REVIEW

Transfusion–associated graft–versus–host disease

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Vox Sanguinis

Transfusion-associated graft-versus-host disease (TA-GvHD) is a rare complication of transfusion of cellular blood components producing a graft-versus-host clinical picture with concomitant bone marrow aplasia. The disease is fulminant and rapidly fatal in the majority of patients. TA-GvHD is caused by transfused blood-derived, alloreactive T lymphocytes that attack host tissue, including bone marrow with resultant bone marrow failure. Human leucocyte antigen similarity between the transfused lymphocytes and the host, often in conjunction with host immunosuppression, allows tolerance of the grafted lymphocytes to survive the host immunological response. Any blood component containing viable T lymphocytes can cause TA-GvHD, with fresher components more likely to have intact cells and, thus, able to cause disease. Treatment is generally not helpful, while prevention, usually via irradiation of blood components given to susceptible recipients, is the key to obviating TA-GvHD. Newer methods, such as pathogen inactivation, may play an important role in the future.

Key words: graft-versus-host, immunosuppression, irradiation, transfusion.

Introduction

Transfusion-associated graft-versus-host disease (TA-GvHD) is a rare complication of transfusion of lymphocytes containing blood components. TA-GvHD occurs when immunocompetent lymphocytes are transfused into a recipient who is unable to mount a host response to the cells due to human leucocyte antigen (HLA) one-way compatibility and/or immunosuppression. This allows engraftment of the transfused cells, which then proceed to reject the host due to immunologic differences.

Clinically, TA-GvHD presents like bone marrow transplant (BMT) or stem cell transplant-associated GvHD. BMT-related GvHD, occurring weeks to months after BMT, presents with an erythematous, maculopapular rash, fever, elevated liver enzymes, often with associated hepatomegaly and jaundice, plus gastrointestinal symptoms, including nausea, vomiting, and diarrhoea. TA-GvHD presents with similar symptoms, but, additionally, the onset of these symptoms occurs earlier along with findings due to marked bone marrow aplasia. Because of the bone marrow failure, the prognosis of TA-GvHD is dismal. Treatment for TA-GvHD is rarely helpful [1]; therefore, prevention is the key to reduce the likelihood of TA-GvHD.

History

Graft-versus-host was apparently first observed by Murphy in 1916. Murphy noted that nodules formed on chick embryos when inoculated with cells from adult animals [2]. Later, Simonsen was able to postulate that the nodules in the embryos were an immunological reaction to the host tissue due to the foreign graft [3]. Simonsen [3] and Billingham [4] independently demonstrated that the reaction also occurs in mice. It was later determined that lymphocytes were the cells responsible for the reaction [5]. After injection of foreign cells into the host, the majority of animals died of what most closely resembles acute graft-versus-host disease, while a minority developed a syndrome termed 'runt disease' [6], akin to chronic GvHD.

Simonsen also defined the conditions that needed to exist for GvHD to occur: (i) grafted cells must be immunologically

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competent, (ii) the host must differ antigenically from the graft in order to be seen as foreign, and (iii) the host must be unable to mount a response against the graft [3]. He is also credited with terming the condition graft-versus-host disease.

Shortly after the first BMTs were performed for rescue from intensive chemotherapy for acute leukaemia patients, there were reports of a 'secondary-like' disease with symptoms similar to those findings seen in 'runt disease' occurring in treated patients [7]. Early BMTs were performed without knowledge of histocompatibility and thus fulfilled the criteria for GvHD described by Simonsen. GvHD was first reported and attributed to transfusion of blood after susceptible, immunodeficient infants [8] and fetuses [9] were transfused with blood containing viable lymphocytes. These patients with the first reported cases of TA-GvHD all died. Prior to these reports, Shimoda [10] reported 12 Japanese patients who developed postoperative erythroderma, of which half died between 6 and 13 days after surgery. The transfusion history was not reported, but it was considered routine at the time to transfuse with fresh blood pre- and postoperatively [11]. It is postulated that at least some of these patients developed TA-GvHD [12].

Pathogenesis

Graft-versus-host is caused by donor T lymphocytes mounting a response to recipient tissues. In TA-GvHD, donor T lymphocytes are derived from blood components containing viable lymphocytes. Typically, in immunocompetent hosts, viable T lymphocytes are destroyed by the recipient's immune system. In susceptible patients, whether immunocompetent or with congenital or acquired cellular immune deficiency, transfused T cells are not destroyed; they proliferate and can induce an immune response 'rejecting' the host tissues. Allogeneic transfused T lymphocytes escape detection under certain host circumstances, including cellular immunodeficiency associated with congenital cellular immune defects, acquired cellular immune defects (either through disease or therapy), or through the host not recognizing the transfused lymphocytes as foreign.

