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Thank you for your request for more information about the efficacy of pathogen-reduced platelets treated with the INTERCEPT® Blood System Pathogen Reduction System for platelets. The INTERCEPT® Blood System for platelets is intended for *ex vivo* preparation of pathogen-reduced platelet components in order to reduce the risk of transfusion-transmitted infection, including sepsis, and as an alternative to gamma irradiation for the prevention of transfusion associated graft-versus-host disease.[1] The INTERCEPT Blood System utilizes a psoralen (amotosalen) and UVA light for inactivation of a broad spectrum of pathogens and donor T-cells.[1]

Executive Summary

- The primary clinical goal of platelet transfusion is to reduce bleeding risk and progression.[2,3]
- In clinical trials evaluating platelet transfusion efficacy, control of Grade ≥2 bleeding is used as the primary endpoint.[4,5]
- Corrected count increment (CCI) is a measure of post-transfusion circulating platelet levels.[6]
    - Multiple large scale clinical trials have shown a lack of correlation between CCI response and bleeding.[7-11]
    - While a low CCI response triggers the need for additional evaluation to determine etiology, including clinical or immune mediated refractoriness, it does not conclusively indicate a lack of platelet efficacy.
- CCI can be impacted by a variety of clinical factors, including: patient condition, platelet dose and processing, and transfusion history.[12]
- INTERCEPT Blood System treated platelets key data:
    - Multiple clinical trials show no statistically significant difference in Grade ≥2 or higher bleeding with INTERCEPT treated platelets, despite mildly reduced CCIs[8,9,13,14]
    - Immune refractoriness, a differentiating factor in a diagnosis of clinical refractoriness, was significantly lower in clinical trials for INTERCEPT treated platelets compared to conventional platelets.[8]
    - Hemovigilance studies of the large-scale, routine use of INTERCEPT treated platelets have shown no impact on clinical hemostasis, increased utilization of platelets and/or Red Blood Cells (RBC), or incidence of refractory response to platelet transfusion.[15-17]

General Considerations on CCI

The CCI measure is used to assess platelet survival and circulation certain time points after transfusion. Platelet corrected count increment (CCI) normalizes the measured increase in circulating platelets observed post-transfusion to the patient's body surface area and dose transfused.

$$\text{CCI is calculated by} = \frac{(\text{platelet increment per } \mu l) \times (\text{body surface area in } m^2)}{\text{Number of platelets transfused } (\times 10^{11})}$$

A low CCI can indicate clinical refractoriness (defined as 2 successive transfusions with 1 hour CCI $< 5.0 \times 10^3$) and therefore triggers an evaluation of clinical refractoriness.[18] CCI response, however, may be reduced for a variety of reasons :

1. Multiple unrelated parameters, including pre-transfusion platelet count, platelet dose, patient body surface area (surrogate measure for blood volume)[19]
2. Functional platelets may be cleared rapidly from circulation as part of the endothelial damage repair process in hemostasis[20]
3. The platelet unit has been stored for > 48 hours, is ABO incompatible, or was gamma irradiated[12]
4. Patient has undergone multiple transfusions [12]
5. Patient condition: fever, palpable spleen, infection, treatment with amphotericin or heparin, female with ≥ 2 pregnancies, or male sex[12]

Thus, CCI is an indicator of the short-term response to platelet transfusion, not platelet function. Unlike a confirmed immunogenic refractory diagnosis, CCI does not correlate with bleeding outcomes.[4,11]

This white paper reviews key clinical trials of INTERCEPT treated PC compared with conventional PC with a focus on differences in CCI.

