Prevention of transfusion-associated graft-versus-host disease with pathogen-reduced platelets with amotosalen and ultraviolet A light: a review

J. Cid
Department of Hemotherapy and Hemostasis, ICMHO, IDIBAPS, Hospital Clinic, University of Barcelona, Barcelona, Spain

Background and Objectives Transfusion-associated graft-versus-host disease (TA-GVHD) is a serious complication of blood component transfusion therapy, caused by donor T lymphocytes. γ-Irradiation or pathogen inactivation methods, capable of inactivating proliferating T cells in blood components, should be selected to prevent TA-GVHD. This review summarizes the published evidence to support the use of pathogen-reduced platelets with amotosalen (150 μM) and ultraviolet A light (UVA, 320–400 nm, 3 J/cm²) for preventing TA-GVHD.

Materials and Methods Available literature on the use of pathogen-reduced platelets to prevent TA-GVHD was reviewed.

Results Observational studies, animal models, in vitro studies and mechanistic studies of pathogen-reduced platelets with amotosalen and UVA light showed that inactivation of T cells are equal or even superior to γ-irradiation.

Conclusion Pathogen-reduced platelets with amotosalen and UVA light can be used as a measure to prevent TA-GVHD.

Key words: pathogen-reduced platelets, platelet transfusion, TA-GVHD.

Introduction
The clinical course of allogeneic hematopoietic progenitor cell (HPC) transplantation is complicated by graft-versus-host disease (GVHD). This condition results when donor T lymphocytes recognize the human leucocyte antigens (HLA) of the recipient as foreign, generating a characteristic immune response [1]. However, GVHD may also result as a complication of blood component transfusion because of the infusion of viable lymphocytes within cellular blood components [2].

Transfusion-associated graft-versus-host disease (TA-GVHD) is a lethal, although rare, complication of blood component transfusion. Three prerequisites are necessary to develop this complication of blood transfusion: (1) differences in histocompatibility between recipient and donor; (2) presence of immunocompetent T cells in the blood component; and (3) inability of the recipient to reject the immunocompetent cells [2].

The clinical picture of TA-GVHD typically appears 8–10 days after transfusion. As seen in GVHD after allogeneic HPC transplantation, a characteristic cutaneous eruption appears, in association with watery diarrhoea, liver function test abnormalities and fever. The development of marrow aplasia with pancytopenia distinguishes TA-GVHD from GVHD occurring after allogeneic HPC transplantation [3]. According to criteria devised by the National Health and Safety Network (NHSN), the diagnosis of TA-GVHD is based on a combination of characteristic clinical findings and a tissue biopsy consistent with GVHD, with imputability established via the demonstration of leucocyte chimerism, specifically donor T lymphocytes in recipient tissue [4].

Treatment of TA-GVHD is only rarely effective, and the prognosis of the disease is almost uniformly fatal [5]. Thus prevention of TA-GVHD in patients groups at risk is critical. These groups of patients are identified based on case reports and small case series published in the
literature. However, the first systematic review of all cases of TA-GVHD in the medical literature challenges the historic emphasis on host immune defects in the pathogenesis of TA-GVHD [4]. Authors found that most patients with TA-GVHD did not have an underlying diagnosis conferring immune compromise, with approximately half not having qualified for irradiated blood components according to current guidelines, based predominantly on patient diagnosis. The majority of cases in that review were attributed to cellular, non-leucoreduced, non-irradiated components that were stored for ≤10 days. According to data reviewed, authors concluded that the dominant mechanism of TA-GVHD in both immunocompetent and immunocompromised hosts is exposure to viable donor T lymphocytes not recognized as foreign by, but able to respond against, the recipient. Therefore, it seems obvious that methodologies capable of inactivating proliferating T cells in blood components should be selected to prevent TA-GVHD [6]. Today, two types of ionizing radiation, γ rays and X-rays, are approved for irradiation of blood components based on more than 40 years of clinical practice [7].

However, new methods of pathogen inactivation in blood components [8], such as amotosalen and ultraviolet A (UVA) light, are effective in inactivating a broad spectrum of viruses, bacteria and protozoa because amotosalen, on illumination with UVA light, forms covalent monoadducts and interstrand cross-links with RNA and DNA [9]. Because of the accepted mechanism of action, contaminating nucleated leucocytes in pathogen-reduced blood components are susceptible targets for inactivation. In this study, I will review the published evidence to support the use of pathogen-reduced platelets with amotosalen (150 μM) and low energy UVA light (320–400 nm, 3 J/cm²) as another methodology to prevent TA-GVHD.

