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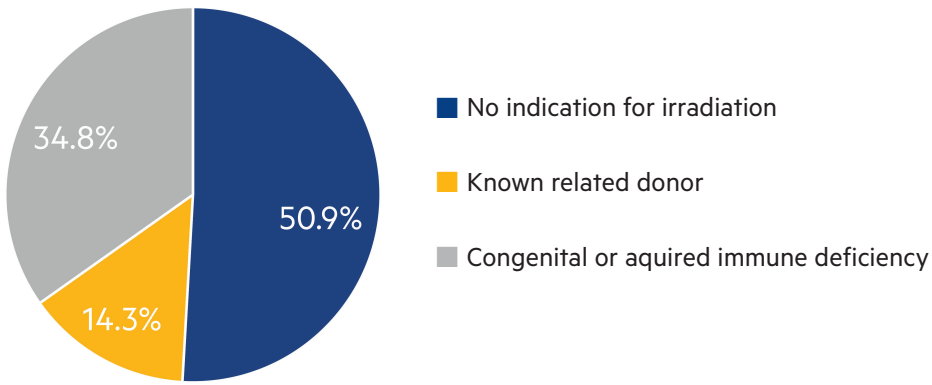
Methodologies for Reducing the Risk of TA-GVHD from Platelet Transfusions

What is Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD)?

TA-GVHD is a rare complication in which viable T-cells (lymphocytes) from the blood donor are transferred through blood transfusion to the blood recipient, engraft, and react against the recipient's cells. While the risk of TA-GVHD may be higher for immune-compromised patients, recent publications demonstrate that the majority of TA-GVHD cases occur in individuals who do not qualify as immune-compromised (Figure 1).[1-3]

Figure 1: More than half of TA-GVHD cases reported occurred in patients with no indication for irradiation[3]



TA-GVHD is a rare, but almost always fatal, transfusion adverse event. While leukoreduction decreases the number of leukocytes (including T-cells) remaining in a blood component, and the recipient's immune system usually reacts against the donor cells, in some instances, donor T-cells go unrecognized and can engraft. This can happen for two reasons:

1. Immunodeficiency: the recipient's immune system has been compromised, for example by chemotherapy or radiation, and lacks the ability to mount the response to remove the "non-self" transfused cells.
2. Partial HLA match between donor and recipient leads to an error in recognition of self-versus-non-self. Immune competency of the recipient is not relevant in these cases.

Symptoms of TA-GVHD typically develop 7-10 days after transfusion and include fever, rash, gastrointestinal symptoms, liver injury, and hypo-proliferative pancytopenia (anemia).[4] Unfortunately, nearly 90% of patients die within the first month after diagnosis.[3] To combat this potentially fatal transfusion event caused by donor T-cells, irradiation of blood components was introduced in the 1990's for immune-compromised patients. Pathogen reduction with the INTERCEPT® Blood System for platelets and plasma, is a U.S. Food and Drug Administration (FDA) approved alternative to irradiation.[5,6] Despite increased awareness and reports of TA-GVHD among immune-competent individuals (figure 1), criteria identifying high TA-GVHD-risk patients are mainly based on immune competency.[3]

Regulatory positions on TA-GVHD Prevention for Transfusion Recipients

Globally, criteria indicating a patient's need for irradiated blood products varies widely.[3,7-10] For example, in the UK, irradiation of platelets it not recommended for patients with specific types lymphomas,[10] in Australia, New Zealand and the Netherlands it depends on additional criteria[7,9] and in Canada and the US it is recommended.[11,12] Overall there is a lack of international consensus on blood product irradiation best practices.

Irradiation by a radioactive source was identified as an effective means to inactivate T-cells.[11] FDA does not explicitly require irradiation of blood products, or the use of irradiated blood products in specific patients. Rather, FDA limits its oversight to ensuring devices deliver predictable doses of ionizing irradiation to blood products, and that these devices are validated.[11] Published studies indicate that doses of 1500 to 2000 cGy reduce mitogen-responsive lymphocytes by 5 to 6 orders of magnitude, while similar effects have also been reported using 1500 to 2500 cGy.[11]

Society Positions on TA-GVHD Prevention for Transfusion Recipients

While the FDA does not regulate the transfusion of irradiated blood components, clinically focused organizations do provide guidance for hospital transfusion services. AABB sets the standards by which all US blood banks are accredited.[13] The Circular of Information (COI), published by the AABB and recognized by FDA, states that "Blood components that contain viable lymphocytes may be irradiated to prevent proliferation of T lymphocytes, which is the immediate cause of TA-GVHD." The COI, does not address which patient groups are at risk,[14] but the AABB standards do.[13]

AABB Standard 5.19.4[13] sets industry standards for prevention of TA-GVHD specifying that:

1. The blood bank or transfusion service shall have a policy regarding the prevention of transfusion-associated graft-vs-host disease.
2. Acceptable methods known to prevent transfusion-associated graft-vs-host disease include irradiation and pathogen reduction technology known to inactivate residual leukocytes that is cleared or approved by the FDA or Competent Authority.

