10^9\) to \(2 \times 10^9\) cells per unit |
| Washed or microaggregate-filtered red blood cells | \(2.5 \times 10^9\) cells per unit |
| Frozen, deglycerolized red blood cells | \(5 \times 10^7\) cells per unit |
| Leukoreduced red blood cells         | \(5 \times 10^8\) cells per unit |
| Apheresis platelets (single unit)    | \(3 \times 10^9\) cells per unit |
| Random donor platelets               | \(4 \times 10^9\) cells per unit |
| Apheresis granulocytes               | \(5 \times 10^9\) to \(10 \times 10^9\) cells per unit |
| Fresh frozen plasma                  | \(8 \times 10^4\) cells per liter |
| Cryoprecipitate                      | 0 cells per unit |

\(^a\) Data derived from Leitman and Holland\(^9\) and van Bekkum.\(^15\)

\(^b\) The number of viable cells in fresh frozen plasma is not adequate to cause transfusion-associated graft-versus-host disease.

\(^c\) The number of viable cells is virtually zero in cryoprecipitate.
polymerase chain reaction (eg, short tandem repeat testing) to establish chimerism.20

PREVENTION OF TA-GVHD AND AVAILABLE IRRADIATION METHODS

TA-GVHD is almost always fatal, with a less than 10% survival rate.21 Currently, the approved method for the prevention of TA-GVHD is the irradiation of cellular blood products using either gamma rays or X-rays. Various studies have shown that the effect of irradiation on lymphocytes is dose dependent: 5 Gy eliminates lymphocyte proliferation, 15 Gy results in an 85% to 90% reduction in mitogen response, and 50 Gy results in a 95% to 98.5% reduction in mitogen response.22–24 Although a minimum dose of 15 Gy causes DNA breakage and prevents T-lymphocyte proliferation, in the United States the recommendation for transfusion practice is that the center of a component bag should receive 25 Gy (versus 50 Gy in some countries), and any other area outside the bag center should receive a minimum of 15 Gy (versus 25 Gy in some countries).25,26

In the United States, most irradiation is performed using self-contained component irradiators. These pieces of equipment are typically sources that emit gamma rays or X-rays. For gamma-ray–emitting devices, cesium-137 is usually the preferred radiation source, primarily because of its long half-life (25–30 years). Table 3 compares the pros and cons of gamma-ray and X-ray instruments as irradiation sources. As an alternative to maintaining a self-contained irradiator, smaller blood banks and transfusion services may choose to use their radiation oncology department’s irradiation equipment, where cobalt-60 is generally the source for gamma rays. In such circumstances, a dose of 25 Gy has been found to be effective for T-lymphocyte inactivation.9,27

BLOOD COMPONENT IRRADIATION

Whole blood, red blood cells, platelets, and granulocytes all may require irradiation because of their viable white blood cell components. Table 4 shows common indications for blood product irradiation. In the past several decades in hospital-based practice, the use of whole blood has been replaced by blood components. Of these latter cellular products, components selected for their HLA compatibility by either typing or crossmatch (eg, red blood cells from first- and second-degree relatives and crossmatched, HLA-matched, and HLA-selected platelets) always require irradiation because of HLA homogeneity and a very high risk of TA-GVHD.9,25,28 General considerations for product irradiation are discussed further below. For a more in-depth discussion of “gray area” indications for irradiation, please see the below section entitled Controversies in Indications for Irradiation.

