Guideline development for prevention of transfusion-associated graft-versus-host disease: reduction of indications for irradiated blood components after prestorage leukodepletion of blood components

Wiersum-Osselton, J.C.; Slomp, J.; Falkenburg, J.H.F.; Geltink, T.; Duijnhoven, H.L.P. van; Netelenbos, T.; Schipperus, M.R.

bjh guideline

Guideline development for prevention of transfusion-associated graft-*versus*-host disease: reduction of indications for irradiated blood components after prestorage leukodepletion of blood components

Johanna C. Wiersum-Osselton,[1] Jennichjen Slomp,[2] J. H. Frederik Falkenburg,[3] Tessa Geltink,[4] Hans L. P. van Duijnhoven,[5] Tanja Netelenbos[6] and Martin R. Schipperus[7]

[1]*TRIP (Transfusion and Transplantation Reactions in Patients) Hemovigilance and Biovigilance Office, Leiden,* [2]*Medlon-Medisch Spectrum Twente, Enschede,* [3]*Department of Hematology, Leiden University Medical Center, Leiden,* [4]*Knowledge Institute of Medical Specialists, Utrecht,* [5]*Elkerliek Ziekenhuis, Helmond,* [6]*Haga Teaching Hospital, The Hague, and* [7]*Department of Hematology, University Medical Center UMCG, Groningen, The Netherlands*

Summary

Transfusion-associated graft-*versus*-host disease (TA-GVHD) is a rare, commonly fatal complication of transfusion preventable by irradiation of blood units. The revision of the Dutch transfusion guideline addressed the question whether irradiation is still necessary if blood components are prestorage leukodepleted. We searched for published cases of TA-GVHD following transfusion of prestorage leukodepleted blood and through contacting haemovigilance systems. Six presumed cases were found, dating from 1998 to 2013. Four out of six patients had received one or more non-irradiated units despite recognised indications for irradiated blood components. In the countries providing information, over 50 million prestorage leukodepleted, non-irradiated, non-pathogen-reduced cellular components were transfused in a 10-year period. Potential benefits of lifting indications for irradiation were considered. These include reduced irradiation costs (€ 1.5 million annually in the Netherlands) and less donor exposure for neonates. Findings were presented in an invitational expert meeting. Recommendations linked to human leukocyte antigen similarity between donor and recipient or intra-uterine transfusion were left unchanged. Indications linked to long-lasting deep T-cell suppression were defined with durations of 6 or 12 months after end of treatment (e.g. autologous or allogeneic stem cell transplantation). Need for continued alertness to TA-GVHD and haemovigilance reporting of erroneous non-irradiated transfusions was emphasised.

Keywords: transfusion-associated graft versus host disease, blood component, leukodepletion, irradiation, immunosuppression.

Transfusion-associated graft-*versus*-host disease (TA-GVHD) can arise if a patient is transfused with a cellular blood component containing T lymphocytes to a recipient whose immune system is unable to clear the donor T cells. The patient develops pancytopenia and other symptoms of GVHD such as rash, and redness of the skin on the palms and soles which can spread over the entire body. Symptoms can include nausea, vomiting, stomach cramps, diarrhoea, loss of appetite, jaundice, abdominal pain, and weight loss. Infiltration of bone marrow, skin and lymphoid tissues by donor lymphocytes can be demonstrated. The only potential cure is by emergency allogeneic haematopoietic stem cell transplantation, if a donor can be found in time. For patients at risk, irradiation of cellular blood components (normally 25 Gy) prevents TA-GVHD.[1,2]

The first and largest group of patients at risk is comprised of those whose cellular immune system is compromised through disease or medical intervention. TA-GVHD has been described in paediatric patients following intra-uterine blood transfusion or with severe combined immunodeficiency. Recipients of haematopoietic stem cell transplantations, patients with Hodgkin lymphoma or treated with T-cell-cytotoxic regimens have been described as risk categories. However, HIV patients, even those with reduced CD4-positive T-cell counts, are not regarded as in need of

Correspondence: Johanna C. Wiersum-Osselton, TRIP National Hemovigilance and Biovigilance Office, Schuttersveld 2, 2316ZA Leiden, The Netherlands.
E-mail: j.wiersum@tripnet.nl

First published online 6 September 2021
doi: 10.1111/bjh.17822

irradiated blood components for prevention of TA-GVHD.[3] The other broad category of patients at risk consists of those who receive blood components of which the human leukocyte antigen (HLA) characteristics are not recognised as foreign by the recipient. Typically this occurs when HLA-compatible components are selected or when a patient is transfused with blood donated by a blood relation. However, HLA similarity between a selected blood component and the recipient may occur purely coincidentally. A literature review by Kopolovic *et al.*[4] identified a total of 348 reported cases of TA-GVHD and found that in 60 of 84 cases (71%) where HLA data was available, donor and recipient shared human leukocyte antigens; this review is discussed further in the *Results* section.

