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Irradiation to prevent a fatal transfusion complication

KRONIKK

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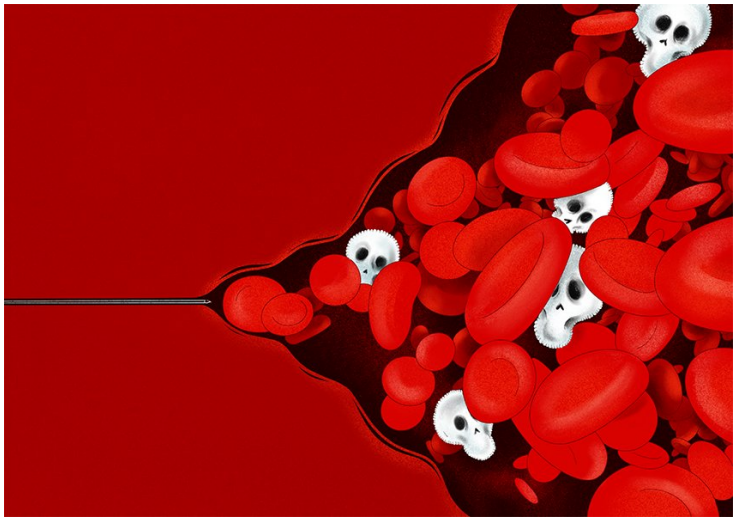
Cellular blood components should be irradiated as a preventive measure against transfusion-associated graft-versus-host disease in severely immunocompromised patients.



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The right blood component for the right patient, based on a correct and well-founded indication, is fundamental to sound transfusion practice (1). Severely immunocompromised patients should be given irradiated blood components to prevent transfusion-associated graft-versus-host disease. It is the responsibility of the doctor ordering the blood to provide the necessary information to the blood bank and to order irradiated blood components.

Transfusion-associated graft-versus-host disease was first described in 1965, and is a rare and usually fatal (> 90 %) complication of transfusion (2, 3).

A review of 348 published cases showed that half the patients who developed the condition had obvious risk, but that they had not received irradiated blood (3). Several countries have guidelines for which patient groups should receive irradiated blood components, but these vary from country to country. In this article we compare the Norwegian guidelines with those of the UK, Canada and Australia/New Zealand. We see that several patient groups are not mentioned in the Norwegian guidelines, and therefore propose harmonisation with the more detailed international guidelines. The new chemotherapies and immunotherapies that lead to severe immunosuppression should be evaluated together with clinicians with

respect to the risk of transfusion-associated graft-versus-host disease. The Norwegian guidelines must be updated continuously in accordance with the evaluations.

Pathophysiology

Passive transfer of immunocompetent T-lymphocytes to the recipient through transfusion leads to transfusion-associated graft-versus-host disease. A blood donor's T-lymphocytes are usually efficiently removed by the recipient's immune system. In a severely immunocompromised recipient, or when donor and recipient share tissue type antigens (human leukocyte antigen, HLA) for which the donor is homozygous, the recipient's immune system is unable to recognise the donor's T-lymphocytes as foreign. As a consequence, the passively transferred T-lymphocytes may attack the recipient's cells, establish and proliferate in the recipient's bone marrow. This leads to severe pancytopenia, which may have a fatal outcome (3).

Transfusion-associated graft-versus-host disease is a rare and usually fatal complication of transfusion

The condition manifests 2–30 days after transfusion, with fever, erythematous maculopapular rash, elevated liver enzyme values, nausea, vomiting and diarrhoea. Because the symptoms are diffuse, and may develop several days after the transfusion, transfusion as a possible trigger may be overlooked. The symptoms can be confused with manifestations of infections or reactions to drugs, which makes diagnosis even more difficult (4). Characteristic findings in biopsies from affected organs (e.g. skin, liver) and/or post-transfusion molecular genetic detection of donor lymphocytes in the patient (chimaerism), are diagnostic. HLA typing of blood donor and patient should be included in the investigation (3).

All blood components that contain viable T-lymphocytes can cause transfusion-associated graft-versus-host disease in susceptible patients. As erythrocyte and platelet concentrates are not produced industrially, they contain some unintended components. In allogeneic haematopoietic stem cell transplantations, T-lymphocytes contribute to a graft-versus-tumour/leukaemia effect, so it is desirable for stem cell products to contain T-lymphocytes. But this is not the case for transfusions (5). The condition has many similarities with graft-versus-host disease, which can develop after allogeneic stem cell transplantation. Both conditions affect skin, gastrointestinal tract and liver, but in contrast to graft-versus-host disease, the one associated with transfusion leads to pronounced and usually irreversible pancytopenia as a result of bone marrow involvement (3). There is no effective treatment for transfusion-associated graft-versus-host disease, so preventive measures are very important (4).