Randomized Controlled Trials of INTERCEPT Treated Platelet Components

SPRINT, a Phase 3 double-blind randomized controlled trial conducted at 12 US centers,[8] compared gamma-irradiated, INTERCEPT treated, platelet components (PC) in platelet additive solution 3 (PAS-3) to conventional, gamma-irradiated, PC in plasma. The primary endpoint was non-inferiority for the incidence of Grade 2 bleeding (World Health Organization, WHO, criteria).[4,5]

SPRINT met its primary endpoint, demonstrating that gamma-irradiated INTERCEPT treated PC were non-inferior to gamma-irradiated conventional PC for incidence of Grade 2 bleeding. Secondary endpoints did not differ between groups, including, Grade 3 & 4 bleeding, RBC transfusion use, and time to first Grade 2 bleeding event.[8] The 1- and 24-hour CCI responses were statistically significantly lower for INTERCEPT treated PC in PAS-3 compared with conventional platelets in plasma. Notably, conventional platelets in PAS are reported to be associated with lower CCIs at 1-hour than conventional platelets in plasma.[21] The interval between transfusions was significantly lower, and the mean number of platelet component transfusions per day was significantly higher, for INTERCEPT treated PC (**Table 1**).[8] However, in SPRINT the proportion of transfusions with platelet component doses $<3.0 \times 10^{11}$ was substantially greater for INTERCEPT treated PC than for control PC (20% versus 12%, $P < 0.01$). CCI response can be impacted by transfused platelet dose.

Murphy et al.[13] reported a sensitivity analysis of the SPRINT study to examine the effect of platelet dose consistency. Patients were divided into two subsets: those receiving all PC doses ≥3.0 x 10^{11} and those receiving one or more PC doses <3.0 x 10^{11}. While differences in PC dose per transfusion, and mean 1-hour CCI, remained significantly lower for the INTERCEPT treated cohorts in comparison to control, the number of PC transfusions per patient was not significantly different (**Table 1**). Incidence of Grade 2 bleeding, the primary endpoint, remained the same when comparing patients receiving INTERCEPT treated versus control platelets, within the dose subgroups. This supports that the functional outcome of platelet transfusion, the reduction or prevention of bleeding, does not correlate with CCI, and INTERCEPT treated PC provided hemostasis as efficaciously as conventional PC.

Table 1. Analysis of Primary and Secondary Endpoints in SPRINT Phase 3 Study

SPRINT	SPRINT[8]			SPRINT[13]- all >±3.0			SPRINT[13]- any <3.0		
	INTERCEPT	control	p	INTERCEPT	control	p	INTERCEPT	control	p
Number of patients	318	327		128	207		190	118	
Grade 2 bleeding %	**58.5**	**57.5**	**NI***	**49**	**52**	**0.65**	**65**	**67**	**0.71**
Grade 3 or 4 bleeding %	4.1	6.1	NI*	2	3	0.49	6	11	0.13
Platelet dose/transfusion ($x10^{11}$) (mean(SD))	3.7	4	<0.001	3.9(0.5)	4.3(0.6)	<0.01	3.5(0.5)	3.6(0.5)	<0.01
Platelet transfusions/patient (mean(SD))	**8.4**	**6.2**	**<0.001**	**4.1(3.2)**	**4.0(3.5)**	**0.59**	**11.3(9.8)**	**10.3(9.5)**	**0.18**
RBC transfusions/patient (mean(SD))	4.8	4.3	0.13	2.9(2.6)	3.1(2.7)	0.57	6.1(4.8)	6.5(5.9)	0.48
1hr CCI (mean)	11.1	16	<0.001	12(6)	16(8)	<0.01	11(6)	15(6)	<0.01
Interval between doses	1.9	2.4	<0.001	2.3(1)	2.6(1.1)	<0.01	1.7(0.9)	2.2(1.0)	<0.01

*NI: non-inferior (study powered to show non-inferiority between test and control groups for bleeding)

Another potential confounding factor to the SPRINT trial was that greater than 99% of the INTERCEPT treated PC also underwent gamma irradiation, a platelet processing procedure shown to reduce CCI.[12] At the time of this trial, data were not yet published on the efficacy of the INTERCEPT system to inactivate T-cells.[22,23] It has since been proven that the INTERCEPT Blood System inactivates T-cells at 99.99% effectiveness. Currently, hospitals use INTERCEPT treatment as an alternative to gamma irradiation for the prevention of transfusion-associated graft-versus-host disease per FDA[1] and AABB Standards.[24]

While SPRINT showed a lower CCI with INTERCEPT-treated PC compared to conventional PCs, a key differentiating factor for a refractory reaction to platelets is immunogenicity. INTERCEPT treated PCs had significantly lower immunogenicity compared to conventional platelets.[8] Norris et al.[25] also reported a trend for decreased alloimmunization in the INTERCEPT arm compared to the conventional arm in the IPTAS study.

