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

Palma Manduzio
Diagnostic Department, Clinical Pathology, ‘Augusto Murri’ Civil Hospital of Fermo, Italy

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 pancyclopenia 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, immunocompetent 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.

Methods and Results

The purpose of this narrative review was analyzing the international guidelines for irradiation of blood components to prevent TA-GVHD. A literature search was conducted using PubMed 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.

Correspondence: Palma Manduzio, Diagnostic Department, Clinical Pathology, ‘Augusto Murri’ Civil Hospital of Fermo, Via A. Murri 21, 63900 Fermo (FM), Italy. Tel.: +39.0734.6252230 - Fax: +39.0734.6252226. E-mail: ina.m77@alice.it

Key words: Transfusion-associated graft-versus-host disease, cellular blood products, irradiation, T lymphocytes, immunodeficiency.

Acknowledgements: The author expresses appreciation to all the laboratory team of Clinical Pathology of Fermo (Italy), in particular Dr Licitra Salvatore (Chief at Clinical Laboratory), Dr Bubbolini Mario, Dr Paci Ornella Onorina, Dr Vallorani Sarah, Dr Arduini Alessandra. The author thanks Dr Leggi Elisabetta for her assistance with the literature and Dr Clementina Fraticelli, Director of Camerino University Library (Macerata). The author is grateful to Dr Pauri Paola, Chief at Clinical Pathology of Jesi (Ancona) and Dr Zaccaria Alfonso, Chief at Hematology Unit of Ravenna for their mentorship.

Conflict of interest: the author declares no competing interests.

Funding: none.

Received for publication: 17 April 2018. Revision received: 4 October 2018. Accepted for publication: 17 July 2018.

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

©Copyright P. Manduzio, 2018 Licensee PAGEPress, Italy Hematology Reports 2018; 10:7724 doi:10.4081/hr.2018.7724
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 | - RBC may be irradiated at any time up to 14 days after collection and must stored for a further 14 days | 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 |

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 >1×10^9/L | Irradiated blood components must be continued until 12 months post-transplant or lymphocytes >1×10^9/L | Indication |
| Recipient of autologous HSCT | Indication | Indefinitely in case of chronic GVHD | Indefinitely in case of chronic GVHD | 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 >1×10^9/L | Possible indication | Indication |
| Hodgkin Lymphoma | Indication | Indefinitely | Indication for at least 2 years after successful treatment or indefinitely | Indication |
| Purine analogues | Indication | Indefinitely | Indication for at least 1 year or indefinitely | Indication |
| Alentuzumab | Indication | Indication includes hematological and autoimmune diseases | Indication | Indication |
| Intrathecal 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 IUT and ET must be irradiated | Neonates require ET should receive irradiated RBC |

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

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.11-14,24-25

Aplastic anemia treated with antithymocyte globulin must receive irradiated transfusions according to all analyzed guidelines.11-14

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, cladribine, deoxycoformycin, 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

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 hemolytic 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.5,26 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 immunocompetent individuals who receive cellular blood components from relatives according to the international guidelines.11-14 For clinical standpoint, it 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 thalasssemia             | 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 transplantation              | No indication | Indication in immunocompromised recipients | - Chemotherapy or radiotherapy in solid tumor - Surgical operation for cancers |
| Solid tumors                            | No indication | No indication                   | Possible indication |
| Non-hodgkin Lymphoma                    | No indication | It may be a possible indication in lymphopenic (lymphocytes <0.5×10^9/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.\textsuperscript{11,12} According to Kopolovic and colleagues, cellular blood components involved in this fatal complication were whole blood (2×10⁹ lymphocytes per unit),\textsuperscript{28} leukoreduced components (5×10⁶ lymphocytes per unit)\textsuperscript{28} and component age inferior to 48 hours.\textsuperscript{27}

Furthermore, this review underlines that HLA antigens shared by the recipient were responsible of TA-GVHD observed in immunocompetent recipient because donor lymphocytes of similar HLA are not recognized as foreign and destroyed by the immune system of recipient.\textsuperscript{27}

