



Transfusion associated graft vs. host disease and how to prevent it

Reakcija presadka proti gostitelju po transfuziji krvi in kako jo preprečimo

Aleksandra Barbarič Kovačič,¹ Slavica Stanišič,¹ Samo Zver^{2,3}

Abstract

¹ Blood Transfusion Centre of Slovenia, Ljubljana, Slovenia

² Department of Hematology, University Medical Centre Ljubljana, Ljubljana, Slovenia

³ Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Correspondence/ Korespondenca:

Aleksandra Barbarič Kovačič, e: aleksandra.barbaric@ztm.si

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Transfusion associated graft versus host disease (TA-GvHD) is a rare but fatal complication of blood components transfusion therapy and has over 90% mortality rate. Transfused donor T lymphocytes react against the recipient's cellular and tissue antigens. Interaction triggers lymphocyte activation and, consequently, destruction of target cells in the recipient's tissues. The reason that immune cells of the recipient do not respond appropriately is an incompetent recipient's immune system and immunodeficiency of the host. Exceptionally, HLA compatibility between the donor and the recipient may cause the same reaction.

Most effective way to prevent TA-GvHD is irradiation of the blood components with ionizing radiation. UVA psoralen based pathogen inactivation is an equally effective preventive measure of TA-GvHD, but it is applicable only to platelets. For this reason, it is important that physicians identify patients at risk of developing TA-GvHD and consequentially always prescribe irradiated blood units. Blood units that need to be irradiated are erythrocytes and granulocytes, with the mentioned exception of platelets. Fresh frozen plasma, cryoprecipitate, blood derived medicines, such as albumins, immunoglobulins, blood clotting factors, and erythrocytes after thawing are not irradiated. The recommended central field irradiation dose is 25-50 Gy.

Izvleček

S transfuzijo povezana reakcija presadka proti gostitelju (*angl.* Transfusion associated graft versus host disease, TA-GvHD) je redek, vendar resen in življenje ogrožajoč zaplet po transfuziji krvnih pripravkov. Posledica, kolikor do nje pride, je bolnikova smrt v več kot 90 % primerov. Po transfuziji krvi se osebi z imunsko pomanjkljivostjo limfociti T iz darovalčeve krvi odzovejo na celične in tkivne antigene prejemnika krvi. Zato darovalčevi limfociti T aktivirajo in uničijo tarčne celice v tkivih prejemnika. Vzrok, da se imunske celice prejemnika ne odzovejo tako, da bi onemogočile darovalčeve limfocite T, je pomanjkljivost imunskega odziva pri prejemniku in le izjemoma vprašanje skladnosti HLA med prejemnikom in darovalcem.

Obsevanje krvnih pripravkov z ionizirajočimi žarki je najbolj učinkovita metoda za preprečevanje TA-GvHD. Patogensko inaktiviranje s psoralenom in UVA-žarki je enakovredno obsevanju, vendar se zaenkrat uporablja samo za trombocitne pripravke. Zato je pomembno, da lečeči zdravnik prepozna bolnike, pri katerih lahko nastane TA-GvHD in za njih naroča zgolj obsevane krvne pripravke. Obsevamo eritrocite, granulocite ter trombocite, kadar niso patogensko inaktivirani. Sveže zmrznjene plazme, krioprecipitata, zdravil iz krvi, kot so albumin, imunoglobulini, faktorji strjevanja krvi ... ter eritrocitov po odmrzovanju ne obsevamo, ker je vsebnost limfocitov T zanesljiva. Priporočen osrednji obsevalni odmerek je znotraj 25–50 Gy.

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1 Introduction

Transfusion-associated graft-versus-host disease (TA-GvHD) is an exceptionally rare but serious complication of the transfusion of various blood components. It mostly appears in immunodeficient patients and only exceptionally in the immunocompetent.

When an immunocompetent person receives a blood transfusion, the donor T lymphocytes are only detectable in the recipient's bloodstream for a few days. They are then removed by the recipient's immune cells. In patients with weakened or immature immune systems or in HLA-homozygous donors and HLA-heterozygous recipients, the allogeneic donor T lymphocytes are not removed from the recipient's bloodstream; they are activated and multiply instead. Specific cytokines are secreted in multiplication and differentiation of T lymphocytes, interferon γ (IFN γ) and interleukin 2 (IL-2) to the greatest extent. This triggers the activation of natural killer cells (NK), macrophages and other lymphocyte subpopulations. This then leads to apoptosis of the recipient's cells and injury of their organs and tissues, which is clinically expressed as TA-GvHD (1,2).