It is recognised that the risk of TA-GVHD is lower when leukoreduced blood components are transfused.[5,6] Thus the United Kingdom's Serious Hazards of Transfusion (SHOT) haemovigilance scheme received four reports of cases of TA-GVHD per year before the introduction of universal prestorage leukodepletion (LD), against a total of three in 20 years since.[5] Two of these occurred shortly before and during the first year of LD (2000–2001) when conceivably the procedure was not as reliable as later. The third arose through a tragic misconception, when a mother's blood was used for intrauterine transfusion without leukodepletion or irradiation in 2012.[7] In the Netherlands universal leukodepletion has been in place since 2001. No case of TA-GVHD has been reported to the TRIP (Transfusion and Transplantation Reactions in Patients) national haemovigilance and biovigilance office, which has been functional since 2003.[8]

The 2011 Dutch national transfusion guideline listing indications for irradiated blood components broadly followed the guidelines of the British Society for Haematology and these were chiefly based on TA-GVHD cases described before countries adopted widespread or universal use of prestorage LD.[9] For the 2018–2020 revision the Dutch guideline, hitherto a single document, was converted to a modular system, allowing for future revisions to be performed per module. A stakeholder meeting, including patient societies, was held to prioritise questions to be addressed by full literature review. Text and recommendations from the previous guideline about aspects which were not selected for full revision were transferred after working-group review.[10] The present paper describes work to address the question 'Is there still a need for irradiation of the currently available leukodepleted cellular blood components?'

Materials and methods

Guideline development

The extreme rarity of TA-GVHD led to an approach which went beyond the standard systematic literature search. If well-documented cases of TA-GVHD following transfusion of prestorage leukodepleted blood components can be found, it can be concluded that the application of irradiation for the patient group(s) in question is not superfluous. The decision about proposed indications for irradiated components should weigh the very small risk of TA-GVHD against the negative effects of irradiation indications in terms of logistics, greater donor exposure of paediatric patients and costs.

In the Netherlands the professional guidelines are developed by working groups consisting of representatives mandated by professional societies. For the transfusion guideline the societies of clinical specialties which regularly prescribe blood transfusions as well as laboratory scientists, nursing professionals, donor physicians and hospital pharmacists were represented. For this particular module, the proposed changes were first sent to key experts from the haematopoietic stem cell transplantation community, paediatrics and neonatology, clinical chemistry, academic centres and the HOVON (the Haemato-Oncology Foundation for Adults in the Netherlands) coordinating body for haematological clinical studies with specific questions for discussion with colleagues about the acceptability of the potential lifting of certain irradiation requirements. Representatives were invited to an invitational expert meeting, leading to minor adjustments. Following this, in accordance with the standard guideline procedures, the draft texts were circulated for public comment followed by revision based on comments received. The finalised proposed guidelines were endorsed by the professional societies.

Literature search and haemovigilance survey

A literature review by Kopolovic *et al.*[4] covering reported cases of TA-GVHD until 2013 was identified, a review already mentioned earlier. We performed a formal literature review from 2013 to April 2018 in Medline (via OVID) and Embase (via Embase.com), including papers in English, Dutch, French, German or Spanish or with an abstract in one of those languages. Publications should comprise data on cases of transfusion-associated GVHD reactions in association with irradiated vs non-irradiated (prestorage) leukodepleted blood components. We also included cohort studies or case reports of cases of TA-GVHD following transfusion of leukodepleted components.

Additionally in 2018 we contacted national haemovigilance systems which are members of the International Haemovigilance Network (IHN) and requested information on any case of TA-GVHD in 2008–2017 following transfusion of a leukodepleted blood component; earlier cases were accepted if the criteria were met. If a case was reported, we requested further clinical and laboratory information along with details of the specifications to which leukodepletion was performed. We requested approximate numbers of leukodepleted, non-irradiated components transfused for the same years.