**Discussion**

A significant decrease of this complication has been noted in Japan since the introduction of irradiation in 1998.\textsuperscript{29} In addition, only 2 fatal TA-GVHD were recognized in UK from 1999 to 2013.\textsuperscript{30} In similar manner, 3 fatal events were documented in USA from 2005 to 2013.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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 leukocytes through nucleic acid modifications.\textsuperscript{18} Furthermore, a large prospective study was recently published regarding transfusion of platelet components prepared with amotosalen-UV A photochemical treatment.\textsuperscript{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.\textsuperscript{5,6,31} No modification of expiration date or quality of platelet units have been recognized.\textsuperscript{32} Limits of new technologies are the paucity of data regarding the long-term follow-up.\textsuperscript{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.\textsuperscript{11-14} Granulocyte units, which contain more lymphocytes (10×10⁹ lymphocytes per unit),\textsuperscript{28} represent a cellular blood component used in selected cases.\textsuperscript{32-35} Similarly, fresh whole blood (2×10⁹ lymphocytes per unit),\textsuperscript{28} which represents a possible therapy for trauma resuscitation,\textsuperscript{36,37} should cause the complication due to a recognized decrease of lymphocytes activity after 2 weeks.\textsuperscript{2}

Further risk categories may include: non-hodgkin lymphoma treated with novel drugs which impact on the cellular immune system\textsuperscript{38} and acute leukemia which receive purine analogs (e.g. clofarabine and fludarabine).\textsuperscript{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), technical 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.\textsuperscript{29} Higher risk categories for TA-GVHD are recipients of haematopoietic stem cell transplantation, severe cellular immunodeficient patients, fetuses and neonates who receive intruterin transfusions, immunocompetent patients who receive cellular components from blood relatives.\textsuperscript{11-14}

