

TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE

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Purposes

Recommendations for the investigation and provision of clinical advice in cases of suspected or proven transfusion-associated graft-versus-host disease.

Method

Recommendations are based on review of the literature and a review of currently accepted practice. The definitions of the types of evidence and the grading of recommendations used in this document originate from the US Agency for Health Care Policy and Research and are provided in the Appendix.

Consultation

NHSBT Transfusion Medicine Clinical Policies Group
NHSBT Transfusion Medicine Clinical Policies H&I Sub-group

Status

Approved by the NHSBT Transfusion Medicine Clinical Policies Group on 18th February 2002.

Summary

Transfusion-associated graft-versus-host disease (TA-GVHD) is rare but usually fatal. Patients at risk of this complication have been clearly defined, as have groups not considered to be at risk. Those components implicated are red cells, platelet concentrates, fresh plasma and granulocyte transfusions. At risk patients should carry the card issued by the Department of Health and receive gamma-irradiated blood components. The dose of gamma irradiation should be a minimum of 25 Gy to any part of the blood component container. In supporting the clinical diagnosis, laboratory testing to demonstrate mixed chimerism is important. The best way to manage TA-GVHD is unknown. All recommendations are Grade C and are based on level IV evidence.

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1 Introduction

TA-GVHD is a devastating but almost entirely preventable complication of transfusion. Twelve cases were reported to the Serious Hazards of Transfusion (SHOT) scheme during the first four years of reporting^{1,2}. No cases have been reported since 2001.

| Year | No. new cases reported | Diagnoses |
|---------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1996-97 | 4 | <ul style="list-style-type: none"> · Congenital immunodeficiency · No patient risk factors · B cell NHL (2 cases) |
| 1997-98 | 4 | <ul style="list-style-type: none"> · Waldenstrom's macroglobulinaemia · B cell NHL · cardiac surgery · autoimmune thrombocytopenia |
| 1998-99 | 4 | <ul style="list-style-type: none"> · myeloma (1 case) · uncharacterised immunodeficiency · cardiac surgery (2 cases) |
| 1999-00 | 0 | Nil |
| 2000-01 | 1 | <ul style="list-style-type: none"> · ALL (1 case) |
| 2001-02 | 0 | Nil |
| 2002-03 | 0 | Nil |
| 2003-04 | 0 | Nil |
| 2004-05 | 0 | Nil |
| 2005-06 | 0 | Nil |
| 2006-07 | 0 | Nil |
| 2007-08 | 0 | Nil |
| 2008-09 | 0 | Nil |
| 2009-10 | 0 | Nil |

Summary

| | |
|--------------------------------------|---|
| B cell malignancies | 6 |
| Cardiac surgery | 3 |
| Congenital/acquired immunodeficiency | 2 |
| Autoimmunity | 1 |
| No risk factors | 1 |

2 Pathogenesis

Normally, recipient lymphocytes are capable of recognising foreign HLA and prevent the development of a donor anti-host immune response. TA-GVHD is the result of engraftment and proliferation of alloreactive donor lymphocytes in transfusion recipients. Mature donor T cells recognise alloantigens in the recipient and become activated leading to cytokine production and lymphocyte proliferation. Inflammation and tissue damage follow^{2,3}. Two factors may allow such a response to develop. Firstly sharing of HLA-haplotypes between donor and

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recipient which occurs when HLA-selected components are transfused or when donations are obtained from relatives. This is particularly true when HLA-homozygous blood components are transfused. This may also occur by chance, particularly in populations with a restricted pool of common HLA haplotypes³. The second factor is defective recipient cell-mediated immunity which may be inherited (e.g. severe combined immune deficiency - SCID) or acquired (e.g. Hodgkin's Disease)². Other factors which may be relevant are the age of the component as the number of viable lymphocytes diminishes with storage. Lymphocyte dose is important but leucodepletion does not prevent TA-GVHD².

3 Clinical features

Typical features of skin rash, fever, diarrhoea, hepatic dysfunction and bone marrow failure appear 1 - 2 weeks after transfusion. The mortality rate is >90%³. TA-GVHD is usually unexpected, prophylaxis has not been given and recognition may be late. All contribute to the poor response to treatment obtained.