We conservatively estimated the number of prestorage leukocyte-depleted, non-irradiated and non-pathogen-reduced cellular components for the years for which we received data

from the IHN haemovigilance systems, including blood component data from 2008 to 2017 or from the year universal prestorage leukodepletion was introduced, if later. This estimated number was deemed to be 'at risk' of causing TA-GVHD despite leukodepletion from random HLA similarity in patients not considered as specifically at risk and therefore not provided irradiated components, or from inadvertent failure to provide irradiated components in patients with recognised indications for irradiated components.

Publicly available information about erroneous transfusion of susceptible patients with non-irradiated components was extracted from material reported by SHOT and TRIP.

Results

The Kopolovic paper presents 348 TA-GVHD cases reported in the literature up to September 2013. Among the reported cases, 121 (35%) of the patients had an immunosuppressed state listed as an indication for irradiated blood components and 50 (14%) had received blood from a related donor. Thus approximately half of the cases with documented clinical details occurred without a recognised indication for irradiated blood components. Twenty-three out of 135 cases where the leukoreduction status was reported occurred following transfusion of leukoreduced blood components but only two were prestorage leukoreduced.[4] The review additionally notes that no cases of TA-GVHD were documented with older (>2 weeks) red blood cells (RBC) or whole blood [in 148/158 (94%) of the reports where the age of the unit was known this was ≤10 days old].

Literature search

The literature search yielded 104 publications from 2013 to 2018 (summarised in supplementary Fig S1). One publication was retained; the GRADE method was applied to assess the likelihood of bias in this report. This study evaluated bleeding parameters in a group of 40 patients randomly assigned to receive irradiated vs non-irradiated platelet units. Occurrence of transfusion reactions was a secondary outcome; no TA-GVHD was reported in either group.[11] This small study was clearly inadequate to address the occurrence of TA-GVHD; thus, there is no published literature in 2013–2018 to provide an evidence base for either retaining or modifying the guidelines for irradiation indications.

Cases reported to haemovigilance systems

Out of 35 haemovigilance systems contacted through the IHN, 18 (51%) responded to the information request. Three systems stated that they are not (yet) adequately covering the occurrence of transfusion reactions in their countries. In Japan universal irradiation of blood components is in place. Thirteen haemovigilance systems had received no reports of TA-GVHD cases. A total of six cases of TA-GVHD were cited by five haemovigilance systems, including the two cases cited by Kopolovic (Table I). Medical information lacked detail and not all cases were conclusively TA-GVHD; we assumed the worst-case scenario that all were indeed cases of TA-GVHD. In four of the six documented cases the patient had a recognised indication for irradiated blood components although time intervals were not precisely known. Two patients did not have a recognised indication.

For additional verification, the transfusion reaction data collected by the European Directorate for the Quality of Medicines & Healthcare were checked for cases of TA-GVHD for the available years (2011–2015) in countries with near-universal leukodepletion.[12] A search of the IHN's database ISTARE covering the same years yielded one possible additional case (2010); the haemovigilance system was approached with a request for additional information but this could not be answered owing to the time interval.

In the countries which provided analysable responses, over 70 million prestorage leukodepleted cellular blood components were distributed, of which over 50 million were not irradiated and therefore at risk to cause TA-GVHD. In all the countries, leukodepletion is performed at least to the standard which is adhered to in the Netherlands ($<10^6$ leukocytes per unit, as monitored by statistical process control). Based on six cases, the incidence of TA-GVHD is estimated at 1 in 8.3 million leukodepleted, non-irradiated cellular components, presumed to be either from random HLA similarity or from inadvertent failure to provide irradiated components.

Patients receiving non-irradiated blood components in error

Reports of cases when patients who should receive irradiated components according to the guidelines are erroneously transfused with non-irradiated blood components but *do not* develop TA-GVHD can lend support to lifting an accepted recommendation for irradiated blood components. Such reports are collected by SHOT and TRIP. A total of 81 cases were reported to TRIP in 2008-2019.[8] Elliot *et al.*[13] analysed cases in the UK in 2010–2019; after exclusion of reports where the indication for irradiation was not stated or not current according to the British Society of Haematology guidelines, 784 incidents were analysed (2 809 units were transfused in total). In no case did TA-GVHD ensue. Extrapolating the SHOT estimation of 2 809 units erroneously transfused to patients who should have had irradiated components gives a figure in the order of 9 000 units in the countries covered by haemovigilance data. Both SHOT and TRIP note that such cases are probably not consistently reported, so this figure represents an underestimation.