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

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

**References**

1. Roback JD, Grossman BJ, Morris T, Millyer CD. Technical manual.\textsuperscript{17}th ed. Bethesda, Maryland: American Association of Blood Banks; 2011.
2. Bordin JO, Heddle NM, Blachman MA. Biological Effects of leukocytes present in transfused Cellular Blood Products. Blood 1994;84:1703-21.
3. Przepiorka D, LeParc GF, Stovall MA et al. Use of Irradiated Blood Components. Practice Parameter. Am J Clin Pathol 1996;106:6-11.
4. Dwyre DM, Holland PV. Transfusion-associated graft-versus-host disease. Vox Sang 2008; 95: 85-93.
5. Appelbaum FR, Forman SJ, Negrin RS, Blume KG. Thomas’ Hematopoietic Cell Transplantation. 4th Ed. Hoboken, NJ: Wiley-Blackwell; 2011.
6. Simon TL, McCullough J, Snyder EL et al. Rossi’s Principles of Transf Med. 5th Ed. Hoboken, NJ: Wiley-Blackwell; 2016.
7. Netto GJ, Saad RD. Diagnostic Molecular Pathology an Increasingly Indispensable Tool for the Practicing Pathologist. Arch Pathol Lab Med 2006;130:1339-48.
8. Clark JR, Scott SD, Jack AL et al. Monitoring of chimerism following allogeneic haematopoietic stem cell transplantation (HSCT): Technical recommendations for the use of Short Tandem Repeat (STR) based techniques, on behalf of the United Kingdom National External Quality Assessment Service for Leucocyte Immunophenotyping Chimerism Working Group. Br J Haematol 2015;168 :26-37.
9. Akay MO, Temiz G, Teke HU et al. Rapid molecular cyogenetic diagnosis of transfusion associated graft-versus-host disease by fluorescent in situ hybridization (FISH). Transf Apher Sci 2008; 38: 189-92.
10. Levine AM, Scadden DT, Zaia JA, and Krishnan A. Hematologic Aspects of Blood Transfusion (ANZSBT) LDT. Guidelines on the use of irradiated blood components prepared by the Australian and New Zealand Society of Blood Transfusion (ANZSBT) LDT. Second Ed. Hoboken, NJ: Wiley-Blackwell; 2011.
11. Australian and New Zealand Society of Blood Transfusion (ANZSBT) LDT. Guidelines for prevention of transfusion-associated graft-versus-host disease (TA-GVHD). 1st Ed. 2011.
12. Treleaven J, Gennery A, Marsh J et al. Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force. Br J Haematol 2011;152:35-51.
13. Asay T, Inaba S, Ohno H et al. Guidelines for irradiation of blood and blood components to prevent post-transfusion graft-versus-host in Japan. Transf Med 2000;10:315-20.
14. New York State Council on Human Blood and Transfusion Services. Guidelines for irradiation of blood and blood components. 4th Ed. 2012.
15. Chu E, De Vita VT. Physicians’ Cancer Hematology Reports 2018; 10:7724
16. Carson JL, Guyatt G, Heddle NM et al. Preventing transfusion-associated graft-versus-host disease. Arch Pathol Lab Med 2015;142:662-7.
17. Kaufman RM, Djulbegovic B, Gernsheimer T et al. Platelet Transfusion: A Clinical Practice Guideline From the AABB. Ann Intern Med 2015;162:205-13.
18. Fast LD. Preventing transfusion-associated graft-versus-host disease: state of the art. International Journal of Clinical Transfusion Medicine 2015;2:1-6.
19. Knutson F, Osselaer J, Pierelli L, et al. A prospective, active haemovigilance study with combined cohort analysis of 19175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. Vox Sanguinis 2015;109:343-52.
20. Gajewski JL, Johnson VV, Sandler SG et al. A review of transfusion practice before, during and after hematopoietic progenitor cell transplantation. Blood 2008;112:3036-47.
21. Weiss B, Hoffmann M, Anders C et al. Gamma-irradiation of blood products following autologous stem cell transplantation: surveillance of the policy of 35 centers. Ann Hemat 2004;83:44-9.
22. Moutouou MM, Page’ G, Zaid I, et al. Restoring T Cell Homeostasis After Allogeneic Stem Cell Transplantation; Principal Limitations and Future Challenges. Front in Immuno 2018;9:1223-37.
23. Xian CL, Jevnikar AM. Transplant Immunology. Hoboken, NJ: Wiley-Blackwell; 2016.
24. New HV, Berryman J, Bolton-Maggs PHB et al. Guidelines on transfusion for fetuses, neonates and older children. Brit J Hemato 2016;175:784-828.
25. New HV, Stanworth SJ, Engelriet CP, et al. Neonatal transfusions. Vox Sang 2009;96:62-85.
26. Janeway CA Jr1, Flavell RA. Immunology at Yale. Immunol Rev 1999;19:105-6.
27. Kopolovic I, Ostro J, Tsubota H et al. A systematic review of transfusion-associated graft-versus-host disease. Blood 2015;126:406-14.
28. Bahar B, Tormey CA. Prevention of Transfusion-Associated Graft-Versus-Host Disease With Blood Product Irradiation. The Past, Present and Future. Arch Pathol Lab Med 2018;142:662-7.
29. Uchida S, Tadokoro K, Takahashi M et al. Analysis of 66 patients definitive with transfusion-associated graft-versus-host disease and the effect of universal irradiation of blood. Transf Med 2013;23:416-22.
30. Serious Hazards of Transfusion (SHOT) Steering Group. The 2012 annual SHOT report. 2013.
31. Bashir S, Naik F, Cardigan R, Thomas S. Effect of X-irradiation on the quality of red cell concentrates. Vox Sang 2011;101:200-7.
32. Zhu M, Xu W, Wang BL, Su H. Hemostatic function and transfusion efficacy of apheresis platelets concentrates treated with gamma irradiation in use for thrombocytopenic patients. Transfus Med Hemo ther 2014;41:189-96.
33. Estcourt LJ, Stanworth SJ, Hopewell S et al. Granulocyte transfusions for treating infections in people with neutropenia or neutrophil dysfunction. Cochrane Database Syst Rev 2016; doi:10.1002/14651858.
34. Pammi M, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropenia (Review) Cochrane Database Syst Rev. 2011; doi: 10.1002/14651858.
35. Klein K, Castillo B. Historical Perspective, Current Status and Ethical issue in Granulocyte Transfusion. Ann of Clin and Lab Sci 2017 47:501-7.
36. McDaniel LM, Etchill EW, Raval JS, Neal MD. State of the art: massive transfusion. Transf Med 2014;24:138-44.
37. McQuilten ZK, Crighton G, Brunskill S et al. Optimal Dose, Timing and Ratio of Blood Products in Massive Transfusion: Results from a Systematic Review. Transf Med Rev 2018;32:6-15.
38. Morrissey KM, Yuraszeck TM, Li CC et al. Immunotherapy and Novel Combinations in Oncology: Current Landscape, Challenges, and Opportunities. Clin Transl Sci 2016;89-104.
39. Stainsby D. Haemovigilance in the United Kingdom and Europe. The Hematol J 2004;5:5175-8.
40. Politis C, Wiersum JC, Richardson C et al. The International Haemovigilance Network Database for the Surveillance of Adverse Reactions and Events in Donors and Recipients of Blood Components: technical issues and results. Vox Sang 2016;111:409-17.
41. Pritchard AE, Shaz BH. Survey of Irradiation Practice for the Prevention of Transfusion-Associated Graft-versus-Host Disease. Arch Pathol Lab Med 2016;140:1092-7.
42. Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. Blood 2008;112:2617-26.
43. Delaney M, Wendel S, Bercovitz RS et al. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016;388:2825-36.
44. Hemdler-Brandstetter D, Ishigame H and Flavell RA. How to define biomarkers of human T cell aging and immunocompetence? Front Immunol 2013;4:1-4.