SAFETY OF IRRADIATED BLOOD PRODUCTS

The main concern for irradiation is the increased potassium amount in the red blood cell products. During storage, potassium content in irradiated blood tends to increase more quickly compared with routine, nonirradiated products, and the amount of potassium is correlated with the radiation dose.23,29 Potassium load could be an important limiting factor for rapid, large-volume transfusions (exchange transfusions, intruterine transfusions, etc) and if there is preexisting hyperkalemia.25 It was shown that reactive oxygen species are increased in irradiated blood components in a dose-dependent and storage time-dependent manner.30,31 Reactive oxygen species cause lipid peroxidation and hemoglobin oxidation31; however, clinical efficacy of erythrocytes, platelets, and granulocytes is not affected by the recommended radiation doses (up to 50 Gy) used in the blood banks.23

GENERAL CONSIDERATIONS

The consensus is that irradiation is required for: (1) all red blood cells and platelets from relatives; (2) all granulocytes; and (3) all crossmatched, HLA-matched, and HLA-selected

| Variable                              | Comparison Between the Radiation Sourcesa |
|---------------------------------------|------------------------------------------|
| Free plasma hemoglobin level          | Similar for both methods                  |
| Extracellular potassium level          | Similar for both methods                  |
| Lymphocyte function                   | Similar for both methods                  |
| Cost                                  | Lower initial cost for X-ray irradiators and lower overall cost for gamma-ray irradiators |
| Access to irradiation source          | X-ray irradiators are advantageous because there is no use of radioactive material |
| Safety concerns                       | Higher for gamma-ray irradiators          |
| Regulations                           | Stricter for gamma-ray irradiators (license and governmental requirements, need for special training, etc) |
| Maintenance needs                     | Less maintenance needs and less downtime for gamma-ray irradiators |

a Data derived from Janatpour et al.48
b Comparisons are done at the radiation doses of 25 Gy (US requirement) and 35 Gy (common EU dose).
For nonrelated donor blood product transfusions, the predicted incidence of TA-GVHD is dependent on the population HLA haplotype frequencies and recipient immunosuppression. In countries with a high risk of TA-GVHD, blood product irradiation recommendations include more clinical scenarios where the patient is immunocompetent, and there may even be practices to universally irradiate all red blood cells and platelets in such environments (eg, Japan).

**PEDIATRIC POPULATION**

In pediatric practice, special considerations should be given based on fetal and neonatal age, maturity, immune status, previous transfusions, and total volume of transfusion. For intrauterine transfusions, general recommendations are that both red blood cells and platelets should be irradiated. Preterm neonates (<4 months) are at risk for TA-GVHD, and the risk increases significantly if the newborn had received prior intrauterine transfusions. Generally, these preterm and young infant patients require blood product irradiation. It is not necessary to provide irradiated blood products to full-term immunocompetent infants older than 4 months. Infants and children with known or suspected T-lymphocyte immunodeficiency syndromes should receive irradiated blood products.

**HEMATOLOGIC MALIGNANCIES**

One major risk for the development of TA-GVHD is lymphoproliferative malignancy, with Hodgkin lymphoma occupying a particular concern. It is universally recommended—by nearly all guidelines—that only irradiated red blood cells and platelets be provided to these patients at any stage of the disease, and this should be a lifelong practice for these patients. It is recommended that patients receiving certain chemotherapeutic medications, as outlined in Table 4, receive irradiated blood products; physicians should seek consultation from transfusion service specialists at their facilities if questions arise about given medications. Many institutions may consider providing irradiated red blood cells or platelets to patients with acute leukemia, myelodysplastic syndrome, aplastic anemia, or non-Hodgkin lymphoma, particularly those treated with medications listed in Table 4; this recommendation applies both to adult and pediatric cases. However, the number of cases of TA-GVHD reported in acute leukemia is quite low, and UK-based guidelines do not recommend for the routine provision of irradiated products to such patients unless there are other circumstances warranting irradiation.

**HEMATOLOGIC STEM CELL TRANSPLANTATION**

Both allogeneic and autologous hematopoietic stem cell transplant recipients should receive irradiated blood products (Table 4). There are variances in initiation and discontinuation of providing irradiated blood products to this patient population. There is no evidence as to when irradiation may be safely discontinued in this patient population. Transfusion service specialists (blood bank director, transfusion medicine consultant, etc) should be available for consultation. In our institution, we provide lifelong irradiated blood products to these patients because of the potential risks of disease relapse and/or graft loss. However, as an alternative, at least 1 British guideline recommends the use of irradiated blood components until there is evidence of hematopoietic engraftment and lymphoid reconstitution.