5.19.4 also specifies that irradiated blood products are required for patients identified as being at risk for TA-GVHD, when the donor of the component is a blood relative, or when the donor is selected for HLA compatibility by typing or cross-matching.[13]

Evidence for the prevention of TA-GVHD

Randomized clinical trials have not been conducted to examine the effectiveness of interventions to prevent TA-GVHD because they would not be ethical. The evidence in support of irradiation is based on guidelines that were developed upon review of case studies and in-vitro assays.[15] These assays suggested that a 2,500cGy dose of radiation at the center of a platelet bag inhibited T-cell activity.[16-18] The irradiation guidelines issued by AABB continue to be based on these case studies. Similarly, there are no randomized trials looking specifically at the prevention of TA-GVHD for the INTERCEPT Blood System, only in vitro T-cell inactivation data.[5,6]

A systematic review published in 2015 examined the literature for case reports globally and found 17 cases of TA-GVHD reported between 1966-1979, 68 between 1980-1989, 197 between 1990-1999, and 66 between 2000- 2013. The majority of the cases occurred in Japan (n=146), the US (n=50) and the UK (n=36).[3] Five of these reported cases (1.4%) were in patients who had received irradiated products. Two of the cases occurred with products exposed to a gamma irradiation dose of 2,500 cGy, 1 with a dose of 1,500 cGy, 1 irradiated via X-Ray, and 1 with no irradiation details available. Over one-third (34.8%) of these TA-GVHD cases occurred in patients with a diagnosis for which irradiated products are indicated according to the AABB standards.

Known related-donor cases represented another 14.4% of cases, and the remaining 50.9% of cases lacked any recipient and donor risk factors outlined in current AABB standards for blood component irradiation. These data question the validity of the current criteria to receive irradiated units being dependent on immunocompromised status.[3]

Gamma Irradiation versus INTERCEPT® Blood System for Platelets

Mechanistic and *in vitro/ex vivo*: Ionizing gamma radiation induces strand breaks in DNA at a rate of approximately 1 break per 37,000 base pairs.[19] In contrast, published data show that the INTERCEPT® Blood System cross-links DNA once per 80-90 base pairs, interrupting DNA >400 times more often than gamma irradiation.[18] Using a limited dilution assay, INTERCEPT treatment exhibited a 4 log[10] reduction of viable T-cells.[5]

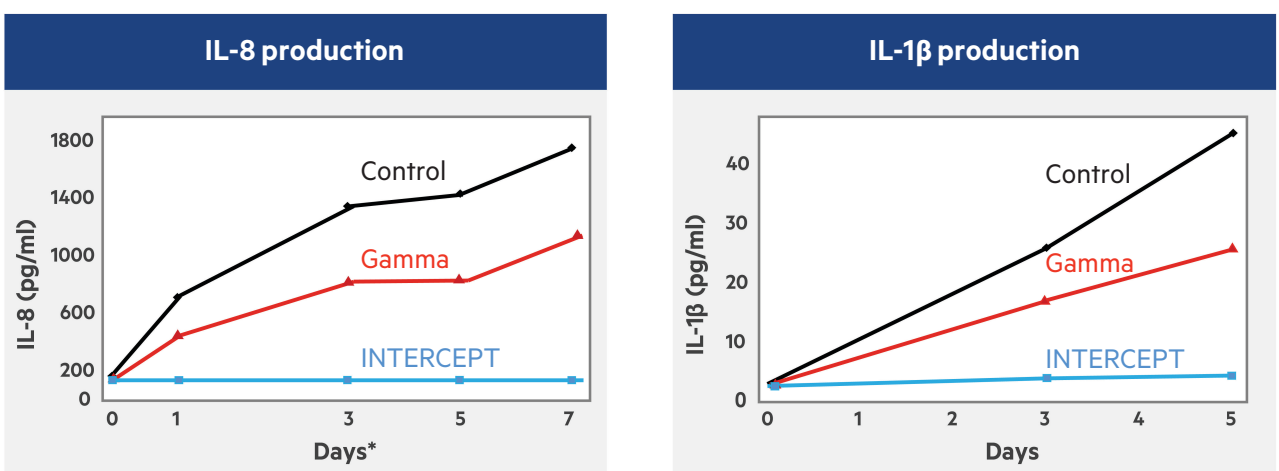
Figure 2: DNA strand breaks from gamma irradiation versus INTERCEPT treatment