TA-GvHD is clinically indistinguishable from the acute form of GvHD following haematopoietic stem-cell transplantation (HSCT). The difference is only in the time it takes for symptoms to appear; TA-GvHD becomes clinically evident sooner, in only a few days. It is usually not

recognized and the clinical course is rapid and always leads to bone marrow aplasia (3).

As no effective treatment exists for TA-GvHD, prevention is key. Patients at risk of developing TA-GvHD need to be identified. They should only receive irradiated blood units and platelets, treated with UVA psoralen-based pathogen inactivation. The knowledge, awareness and approach of the attending physician and transfusion medicine specialist is crucial (4).

Blood units (erythrocytes, granulocytes, platelets that have not been pathogen inactivated, and fresh blood plasma that has not been frozen) are always irradiated prior to transfusion. For platelets, the equivalent to irradiation is UVA psoralen-based pathogen inactivation.

Fresh frozen plasma, cryoprecipitate, blood-derived medicines, such as albumins, immunoglobulins, blood clotting factors, and erythrocytes after thawing and washing do not need to be irradiated since their T lymphocyte content is negligible (4,5).

2 History

In 1955, Shimoda first described cases of so-called postoperative erythroderma (POED) in 12 patients who received fresh blood from their relatives (1,2). All of them became ill with fever and rash 6–13 days following the transfusion and later

died. At first, the cause was presumed to be an allergic drug reaction. Only later was it recognized that these were the first described cases of TA-GvHD. The first case of TA-GvHD in an immunocompetent patient was described in Japan in 1984. More than 340 cases have been described in the literature so far. The disease is often not recognized, so the number of published TA-GvHD cases in the literature is certainly lower than the actual number (2).

3 Patient factors important for the development of TA-GvHD

- **A weakened or immature immune system of the blood unit recipient**

Patients at highest risk for the development of TA-GvHD are those with congenital or acquired immunodeficiency. Because of their weakened immune systems, these patients do not mount an appropriate immune response to donor lymphocytes, which survive in the recipient's body and multiply in the bone marrow. They cause apoptosis of bone marrow cells and injure the recipient's tissues.

- **The recipient is immunocompetent, but there is a partial HLA compatibility between the donor and recipient, which leads to the recipient's immune system not recognizing the donor T lymphocytes as foreign, so they are not removed from the bloodstream.**

Partial HLA compatibility between the HLA-homozygous recipient and an HLA-heterozygous volunteer blood donor is associated with the highest risk for the development of TA-GvHD in immunocompetent patients. The HLA compatibility "blinds" the recipient's otherwise immunocompetent cells to allow implantation of donor T lymphocytes, which then trigger TA-GvHD. The HLA immune tolerance of the recipient's immune system

is not welcome in such cases. The risk for patients with a specific HLA haplotype to receive blood from a donor, HLA-homozygous for this haplotype, in a heterogenous white population in the USA is 1/17,700–39,000. In Germany, the risk for the development of TA-GvHD is 1/6,900–48,500, and in Japan, the risk is significantly higher at 1/1,600–7,900. The differences can be explained by regions with reduced genetic variability (6). For this reason, Japan introduced the irradiation of all blood units in 2000, and since then, no cases of TA-GvHD have been reported there (7). In Slovenia, this is a realistic possibility especially for treatment with granulocyte products. Not uncommonly, the donors are relatives of the patient.