After recognition of the host tissue as foreign, cytokines, released from transfused T lymphocytes, drive the inflammatory response. Inflammatory cytokines activate inflammatory cells – NK cells, macrophages, and other T cells – that result in destruction of target host tissues, seen clinically as GvHD. In BMT-related GvHD, the balance between Th1 and Th2 T lymphocytes affects the extent of GvHD and engraftment [13]. Immunomodulating medications used in BMT patients (e.g. rapamycin) alter the Th1/Th2 ratio in addition to inhibiting inflammatory cytokines [14] as one of their mechanisms of action. The role of T lymphocyte subtypes and cytokines has not been well-studied in TA-GvHD.

T lymphocytes and other immune cells recognize other cells as self or non-self by identification of the proteins derived from the major histocompatibility complex (MHC) of genes. Of the MHC genes, the most widely recognized group of genes and proteins are in the human leucocyte antigen group. HLA proteins are cell membrane proteins that are used by the immune system to recognize self antigens from foreign cells when bound to T cell antigens. It is the lack of recognition as different that can lead to tolerance of foreign cells – and potentially GvHD. Populations with less HLA diversity, such as Japanese, have a higher incidence of TA-GvHD due to the higher probability of shared HLAs in transfused lymphocytes. In fact, it has been estimated that the incidence of TA-GvHD in the Japanese population is potentially 10–20 times higher than in the North American Caucasian population [15]. TA-GvHD occurs more frequently in Japanese immunocompetent patients and is likely due to receiving HLA homozygous haplotype blood components from unrelated donors [15] (as detailed later).

Transfused lymphocytes can occasionally remain viable, persist in the host, and not cause apparent disease in a condition termed microchimerism [16]. The reason why microchimerism occurs and does not cause overt disease is not completely understood, but, like most cases of TA-GvHD, is believed to involve cellular immune defects [16].

Clinical features

Graft-versus-host following stem cell transplants (e.g. bone marrow or peripheral blood progenitor cells) primarily affects the skin, the gastrointestinal tract and the liver. A febrile illness and skin manifestations usually are the initial presenting signs of GvHD. Skin lesions can range from erythematous macules to haemorrhagic bullae. Erythematous lesions can coalesce to encompass large areas of skin. Skin lesions can initially mimic viral exanthems and drug reactions. Gastrointestinal manifestations include diarrhoea, which can be profound. Hepatic dysfunction associated with GvHD is usually assessed by laboratory tests showing an intrahepatic cholestatic picture. Elevated alkaline phosphatase, transaminases and direct bilirubin values will often be noted, along with clinical jaundice.

As the bone marrow and immune system cells are of donor origin in bone marrow or stem cell transplant-related GvHD, the bone marrow is not affected. However, with TA-GvHD, the bone marrow is of recipient origin. With TA-GvHD, the marrow is uniformly affected and is the source of greatest morbidity and mortality. Bone marrow failure with pancytopenia, especially neutropenia, progressively develops with death often occurring due to infection and/or bleeding complications. Skin, gastrointestinal, and liver signs and symptoms similar to BMT-related GvHD also occur in patients with TA-GvHD.

Bone marrow transplant-related GvHD is divided into acute and chronic forms. The acute form generally occurs 10–35 days after transplant. The chronic form generally occurs after 35 days, but can occur months after transplant with or without antecedent acute GvHD. Occasionally, chronic GvHD can occur earlier than 35 days. GvHD occurs fairly commonly in BMT patients with 30–70% of recipients developing some degree of the acute form, the chronic form, or both [17]. The mortality from GvHD is between 5 and 10% of BMT recipients even with therapy.

Although much less common, TA-GvHD is a more fulminant and lethal condition. Signs and symptoms of TA-GvHD usually begin 2–30 days after transfusion. TA-GvHD follows 0·1–1·0% of transfusions in susceptible recipients [17]. As bone marrow failure is almost uniform in patients with TA-GvHD, the mortality rate of TA-GvHD is 87–100%.