Current recommendations

The importance of the extensive proliferation of transfused donor T cells for the development of TA-GVHD and the inability to reverse the consequences of the donor antirecipient T-cell responses once initiated caused investigators to focus on identifying treatments that could prevent donor T-cell proliferation without interfering with the function of the transfused RBCs or platelets. One first approach was using leucoreduction filters that have the ability to deplete three logs of white blood cells (WBC) [10]. However, isolated cases of individuals who develop TA-GVHD after transfused with leucoreduced blood components have been reported [11]. Thus, while there may be many benefits to the use of leucoreduction, it does not necessarily prevent the development of TA-GVHD.

Therefore, a second approach was exposing blood components to irradiation. Irradiation of cellular components with ionizing radiation results in the inactivation of T lymphocytes by damaging nuclear DNA either directly, or by generating ions and free radicals that have damaging biological actions. This prevents post-transfusion T-cell proliferation in response to host antigen-presenting cells, which, in turn, abrogates TA-GVHD [2]. An in vitro limiting dilution assay (LDA) was used to measure the effect of irradiation on T-cell proliferation. The results of these in vitro studies led to adoption of a dose of 25–30 Gy γ-irradiation as a standard for the inactivation of T lymphocytes in blood components [12]. According to the previous data, regulatory agencies as well as expert guidelines recommend treatment with ionizing irradiation for the prevention of TA-GVHD. Interestingly, the American Association of Blood Banks (AABB) recommends a dose of 25 Gy to the central area of the component with no portion receiving <15 Gy [13]; the European Committee (Partial Agreement) on Blood Transfusion recommends that no part of an irradiated blood component receives a dose <25 or >50 Gy [14]; and the Japanese Society of Blood Transfusion’s guidelines recommends a dose between 15 and 50 Gy [15]. The range of dose reported is acceptable given the physics of irradiation, but the minimum of 15 Gy should be reconsidered because some case reports of TA-GVHD after transfusion of blood components irradiated at 15 and 20 Gy have been described [16–18].

In contrast to previous differences in the dose of γ-irradiation, all guidelines state that platelets can be irradiated at any stage in their 5-day storage, and thereafter irradiated platelets can be stored up to their normal shelf life of 5 days after collection [13–15, 19].

LDA evidence to establish 25 Gy γ-irradiation limit

The paper published in 1994 by Pelszynski et al. was the basis to establish the minimum γ-irradiation dose of blood components [12]. Authors used an LDA that provided quantitative data on very low frequencies of proliferating T cells, in contrast to previous, less sensitivity methods, such as mixed lymphocyte culture (MLC). While MLC detects only a 1–2 log decrease (90%–99% decrease) in functional T cells, under standard conditions, the LDA assay can detect >5 log reduction in functional T cells. Authors collected whole blood into PL 146 or PL 2209 plastic containers (Baxter), they prepared red blood cells (RBC) by centrifugation, and ADSOL preservative solution (Fenwal) was added within 8 h of phlebotomy. One-day-old RBC units were individually irradiated in blood bags with a 137Cs source (Isomedix; Nordion, Kanata, Ontario, Canada) with doses of 5, 10, 15, 20, 25 and 30 Gy, © 2017 The Authors.

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sequentially, and compared with unirradiated samples. According to results reported, no T-cell growth was detected in irradiated RBC units in PL 146 container at doses ≥25 Gy, and in irradiated RBC units in PL 2209 container at doses ≥20 Gy. This implies frequencies of less than one proliferating T cells in 10⁶, which corresponds to the LDA’s limits of detection. This represents at least a > 5 log reduction. Authors also performed a comparison of ¹³⁷Cs γ-irradiation with a linear accelerator (Varian, Palo Alto, CA, USA) that delivered a dose rate of 3.5 Gy per min at the internal midplane of the bag. At equivalent radiation dose rates, comparable T-cell inactivation was obtained, and no T-cell growth was observed with the two γ-irradiation sources at 25 Gy. Finally, the ability of γ-irradiation to inactivate T lymphocytes in 7- and 21-day-old stored RBC units at 1–6°C in both PL 146 and PL 2209 containers was studied. Viable T cells capable of proliferation were present in stored RBC units, although at a lower frequency and number than those in the 1-day-old RBC units. Data showed that T cells were susceptible to inactivation by γ-irradiation at both days 7 and 21, with no T-cell growth detectable after irradiation with 25 Gy.

