

**INTERCEPT™ for Pathogen Inactivation in Platelet Concentrates  
Effectively Prevents Transfusion-Associated  
Graft-Versus-Host Disease (TA-GVHD)**

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# INTERCEPT for Pathogen Inactivation in Platelet Concentrates Effectively Prevents Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD)

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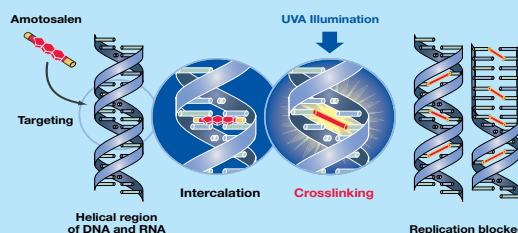


## Background

INTERCEPT™ technology allows pathogen inactivation (PI) in platelet concentrates (PCs) through the combined use of a psoralen (amotosalen, or S-59) and UVA (320-400 nm) light (Figure 1). The method has been shown to be highly effective in inactivating a broad spectrum of bacteria, viruses, and protozoa, and to be devoid of toxicity. INTERCEPT technique is effective in inhibiting both T-cell proliferation and cytokine synthesis. Furthermore, when compared to 2,500 cGy gamma irradiation, which is the standard treatment of cellular blood components for prophylaxis of TA-GVHD, INTERCEPT treatment has a significantly higher efficacy margin than gamma irradiation. High levels of viable T cells (>5 logs) were inactivated by both techniques (Table 1). However, the amotosalen concentration could be reduced more than 1,500-fold in INTERCEPT treatment without affecting the T-cell inactivation efficacy compared to a 2-3 log reduction of T-cell inactivation when the dose of gamma was reduced by 2-fold. INTERCEPT treatment induces a significantly higher degree of DNA modification compared to gamma irradiation (Table 1). INTERCEPT treatment completely inhibited cytokine synthesis of lymphocytes during storage of PCs while gamma irradiation had only a partial effect (Figure 2). INTERCEPT was introduced in routine clinical use at Mont-Godinne University Hospital in October 2003. At the same time gamma-irradiation of PCs was stopped. This policy was also followed in patients receiving hematopoietic stem cell transplants (HSCT).

**Figure 1: INTERCEPT Mechanism of Action**

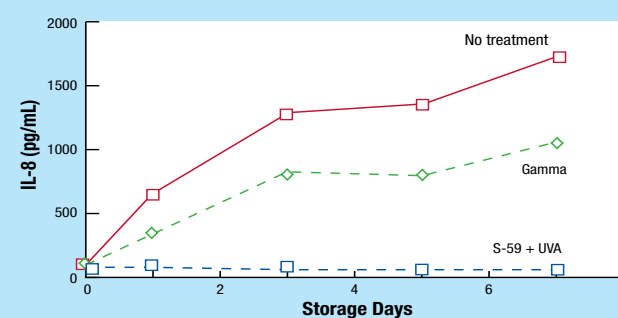
The INTERCEPT Blood System uses a combination of amotosalen HCl and long wavelength ultraviolet A (UVA) light. The amotosalen compound penetrates cellular and nuclear membranes and intercalates into the helical regions of DNA and RNA. Covalent crosslinks to the nucleic acid base pairs form upon exposure to UVA light, blocking DNA and RNA replication. This process inactivates leukocytes and pathogens, rendering them unable to cause disease, while retaining the function of plasma/platelets, which do not require nucleic acid replication for therapeutic efficacy.



**Figure 2: Inhibition of cytokine synthesis during platelet storage after INTERCEPT treatment compared to gamma-irradiation\***

Comparison of IL-8 generation during 7 days of storage of identical PC aliquots containing  $1.7 \times 10^6$  WBCs/mL. The PC treated with 2500-cGy gamma-radiation (---◇---) showed partial inhibition of IL-8 synthesis relative to the untreated (control) PC (---□---). The PC that was subjected to PCT (Photochemical Treatment) with 150 μM S-59 (---□---) showed complete elimination of IL-8 synthesis.