Laboratory/pathological findings/diagnosis

Transfusion-associated graft-versus-host disease is a clinical diagnosis and should be suspected following a transfusion in the presence of fever, rash, liver dysfunction and gastrointestinal symptoms. Confirmation of GvHD, whether due to BMT or transfusion, can be supported by biopsies from the skin (most commonly), liver or bowel. The histopathological skin findings supportive of a diagnosis of GvHD are epidermal mononuclear infiltrates, basal membrane degeneration, and bullae formation in the absence of eosinophils [18]. The presence of eosinophils would be more supportive of a drug reaction, which is often in the differential diagnosis of GvHD [19]. Ulceration can be present in advanced cases of GvHD. In the liver, a portal triad lymphocytic infiltrate is seen without evidence of acute inflammatory cells [20]. Again, these histopathological findings are not specific for GvHD and analysed in the context of clinical findings. Similarly, gastrointestinal pathology findings include lymphocytic infiltrates with apoptotic epithelial cells [20]. However, for TA-GvHD, if a bone marrow aspirate or biopsy is obtained, marrow failure is confirmed by the presence of aplastic anaemia or a markedly hypocellular marrow with a lymphohistiocytic infiltrate. Haemophagocytosis has also been seen [21].

As the pathophysiology of TA-GvHD involves similarities and differences in HLAs, the determination of genetic chimerism, demonstrating donor HLAs, which can be readily determined by polymerase chain reaction in peripheral blood, supports the diagnosis of TA-GvHD [16,22,23]. HLA-typing of the buccal mucosa can be used to determine the HLA type of the host if not already known. In patients with suspected TA-GvHD, chimerism can be detected in skin with determination of both graft and host HLA subtypes in the affected areas. Occasionally, engrafted lymphocytes from transfused blood can exist in tissues without causing disease [16], most frequently seen in trauma patients [24]. This

'microchimerism' without disease has also been documented in pregnant and postpartum women and has been implicated in autoimmune diseases [25,26]. As the goal of allogeneic bone marrow or peripheral blood stem cell transplant is bone marrow engraftment, chimerism is the expected outcome of the treatment.

Although not measured diagnostically, inflammatory cytokines are involved in active GvHD due to the T cell-mediated cytokine storm [27]. Most notably, interleukin 1 (IL-1), IL-2, and tumour necrosis factor α (TNF-α), via Th1 and Th2 T lymphocytes, are thought to play a role in GvHD [27]. This is important to keep in mind in oncology patients on chemotherapy as these cytokines in particular are being used as targets for therapy in GvHD (daclizumab and basiliximab for IL-2 and infliximab and etanercept for TNF-α) [28]. As TA-GvHD is fulminant, little study of cytokines has been possible.

Blood components associated with TA-GvHD

Any non-frozen blood component containing viable lymphocytes can potentially cause TA-GvHD, even fresh plasma. Frozen components, although shown to contain some viable lymphocytes after thawing, have not been definitively proven to have caused TA-GvHD [29]. It has been estimated that TA-GvHD can occur with as few as 8×10^4 lymphocytes transfused; however, despite the presence of greater than 1×10^7 lymphocytes in previously frozen red blood cells (RBCs), TA-GvHD has not been documented with use of this component [29].

Fresh blood (< 3 days) has been shown to have caused TA-GvHD more commonly than blood that has been stored for longer time (> 7 days) [30], presumably due to decreased viability of lymphocytes on refrigerator storage. Granulocyte transfusions (which contain many lymphocytes) given fresh to immunocompromised patients have an increased propensity for causing TA-GvHD. No documented cases of TA-GvHD have been attributed to fresh-frozen plasma (FFP). Even though FFP may contain viable lymphocytes post-thaw, in general, it is not considered to be a component likely to cause TA-GvHD. Thus, there is no consensus on whether FFP should be irradiated prior to infusion into susceptible recipients. Any blood component from relatives is considered to be at higher risk for causing TA-GvHD due to shared HLAs between donor and recipient. This risk is accentuated in populations with less HLA diversity, such as Japanese.

Patients at risk for TA-GvHD

As GvHD is an interaction between graft and host, both predisposing graft (transfused blood) and host factors are involved in TA-GvHD. The goal is to avoid TA-GvHD by reducing the likelihood of the blood component causing the

disease, generally through irradiation. Concerning host factors, it is of utmost importance to identify patients who are at higher risk of developing TA-GvHD. When transfusion is indicated, these patients require the use of components in which the passenger lymphocytes have been inactivated by some process – usually irradiation; however, pathogen inactivation processes can accomplish this also.