In conclusion, based on the LDA assay, γ-irradiation at a dose of ≥25 Gy is capable of inactivating T-cell proliferation in 1-, 7- and 21-day-old RBC units stored in PL 146 and PL 2209 containers. That means that less than one proliferating T cells in 10⁶ is present in RBC units because this corresponds to the LDA’s limits of detection. Based on the combined data of these studies, authors recommended a dose of 25 Gy as a measure to inactivate T cells in RBC units. Since then, as stated before, a dose of 25–30 Gy γ-irradiation was adopted as a standard for the inactivation of T lymphocytes in blood components.

Types of evidence for efficacy of interventions against TA-GVHD

Evidence-based medicine (EBM) requires the integration of the best research evidence with physician’s clinical expertise and patient’s unique values and circumstances [20]. Best research evidence is the foundation of EBM, and the term best research evidence refers to clinically relevant research, often from the basic sciences of medicine, but specially from patient-centred clinical research into the accuracy and precision of diagnostic tests, the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative and preventive regimens [21]. In the present scenario, health professionals involved in the blood transfusion arena are following recommendations received from authorities. After reviewing the previous studies that became the basis to support the use of γ-irradiation to prevent TA-GVHD, it is clear that the level of evidence is low according to the most recent use of the GRADE system, which takes into account the methodological quality of supporting evidence [22]. High-quality randomized controlled trials using irradiation or pathogen inactivation methods to prevent TA-GVHD are not available, and these trials would not be ethical or feasible to perform because this complication of blood transfusion is rare, and the prognosis of the disease is almost uniformly fatal.

However, observational studies [23], animal models [24], in vitro studies [25] and mechanistic studies [25] are available for pathogen-reduced blood components with amotosalen and UVA light. All these studies will be reviewed in the following section and compared with similar studies performed with irradiated blood components.

Data on pathogen-reduced blood components with amotosalen and UVA light

Observational studies

Since 2002, the INTERCEPT™ Blood System for platelets (Cerus Corporation BV, Amersfoort, the Netherlands) has been approved for use in Europe through CE Mark registration. Blood centres in Belgium, Italy, Norway and Spain implemented routine production in 2003 [23]. As of September 2016, over 3.5 million pathogen-reduced platelets have been produced for transfusion to patients. European centres using INTERCEPT platelets have replaced the use of γ-irradiation to prevent TA-GVHD, and postmarketing haemovigilance programmes include a definition of TA-GVHD and are capable of detecting such rare cases. Therefore, according to reported data on haemovigilance systems, no cases of TA-GVHD have been reported after transfusing ≥2 000 000 INTERCEPT platelets to ≥300 000 patients (Table 1).

As stated before, based on more than 40 years of clinical practice, γ-irradiation has been shown to be effective in reducing the incidence of TA-GVHD. However, TA-GVHD cases after receiving irradiated blood components at 15 Gy [17, 18], 20 Gy [16] or even 25 Gy [4] have been reported.

Animal models

Grass et al. performed an in vivo study to establish the inactivation of T cells with amotosalen and UVA light [24]. In that study, authors used a well-characterized parent to F₁ murine transfusion model. Affected mice exhibit clinical signs and findings analogous to human TA-GVHD. In this model, parental A mice were used as donors and hybrid offspring B6AF₁ (C57BL/6 × A) mice as recipients. Strain A donor mice are homozygous at the
H-2 locus, and the recipient B6AF1 mice are heterozygous. Donor A cells recognize the B6 antigens on recipient cells as foreign and initiate acute TA-GVHD, while the recipient B6AF1 host cells recognize the donor cells as self and fail to reject them. Four experimental groups were analysed as follows: control group mice received syngeneic splenic leucocyte transfusions, GVHD group mice received untreated allogeneic splenic leucocytes, \( \gamma \)-irradiation group mice received 25 Gy-irradiated allogeneic splenic leucocytes and pathogen-reduced group mice received allogeneic splenic leucocytes treated with 150 \( \mu \)M amotosalen and illuminated with 2.1 J/cm\(^2\) of UVA light. One day before transfusion, and weekly after transfusion for 10 weeks, recipient animals were scored for clinical signs of TA-GVHD. While all animals in the GVHD group developed clinical lesions of TA-GVHD, the animals of the rest of groups remained healthy and did not develop detectable TA-GVHD (Fig. 1). This study demonstrated that amotosalen/UVA had the same effect on splenocytes as \( \gamma \)-irradiation, preventing TA-GVHD in this model.