Prevention

The quantity of T-lymphocytes in blood components has a bearing on transfusion-associated graft-versus-host disease. In 2001, leukocyte reduction was introduced as standard in blood component production in Norway. The requirement is $< 10^6$ residual leukocytes per unit, and the risk of transfusion-associated graft-versus-host disease is therefore substantially reduced (6). However, leukocyte reduction is not sufficient, as the condition has also been reported after transfusion with leukocyte-reduced blood components (7).

We see that several patient populations are not mentioned in the Norwegian guidelines, and therefore propose harmonisation with the more detailed international guidelines

Effective prevention of transfusion-associated graft-versus-host disease is achieved by irradiating blood components with doses of ionising radiation (25–50 Gy). This inhibits lymphocyte proliferation, while maintaining the viability and thus the clinical efficacy of erythrocytes and platelets. After irradiation of erythrocyte concentrates, however,

potassium leakage from the erythrocytes increases gradually, leading to a rise in potassium in the additive solution (8). Furthermore, haemolysis increases in irradiated erythrocyte concentrates (9). To limit haemolysis and restrict the potassium content, the storage time for irradiated erythrocyte concentrates is shortened from the normal 35 days to 28 days after collection.

For exchange or intrauterine transfusions, however, erythrocyte concentrates must be used within 24 hours following irradiation, because fetuses and neonates are more vulnerable to severe hyperkalaemia.

Platelet concentrates can be stored for up to seven days, and can be irradiated throughout the storage period (9). Their shelf life is not shortened, as irradiation does not affect platelet function. The condition can also be effectively prevented by using a pathogen reduction method (10), whereby both lymphocytes and any microbial agents are deactivated through irreversible nucleic acid damage. Octaplasma and plasma products do not contain cells and do not require irradiation.

Viable T-lymphocytes persist in blood components for up to two weeks (11). Thus, the fresher the blood, the higher the risk of transfusion-associated graft-versus-host disease. Irradiation of fresh blood components is therefore particularly important.

Not all hospitals have an irradiator, and procuring irradiated blood components from a tertiary blood bank can be a logistical challenge. It is important that essential transfusion treatment is not delayed. If irradiated blood components cannot be procured, efforts should be made to give blood that is over 14 days old, to prevent the transfer of viable T-lymphocytes.

Indications for irradiation

A comparison of guidelines from different countries shows that there is a lack of consensus as to which patient populations should receive irradiated blood components (7, 9, 12–14). The guidelines are generally based on the risk of HLA compatibility between donor and patient, and the risk of immunosuppression on the basis of diagnosis and/or certain immunosuppressive treatments (7, 9, 12–14). There are no randomised studies in this field, and the guidelines are therefore based mainly on empirical data. The UK, Canada and Australia/New Zealand have good, evidence-based, and up-to-date transfusion guidelines with which it is natural to compare the Norwegian guidelines.

There is no effective treatment for transfusion-associated graft-versus-host disease, so preventive measures are very important

The Norwegian guidelines are liberal with regard to indication for irradiation of blood components but specify a list of indications that must be regarded as a minimum (9, 13) (Box 1). Some hospitals use broader indications than those in this list. The guidelines of other countries contain additional and more detailed indications and include more diagnoses and immunosuppressive drugs than the Norwegian guidelines (7, 9, 12–15). In Japan, where the population is relatively homogenous, all cellular blood components are irradiated for all patients (11). We therefore want to draw attention to several indications that should also be included in the Norwegian guidelines.

Box 1 Patient populations where irradiation is indicated according to the Norwegian guidelines (9, 13).

Fetuses in need of intrauterine transfusions
Prematures (weight < 1 500 g)
Patients who receive transfusions with HLA-compatible platelet concentrates
Patients who receive blood components from relatives

Patients who receive allogeneic haematopoietic stem cell transplants. The requirement applies for one month before and at least 12 months after transplantation
Patients who receive autologous haematopoietic stem cell transplants. The requirement applies for one month before and 3–6 months after transplantation
Patients with severe immunodeficiencies
Patients who are severely immunocompromised due to disease or treatment, for example chemotherapy with purine analogues (fludarabine) or immunomodulatory monoclonal antibodies. Patients who are treated with purine analogues should receive irradiated components life-long.