4 Patients – other than stem cell transplant donors/recipients

4.1 Patient groups considered to be at risk

- Recipients of donations from first or second degree relatives.
- Patients receiving HLA-matched platelets.
- Intra-uterine transfusion of red cells or platelets.
- Exchange transfusions (especially after Intra-uterine transfusion); Red cell or platelet transfusions given after birth to infants who have received either red cells or platelets in utero, should be irradiated and this practice should continue up to the age of one year
- Recipients of allogeneic stem cell transplants (SCT) until GVHD prophylaxis is completed and/or lymphocyte count $>1 \times 10^9/L$.
- Hodgkin's disease
- Patients treated with purine analogues, e.g. fludarabine, cladribine or deoxycoformycin.

4.2 Cardiac surgery

In children irradiated components should be given if there is suspicion of Di George syndrome, lymphopenia or other immune deficiency state that might compromise T lymphocyte function. In adults irradiated blood is not currently indicated but the Serious Hazards of Transfusion scheme has suggested that this recommendation should be kept under review.

4.3 Patients not at risk

- Solid organ transplant - TA-GVHD has been documented in recipients of liver, lung and kidney transplants but this is ordinarily associated with the transfer of donor lymphoid tissue with the graft.
- HIV.
- Solid tumours.
- Non-Hodgkin's lymphoma - currently under review by the BCSH.

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5 Stem cell donors and recipients

- Donors of allogeneic marrow who receive transfusions. These donors are not themselves at risk but viable third party lymphocytes may be collected and transplanted. If transfusions are given during the harvest they must be irradiated.
- Patients undergoing autologous SCT. Irradiation of transfusions should be commenced 7 days prior to HPC harvesting to prevent collection of viable allogeneic lymphocytes which could cause TA-GVHD after reinfusion. Irradiated components are continued for 3 months or 6 months if the patient received total body irradiation.
- Patients with an underlying primary immunodeficiency which comprises T lymphocyte function (except chronic mucocutaneous candidiasis).

6 Diagnosis

6.1 Haematological and histopathological features

There is usually profound pancytopenia and bone marrow hypoplasia. The skin biopsy findings may be non-specific but support the diagnosis of TA-GVHD. These include cell necrosis, dyskeratosis and infiltration with mononuclear cells.

6.2 Laboratory features

Diagnosis depends on finding evidence of donor-derived cells or chromosomes or DNA in the blood and/or affected tissues of the recipient (mixed chimerism) on more than one occasion. Note that transfused donor leucocytes may remain in otherwise healthy recipients from a few days to several years.

6.3 Testing

The best strategy for supporting a clinicopathological diagnosis of TA-GVHD is to establish that there is mixed chimerism in patient samples. Chimerism may be based on cytogenetic or DNA analysis. Samples should be obtained from the recipient before and after the transfusion and from the donors from whom blood components have been transfused. Analysis is then performed of polymorphic sites at HLA loci or elsewhere. These include analysis of variable number tandem repeat (VNTR) and short tandem repeat (STR) profiles^{4,5}.

Alternative tissues for DNA extraction include skin (both affected and unaffected areas) and hair follicles or nail clippings (which represent the 'pretransfusion' sample equivalent). Post-mortem samples, e.g. spleen or bone marrow, may also be used. Skin samples are necessary to establish presence of donor derived lymphocytes in lesions. If only a peripheral blood sample is obtained it would be difficult to confirm TA-GVHD as donor derived lymphocytes can exist in peripheral blood of healthy transfused patients.

A routine service for the investigation of TA-GVHD is provided by the NHSBT network of H&I laboratories.

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7 Investigations

7.1 Donor samples required

- Fresh samples from the donor.
- 10 - 20 mL EDTA.
- Practical only if manageable numbers e.g. 10 or less component transfusions are implicated.

Decision to base the diagnosis on analysis of patient material only should be discussed with an NHSBT H&I Consultant. Where it is intended that some/all donor components are not to be analysed a check should be made to ascertain whether any non-irradiated blood components were transfused to an at-risk patient and in this case these components or donor samples must be investigated.