- **The number of viable T lymphocytes in a blood unit**

Although the smallest number of viable T lymphocytes in a blood unit necessary for the development of TA-GvHD is not known, the data from the literature show that at least 1×10^7 of T lymphocytes/kg of the patient are needed for TA-GvHD to develop after their multiplication, proliferation, and apoptosis of the recipient's tissues. Blood units that meet this "condition" are whole blood (not available anymore in Slovenia), concentrated erythrocytes ($1-2 \times 10^9$ per therapeutic dose, TD); whole blood-derived platelets (4×10^7 per TD); apheresis platelets (3×10^8 per TD); granulocyte concentrates ($5-10 \times 10^9$ per TD); nonfrozen liquid plasma, which has not been used in Slovenia for several years. Fewer than 1×10^7 /kg of the patient of lymphocytes are present in frozen deglycerized erythrocytes (5×10^7 per TD) and fresh frozen plasma (8×10^4 per TD). Cryoprecipitate, which is also not used in Slovenia anymore, does not contain T lymphocytes. (8). Transfusion centres are responsible for an adequately low content

of T lymphocytes in blood units, using modern preparation and processing methods to guarantee their quality.

- **The volume and age of the blood unit**

The lifespan and activity of lymphocytes depend on the age of the blood product. Lymphocytes are most viable in the first three days after blood collection, then their activity falls exponentially. Studies have shown that there are no active T lymphocytes in erythrocyte products after three weeks. Therefore, the transfusion of fresh blood (not available for treatment in Slovenia) is an additional risk factor for patients already at risk for TA-GvHD (9).

4 Patient groups at risk for the development of TA-GvHD

Paediatric patients: In the paediatric population, the most at-risk for TA-GvHD are neonates with a low birth weight and the prematurely born—the latter especially if they previously received intrauterine transfusions (IUT), children with congenital deficiencies of cell-mediated immunity (e.g. thymic hypoplasia – DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID)), and children with severe immunodeficiency due to chemotherapy or radiation for the treatment of oncological or autoimmune diseases. All of them should only be treated with irradiated blood units (8).

Patients with haematological diseases: Adults and children with Hodgkin's lymphoma; patients with non-Hodgkin's lymphoma and acute leukaemia who receive treatment with nucleoside analogues (clofarabine, cladribine, fludarabine, nelarabine); some believe that irradiated blood units should also be used in patients treated with bendamustine (5); patients treated with anti-lymphocyte globulin (aplastic anaemia, myelodysplastic

syndrome); patients with deficiency of cell-mediated immunity.

Haematopoietic stem-cell transplantation: After allogeneic or autologous HSCT, patients should only be treated with irradiated blood units, without exception. Irradiation begins at the start of conditioning for HSCT. To avoid TA-GvHD, patients require irradiated blood units for at least 6 months after allogeneic HSCT and 3 months after autologous HSCT or for as long as the number of lymphocytes is below $1 \times 10^9/L$, if the patient is receiving immunosuppressive drugs. In case of chronic GvHD, only irradiated blood units should be used. Should donors of bone marrow and hematopoietic stem cells from peripheral blood need a transfusion of allogeneic blood units seven days before or during the harvesting procedure, such blood units should also be irradiated. Solid organ transplant recipients do not need irradiated blood units unless they are treated with immunosuppressive drugs (5,10).

The drugs are listed in [Table 1](#).

Solid tumours: TA-GvHD is not always associated with the type of tumour but with the type and intensity (degree of immunosuppression) of chemotherapy, which causes immunosuppression and creates the conditions for the growth of donor T lymphocytes. Cases of TA-GvHD in patients with neuroblastoma, rhabdomyosarcoma, lung cancer, etc., are described in the literature (2).

Indications for irradiation of blood units are listed in [Table 2](#).

5 Clinical features of TA-GvHD

The clinical features are varied and only appear with a delay after receiving a blood unit. Establishing a diagnosis is, therefore, often difficult. The first symptoms and

Table 1: Generic and brand names of drugs, capable of causing the development of TA-GvHD.

Immunosuppressive drugs, capable of causing the development of TA-GvHD	
Generic name	Brand name in Slovenia
fludarabine, nelarabine	Fludara
cladribine (2-CDA)	Litak
deoxycoformycin	Pentostatin
alemtuzumab (anti-CD52)	Lemtrada, Campath
anti-thymocyte globulin (ATG)	Atgam
bendamustine	Bendamustine actavis, Levact, Lynetoril
clofaribine	Evoltra

signs appear 4–30 days after a blood unit transfusion, which makes it difficult to establish a diagnosis as the link between the transfusion and TA-GvHD is often missed. The clinical features are characteristic of acute or chronic GvHD, as is seen with treatment of allogeneic HSCT.