Establishing proposals to adjust indications for irradiation

Table II shows the proposed revisions as initially developed by the group and circulated to experts for discussion prior to

Table I. Transfusion-associated graft-*versus*-host disease reported to haemovigilance systems following transfusion of prestorage leukodepleted cellular blood components.

Country*	Year	Patient condition	Indication for irradiated components	Type of blood component	Remark
United Kingdom	1998–1999	Patient 1: Multiple myeloma	No	LD RBC	These two cases are included in the Kopolovic review.
	2000–2001	Patient 2: Relapsed ALL; donor chimerism on biopsy	No	LD RBC+ LD plts	
France	2003	AML, 2× auto SCT in January and March 2003 (without total body irradiation)	Yes	From 2 days before first SCT 50 LD RBC, 47 apheresis plts, 1 pooled plt concentrate; in addition the patient received irradiated RBC and apheresis plts	'Lyell's syndrome + skin biopsy consistent with TA-GVHD,' however no pancytopenia
Italy	2009	Recent autologous SCT, haemorrhage	Yes	LD RBC+ Apheresis plts	Fever, 'GVHD signs'
Greece	2013	ALL, treated with fludarabine Signs of TA-GVHD < 30 days after two non-irradiated RBC units	Yes	Non-irradiated RBC; in addition irradiated RBC, plasma, plts; all LD	Bone marrow: hypoplasia + infiltration with small T lymphocytes
Spain	2011	Hodgkin lymphoma	Yes† (No information about staging)	2 LD RBC	Pancytopenia, erythema and diarrhoea; lymphocytic infiltrate in skin biopsy

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; LD, leukodepleted; RBC, red blood cells; plts, platelets; SCT, stem cell transplantation; TA-GVHD, transfusion-associated graft-*versus*-host disease.

*Countries that responded to the survey were: China, Croatia, Denmark, France, Greece, Italy, Japan, Malta, Namibia, Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, Pakistan, United Kingdom.

†In contrast to the British Society for Haematology guidelines, the former Dutch guidelines recommended lifelong provision of irradiated components only for Hodgkin lymphoma stage III or IV.

finalising the revised recommendations. The indications based on HLA similarity and for granulocyte transfusions were retained with little debate, as were those for children with congenital combined immunodeficiency and for intrauterine transfusions and until six months after due date. These indications concern relatively small numbers of transfusions. As suggested by the paediatric haematologists (for reasons detailed below) the group proposed lifting the recommendation for 'top-up' transfusions for infants born prematurely.

There was no change for haematopoietic stem cell transplantation, donor lymphocyte infusion or treatment with anti-thymocyte globulin (ATG) for aplastic anaemia or leukaemia. Among indications related to Hodgkin lymphoma and immunosuppressive medication, the group commuted lifelong irradiation indications to temporary because of absent evidence for a lifelong need. Automatic inclusion of new medicines of certain groups (such as purine/pyrimidine agonists) in the requirements was deemed to be unacceptable, so the recommendation was altered and is now based on the official product information because this is assessed on the basis of evidence at registration of a medicine and ongoing subsequent pharmacovigilance monitoring. Despite the lifting of some recommendations, the proposals do not attempt to overrule (investigational) study treatment protocols if they require provision of irradiated components for specific reasons, e.g. monitoring of residual disease.

The invitational expert meeting was attended, in addition to working-group members, by five academic clinicians, representing neonatology as well as adult and paediatric haematologists from the Dutch transplantation centres. (There are eight academic transplantation centres where allogeneic stem cell transplantations and solid organ transplantations are performed, while a further four teaching hospitals perform autologous haematopoietic stem cell transplantations; experts from all the academic centres had previously been sent the proposals for consultation, as explained above.) The literature review and haemovigilance data were presented followed by discussion of the proposed adjustments to the criteria, as shown in Table II. Experts stressed the extreme rarity of TA-GVHD and lack of adequate evidence to rationalise decisions to continue (or lift) specific indications.

