Transfusion-associated graft-versus-host disease: A concise review

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Abstract

Transfusion-associated graft-versus-host disease (TA-GVHD) represents a rare fatal event observed in immunocompromised patients and immunocompetent individuals. The main clinical features of this transfusion reaction are pancitopenia and multiorgan failure (skin, liver, gut). The possible pathogenesis includes donor T lymphocyte proliferation in blood, their engraftment and host tissue attack. The purpose of this narrative review was analyzing the international guidelines for irradiation of cellular blood components to prevent TA-GVHD. A literature search was conducted using PubMed articles published between January 2000 to July 2018. American, Australian, British and Japanese transfusion guidelines have been compared regarding clinical indications. The contribution of manuscripts has been focused on recipients of Haematopoietic Stem Cell Transplantation, severe cellular immunodeficient patients, fetuses and neonates, immunocompentent individuals. Furthermore, 348 cases of TA-GVHD in the last five decades have been documented according to a recent systematic review. The standard of care to prevent this complication is gamma or x irradiation of cellular blood products. New treatments with pathogen inactivation appear safe and effective against proliferating white blood cells and T cells. Further clinical and biological studies are necessary to better characterize immunocompetence of T cells and select alternative preventive strategies.

Introduction

Cellular blood products which include red blood cells (RBC), platelets (PLT), granulocyte units and non-frozen plasma carry the risk for TA-GVHD.[1,2] This transfusion complication is documented in immunocompromised patients and in immunocompetent individuals.[1-3] Clinical features of the reaction include erythema, diarrhea, hepatitis, aplasia which occurred more commonly within 1-2 weeks of transfusion history. Laboratory features include pancytopenia, elevated alkaline phosphatase, increased transaminases and elevated bilirubin. A suggestive skin, liver or gut biopsy may recognize mononuclear infiltrates of lymphocytes. The possible pathogenesis includes donor T lymphocyte proliferation in blood components, their engraftment and host tissue attack (skin, liver, gut and bone marrow).[4,6]

Chimerism or engraftment analysis of T lymphocytes through molecular assays (*e.g.* short tandem repeats analysis or a variable number of tandem repeat studies) may be helpful in case of suspect of the syndrome.[7,8] Alternatively, fluorescent in situ hybridization for the X and Y chromosomes may be considered in case of sex-mismatched between donor and recipient.[9]

TA-GVHD cases has been reported in immunodeficient recipients (newborn, hematological patients, recipient of haematopoietic stem cell transplantation) and in immunocompetent individuals who receive blood components from a family member (donor and recipient were partially matched for Human Leucocyte Antigen (HLA)) or in Japanese population (in which high degree of homozygosity of HLA has been documented).[1-9] Interestingly, no reports of the reaction has been noted in acquired immunodeficiency syndrome (AIDS) probably because the donor lymphocytes are not able to survive and proliferate adequately in this recipient and initiate the immune response which results in host tissue attack.[10] Certainly, unknown mechanisms may be involved in its pathogenesis.[1-9] The focus of this review was the analyis of the international guidelines for irradiation of blood components for clinical practice.[11-16] New data are recently published regarding alternative preventive methods.[17,18]

Methods and Results

The purpose of this narrative review was analyzing the international guidelines for irradiation of blood components to prevent TA-GVHD.[11-16] A literature search was conducted using Pub Med for articles published from January 2000 to July 2018 using the terms *TA-GVHD and guidelines for irradiation of cellular blood products* and *TA-GVHD and systematic review*. Only articles published in English were considered. The contribution of manuscripts was focused on recipients of Haematopoietic Stem Cell Transplantation (HSCT), severe cellular immunodeficient patients, fetuses and neonates, immunocompetent individuals. The results were complemented by clinical experience.