7.2 Recipient samples required

- Blood sample prior to transfusion (any amount available).
- Blood samples after transfusion, 10 - 20 mL EDTA.
- Hair follicle or nail clipping samples (in saline) are an alternative source of pre-transfusion DNA, but could be taken after the transfusions were given.
- Affected and unaffected skin (send biopsy in sterile saline or culture medium).
- Bone marrow (if being performed anyway; 1 mL in EDTA).
- Spleen (post-mortem; sample in sterile saline).

7.3 Additional samples

Follow-up samples (typically blood) may provide valuable information about temporal changes to the DNA profile, particularly in cases where not all of the above samples are available.

7.4 Samples are sent to the local blood centre and will be referred to the appropriate H&I laboratory. Investigations will be performed at the H&I laboratory. In each centre or group of functionally linked centres an NHSBT H&I Consultant will take responsibility for ensuring that essential clinical data and samples are provided to and discussed with the senior scientists in the H&I laboratory. A copy of the final report should be sent to the NHSBT H&I Consultant and/or other Consultant Haematologists involved at NHSBT blood centres.

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8 Prevention

- 8.1 At risk patients should carry the card presently issued by DoH to hospitals. This card indicates that the cellular blood components must be irradiated.⁶
- 8.2 Leucocyte depletion - NOT adequate alone for at risk patients as defined above. Removes 3-4 log T cells from whole blood so may reduce risk in immunocompetent patients.⁷
- 8.3 Gamma irradiation - standard method at present. Needs 25 Gy to all parts of pack, with no part receiving more than 50 Gy. Appropriate radiation sensitive labels must be used so that it can be verified that the dose of radiation has been given.
- 8.4 Psoralen (S59) + ultra-violet A - this method is under trial for pathogen inactivation of platelets, but there is also prevention of TA-GVHD in an animal model. FDA have recently allowed trials of this method to proceed without gamma irradiation in susceptible patients.

9 Blood components (BC)

BC implicated in TA-GVHD are red cells, platelet concentrates, fresh plasma and granulocyte transfusions.

Those not implicated are frozen-thawed RBC, fresh frozen plasma (FFP), cryosupernatant plasma (CSP), cryoprecipitate and fractionated plasma products.

BC storage after irradiation

- IUT / ET red cells - 24 hours.
- Other red cells including neonatal top-up transfusions - irradiate within 14 days of collection and store for not greater than 14 days post-irradiation.
- Platelets. Irradiate at any stage in shelf life - no effect on total shelf life of 5 days except 24 hours for IUT platelets.
- Granulocytes. Transfuse as soon as possible after preparation/irradiation.

10 Management

10.1 Suspected or proven TA-GVHD

The NHSBT Consultant involved (H&I or other) should, for patients not under the care of a haematologist, recommend transfer to an appropriate specialist unit. He/she should recommend that the case should be discussed with a haematologist with experience of managing patients with acute GVHD.

- The best advice is to start treatment promptly including supportive care with blood component transfusions, broad spectrum antibiotics and antifungal agents as appropriate.
- A number of drugs have been used in acute GVHD. Cyclosporin A and methotrexate are used to prevent GVHD and steroids are first line treatment when it develops. Steroid-refractory GVHD is treated with a number of agents including ATG, FK506, anti-T cell and IL-2 receptor

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mononuclear antibodies and mycophenolate mofetil. The role of these agents in TA-GVHD is uncertain.

10.2 Management where at-risk patients have received non-irradiated blood components

- In the most recent data set reported to SHOT 68 cases were reported where non-irradiated BCs were given inappropriately. None of these developed TA-GVHD.
- Establish which blood components are involved.
- HLA type patient and store mononuclear cell and DNA samples.
- Consider testing to establish molecular profiles (see above).
- There should be careful clinical observation of the transfusion recipient with institution of treatment and review of appropriate laboratory investigation (see 5.3 and 6 above) if any clinical features of TA-GVHD appear.

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Appendix

Key to evidence statements and grades of recommendations

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research and are set out in the following tables.

STATEMENTS OF EVIDENCE

- Ia Evidence obtained from meta-analysis of randomised controlled trials.
- Ib Evidence obtained from at least one randomised controlled trial.
- IIa Evidence obtained from at least one well-designed controlled study without randomisation.
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.
- III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

GRADES OF RECOMMENDATIONS

- A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.**
(Evidence levels Ia, Ib)
- B Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.**
(Evidence levels IIa, IIb, III)
- C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.**
(Evidence level IV)