Recent work using T-cell receptor sequencing has demonstrated that in individuals with a normal diversity of $CD4^+$ and $CD8^+$ clones, at least in the range of 1–6% of such clones are capable of mounting an allo-reactive response to

(mismatched) allo-HLA molecules.[14] If we consider the risk of TA-GVHD to be dependent on the relative number of immune-compentent cells of the donor and the recipient, a patient with immune reconstitution will easily generate a large number of cells able to mount an immune response to prevent TA-GVHD. Indications based on suppressed immunity of the patient should be determined according to clinical states with deep T-cell suppression and its duration.

Table II. Listed indications for provision of irradiated blood components in the former (2011) and the revised (2020) Dutch guidelines.

2011 Dutch guideline	Proposed revision prior to expert meeting	Revised guideline following expert meeting, as submitted to professional societies for endorsement (2020)
A. Indications based on HLA similarity		
Transfusion between 1st up to and including 3rd-degree relatives of cell-containing blood components	Unchanged	Unchanged
HLA-compatible platelet concentrates	Unchanged	Unchanged
B. Granulocyte transfusions	Unchanged	Unchanged
C. Indications based on immune status of the patient		
Children with congenital combined immuno-deficiency (SCID)	Unchanged	Unchanged
Intra-uterine transfusions (IUT), thereafter until 6 months after the due date	Unchanged	Unchanged
Premature babies (<1500 g birth weight) and/or pregnancy <32 weeks (up to 6 months after due date)	Not routinely required; also not routinely required following exchange transfusion unless previous IUT	Not routinely required
Acquired immuno-deficiency as is the case with: -allogeneic stem cell transplantation (for at least 6 months after transplantation if total body irradiation formed part of the conditioning; see other considerations); -autologous stem cell transplantation (for at least 3 months after re-infusion)	Unchanged	Allogeneic stem cell transplantation: until 1 year after last medication/ intervention Autologous stem cell transplantation: until 6 months after transplantation
After use of donor lymphocyte infusion (DLI) or infusion of cytotoxic T lymphocytes (CTL) for 1 year after transfusion	Unchanged	Unchanged
(Investigational) treatment protocols where the use of irradiated components is specified	Unchanged	Unchanged
Peripheral blood stem cell apheresis: from mobilization until after collection	Not routinely required	Not routinely required
Bone marrow collection: from 6 weeks prior to collection until after collection	Not routinely required	Not routinely required
Use of purine/pyrimidine agonists and related medication (e.g. fludarabine, pentostatin, cladribine) for 1 year after cessation of the therapy	Treatment with fludarabine for 1 year after cessation; treatment with a purine/pyrimidine agonist or similar medication, if the approved product information warns of TA-GVHD risk, but otherwise not routinely required	Patients with long-lasting T cell suppression after medication: fludarabine or other T-cell-depleting medication if the approved product information warns of TA-GVHD risk, for 6 months after cessation of the therapy
In the case of anti-T-cell treatment (ATG, anti-CD52 and other T cell monoclonals) for aplastic anaemia or leukaemia: from the start of the administration through to 6 months after completion of the treatment	In the case of anti-T-cell treatment (ATG, anti-CD52 and other T-cell monoclonals), unchanged for aplastic anaemia or induction for allogeneic transplantation of leukaemia patients; otherwise not routinely required	Medication which in combination with patient's illness gives a long-lasting T-cell suppression, such as anti-CD52 treatments for haematological diseases and anti-thymocyte treatment for aplastic anaemia: from the initiation of treatment till 6 months after completing treatment

Table II. (*Continued*)

2011 Dutch guideline	Proposed revision prior to expert meeting	Revised guideline following expert meeting, as submitted to professional societies for endorsement (2020)
Hodgkin lymphoma stage III or IV (with bone marrow infiltration)	Not routinely required	Not routinely required
	NEW For all transfused patients, be aware of risk of TA-GVHD; if TA-GVHD is suspected, confirm diagnosis through histology and demonstration of circulating donor lymphocytes NEW Report all cases where a patient with a recognised indication for irradiated blood components receives a non-irradiated component in error	NEW For all transfused patients, be aware of risk of TA-GVHD; if TA-GVHD is suspected, confirm diagnosis through histology and demonstration of circulating donor lymphocytes NEW Report all cases where a patient with a recognised indication for irradiated blood components receives a non-irradiated component in error

ATG, anti-thymocyte globulin; HLA, human leukocyte antigen; TA-GVHD, transfusion-associated graft-*versus*-host disease.

