

Hemostasis Endpoints in Platelet Transfusion Clinical Trials with Differential Follow-up



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Background

The primary objective of platelet component (PC) transfusion is to prevent bleeding. Many of the endpoints used to assess PC transfusion efficacy combine different types of bleeding (WHO Grades 2 through 4) into a single composite endpoint. To simplify the assessment of hemostasis, clinicians and statisticians have dichotomized bleeding outcomes during platelet support into presence or absence of bleeding. However, such simplified classification does not consider the issue of recurrent bleeding nor differences in days of observation during the platelet transfusion support period. **Study population:** The SPRINT trial evaluated the hemostatic efficacy of conventional PC (C-PC) compared to pathogen inactivated PC (PI-PC) in a patient population with hematologic malignancies largely (78%) treated with HSCT for up to 28 days of transfusion (McCullough, Vesole *et al.* 2004). The primary endpoint was the proportion of patients with Grade 2 bleeding, and days with Grade 2 bleeding was analyzed as a secondary endpoint.

Results

Table 1: Model Predicted Mean Days of Observation – SPRINT clinical trial

Patient Types	Potential Confounders			Estimate of Mean Days of Observation
	Grade ≥ 2 Bleeding Prior to 1st Study Tx	GVHD	TBI	
Chemotherapy Patients	-	-	-	14.97
	+	-	-	17.29
	-	-	+	18.66
	+	-	+	21.54
Autologous HSCT Patients	-	-	-	9.93
	+	-	-	11.46
	-	-	+	12.37
	+	-	+	14.29
Allogeneic HSCT Patients	-	-	-	16.13
	-	+	-	17.83
	+	-	-	18.62
	-	-	+	20.10
	+	+	-	20.59
	-	+	+	22.23
	+	-	+	23.21
	+	+	+	25.66

+ = confounder present
- = confounder absent

Table 2: Parameter Estimates (log scale) from the Negative Binomial Model that Predicts Rate of Grade 2 Bleeding

Parameter	Maximum Likelihood Estimate	Standard Error	Wald 95% CI	p-Value
Intercept (b_0)	-2.076	0.089	[-2.250, -1.902]	< 0.0001
Treatment (b_A) (Ref=0, INT=1)	0.139	0.107	[-0.071, 0.349]	0.1946
Bleeding at entry (b_B) (No=0, Yes=1)	0.970	0.132	[0.711, 1.229]	< 0.0001
GVHD (b_G) (No=0, Yes=1)	0.338	0.194	[-0.042, 0.718]	0.0816
Total Body Irradiation (b_T) (No=0, Yes=1)	0.265	0.119	[0.032, 0.498]	0.0264

When one considers the days of observation for each patient, there is no significant difference in the rate of Grade 2 bleeding between the treatment arms when one controls for Grade 2 or greater bleeding prior to study transfusion, TBI, and GVHD.

Many of the endpoints used to assess PC transfusion efficacy combine different types of bleeding (WHO Grades 2 through 4) into a single composite endpoint. However, the most severe bleeding is not affected by increasing platelet transfusions, but requires additional interventions such as plasma transfusion. **Figure 3** displays SPRINT clinical trial data from patients that experienced both Grade 2 and Grade 3 or 4 bleeding. Most of the data points are below the diagonal indicating that Grade 3 or 4 bleeding generally occurred prior to Grade 2 bleeding in this study and 70% were associated with plasma phase coagulopathy.

Of the 4 confounders described, the two that exhibited the greatest impact in predicting the number of days of observation are: Grade 2 or greater bleeding prior to the initial study transfusion and type of HSCT. **Table 1** provides the model estimated days of follow-up and the impact of the 4 confounders on the days of transfusion support and thus the days of observation.

Mean days with Grade 2 bleeding (M) is best described by the following negative binomial regression model, i.e.,

$$\log(M) = \log(\text{days of follow-up}) + b_0 + b_A I_{Tt} + b_B I_{Bleed} + b_G I_{GVHD} + b_T I_{TBI}$$

$$\log(M/\text{days of follow-up}) = \log(R) = b_0 + b_A I_{Tt} + b_B I_{Bleed} + b_G I_{GVHD} + b_T I_{TBI}$$

where

$$I_{Tt} = \begin{cases} 0, \text{Reference group} \\ 1, \text{INTERCEPT group} \end{cases}$$

$$I_{Bleed} = \begin{cases} 0, \text{No bleeding or less than Grade 2 bleeding prior to study} \\ 1, \text{Grade 2 or greater bleeding prior to study transfusion} \end{cases}$$