**CONTROVERSIES IN INDICATIONS FOR IRRADIATION**

Some controversy remains regarding whether plasma and frozen/deglycerolized components require irradiation. As seen in Table 1, the number of T lymphocytes is different in various blood components. To date, there have not been any confirmed cases of TA-GVHD after transfusion of fresh frozen plasma, cryoprecipitate, any fractioned plasma products, or frozen deglycerolized cells, so these components do not require irradiation for the prevention of TA-GVHD. There is only a single case in the medical literature where plasma was implicated in TA-GVHD, but that component was fresh plasma. The US Circular of Information lists “liquid plasma” as a viable option for the initial treatment of patients who are undergoing massive transfusion and who have clinically significant coagulation deficiencies (ie, trauma patients). It should be noted that liquid plasma does contain viable T lymphocytes, which may cause TA-GVHD, and, like red blood cells and platelets, this product should be irradiated under the conditions stated in Table 4.

In addition, at our facility, we are frequently asked whether recipients of solid organ transplantation require irradiated blood products. It is not necessary to provide, at baseline, irradiated blood products in solid organ transplantation, even after transplantation when patients are receiving immunosuppressive therapies (unless patients are being treated with the medications listed in Table 4). Following a solid organ transplantation, the passenger lymphocytes in the donor organ, rather than the transfused blood products, are reported to be the cause of GVHD. From an evidence-based standpoint, there is even 1 study that suggested recipients of solid organ kidney transplant had superior outcomes when they received nonirradiated blood components. It should be noted that there have not been any reported cases of TA-GVHD in humoral immunodeficiency syndromes or in conditions with primary neutrophil dysfunction, so these patients do not require irradiated blood products.

Many blood banks and transfusion services use leukoreduced blood components. Theoretically, leukoreduction (also known as leukodepletion or leukofiltration) could remove a sufficient number of white blood cells to limit TA-

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**Table 4. General Recommended Situations for Red Blood Cell and Platelet Irradiation**

| Donations to a first- or a second-degree relative |
|-----------------------------------------------|
| HLA-selected, HLA-matched, and crossmatched products |
| Intrauterine and neonatal transfusion |
| Congenital cellular immunodeficiency patients |
| Hodgkin lymphoma patients |
| Patients treated with purine analogs, purine antagonists, bendamustine, alemtuzumab, and antithymocyte globulin |
| Both allogeneic and autologous hematopoietic stem cell transplant recipients: |
| (1) From initiation of conditioning treatment until the end of immunosuppressive therapy |
| (2) Within 7 days before donation |

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*a It should be noted that practice variations for blood product irradiation are present for patients with different needs (eg, patients receiving immunosuppressive treatments). National health agencies may mandate stricter use of irradiated blood products. All HLA-matched or HLA-selected platelets should be irradiated. All granulocyte concentrates should be irradiated.*
GVHD; however, there have been 23 reported cases of TA-GVHD after transfusion of leukoreduced red blood cells in the literature, indicating leukoreduction alone is not adequate to prevent TA-GVHD.

Finally, there remain some questions as to when to begin and end irradiation for patients. As we noted previously in the setting of hematologic stem cell transplantation, there is great variability in the approach to irradiation regarding timing. Although there are no clear-cut evidence-based answers, as an example, at the authors’ institutions it is our institutional practice to provide irradiated blood products to patients with acute leukemia, all types of lymphoma, myelodysplastic syndrome, neuroblastoma, rhabdomyosarcoma, and glioblastoma multiforme at any time and at any stage of their disease, which includes remission states. This is done in the event that the patient might have an unexpected recurrence of his or her disease. However, and as noted previously, it is always best to consult with one’s own transfusion service regarding local policies on the timing of irradiation.