In the absence of evidence for specific durations, clarity of guidance improves adherence and therefore also safety. Thus, the groups were broadly subdivided. Irradiated components are recommended lifelong for severe congenital immunodeficiency and for one year after end of treatment in the case of allogeneic transplantation or donor lymphocyte infusion. A six-month duration is recommended for more moderate states of immunosuppression, e.g. after intra-uterine transfusion, autologous transplantation or anti-T-cell treatment, e.g. ATG for haematological indications. This is in line with the practical experience that after six months immune recovery is sufficient to be able to stop the antiviral prophylaxis and start a re-vaccination programme. For purine analogues and similar medication, advice to irradiate was limited to those drugs where the approved drug information specifically warns about an associated risk of TA-GVHD. Treatment with ATG in the organ transplantation setting affects transfused cells as well as recipient cells. Shortly after the ATG treatment is ended the host will have recovered sufficient immune competence.

The potential benefits of lifting indications for irradiation were considered. Although no formal economic evaluation was performed, irradiation carries financial costs which are significant (circa € 1.5 million/year in the Netherlands) due to a standard surcharge on each product. These costs and the logistic burden will decrease with the lifting of some indications. In this country irradiation is performed by the (national) blood establishment, necessitating parallel stocks in hospital transfusion laboratories, which are responsible for component selection and issue. For paediatric transfusions the limited post-irradiation storage of RBC units logistically prevents the use of paediatric units from the same donation for subsequent transfusions. Reduced donor exposure for premature-born infants requiring repeated transfusions means reduced risks of possible infections or donor-related transfusion reactions, and these risks are clearer than the residual concern about TA-GVHD. An additional consideration is the increase of haemolysis and free potassium in irradiated, stored RBC units and the susceptibility of infants to hyperkalaemia.[15,16] The former indication for irradiation of units for exchange transfusion and for infants born prematurely was therefore lifted. Intra-uterine transfusion (and subsequently transfusions up to six months from the due date) was retained as an indication because of the large volume of fresh blood transfused to these extremely vulnerable patients.[17]

Previous recommendations were for patients with Hodgkin lymphoma, even those in remission after treatment, to receive irradiated components lifelong because of early reports of late TA-GVHD and a long-lasting immune-deficient state.[18] In the Netherlands the advice was formerly limited to stages 3 and 4, as opposed to all stages in the UK.[1,9] In the absence of recent TA-GVHD cases in patients with Hodgkin, removal of this indication was proposed for patients who do not require irradiated components based on treatment given for their lymphoma. Finally, the requirement for irradiated components for transfusions in the week prior to stem cell harvest was lifted. The listed indications in the revised guideline are shown alongside those of the former guideline in Table II.

Discussion

This paper describes the evidence-gathering and changes in the Dutch recommendations for provision of irradiated blood components for patients potentially at risk for TA-GVHD. The literature search provided no evidence to support decisions about maintaining or removing indications for irradiated components. A survey of haemovigilance systems for cases of TA-GVHD associated with prestorage

leukoreduced blood components yielded a total of six potential cases, of which at least two had no recognised indication for irradiated components, associated with over (estimated) 50 million leukoreduced, non-irradiated and non-pathogen-reduced components. The main changes to the Dutch recommendations are the lifting of indications for neonatal exchange transfusions, infants born prematurely and Hodgkin lymphoma along with shortening of the time period to six months following purine agonist or similar medication carrying a warning about TA-GVHD risk. If only a short period of immune suppression is induced by medication such as ATG in the organ transplantation setting, there is no recommendation to transfuse irradiated blood components. The changes are small but go further than the recently revised British recommendations. On the other hand, the British guidelines recognise that the large group of organ recipients on prophylactic immunosuppressive drugs against graft rejection appears not to be at risk and formally endorse the practice of not providing irradiated components.[1]

A potential argument against relying on leukodepletion for protecting groups potentially at risk of TA-GVHD is the possibility of leukodepletion failure since residual leukocytes are not measured in every unit. Under statistical process control, in line with European standards, at least 99% of all units of cellular components should contain less than 5 million leukocytes, and at least 90% less than 1 million leukocytes. The range of the number of residual leukocytes per unit can be calculated based on quality control parameters. Although it is currently not known how many viable lymphocytes are required to cause TA-GVHD, theoretically it is possible that a small percentage of distributed cellular components contain residual T cells able to cause TA-GVHD in an immune-compromised recipient.