Characteristics of irradiated cellular blood products according to the international guidelines are summarized in Table 1.[11-16] Clinical indications and controversies regarding possible benefit of irradiation policy are discussed in Tables 2 and 3, respectively.[11-16]

Recipients of haematopoietic stem cell transplantation

In *allogenic hematopoietic stem cell transplantation* (HSCT) irradiation of blood components must be started at a least 7 days prior HSCT (the time of initiation of conditioning regimen) and continued until 6 or 12 months after the procedure or until lymphocytes is more than 1×10^9/L. This caution

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should be considered indefinitely in case of chronic graft-versus-host-disease or evidence of immune derangement according to the British, Australian and American guidelines.[11-16,19] In similar manner, irradiation of RBC or PLT units must be started at a least 7 days prior *autologous HSCT* (the time of initiation of conditioning regimen) until 3 months after the procedure or 6 months in case of total body irradiation conditioning.[11-16,20] Importantly, immune reconstitution is recognized a complex and multistep phenomenon in allogenic and autologous hematopoietic stem cell transplantation.[21,22] In fact, only a quantitative analyisis may be performed by flow cytometry.[5,23]

Table 1. International guidelines for irradiation of cellular blood products, main features.

Main features	American (New York) 2012	British 2011	Australian and New Zealand 2011	Japanese 2000
Blood product	All blood components should be irradiated with the exception of frozen RBC and frozen plasma and their products, peripheral blood stem cells. Bone marrow, cord blood, donor lymphocytes	- RBC may be irradiated at any time up to 14 days after collection and must stored for a further 14 days - PLT can be irradiated at any stage during storage - Granulocyte should be irradiated and transfused as soon as possible	- RBC may be irradiated at any time up to 14 days after collection and must stored for a further 14 days - PLT can be irradiated at any stage during storage - Granulocyte should be irradiated and transfused as soon as possible	All blood components should be irradiated with the exception of frozen plasma and their products
Irradiation type and dose	25 Gy	Gamma or X irradiation of 25 Gy, no more than 50 Gy	Gamma or X irradiation of 25 Gy	15-50 Gy, no more than 50 Gy

RBC (red blood cells), PLT (platelets), Gy (Gray).

Table 2. International guidelines for irradiation of cellular blood components, clinical indications.

Main features	American (New York) 2012	British 2011	Australian and New Zealand 2011	Japanese 2000
Recipient of allogenic HSCT	Indication	- Irradiated blood components must be started 7 days prior HSCT until 6 months post-transplant or lymphocytes $>1\times10^9$/L - Indefinitely in case of chronic GVHD	Irradiated blood components must be continued until 12 months post-transplant or lymphocytes $>1\times10^9$/L	Indication
Recipient of autologous HSCT	Indication	Irradiated blood components should be started 7 days prior HSCT until 3 months or 6 months in case of TBI conditioning regimen	Irradiated blood components must be started 7 days prior HSCT until 3 months or 6 months in case of TBI conditioning regimen	Indication
Autologous stem cell harvesting	Indication	Irradiated blood components should be started 7 days prior autologous stem cell harvesting	Indication	No data reported
Congenital T cell immunodeficiencies	Indication	Indication in all severe syndromes	Indication	Indication
Aplastic Anemia and anti-thymocyte globulin	Indication	Until lymphocyte $>1\times10^9$/L	Possible indication	Indication
Hodgkin Lymphoma	Indication	Indefinitely	Indication for at least 2 years after successful treatment or indefinitely	Indication
Purine analougeus	Indication	Indefinitely	Indication for at least 1 year or indefinitely	Indication
Alentuzumab	Indication	Indication includes hematological and autoimmune diseases	Indication	Indication
Intrauterine transfusion (IUT), exchange transfusion (ET), neonatal alloimmune thrombocytopenia (NAIT)	Blood for IUT and ET should be irradiated	- Blood for IUT should be irradiated until 6 months after expected date of delivery - Blood for ET after IUT should be irradiated until 6 months after birth - RBC less than 5 days of age should be used for IUT or ET and transfused within 24 hours of irradiation	- Blood for IUT and ET must be irradiated - Platelets must be irradiated to treat NAIT until 6 months after birth	Neonates require ET should receive irradiated RBC
Cellular blood components from relatives	Indication	Indication	Indication	Indication

HSCT (hematopoietic stem cell transplantation), GVHD (graft-versus-host disease), TBI (total body irradiation), IUT (intrauterin transfusion), ET (exchange transfusion), NAIT (neonatal alloimmune thrombocytopenia).