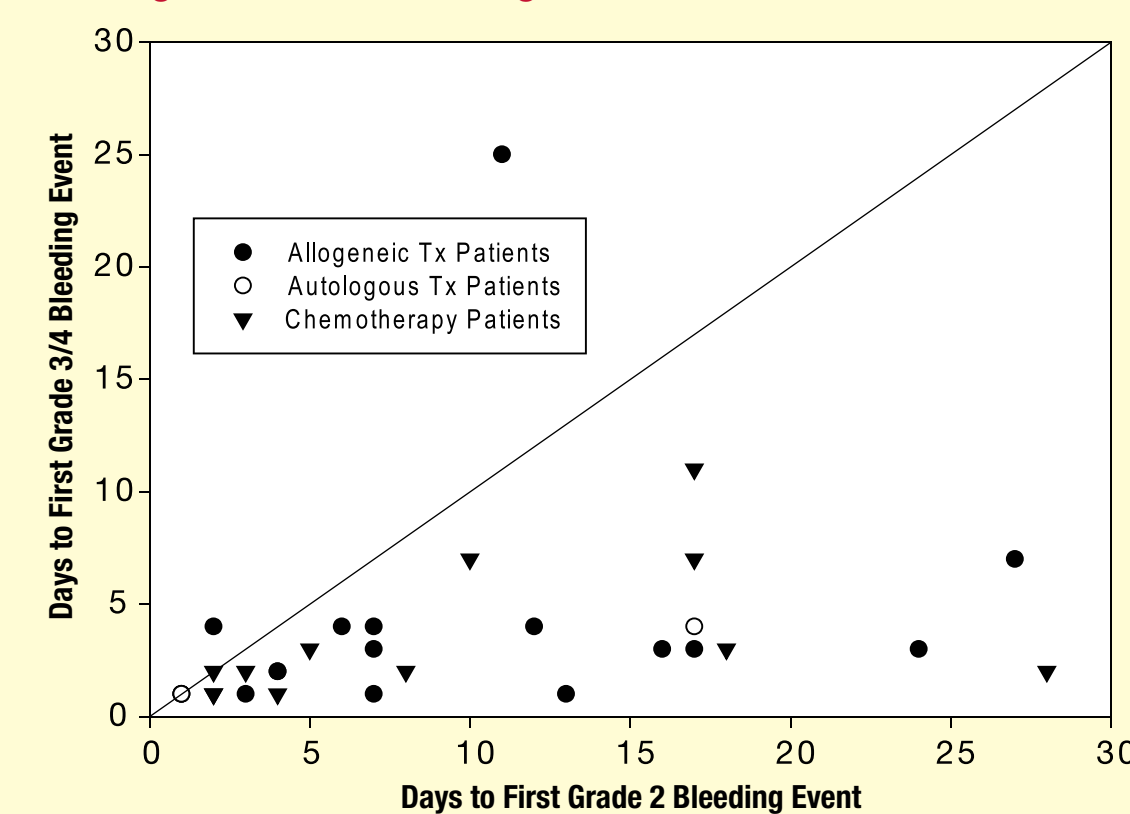
$$I_{GVHD} = \begin{cases} 0, \text{Patient not diagnosed with GVHD} \\ 1, \text{Patient diagnosed with Graft Versus Host Disease (GVHD)} \end{cases}$$

$$I_{TBI} = \begin{cases} 0, \text{Patient did not receive TBI} \\ 1, \text{Patient received Total Body Irradiation (TBI)} \end{cases}$$

Note: The SPRINT clinical trial stratified for type of HSCT. Thus, it is not necessary to include this covariate in the model.

As a consequence of the model formulation, the log rate of Grade 2 bleeding (per unit day) for the Reference group is $\log(R_r) = b_0$ and for the INTERCEPT group is $\log(R_i) = b_0 + b_A$. Therefore, b_A represents the difference in the log rate of Grade 2 bleeding between the INTERCEPT and Reference groups. Table 2 presents the model parameter estimates.

Figure 3: Lack of Temporal Relation Between the Onset of Grade 3 or 4 Bleeding and Grade 2 Bleeding



Aims

- To examine the methods for analysis of recurrent bleeding during a period of platelet transfusion support.
- To examine the temporal relationship of Grade 2 bleeding to Grade 3 and Grade 4 bleeding.

Methods

Days with Grade 2 bleeding is a recurrent event endpoint (with a positively skewed distribution, **Figure 1**). Data from the SPRINT trial describing the days with Grade 2 bleeding and the days of transfusion support were utilized to develop a model to identify and evaluate key covariates that could impact days with Grade 2 bleeding. Statistical models were developed to evaluate the impact of the following key factors:

- Type of HSCT (allogeneic versus autologous).
- Total body irradiation (TBI) during HSCT preparative regimen.
- Transplant-related GVHD.
- Grade 2 or greater bleeding prior to the initial study platelet transfusion.