The lethal nature of TA-GVHD requires a robust approach with clear recommendations.[19] Evidence-based guidelines are limited when there is inadequate evidence in the peer-reviewed literature. The search for TA-GVHD cases in haemovigilance data is an important supplementary source of information since individual cases are not necessarily published in journals. Possible under-recognition and under-reporting in haemovigilance was discussed by the expert group. Transplanted patients may have acute or chronic GVHD and transfusion may not be considered as a potential cause of less serious GVHD although unexplained *de novo* pancytopaenia could point at transfusion as an (unlikely) cause. However, the guidelines aim to prevent fulminant TA-GVHD with pancytopaenia and a fatal outcome, which is less likely to be missed.

For the present revision the costs were also considered allowing for acceptance of a possible slightly increased risk which cannot be quantified. Although no formal economic evaluation was performed, irradiation carries financial costs which are significant and can be predicted to increase if indications are left unchanged. Several irradiation indications—indications where there was weak evidence of risk with the current leukodepleted components—were removed based on absence of evidence to continue. Others were actually lengthened in the interests of clear recommendations based on clinical states. The updated guideline proposals were formally endorsed by the professional societies.

Our study addressed indications for irradiation for the prevention of TA-GVHD. Use of irradiation prior to harvest of lymphocytes for advanced-therapy medicinal products, e.g. CAR-Ts, was outside the scope of the literature search. The working group advises that irradiated components should be considered for a week prior to such harvest in view of the subsequent modification and culturing as well as difficulty distinguishing between cells of donor and autologous origin as a cause of GVHD which may arise. A future literature search is recommended to cover this area.

Differences between countries in approach to prevention of TA-GVHD are understandable. The level of HLA diversity in the population is relevant: thus universal irradiation of blood components is employed in Japan because of a relatively limited HLA diversity and this successfully prevented cases of TA-GVHD before leukodepletion was introduced.[6] Of note, pathogen reduction technologies will also inactivate residual leukocytes, rendering irradiation unnecessary for blood products treated for pathogen reduction.[20] Blood processing and supply chain logistics have an impact, with consequences of subsequent storage and donor exposure being different in situations where irradiation is performed in the hospitals. If there is an urgent need for transfusion, this should not be withheld if no irradiated unit is available. Given the finding in the Kopolovic review that no cases of TA-GVHD were documented with older (>2 weeks) RBC or whole blood, consideration should be given to preferential selection of an older unit in such a situation. Attention is drawn to this approach in the British guideline.

It is important to realise that TA-GVHD, while exceedingly rare even with non-leukodepleted blood components, can also occur in patients who do not have any of the stated indications. Any suspected case should be investigated and if confirmed, reported to the haemovigilance system. If patients who should be given irradiated blood have been erroneously transfused with non-irradiated components this should also be reported, both to strengthen the (haemovigilance) evidence base and for sharing lessons about how to avoid repetition.

Conclusion

The national guideline revision for TA-GVHD prevention in the Netherlands, where universal leukodepletion of blood components is in place, took account of a systematic search of the literature and of findings of national haemovigilance systems. A number of the former indications for provision of irradiated cellular blood components have been dropped. Recommendations have been continued for situations of HLA similarity and for patient groups based on states of long-lasting deep T-cell suppression, as summarised in Table II.

Acknowledgements

The authors acknowledge assistance from literature specialists of the Knowledge Institute of Medical Specialists who performed the literature search and Eva Volmeijer who provided methodological support. Klasien Bergman, Peter te Boekhorst, Mette D Hazenberg, and Jaap Jan Zwaginga attended the expert meeting and advised on clinical acceptability of the proposed changes. The authors thank the haemovigilance system correspondents for responding to the survey questions.

Funding information

Meeting facilities, methodological and literature search support for the guideline revision was provided by the Royal Dutch Medical Association. No additional funding was received.

Author contributions

JCW-O and JS designed the study, JCW-O collected the haemovigilance and component distribution data and drafted the paper, TG performed the literature analysis, HLPD provided information on costs of irradiation. All authors interpreted the data and contributed to the guideline development. All authors critically reviewed or revised the paper and agree to its submission.

Conflicts of interests

The authors have no competing interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Literature search summary and results.