Gamma irradiation 1:37,000 strand-break:base pair

Psoralen/UVA Light-Treated Platelets 1:83 amotosalen adduct formed:base pair[18,19]

Further, the efficacy of INTERCEPT treatment and gamma irradiation at inhibiting T-cell activity can be measured by the T-cell capacity to synthesize IL-1 and IL-8 in the platelet unit. While INTERCEPT-treated platelets express almost no IL-1 and IL-8 at the end of 5 days, gamma-irradiated platelets show only a ~50% reduction in cytokine concentrations in comparison to control (Figure 3).[20]

Figure 3: INTERCEPT treatment reduces cytokine production in platelet units over time[20]



Although infrequent, failure of gamma irradiation to prevent TA-GVHD has been reported with doses of 1,500 to 2,000 cGy.[21]

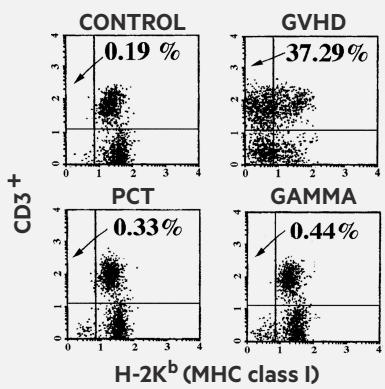
Animal Model

Although clinical trials assessing TA-GVHD prevention are not feasible in humans, murine studies are. Heterozygous- A/B mice infused with splenic leukocytes from one of their parents (A/A) were shown to develop TA-GVHD (Figures 4A and 4B). Both gamma irradiation, and photochemical treatment (PCT: S-59/UVA light treatment, the active components of INTERCEPT), prevented the clinical and laboratory findings of GVHD (positive control). Flow cytometry (Figure 4B) shows the effectiveness of PCT and gamma at minimizing the residual that can be seen in the GVHD mice (37.29%). While PCT showed less than gamma (0.33% and 0.44% respectively) this difference was not statistically significant.[22]

Figure 4A: Evaluation of gamma or INTERCEPT treatment on preventing TA-GVHD from A/A donor into AB recipient mice

Treatment Condition	Donor Type	Recipient Type	Result of Transfusion
Control	A/B	A/B	No adverse events
Positive Control	A/A	A/B	TA-GVHD
2,500c Gy Gamma	A/A	A/B	No adverse events
INTERCEPT	A/A	A/B	No adverse events

Figure 4B: Engraftment of donor T cells in spleens of recipient mice



National active hemovigilance (HV)

The INTERCEPT® Blood System received Conformité Européenne (CE) Mark approval to replace gamma irradiation for inactivation of donor T-cells in platelet components for the prevention of TA-GVHD 13 years ago. Hemovigilance (HV) data from nearly 1.6 million INTERCEPT treated platelet components transfused to US and EU patients between 2003-2019 have demonstrated no cases of TA-GVHD when gamma irradiation was replaced with INTERCEPT treatment (Table 1).

Table 1: Multi-center HV network

Study	INTERCEPT treated platelet doses	Patients	Outcome	Timing
HV1[22]	5,106	651	No Transfusion-Transmitted Bacterial Infections (TTBI)	2003 - 2005
HV2[22]	7,437	1,400		2005 - 2007
HV3[22]	6,632	2,016		2006 - 2010
HV5[22]	2,373	698	No Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD)	2013 - 2016
HV France[24,25]	947,434	~158,000		2006 - 2019
HV Switzerland[26,27]	318,364	~53,000		2011 - 2019
HV Belgium[28]	291,879	~48,000		2009 - 2016
Total	**1,579,225**	~264,000	No TTBIs No TA-GVHD	2003 - 2019

Conclusion

IINTERCEPT® Blood System is FDA approved as an alternative to gamma irradiation for the prevention of TA-GVHD by reducing contaminating T-cell activity.[5,6] AABB Standard 5.19.4.1 requires a method to prevent TA-GVHD, and includes pathogen reduction as an option.[13] FDA approval, and inclusion of the pathogen reduction (i.e. INTERCEPT® Blood System) in the AABB standards as a risk reduction strategy against TA-GVHD is supported by extensive in vitro and hemovigilance data.

For more information or additional questions please reach out to: hospitalsupport@cerus.com

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