In assessing the number of days with Grade 2 bleeding, the amount of time a patient is platelet dependent must be considered (**Figure 2**). The longer a patient is monitored, the more likely Grade 2 bleeding will be observed. The model needs to be adjusted for the varying length of per patient observation.

Figure 1: Days with Grade 2 Bleeding are Positively Skewed – SPRINT Clinical Trial

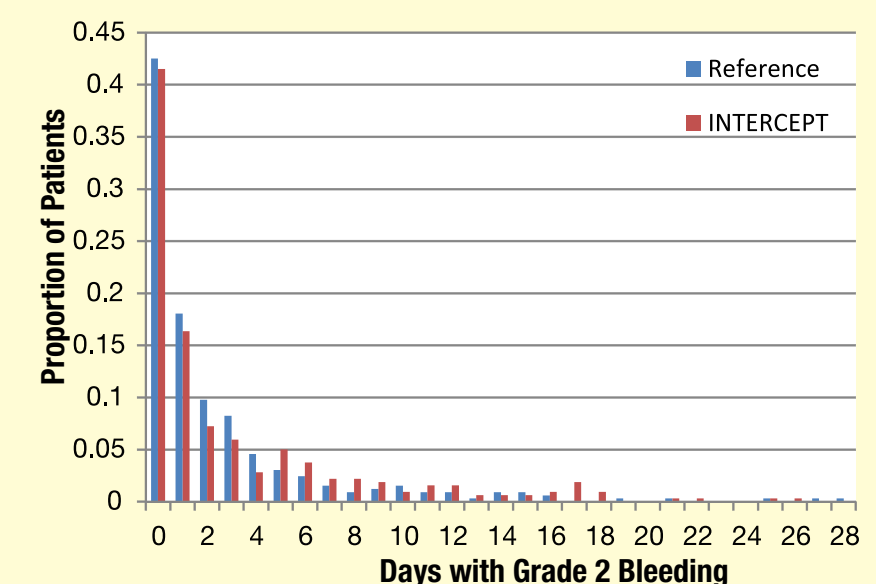
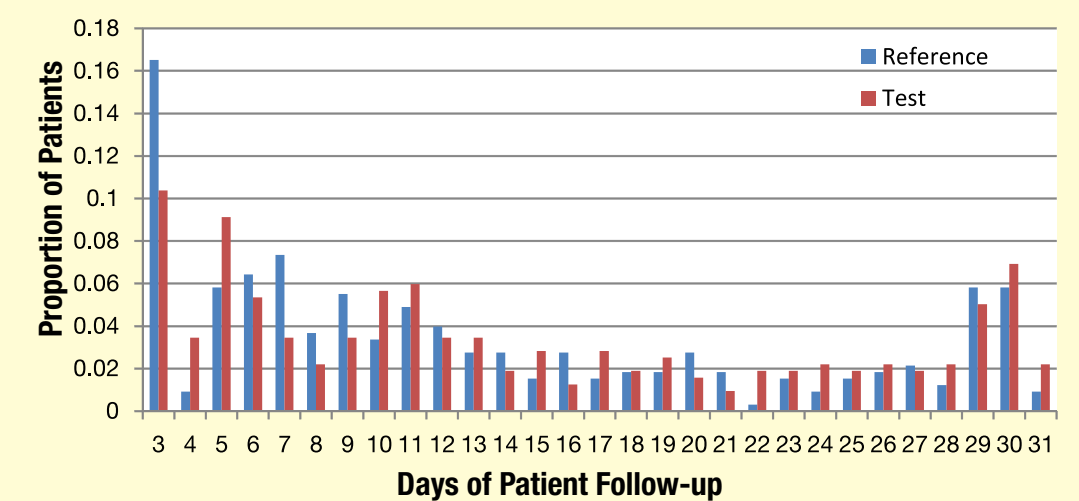


Figure 2: Distribution of the Number of Days is Highly Variable – SPRINT Clinical Trial



References

McCullough, Vesole *et al.* (2004) Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial. *Blood* 104(5): 1534-41.

Conclusions

- Mean days with Grade 2 bleeding was not significantly different between INTERCEPT and Reference groups, when appropriately analyzed.
- Grades 3 and 4 bleeding generally occurred before Grade 2 bleeding and were commonly associated with plasma phase coagulopathy.
- Grade 2 bleeding was not predictive of Grade 3 or 4 bleeding, and different bleeding grades should not be combined in a composite endpoint.

Presented at the American Association of Blood Banks Annual Conference & CCTXPO (AABB)

San Diego, California • October 22nd - 25th, 2011