References

1. Foukaneli T, Kerr P, Bolton-Maggs PHB, Cardigan R, Coles A, Gennery A, et al; on behalf of the British Society for Haematology Guidelines Transfusion Task Force. Guidelines on the use of irradiated blood components. *Br J Haematol*. 2020;**191**:704–24. https://doi.org/10.1111/bjh.17015
2. 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.
3. Anderson KC, Goodnough LT, Sayers M, Pisciotto PT, Kurtz SR, Lane TA, et al. Variation in blood component irradiation practice: implications for prevention. *Blood*. 1991;**77**:2096–102.
4. Kopolovic I, Ostro J, Tsubota H, Lin Y, Cserti-Gazdewich CM, Messner HA, et al. A systematic review of transfusion-associated graft versus-host disease. *Blood*. 2015;**126**:406–14.
5. Williamson LM, Stainsby D, Jones H, Love E, Chapman CE, Navarrete C, et al. The impact of universal leukodepletion of the blood supply on hemovigilance reports of posttransfusion purpura and transfusion-associated graft-versus-host disease. *Transfusion*. 2007;**47**:1455–67.
6. Uchida S, Tadokoro K, Takahashi M, Yahagi H, Satake M, Juji T. Analysis of 66 patients with definitive transfusion-associated graft-versus-host disease and the effect of universal irradiation of blood. *Transfus Med*. 2013;**23**:416–22.
7. Bolton-Maggs PHB, Poles D, Watt A, Thomas D, Cohen H & Serious Hazards of Transfusion (SHOT) Steering Group ; on behalf of the . The 2012 annual SHOT report. 2013. Available from: https://www.shotuk.org/wp-content/uploads/myimages/SHOT-Annual-Report-20121.pdf
8. TRIP reports on haemovigilance, extended version. Available from: https://www.tripnet.nl/en/publications/trip-reports/
9. Treleaven J, Gennery A, Marsh J, Norfolk D, Page L, Parker A, et al. Guidelines on the use of irradiated lood components prepared by the British Committee for Standards in Haematology blood transfusion task force. *Br J Haematol*. 2011;**152**:35–51.
10. Dutch transfusion guideline available (in Dutch). Available from: https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/startpagina_-_bloedtransfusiebeleid.html
11. Zhu M, Xu W, Wang BL, Su H. Hemostatic function and transfusion efficacy of apheresis platelet concentrates treated with gamma irradiation in use for thrombocytopenic patients. *Transfus Med Hemother*. 2014;**41**:189–96.
12. European Directorate for the Quality of Medicines and Healthcare. Reports on the collection, testing and use of blood and blood components in Europe. Available from: https://www.edqm.eu/en/blood-transfusion-reports-70.html
13. Elliot J, Narayan S, Poles D, Tuckley V, Bolton-Maggs PHB. Missed irradiation of cellular blood components for vulnerable patients: Insights from 10 years of SHOT data. *Transfusion*. 2020. Epub ahead of print. https://doi.org/10.1111/trf.16189
14. DeWolf S, Grinshpun B, Savage T, Lau SP, Obradovic A, Shonts B, et al. Quantifying size and diversity of the human T cell alloresponse. *JCI Insight*. 2018;**3**:e121256.
15. Moroff G, Holme S, Aubuchon JP, Heaton WA, Sweeney JD, Friedman LI. Viability and in vitro properties of AS-1 red cells after gamma irradiation. *Transfusion*. 1999;**39**:128–34.
16. Strauss RG. Red blood cell storage and avoiding hyperkalemia from transfusions to neonates and infants. *Transfusion*. 2010;**50**:1862–5.
17. Naiman JL, Punnett HH, Lischner HW, Destine ML, Arey JB. Possible graft-versus-host reaction after intrauterine transfusion for Rh erythroblastosis fetalis. *N Engl J Med*. 1969;**281**:697–701.
18. Spitzer TR, Cahill R, Cottler-Fox M, Treat J, Sacher R, Deeg HJ. Transfusion-induced graft-versus-host disease in patients with malignant lymphoma. A case report and review of the literature. *Cancer*. 1990;**66**:2346–9.
19. Loingsigh SN, Flegel WA, Hendrickson JE, Tormey CA. Preventing transfusion-associated graft-versus-host disease with blood component irradiation: indispensable guidance for a deadly disorder. *Br J Haematol*. 2020;**191**:653–7.
20. Prowse C. Component pathogen inactivation: a critical review. *Vox Sang*. 2013;**104**:183–99.