The latter, however, does not feature bone marrow aplasia on a bone marrow biopsy, as is characteristic of TA-GvHD. The skin, intestines and liver are primarily affected, but any organ system can also be involved. A skin rash is usually the first clinical sign, appearing in an erythematous

Table 2: Patients with indications for blood unit irradiation.

Paediatric patients	
• Intrauterine transfusions (IUT)	
• Exchange transfusions (ET)	
• Neonates with a low birth weight and the prematurely born	
• Children with congenital deficiencies of cell-mediated immunity (DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID). All are indications for lifelong blood unit irradiation	
Haematologic patients (children and adults)	
• Haematopoietic stem-cell transplantation (HSCT) (autologous for 3 months and allogeneic for 6 months after HSCT)	
• Acute myeloblastic leukaemia (AML)	When treated with purine analogues
• Acute and chronic myeloblastic leukaemia (ALL, CLL)	
• Non-Hodgkin lymphoma (NHL)	
• Hodgkin lymphoma	Lifelong
• Solid organ transplant recipients, when they are treated with alemtuzumab	
• Recipients of blood units from biological relatives	
• Recipients of blood units from HLA-compatible donors	
• Recipients of granulocyte concentrates	

or maculopapular form and usually progressing to generalised erythroderma or, in extreme cases, to toxic epidermal necrolysis. The most common intestinal signs and symptoms are anorexia, vomiting, elevated transaminases, hepatomegaly, abdominal pain and profuse diarrhoea (up to 7–8 L/day). Bone marrow involvement is manifested by pancytopenia in the peripheral blood, a consequence of bone marrow aplasia. Clinically, such patients may have a fever (febrile neutropenia) and are vulnerable to respiratory and urinary tract infections or they can experience spontaneous bleeding (11).

TA-GvHD mortality exceeds 90% due to a lack of effective treatment. Prevention is the only acceptable course. TA-GvHD is confirmed with histological examination of the affected organ or tissue or with confirmation of lymphocyte chimerism.

In neonates, TA-GvHD is overlooked more often than in adults as it appears later; the clinical features are often attributed to prematurity itself and comorbidities. Cutaneous erythema, usually the first clinical sign of the disease, is often attributed to incubator use or phototherapy with liver immaturity (12).

6 Diagnosis and treatment of TA-GvHD

The first and most important step in diagnosing TA-GvHD is to think of the disease in time. It can be easily missed as it can be attributed to general poor condition, viral, bacterial or fungal infections, autoimmune diseases or side effects of treatment. A good history, focused on possible immunodeficiency, is key when admitting patients for treatment planning.

If pancytopenia, skin rash or intestinal problems appear in the first month following a blood transfusion, TA-GvHD should always be thought of and a consultation

with attending transfusion medicine specialist should be sought. They will check whether the received blood units were irradiated or pathogen inactivated (2).

TA-GvHD is confirmed with flow cytometry, with which we can detect donor lymphocytes in the recipient's peripheral blood, or histologically with the proof of presence of donor HLA antigens or DNA.

Donor T lymphocyte detection techniques are HLA typing, variable numbers of tandem repeats (VNTR), karyotyping or analysis of microsatellite DNA loci. Donor DNA can be isolated from blood or cell infiltrations and confirmed with a polymerase chain reaction (PCR).

No effective treatment for TA-GvHD is known. Treatment with immunosuppressive drugs, including corticosteroids, is almost without effect. Trials of treatment with cyclosporine, anti-lymphocyte globulin, methotrexate, azathioprine, serine protease inhibitors, chloroquine and OKT3 have been described (13,14). Even treatment with combinations of drugs, for example cyclosporine and anti-CD3 monoclonal antibodies or anti-lymphocyte globulin and steroids, has not brought the desired results (15). Treatment with extracorporeal photopheresis (ECP) with the aim of triggering donor lymphocyte apoptosis and acting as an anti-inflammatory can be tried. Allogeneic HSCT is the only successful treatment method, but it is rarely considered as there is usually not enough time to find for a suitable donor. This could change, however, with the advent of haploidentical HSCT. A poor response to treatment and high mortality sadly remain characteristic of TA-GvHD.