Severe cellular immunodeficient patients

Neonates and infants must receive, definitely, irradiated blood components in case of *congenital T cell immunodeficiencies* or before a confirmed diagnosis.[11-14]

Aplastic anemia treated with antithymocyte globulin must receive irradiated transfusions according to all analized guidelines.[11-15]

In case of *Hodgkin Lymphoma,* a significantly T-cell immunosuppressed disease, all international guidelines confirm that patients should receive irradiated cellular blood components for at least 2 years following successful treatment or indefinitely according to the British and Australian guidelines, respectively.[11-15]

In similar manner, *patients treated with alemtuzumab or purine analogues* (fludarabine, cladribrine, deoxycoformicin, bendamustine and clofarabine), represent another mandatory indication of the irradiation of blood components for 1 year or longer (following successful treatment).[11-15]

Fetuses and neonates

Irradiation of blood products is recommended for *intrauterine transfusion* (IUT) according to the international guidelines.[11-14,24,25] On the other hand, indication of irradiation of red blood cells for *exchange transfusion* (ET) after IUT varies in different countries.[11-14,24.25]

In line with the international guidelines RBC less than 5 days of age must be used for IUT or ET and transfused within 24 hours of irradiation to reduce the risk of increased serum potassium level.[11-14] The IUT is an invasive procedure performed for the treatment of fetal anemia frequently due to severe haemolytic disease of the fetus and newborn (HDFN) due to maternal alloimmune antibodies against red cell antigens of fetus (more commonly Rh, Kell, Duffy, Kidd and MNSs antigens) or parvovirus infection. The ET is a procedure performed to treat resistant icterus due to HDFN or severe anemia. Furthermore, Australian guidelines underline the importance of irradiated platelets in *neonatal alloimmune thrombocytopenia* (NAIT).[11] This complication is due to maternal alloimmune antibodies against platelet antigens of fetus, more commonly against human platelet antigen 1a (HPA-1a).

Prematures and low-birth weight babies may represent a possible high-risk category according to several expert opinions and guidelines.[24,25] Open question regards how long this caution should be considered after birth due to the possible immature thymus dysfunctions.[6,26] Briefly, the majority of guidelines suggest that irradiation policy should be continued for at least 6 months after birth.[11-14]

Immunocompetent individuals and other risk categories

Irradiation of cellular blood products is recommended for immuncompetent individuals who receive cellular blood *components from relatives* according to the international guidelines.[11-14] For clinical standpoint is mandatory the appropriate indications and use of blood products, avoid transfusions from first and second relatives.

A systematic review of 348 cases published by Kopolovic, which includes all cases published in the last 5 decades without restriction of language, confirm that a small percentage (more specifically 5%) of the cases appears in *non-high risk setting* according to the current guidelines.[27]

Few data regard the minimum number

Table 3. International guidelines for irradiation of cellular blood products, controversies.

Diagnosis or treatment	British 2011	Australian and New Zealand 2011	Japanese 2000
Acute Leukemia	No indication	Possible indication	Possible indication
Chronic Myeloid Leukemia	No data reported	Possible indication	No data reported
Haemophilia and thalassemia	No data reported	No indication	No data reported
Massive transfusions	No data reported	Possible indication	Indication
Cardiovascular surgery	No indication	Possible indication	Indication
Solid organ tranplantation	No indicated unless alentuzumab use	No indication	Indication in immunocompromised recipients
Solid tumors	No indication	No indication	- Chemotherapy or radiotherapy in solid tumor - Surgical operation for cancers
Non-hodgkin Lymphoma	No indication	It may be a possible indication in lymphopenic (lymphocytes $<0.5\times10^9$/L) patients who receive chemotherapy or radiotherapy	Possible indication
T cell Lymphoma	No data reported	Possible indication	No data reported
Rituximab	No indication	No indication	No data reported
High dose steroids	No data reported	Possible indication	Indication
Acquired immunodeficiency syndrome	No indication	No indication	No data reported
Elderly	No data reported	No data reported	Indication in recipient of blood transfusion of >65 years old
Premature babies and low-birth weight babies	No data reported	Prematures babies (<28 weeks) and low-weight babies (<900 gr) may be a possible indication for at least 7 months	Low-weight babies may be a possible indication

of lymphocytes necessary to cause TA-GVHD.[11,12] According to Kopolovic and colleagues, cellular blood components involved in this fatal complication were whole blood (2×10^9 lymphocytes per unit),[28] leukoreduced components (5×10^6 lymphocytes per unit)[28] and component age inferior to 48 hours.[27]