The patients most vulnerable to TA-GvHD are those with congenital or require cellular immunodeficiencies that leave the patient unable to recognize and destroy foreign cells. Patients with identified congenital cellular immunodeficiency defects, such as severe combined immunodeficiency disorder and DiGeorge syndrome, should always be given irradiated blood components when transfusion is needed. It is generally accepted that premature infants are in an immunocompromised state and should receive irradiated blood components, even up to 7 months of age. Similarly, intrauterine transfusions also require irradiated components. It has been suggested that all newborns, who have not had an opportunity to demonstrate immune competence, should receive irradiated components [31].

Acquired cellular immunodeficiency, whether from a disease state or from therapy related to treatment of a disease, is an indication for use of irradiated blood components. It is universally accepted that all bone marrow or stem cell transplant patients should receive irradiated blood components. Both allogeneic and autologous BMT recipients should receive irradiated components due to the immunosuppression of the conditioning chemotherapy. Patients diagnosed with Hodgkin's lymphoma, non-Hodgkin's lymphoma and acute leukaemias are often considered immunodeficient and, therefore, given irradiated blood components, regardless of type of chemotherapy or radiation therapy given. Additionally, some patients with solid tumours treated with very aggressive multiagent chemotherapy regimens are often severely immunosuppressed and may be given irradiated blood components. Concerning specific chemotherapeutic agents, fludarabine is worth noting. Fludarabine is a synthetic purine antimetabolite used to treat lymphoid malignancies. It has been shown to cause lymphocytopenia with sustained reduction of CD4+ T lymphocytes [32]. Fludarabine treatment has been associated with susceptibility to TA-GvHD [33–37]. Similarly, a related nucleoside analogue chemotherapeutic agent, cladribine (2-CDA), has also been associated with severe lymphocytopenia and TA-GvHD [38]. The immunosuppressive effect of these two drugs has been noted for extended periods long after cessation of treatment [39,40]. It is therefore recommended that prior treatment with fludarabine and 2-CDA, whether for a malignant or non-malignant disease, should be considered an indication for irradiation of blood components, even if the treatment was in the distant past. Interestingly, patients with human immunodeficiency virus (HIV) infection and even acquired immune deficiency syndrome (AIDS) are immunosuppressed, but have not been shown to be at risk of TA-GvHD. Therefore, patients with HIV infection/AIDS are not routinely given irradiated blood components. Similarly, microchimerism is uncommon after transfusion in HIV+ patients. It has been postulated that TA-GvHD and microchimerism do not occur in HIV+ patients because, despite tolerance of donor leucocytes, donor leucocytes are unable to proliferate in these patients [41].

Shared HLA is another major factor in susceptibility to TA-GvHD. The chances of a transfusion recipient sharing an HLA haplotype with an unrelated blood donor are low and depend on the heterogeneity of the population. It has been estimated that the likelihood of receiving HLA-compatible (homozygous HLA haplotype to a heterozygous individual sharing one of the same haplotypes) blood during an unrelated transfusion is 1 in 874 in Japan, and much less – approximately nine times less likely – in Caucasian populations [30,42]. This has been demonstrated in the literature with most of the case reports of TA-GvHD in immunocompetent individuals occurring in Japan. Additionally, in areas where irradiation is not readily available and relatives are used as blood donors, TA-GvHD occurs, but is often not diagnosed [43].

Individuals receiving HLA-matched blood components are at risk for TA-GvHD and should always receive irradiated blood components. Similarly, as relatives share HLA haplotypes, directed donations from relatives should always be irradiated before being transfused.

Recipients of solid organ transplants have, on occasion, been reported with TA-GvHD [44,45]; however, most solid organ transplant recipients are not believed to be at higher risk of TA-GvHD. Most cases of GvHD in solid organ transplant recipients are believed to have developed the condition secondary to 'passenger' lymphocytes from the transplanted organ and not from transfused blood [46].

Ultimately, it is the responsibility of transfusion services, in collaboration with clinicians, to develop procedures for identifying individuals at risk of TA-GvHD and to ensure that irradiated components are given to them. Some US hospitals, such as the Clinical Center at the National Institutes of Health, MD Anderson in Houston, and Children's Hospital of Philadelphia, give irradiated blood components to all their patients (whether considered at risk for TA-GvHD or not). As their populations differ, the recommendations for blood irradiation differ somewhat between Japan, the USA, and the UK (Table 1).