TRANSFUSIONS TO FETUSES AND NEONATES

According to the British guidelines, children who have had exchange or intrauterine transfusion must receive irradiated blood components until they are six months old, counting from the expected due date (14). Although it is not a national recommendation, this is also practised by some blood banks in Norway, if the bank receives the necessary information. Neonates may have an undetected underlying congenital immune deficiency with increased risk of transfusion-associated graft-versus-host disease. Irradiation should therefore be considered for neonates in need of transfusion (7). These indications should be included in the Norwegian guidelines.

HODGKIN'S LYMPHOMA

The Norwegian guidelines have no recommendation concerning irradiated blood components for patients with Hodgkin's lymphoma. However, transfusion-associated graft-versus-host disease with fatal outcomes has been reported for this patient population, also long after treatment is completed (16). Several countries accordingly recommend irradiated blood components for patients with Hodgkin's lymphoma, irrespective of cancer stage, and life-long (7, 14, 15). This indication should be included in the Norwegian guidelines.

ANTITHYMOCYTE GLOBULIN

Several countries recommend life-long treatment with irradiated blood components for patients with aplastic anaemia who receive antithymocyte globulin (ATG) (7, 12, 14). The risk is probably not associated with the underlying condition, but with the antithymocyte treatment, which reduces and inhibits T-cell function (7). Antithymocyte globulin is also used in haematopoietic stem cell transplantation and in the treatment of steroid-resistant rejection following a kidney transplantation (17). These indications are not included in the Norwegian guidelines but should be.

The fresher the blood, the higher the risk of transfusion-associated graft-versus-host disease

PURINE ANALOGUES AND BENDAMUSTINE

Purine analogues (for example fludarabine) are used in haematological malignancy and multiple sclerosis (MS). This drug group causes severe lymphocytopenia with long-term reduction of CD4-positive T-lymphocytes and increased risk of transfusion-associated graft-versus-host disease. As a result, irradiation is recommended life-long, also in the Norwegian guidelines (7, 9, 12–14, 18). Bendamustine, which is an alkylating cytostatic drug and has a possible additional effect as a purine analogue, is included in the guidelines of several countries, and should be included in the Norwegian guidelines (7, 14).

ALEMTUZUMAB

Alemtuzumab is a humanised monoclonal antibody against CD52 which is largely expressed on the cell surface of normal and malignant B- and T-lymphocytes and leads to pronounced lymphocyte depletion. Alemtuzumab is used to treat chronic lymphocytic leukaemia and is included in some protocols for allogeneic haematopoietic stem cell transplantation as prophylaxis against graft-versus-host-disease, in kidney transplant

protocols and for multiple sclerosis (19, 20). There is some variation in the recommendations of different countries. Some countries recommend life-long use of irradiated blood components following alemtuzumab treatment, irrespective of indication, while others do not recommend irradiation in treatment of multiple sclerosis and vasculitis (7, 12, 14). The inclusion of alemtuzumab in the Norwegian guidelines should therefore be considered.

CAR-T THERAPY

Chimeric antigen receptor T-cell (CAR-T) therapy, which is used for some acute leukaemia and lymphoma patients, causes severe immunosuppression. Irradiation of blood components is considered to be indicated in the guidelines of some countries (14). This treatment should also be included in the Norwegian guidelines.

DOSE-RELATED IMMUNOSUPPRESSIVE EFFECT

The risk of transfusion-associated graft-versus-host disease can be dose-dependent, as higher doses of immunosuppressive drugs lead to more severe immunosuppression. For some indications, it is unclear how long irradiated blood components will be needed after the completion of immunosuppressive treatment. British guidelines recommend considering the need for irradiation of blood components when new, high efficacy immunosuppressive and biological drugs are taken in clinical use (7, 12, 14). This should also be included in the Norwegian guidelines.

Conclusion

Several conditions carry increased risk of transfusion-associated graft-versus-host disease, and there is no effective treatment. The condition is associated with very high mortality (> 90 %). Preventive measures such as irradiation are therefore very important. The Norwegian guidelines as to which patient groups should receive irradiated blood components, based on diagnosis and drugs used previously or currently, should be updated. The indications should be described in discipline-specific guides, so that clinicians are aware of the indications for irradiation.

REFERENCES:

1. Legeforeningen. Gjør kloke valg. https://www.legeforeningen.no/kloke-valg/anbefalinger/fagmedisinske-anbefalinger/norsk-forening-for-immunologi-og-transfusjonsmedisin/ Accessed 7.6.2020.