In vitro studies

In 1998, Grass et al. performed an in vitro study to evaluate the efficacy of amotosalen for inactivation of contaminating leucocytes in platelet components [25]. Authors tested three different psoralens and used four biological and molecular assays to demonstrate the efficacy of psoralens inactivating leucocytes.

First, using the LDA assay, treatment with 150 \( \mu \)M of amotosalen and 1.0–3.0 J/cm\(^2\) UVA light inactivated >5.4 ± 0.3 log of T cells in single donor platelethphasis units. Authors also determined the minimum dose of amotosalen required to inactivate T cells after illumination with 1 J/cm\(^2\) of UVA light was 0.05 \( \mu \)M. This concentration of amotosalen is 3000-fold lower than the currently 150 \( \mu \)M and 3 J/cm\(^2\) UVA of amotosalen used to inactivate blood components (Fig. 2). In contrast, the safety margin for the 25 Gy \( \gamma \)-irradiation is limited because TA-GVHD cases after \( \gamma \)-irradiation with 20 Gy have been reported. That dose is only a 1.25-fold lower than the effective dose (Fig. 2).

Second, in another group of experiments, authors used random donor platelet concentrates with a final leucocyte content of 4.33 \( \times \) 10\(^6\)/ml to measure the cytokine IL-8 content during 5 days of storage as a typical cytokine produced by leucocytes that has been implicated in transfusion adverse events. Concentrations of IL-8 were found to increase to high levels in the control platelet concentrate. The level of IL-8 increased from day 0 to day 5 suggesting that active synthesis of IL-8 by viable leucocytes was occurring during storage. Similar results, although with partially reduced levels of IL-8 synthesis, were obtained for the platelet concentrate treated with
the clinical dose of \( \gamma \)-irradiation (25 Gy). In contrast, treatment with 150 \( \mu \)M of amotosalen and 1.9 J/cm\(^2\) of UVA light resulted in complete inhibition of IL-8 synthesis. During the 5 days of platelet storage, the IL-8 level did not rise above the day 0 baseline level. The observations are probably due to the fact that the treatment with amotosalen/UVA created adducts and cross-links and did not allow the transcription of new IL-8 molecules from mRNA post-treatment [9].

Third, authors also confirmed the leucocyte inactivation at the molecular level by measurement of amotosalen-DNA adduct formation. While no amotosalen-DNA adducts were detected in leucocytes of platelet samples either untreated or treated with either amotosalen or UVA alone, the extent of amotosalen photomodification of leucocyte genomic DNA correlated with the concentration of amotosalen. Using 1.9 J/cm\(^2\) of UVA light, 150 \( \mu \)M of amotosalen induced 12 \pm 3 adducts per 1000 bp (or one per 83). In comparison, irradiation (25 Gy) induces DNA strand breaks at a level of one per 37 000 bp [25, 26].

A recent in vitro study compared T-cell inactivation in human plasma with either \( \gamma \)-irradiation or amotosalen [27]. Authors used a highly sensitive LDA method that allowed the culture of 10\(^7\) cells in a single well and the detection of proliferating T cells with high sensitivity. The treatment of T cells with amotosalen and UVA light gave more robust T-cell inactivation (>6.2 log) than with 25 Gy \( \gamma \)-irradiation that was found to inactivate more than 4.2 log but <6.2 log.

**Combination of \( \gamma \)-irradiation and amotosalen**

As stated in the section of current recommendations, irradiated platelets can be stored up to their normal shelf life of 5 days after collection. This recommendation by international guidelines is based on earlier transfusion studies where irradiation of platelets did not influence post-transfusion platelet increments [28-30]. However, three more recent studies showed decreased transfusion efficacy of irradiated platelets [31-33].

In 2005, Slichter et al. published a re-analysis of the TRAP trial database to evaluate patient- and product-related characteristics that might influence post-transfusion platelet responses [31]. Authors showed that \( \gamma \)-irradiation of the platelets prior to transfusion decreased 1-h post-transfusion increments by 2.8 \( \times \) 10\(^{-3}\) [1] \( P < 0.001\) but had no effect on 18- to 24-h post-transfusion platelet increments or platelet transfusion interval. Authors also showed that \( \gamma \)-irradiation was associated with a significant increase in platelet refractory rates (hazard ratio 1.45; 95% CI: 1.01-2.07; \( P = 0.04\)).