Treatment and prevention

Transfusion-associated GvHD has a nearly 100% mortality rate. As the clinical signs and symptoms are non-specific and can mimic viral and drug reactions, diagnosis is often missed or delayed. Even with prompt diagnosis, the prognosis is poor [43]. Immunosuppression, via medications used to

Table 1 Comparison of recommendations for irradiation of blood components for the USA [54,73], UK [11,56], and Japan [55]

USA	UK	Japan
Irradiation of blood components required		
1. Blood component from relative.	1. Blood component from relative.	1. Blood component from relative.
2. HLA-compatible blood components.	2. HLA-compatible blood components.	2. HLA-compatible blood components.
3. Intrauterine transfusions.	3. Intrauterine transfusions.	3. Intrauterine and low birth weight neonate transfusions.
4. Neonatal exchange transfusions.	4. Neonatal exchange transfusions.	4. Neonatal exchange transfusions.
5. Congenital T cell immunodeficiency defects.	5. All granulocyte products.	5. Congenital T cell immunodeficiency defects.
6. Allogeneic BMT or PBSC transplant patients.	6. Congenital T cell immunodeficiency defects.	6. Allogeneic BMT or PBSC transplant patients.
7. Autologous BMT or PBSC transplant patients.	7. Allogeneic BMT or PBSC transplant patients.	7. Autologous BMT or PBSC transplant patients.
8. Patients with Hodgkin's disease.	8. Autologous BMT or PBSC transplant patients – at least 3 months post-transplant.	8. Any RBCs ≤ 3 days old.
9. Patients treated with fludarabine or related purine analogue.	9. Patients with Hodgkin's disease.	9. Frozen/thawed RBCs and fresh plasma when given to patients at risk.
	10. Patients treated with fludarabine or related purine analogue.	10. Cardiovascular surgery patients.
		11. Oncology surgery patients.
		12. Immunocompromised recipients of organ transplantation.
		13. Patients ≥ 65 years old.
		14. Massive blood loss or severe trauma.
		15. Consider irradiated blood products for patients with lymphomas, leukaemias, other haematopoietic malignancies, and solid organ tumours treated with high-dose chemotherapy or radiation.
Irradiation of blood components not recommended		
1. Fresh-frozen plasma.	1. Fresh-frozen plasma.	1. Fresh-frozen plasma.
2. Frozen/thawed RBCs.	2. Frozen/thawed RBCs.	
3. Cardiovascular surgery patients.	3. Cardiovascular surgery patients.	
4. Patients with solid tumours.	4. Patients with solid tumours.	
5. Patients with solid organ transplants.	5. Patients with solid organ transplants.	

HLA, human leucocyte antigen; BMT, bone marrow transplant; PBSC, peripheral blood stem cell; RBC, red blood cells.

treat BMT-related GvHD, has not been effective in the treatment of TA-GvHD. Corticosteroids, antithymocyte globulin, methotrexate, cyclosporin, azathioprine, serine protease inhibitors, chloroquine and OKT3 have all been used with poor results [1,47,48]. Only a few survivors of TA-GvHD have been documented [1,49,50]; in one survivor, another peripheral stem transplant was performed [1]. Photopheresis, also a well-documented treatment option for BMT-related GvHD, has been proposed [51], but never been reportedly used (at least successfully) for the treatment of TA-GvHD.

As treatment is almost always unsuccessful, the main thrust for decreasing the risk of TA-GvHD is prevention. Irradiation of cellular blood components has been the mainstay in prevention of this disease. In fact, up to this point, it is the only process shown to consistently and reliably prevent TA-GvHD in humans. Therefore, patients at risk need to be identified and must be given irradiated blood components. The dose of radiation recommended varies, but generally ranges from 15 to 50 Gy. Doses of ionizing radiation in this range inhibit lymphocytes from replication while maintaining other cellular functions [52,53]. Irradiation is usually delivered via devices with a caesium-137 or cobalt-60 source, but machines intended to deliver γ-irradiation as therapy have been used in the past. AABB recommends a dose of 25 Gy to the central portion of the blood component with no portion of the bag receiving less than 15 Gy [54]. The Japanese Society of Blood Transfusion's guidelines recommend a similar dose of radiation for the prevention of TA-GvHD [55]. Other bodies, such as the Council of Europe, have recommended delivering somewhat higher doses of radiation, but not greater than 50 Gy [56].