7 Prevention of TA-GvHD

TA-GvHD is an incurable disease with a high mortality rate. Prevention is thus key. Methods of prevention are: blood unit

irradiation, UVA psoralen-based pathogen inactivation of platelets and reducing the number of T lymphocytes in a blood unit (4).

The most effective method for inactivating lymphocytes in a blood unit is with ionizing radiation. With irradiation, the DNA of nucleated cells is denatured, thus preventing them from dividing, which prevents the multiplication of all lymphocyte subpopulations. At the Blood Transfusion Centre of Slovenia (BTC), irradiation of blood units has been used since 2007 for all Slovenian patients. The Gammacell 1000 Elite irradiator is used for this purpose. The source of radiation is the Cs-137 isotope. The ordinary radiation dose for all blood products is 30 Gy. Since 2020, the new Radgil 2 irradiation has been used and is equally effective as the Gammacell 1000 Elite. Its advantage is greater safety for providers as X-rays are used as the source of radiation. There is no data in the literature on X-rays causing slight damage to blood cell membranes.

The British Council for Standards in Haematology (BCSH) recommends a radiation dose of 25–50 Gy (5). The American Association of Blood Banks (AABB) recommends a minimal radiation dose of 25 Gy with no part of the blood unit receiving less than 15 Gy, but no more than 50 Gy (16). The same recommendations are in use in Japan (7). With a radiation dose of 30 Gy, we are therefore following the published recommendations in Slovenia.

Another effective way to prevent the development of TA-GvHD is pathogen inactivation. A combination of psoralen (amotosalen) and UVA rays is used to prevent the replication of viruses, bacteria, parasites and also lymphocyte proliferation. Pathogen inactivation with Intercept® (amotosalen/UVA) is used by the BTC. Currently, the method is only suitable for whole blood-derived platelets

and apheresis platelets. Irradiation is not needed after platelets have been inactivated with psoralen.

The smallest number of T lymphocytes that are capable of causing TA-GvHD has not yet been established. The number of lymphocytes in blood units could be reduced with filtration or washing. These procedures are not effective enough, however, to prevent the development of TA-GvHD. This is confirmation that TA-GvHD can develop in immunocompetent patients after transfusion of filtered blood units (4).

8 Side effects of irradiation on blood unit quality

Irradiation of erythrocyte products damages the erythrocyte membrane by damaging the Na⁺/K⁺ pump, reducing erythrocyte viability. This leads to an increase in the extracellular concentration of K⁺ and an influx of Na⁺ into erythrocytes as a consequence of ATP depletion in erythrocytes. ATP is, of course, the “fuel” for the Na⁺/K⁺ pump. Conversely, the haemoglobin and lactate dehydrogenase (LDH) levels in the supernatant of the irradiated blood unit rise. The changes in the membrane and the impaired operation of the Na⁺/K⁺ pump affect the durability of the erythrocyte membrane, which can lead to haemolysis due to lower membrane compliance. After erythrocyte irradiation, the K⁺ concentration in a stored blood unit rises by 1–2 meQ/day. Caution is therefore recommended in patients with kidney failure, intrauterine transfusion (IUT) and exchange transfusion (ET). The time between irradiation and transfusion is limited to 24 hours in such cases (9). Irradiation of platelets does not affect their number, morphology or function. As most platelet products in Slovenia go through UVA psoralen-based pathogen

inactivation, they do not need additional irradiation. Following irradiation, the basic functions of granulocytes (chemotaxis, phagocytosis and generation of free radicals) are not altered, so their function is not impaired.

9 Conclusion

TA-GvHD is an extremely rare but life-threatening complication of blood transfusion with a dismal prognosis. Therefore, it is necessary to spread knowledge and raise awareness in the profession on how to prevent this complication. Awareness of the disease should reach all healthcare workers, physicians, transfusion medicine specialists and the patients

themselves. The patients at risk of developing TA-GvHD need to be identified and provided with safe, irradiated blood units. Patients need to be aware of their medication and whether they are immunodeficient. Only in this way can they warn their physician of the possible complication. Cooperation, dialogue between all involved in the patient's management, and flow of information between clinicians and transfusion medicine specialists are key. The responsibility of the transfusion medicine specialist lies in ensuring the irradiation of blood products is done in accordance with established standardized procedures and that the quality meets the maximum safety requirements for the recipient.

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