In 2008, Julmy et al. published a study where \( \gamma \)-irradiation of platelets were associated with a significantly decrease in platelet transfusion efficacy measured either by 1-h per cent platelet recovery (PPR: −3.6%; 95% CI: −6.1 to −1.0; \( P = 0.007\)) or by 1-h corrected count increment (−1.5%; 95% CI: −2.6 to −0.3; \( P = 0.013\)) [32]. In 2014, the same group of authors reported a larger study, and they showed that \( \gamma \)-irradiation of platelets was associated with a decrease in transfusion efficacy when compared with non-irradiated platelets (mean PPR 32.7% vs. 39.3%; \( P = 0.014\)). However, this was due to irradiation of platelets in advance (\( \geq 24\) h) (mean PPR 27.7%; \( P < 0.001\)), while the efficacy of irradiated platelets at the day of transfusion was not significantly inferior than that of non-irradiated platelets (mean PPR 35.0%; \( P = 0.092\)) [33].

Interestingly, in a clinical study conducted in Switzerland [34] where haematologic patients were assigned to either receive \( \gamma \)-irradiated platelets (\( n = 76\)) or an equivalent dose of amotosalen/UVA-treated platelets (\( n = 44\)), it was found that there were no statistically significant differences between the groups for 1 h CCI (11.4 ± 4.9 vs. 11.0 ± 4.9) or 24 h CCI (3.3 ± 3.9 vs. 4.2 ± 5). This was

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**Fig. 2** Safety margin for developing TA-GVHD after receiving blood components \( \gamma \)-irradiated with 25 Gy or pathogen-reduced with 150 \( \mu \)M of amotosalen and 3.0 J/cm\(^2\) UVA light.
in contrast to the results in the SPRINT clinical trial [35] also conducted with patients from the same population, where the 1 h CCI between the Test arm \((n = 318)\), that combined amotosalen/UVA with \(\gamma\)-irradiation and the Control \((n = 327)\) that was only exposed to \(\gamma\)-irradiation, was different \((11.1\ \text{vs.}\ 16.0)\), despite the fact the control of bleeding with the transfusion of either the test or control products was equivalent.

Taking into account the previous observations of decreased transfusion efficacy following \(\gamma\)-irradiation of platelets as well as the loss of platelets during the process of pathogen inactivation with amotosalen and UVA light, I consider that their combined use is unnecessary and not recommended because both methods have the same reason for use, and they both may cause a reduction to platelet circulation post-treatment.

**Conclusions**

A randomized, double-blind, placebo-controlled trial to prevent TA-GVHD is not available neither for \(\gamma\)-irradiation, nor for pathogen-reduced blood components with amotosalen and UVA light. However, \(\gamma\)-irradiation of blood components is the current accepted measure to prevent TA-GVHD based on *in vitro* data and empirical experience. As I reviewed in this study, observational studies [23], animal models [24], *in vitro* studies [25, 27] and mechanistic studies [25], are available for pathogen-reduced blood components with amotosalen and UVA light, and all those studies showed that inactivation of T cells is equal or even superior to \(\gamma\)-irradiation.

No TA-GVHD cases have been reported in Europe in the period of 2002–2016 after the transfusion of 3.5 million units of pathogen-reduced platelets or plasma with amotosalen and UVA light [23]. A TA-GVHD mouse model showed inhibition of TA-GVHD with the use of pathogen-reduced platelets with amotosalen and UVA light [24]. LDA *in vitro* data showed inactivation of T cells to the limit of detection, even at amotosalen concentrations and UVA light doses that were 3000-fold below the commercial settings [25, 27]. Amotosalen plus UVA had 1:83 DNA bp adduct formation, which resulted in inhibition of protein production and nucleic acid function [25]. In comparison, \(\gamma\)-irradiation had 1:37 000 DNA bp adduct formation.

In conclusion, pathogen-reduced platelets with amotosalen and UVA light can be used as a measure to prevent TA-GVHD based on *in vitro* data and empirical experience, as \(\gamma\)-irradiation has been used until today. Obviously, without a randomized, double-blind, placebo-controlled trial, an absolute assessment of the prevention of TA-GVHD with pathogen-reduced platelets with amotosalen and UVA light may not be possible. However, routine use and haemovigilance follow-up both through national haemovigilance systems, with clinical studies or the quality systems in place, have not detected any cases of TA-GVHD associated with the transfusion of pathogen-reduced components with the UVA/amotosalen system.

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