Although the most common method of achieving irradiation to blood products has been γ-irradiation, X-ray irradiation is a reasonable alternative to γ-irradiation with some notable advantages when compared to γ-irradiation [57]. X-ray machines are less expensive and do not have a radioactive

source, resulting in less regulatory requirements. Like γ-irradiation, X-ray radiation has been shown to inhibit lymphocyte function with similar effects on RBC permeability as measured by extracellular potassium and haemoglobin leakage [57]. A recent report noted that γ-irradiated RBCs showed decreased deformability that occurred soon after irradiation treatment; no increased RBC aggregation was noted after γ-irradiation treatment, however [58]. Due to the leakage of potassium from RBCs after irradiation, many institutions wash irradiated RBCs prior to transfusion to infants in order to reduce the level of potassium in the components. Washing RBCs after irradiation results in a lower potassium concentration when compared to washing RBCs prior to irradiation [59]. The effect of reduced potassium in washed irradiated RBCs will persist for at least 2–3 h after washing [59]. It is therefore recommended that irradiated RBCs that are subsequently washed should be transfused within 3–4 h to ensure that the extracellular potassium levels remain below 5 mEq/L (potassium generally < 2 mEq in RBCs at time of washing).

Universal leucoreduction (UL) has been implemented in many blood centres around the world and some countries (e.g. in Europe) primarily for its documented benefit in reduction of leucocyte-associated viral transfusion-transmitted infectious diseases [60], for its reduction of alloimmunization [61], and for its reduction of non-haemolytic transfusion reactions [62,63]. UL has also been shown to lower the incidence of TA-GvHD in recipients, as reported in the Serious Hazards of Transfusion (SHOT) study [64]. Thirteen cases of TA-GvHD were reported in the UK between 1996 and 2001, three of which were cardiac surgery patients (one of which received fresh blood). No reports of TA-GvHD in immunocompetent patients have been reported to SHOT since 2001 [64]. As TA-GvHD is a relatively rare disease in the era or irradiation, documenting an overall reduction in incidence based on UL is difficult without a large study based on a large database.

Pathogen-inactivation (PI) technologies, originally designed to eliminate the risk of micro-organisms in blood components via nucleic acid inactivation, have been shown to be a promising advancement in the reduction of TA-GvHD. PI systems involve treatment of the blood component with ultraviolet light after infusion of a photoactivating chemical, such as riboflavin, or a psoralen-based compound [65–68]. Two substances that also target nucleic acids but do not require photoactivation, PEN 110, an ethyleneimine derivative, and S-303, are also under investigation [69,70]. These substances have been shown *in vitro* [67–70] and *in vivo* (mouse model) [65,66] to reduce or eliminate lymphocyte proliferation, a key component in TA-GvHD.

Only a few studies have evaluated PI-treated components (platelets and plasma thus far) in phase III trials. Trials in Europe have found that the safety profile of the PI-treated platelets (as measured by transfusion reactions) so far

appears similar to that of non-PI treated platelets [71]. As TA-GvHD is rare, the effect of PI on the incidence of TA-GvHD cannot be assessed. However, some centres in Europe using PI-treated platelets no longer irradiate them to prevent TA-GvHD.

Unlike irradiation, PI also has the benefit of preventing antigen presentation and resultant cytokine production. Cytokine production, including IL-1, IL-2 and TNF-α, has been shown to be reduced after stimulation if pre-treated with riboflavin and photoactivation [72]. Other *in vitro* studies have demonstrated a reduction in alloantibodies after photoactivation [65–68]. Therefore, PI may result in reduction in cytokines involved in non-haemolytic transfusion reactions as well as the production of alloantibodies involved in transfusion reactions [65–68].

As TA-GvHD is rare and prevention maintains the incidence at a low level, it would be difficult to justify PI or UL solely for this disease. The reduction or elimination of TA-GvHD may be a beneficial by-product of implementing UL and/or PI. The only way to determine if separate measures (i.e. continual identification of susceptible blood recipients and giving irradiated components) are needed is to monitor and measure the incidence of TA-GvHD. If PI and/or UL can greatly reduce or eliminate TA-GvHD in the future, this reduction or elimination of a disease with no cure puts some justification into the use of these new technologies. As a benefit, it will help reduce the necessity of irradiation and the inherent potential of human error in the identification of susceptible patients.

In summary, TA-GvHD occurs as early as 2 days after transfusion in a susceptible recipient of cellular blood components beginning with fever, a rash, diarrhoea and liver dysfunction. Pancytopenia results with subsequent transfusion dependence and ultimately death within 3 weeks due to infection from the neutropenia. Treatment outcome is poor. Prevention remains the key to reduce the incidence of TA-GvHD. Provision of irradiated cellular blood components for susceptible recipients has been the mainstay for prevention of the disease. In the future, PI, with or without UL, may eliminate the need to identify at risk patients of TA-GvHD.

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