Furthermore, this review underlines that HLA antigens shared by the recipient were responsible of TA-GVHD observed in *immunocompent recipient* because donor lymphocytes of similar HLA are not recognized as foreign and destroyed by the immune system of recipient.[27]

Discussion

A significant decrease of this complication has been noted in Japan since the introduction of irradiation in 1998.[29] In addition, only 2 fatal TA-GVHD were recognized in UK from 1999 to 2013.[30] In similar manner, 3 fatal events were documented in USA from 2005 to 2013.[6]

Gamma or X irradiation of blood products is considered the gold standard to prevent the complication due to the capability of damage DNA of white blood cells (WBC).[11-14] The maximum expiration time of red blood cell post-irradiation varies from 28 to 14 days according to the American and British Standards, respectively.[16,30]

New preventive treatments with pathogen inactivation appear effective against proliferating WBC and T cells and useful to treat all cellular blood products (RBC, platelets, whole blood, plasma). More recently, Fast L. summarized the main technologies (*e.g.* solvent detergent, methylene blue, UV-light etc) which interfere with the replication of pathogens and leucocytes through nucleic acid modifications.[18] Furthermore, a large prospective study was recently published regarding transfusion of platelet components prepared with amotosalen-UVA photochemical treatment.[19]

Limits of irradiation of RBC products include reduction of the expiration date and the increase of its cost. In addition, RBC irradiation is time consuming, rises the serum potassium level and causes hemolysis therefore it favors possible complications in neonates, renal failure or in massive transfusions.[1,6,31] No modification of expiration date or quality of platelet units have been recognized.[32] Limits of new technologies are the paucity of data regarding the long-term follow-up.[18,19]

Controversies regard which cellular blood products are more commonly involved in the reaction and additional possible risk categories for TA-GVHD remain after literature search.[11-14] Granulocyte units, which contain more lymphocytes (10×10^9 lymphocytes per unit),[28] represent a cellular blood component used in selected cases.[32-35] Similarly, fresh whole blood (2×10^9 lymphocytes per unit),[28] which represents a possible therapy for trauma resuscitation,[36,37] should cause the complication due to a recognized decrease of lymphocytes activity after 2 weeks.[2]

Further risk categories may include: non-hodgkin lymphoma treated with novel drugs which impact on the cellular immune system[38] and acute leukemia which receive purine analogs (*e.g.* clofarabine and fludarabine).[11-14]

In addition, in some cases it is hard to confirm the clinical suspect of TA-GVHD (due to attenuated manifestations of the syndrome, confounding factors (infections, autoimmunity), techinical issues of HLA type (pancytopenia)).

Conclusions

In populations in which more homogeneity of HLA exists, such as documented in Japan, a stricter policy regarding irradiation of cellular blood products is successful.[29] Higher risk categories for TA-GVHD are recipients of haematopoietic stem cell transplantation, severe cellular immunodeficient patients, fetuses and neonates who receive intrauterin transfusions, immunocompetent patients who receive cellular components from blood relatives.[11-14]

Controversies remain regard which cellular blood products are more commonly involved in the reaction and additional risk categories for TA-GVHD [27,38] Haemovigilance, a *systematic surveillance of adverse reactions and adverse events related to transfusion*, is an effective tool for improving transfusion practice internationally.[39,40]

The gold standard procedure to prevent this complication is 25 gamma or x irradiation of blood components.[11-14] New preventive treatments with pathogen inactivation appear effective against proliferating white blood cells and T cells.[18,19] Further clinical and biological studies are necessary to better characterize immunocompetence of T cells and compare preventive approaches for TA-GVHD.[41-44]

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