\*Hei et al. *Transfusion* 1999; 39:239-248



**Table 1: Inactivation of Leukocytes in Platelet Concentrates by INTERCEPT Compared to Gamma-irradiation\***

Assay	Measurement	INTERCEPT (S-59 + UVA)	Gamma Irradiation (2,500 cGy)
T-cell inactivation	Log reduction	>5.4 ± 0.3	>5.0
DNA modification	per 10,000 base pairs	120	0.27

\*Grass et al. *Blood* 1998;91:2180-2188

## Aims

To evaluate the incidence of TA-GVHD in patients undergoing hematopoietic stem cell transplants and supported by transfusions of INTERCEPT platelet concentrates.

## Methods

Gamma-irradiation was stopped for all PC's with routine implementation of INTERCEPT pathogen inactivation in our transfusion center in October 2003. Transfusion records of all HSCT patients were analyzed for PC transfusion post-graft, and patient files were reviewed for evidence of TA-GVHD according to standard criteria (Anderson KC, *N Eng J Med*, 1990; 323:315-21).

Platelet components were collected on the Amicus Cell Separator® (Fenwal Inc, Lake Zurich, IL)

with process leukoreduction. Platelets were suspended in InterSol with a ratio to plasma of approximately 65:35%. Platelet components containing  $2.5$  to  $7.0 \times 10^{11}$  platelets in 255-420 mL were processed using integrated INTERCEPT processing sets to inactivate pathogens and leukocytes. INTERCEPT platelet components were issued the day after collection and stored for up to 7 days.

## Results

Between November 2003 and December 2009, a total of 186 patients received HSCT (Table 2). One-hundred-fifty-one (151) patients had received autologous HSCT with myeloma (n=81, or 54%) and non-hodgkin's lymphoma (n=48, or 32%) being the most frequently diagnosed malignancies. Twenty (20) patients had received allogeneic HSCT with acute myelogenous leukemia (n=13, or 65%) being the most frequent malignancy. Fifteen (15) patients had received mini-allogeneic HSCT with a variety of hematological oncology disorders. After transplant, these patients received a total of 3,645 INTERCEPT PC transfusions (Table 3). The mean number of transfusions per patient was 19.6, and ranged from 0 - 158 transfusions. No patient developed TA-GVHD.

**Table 3: TA-GVHD Outcome of Hematopoietic Stem Cell Transplant (HSCT) Patients**

	Results
Number of HSCT patients	186
Number of Transfusions with INTERCEPT PC	3,654
Gamma-irradiation	0%
Mean transfusion per patient (range)	19.6 (0-158)
Incidence of TA-GVHD	0

**Table 2: Distribution by Diagnosis for Hematopoietic Stem Cell Transplant (HSCT) Patients Supported with INTERCEPT Platelet Components**

Patient diagnosis	Auto-HSCT	Allo-HSCT	Mini-allo-HSCT	Total (%)
Myeloma (MM)	81		1	82 (44.1%)
Non-Hodgkin's Lymphoma (NHL)	48		2	50 (26.9%)
Hodgkin's Disease (HK)	10			10 (5.4%)
Acute Myelogenous Leukemia (AML)	6	13	2	21 (11.3%)
Acute Lymphocytic Leukemia (ALL)	1	4		5 (2.7%)
Chronic Myelogenous Leukemia (CML)		1		1(0.5%)
Chronic Lymphocytic Leukemia (CLL)	3		1	4 (2.2%)
Acute Myelofibrosis (AMF)			3	3 (1.6%)
Myelodysplasia (MDS)			3	3 (1.6%)
Solid Tumor	1		2	3 (1.6%)
Amyloidosis	1			1 (0.5%)
Agnogenic aplasia (AA)		2		2 (1.1%)
Polycythemia Vera (PV)			1	1 (0.5%)
<b>Total</b>	<b>151</b>	<b>20</b>	<b>15</b>	<b>186</b>

## Conclusions

- INTERCEPT treatment alone, without gamma irradiation, provides an effective prophylaxis for TA-GVHD in patients undergoing hematopoietic stem cell transplant and supported by INTERCEPT platelet transfusion.
- The lack of TA-GVHD in HSCT patients supported by INTERCEPT PC transfusions was attributed by the effective inactivation of T-cells.
- As of today, more than 500,000 transfusions of INTERCEPT products have been administered into patients in routine clinical practice, of which more than 60,000 transfusions were documented in a hemovigilance program, no cases of TA-GVHD were reported.