In euroSPRITE, a European phase 3, double-blind, randomized trial, INTERCEPT treated PCs (non-irradiated) were compared to conventional gamma-irradiated PCs using 1-hour CCI and platelet count increments (CI) as primary endpoints. 1-hour CCI responses were not significantly different for the two groups (INTERCEPT treated 13,100 ± 5,400 (n=52); irradiated 14,900 ± 6,200 (n=51); p =0.11).[9] Furthermore, longitudinal regression analysis of all transfusions found that equal doses of INTERCEPT treated and irradiated PCs were transfused.[9]

A recent study by Sim *et al.*[26] showed that INTERCEPT treatment of non-leukoreduced platelets resulted in significantly fewer patients with low 1 hour CCIs/meeting refractory criteria than gamma-irradiated non-leukoreduced platelets. While the combined effect of irradiation and INTERCEPT treatment on PCs has not been systematically studied, euroSPRITE and Sim et al suggests that the

reductions in CCI observed in SPRINT[8,13] may partly be due to the effect of treating platelets with both irradiation and INTERCEPT.

HOVON, a European study comparing irradiated INTERCEPT treated PC to conventional irradiated PC, was stopped early because of increased bleeding in the INTERCEPT arm. This study was not powered for assessment of bleeding, nor was it evaluated according to WHO criteria. Results from this study have never been replicated.[27]

Hemovigilance Studies of INTERCEPT Treated PCs

INTERCEPT treated PC retain hemostatic function in routine use as supported by large-scale hemovigilance (HV) programs consistently demonstrating that conversion to INTERCEPT treated PC does not lead to increased utilization of PC or RBC. HV data from regional blood centers in Belgium, France, and Austria evaluated utilization of PC and RBC during the periods before and after conversion to INTERCEPT treated PC (**Table 2**). Belgian[15] and Austrian[16,28] reports show no difference in number of PC transfused per patient between conventional and INTERCEPT treated PC. The cohort transfused with INTERCEPT treated PC in France[17] did receive significantly more PC in comparison to control, however, the total platelet dose per patient did not differ between cohorts. During the time period assessed, Cazenave *et al.*[17] noted that platelet content per PC unit was intentionally reduced in France. Therefore, total platelet dose per patient, rather than number of PC transfused, reflects the product's hemostatic capacity. This did not change with transition to INTERCEPT treated PC. Additionally, RBC use per patient did not differ between patient cohorts. These HV programs demonstrate no indication of a loss of hemostatic efficacy comparing INTERCEPT and conventional PC.

Table 2. Hemovigilance Programs in Belgium, France, and Austria

Hemovigilance Studies	Mt. Godinne, Belgium[15]			EFS Alsace, France[17]			Innsbruck, Austria[16]		
	Test (n = 795)	Control (n = 668)	p	Test (n = 2069)	Control (n = 1678)	p	Test (n = 1694)	Control (n = 1797)	p
PC/patient (mean(SD))	10.1(20.9)	9.9(19.5)	0.88	6.4	5.5	<0.05	4.5(8.9)	4.8(9.7)	0.44
Total PC dose/patient	36.7(76.5)	41.5(82.8)	0.24	26.9	24.1	Anova not significant	n/a	n/a	n/a
RBC use/patient	15.0(21.0)	15.1(20.5)	0.9	13.6	13.1	Anova not significant	10.2(13.9)	10.8(15.3)	0.22

Conclusion

While some studies have reported a decrease in CI and CCI associated with transfusion of INTERCEPT treated PC relative to conventional PC, multiple studies have shown that hemostasis and platelet utilization remain similar, indicating that INTERCEPT treated PC are effective for bleeding control. Platelet utilization, and use of other blood products, has not been shown to be increased in routine clinical use of INTERCEPT® Blood System pathogen-reduced platelets.

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