REGULATIONS

Blood products are tightly regulated treatment modalities, and practice differences are common between physician specialties and between countries. Several government agencies, such as the National Health Service in the United Kingdom, the Japan Society of Blood Transfusion in Japan, and the Istituto Superiore di Sanità in Italy, publish guidance documents with regular updates. In contrast, the United States does not provide a national guideline for blood product irradiation, and this gap is filled by organizations such as the American Association of Blood Banks. A 2014 survey conducted by the College of American Pathologists demonstrated that the 3 most common indications for blood product irradiation were “transfusion from blood relatives” (78.6%), “HLA-matched or partially matched products” (68.9%), and “neonatal exchange transfusion” (66.3%). These numbers are worrisome because general guidance requires universal irradiation (100%) for these indications, but depending on the scenario, 21.4% to 33.7% of responders do not perform irradiation, despite the requirement. Interestingly, per the US Food and Drug Administration, from 2005 to 2015 there have been only 3 reported cases of death caused by TA-GVHD (1 case each in 2005, 2010, and 2011) in the United States.

A 28-day rule is in practice in the United States to overcome the possibility of causing hyperkalemia in the patient, where the expiration date of the irradiated product is shortened to 28 days from irradiation or the original expiration date, whichever is earlier. Application of this rule is different in some countries; for example, in Japan there is a 21-day shelf life rule, and in the United Kingdom there is a 14-day shelf life rule for the irradiated red blood cells. Platelet products do not need shelf life adjustments.

CHALLENGES AND PITFALLS

A 2015 systematic review from 6 databases (Medline, Embase, the Cochrane library, Web of Science, British Medical Journal case reports, and the International Society of Blood Transfusion proceedings) identified 348 unique cases in the medical literature of TA-GVHD and found that 34.8% of the cases occurred in recipients who would warrant blood component irradiation based on underlying diagnosis. Interestingly, 5 reported cases received irradiated products where proper irradiation practices were questioned. The authors also addressed the fact that most of the reported cases were immunocompetent individuals who received transfusions and lacked factors addressed in the current guidelines for blood product irradiation. This finding could not be explained simply by saying that the products were from genetically homogenous donors, because the reported cases were from 26 countries in which there is high genetic heterogeneity. Future studies should be conducted on this topic, which might require a generalized approach to blood product irradiation using the newer guidelines, or alternatives (as discussed below) that may help to mitigate TA-GVHD risks.

ALTERNATIVES AND FUTURE ASPECTS

Pathogen reduction and pathogen inactivation are terms used interchangeably in medical practice—pathogen inactivation is the generally accepted term and is seen more commonly in medical literature, but pathogen reduction is the preference for most of the regulatory agencies because what most of these novel methods do is “log reduction” in the number of infectious agents in the blood product. When a psoralen-based method (150 μM amotosalen and 3 J/cm² ultraviolet A [UVA] treatment) for pathogen reduction is applied to platelet concentrates, a more than 10⁵ log/mL viable lymphocyte reduction is observed by T-cell clonal expansion assay with limiting dilution analysis; this amount of reduction is the same as that provided by routine irradiation procedures. In January 2016, the US Food and Drug Administration approved the use of the INTERCEPT Blood System (Cerus Corp, Concord, California) in the United States for apheresis platelets in order to reduce the risk of TA-GVHD using amotosalen plus UVA in place of irradiation.

Riboflavin plus UVA/UVB treatment by the Mirasol System (Terumo BCT Inc, Lakewood, Colorado) of whole blood was shown to be effective in both in vitro and in vivo studies (4.7-log reduction of viable T cells by limiting dilution assay) for the prevention of TA-GVHD and provided an alternative modality for the irradiation procedure for platelet and red blood cell products mutually. Both the Mirasol and INTERCEPT pathogen reduction systems have received CE Mark approvals and are being used in lieu of irradiation in some European countries for the prevention of TA-GVHD from apheresis platelets. Other chemical compounds, such as S-303, are under investigation for pathogen reduction and prevention of TA-GVHD.

CONCLUSIONS

TA-GVHD is a transfusion-transmitted disease and is preventable with irradiation of blood products. It is ironic that both the cause of discovery and treatment modalities of this condition are the same—irradiation.

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