2. Hathaway WE, Githens JH, Blackburn WR et al. Aplastic anemia, histiocytosis and erythrodermia in immunologically deficient children. Probable human runt disease. N Engl J Med 1965; 273: 953–8. [PubMed][CrossRef]

3. Kopolovic I, Ostro J, Tsubota H et al. A systematic review of transfusion-associated graft-versus-host disease. Blood 2015; 126: 406–14. [PubMed][CrossRef]

4. Fast LD. Developments in the prevention of transfusion-associated graft-versus-host disease. Br J Haematol 2012; 158: 563–8. [PubMed][CrossRef]

5. Sweeney C, Vyas P. The Graft-Versus-Leukemia Effect in AML. Front Oncol 2019; 9: 1217. [PubMed][CrossRef]

6. Lovdata. Blodforskriften. https://lovdata.no/artikkel/blodforskriften/814 Accessed 9.8.2020.

7. Guidelines for prevention of transfusion-associated graft-versus-host disease (TA-GVHD). Sydney: Australian and New Zealand Society of Blood Transfusion Ltd, 2011. https://anzsbt.org.au/wp-content/uploads/2018/06/PreventionofTA-GVHD.pdf Accessed 31.5.2020.

8. 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.

[PubMed][CrossRef]

9. Veileder for transfusjonstjenesten i Norge, Utgave 7.3.2017. Oslo: Helsedirektoratet, 2017. https://www.helsedirektoratet.no/veiledere/transfusjonstjenesten-i-norge-utgave-73/Transfusjonstjenesten%20i%20Norge%20utgave%207.3%20%E2%80%93%20Veileder.pdf/_/attachment/inline/6222d24e-ebdc-4588-a51f-735cc17f58c6:ddb6d627e05b9f68918723bf59407db19602a601/Transfusjonstjenesten%20i%20Norge%20utgave%207.3%20%E2%80%93%20Veileder.pdf Accessed 31.5.2020.

10. Cid J. Prevention of transfusion-associated graft-versus-host disease with pathogen-reduced platelets with amotosalen and ultraviolet A light: a review. Vox Sang 2017; 112: 607–13. [PubMed][CrossRef]

11. 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. Transfus Med 2013; 23: 416–22. [PubMed][CrossRef]

12. Prokopchuk-Gauk O. Clinical Guide To Transfusion, Chapter 15: CMV Seronegative, Irradiated and Washed Blood Components. https://profedu.blood.ca/en/transfusion/guide-clinique/cmv-seronegative-irradiated-and-washed-blood-components Accessed 31.5.2020.

13. Norsk forening for immunologi og transfusjonsmedisin. Klinisk transfusjonshåndbok. https://www.legeforeningen.no/contentassets/91aac334a9904f7abe1ba881fa40792a/tranfusjonshandboken-010217.pdf Accessed 31.5.2020.

14. Foukaneli T, Kerr P, Bolton-Maggs PHB et al. Guidelines on the use of irradiated blood components. Br J Haematol 2020; 191: 704–24. [PubMed][CrossRef]

15. Manduzio P. Transfusion-associated graft-versus-host disease: A concise review. Hematol Rep 2018; 10: 7724. [PubMed][CrossRef]

16. Spitzer TR, Cahill R, Cottler-Fox M et al. Transfusion-induced graft-versus-host disease in patients with malignant lymphoma. A case report and review of the literature. Cancer 1990; 66: 2346–9. [PubMed][CrossRef]

17. Bamoulid J, Staeck O, Crépin T et al. Anti-thymocyte globulins in kidney transplantation: focus on current indications and long-term immunological side effects. Nephrol Dial Transplant 2017; 32: 1601–8. [PubMed]

18. Leitman SF, Tisdale JF, Bolan CD et al. Transfusion-associated GVHD after fludarabine therapy in a patient with systemic lupus erythematosus. Transfusion 2003; 43: 1667–71. [PubMed][CrossRef]

19. Brierley CK, Jones FM, Hanlon K et al. Impact of graft-versus-lymphoma effect on outcomes after reduced intensity conditioned-alemtuzumab allogeneic haematopoietic stem cell transplantation for patients with mature lymphoid malignancies. Br J Haematol 2019; 184: 547–57. [PubMed][CrossRef]

20. Hui YM, Regan F, Willecombe M et al. Use of non-irradiated blood components in Campath (alemtuzumab)-treated renal transplant patients. Transfus Med 2016; 26: 138–46. [PubMed][CrossRef]

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