SUPPLEMENTARY APPENDIX

Risk of bleeding and use of platelet transfusions in patients with hematologic malignancies: recurrent event analysis

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Appendix:

Supplementary Table 1: Multivariate recurrent event analysis model summaries

Parameter		Main model (n=598) (Analysis 2a)			Thrombocytopenia model (n=588) (Analysis 2b)			Fever model (n=469) (Analysis 2c)		
		Hazard ratio (95% CI)		P value	Hazard ratio (95% CI)		P value	Hazard ratio (95% CI)		P value
Treatment arm	No-prophylaxis	1.25	(1.04 to 1.52)	0.01	1.16	(0.94 to 1.41)	0.1	1.25	(0.96 to 1.62)	0.1
	Prophylaxis	1.00			1.00			1.00		
Red cell transfusion in the previous 3 days?	Yes	1.24	(1.03 to 1.50)	0.02	1.32	(1.09 to 1.60)	0.002	1.11	(0.83 to 1.47)	0.5
	No	1.00			1.00			1.00		
Sex	Female	1.33	(1.10 to 1.61)	0.0002	1.19	(0.98 to 1.43)	0.07	1.08	(0.83 to 1.41)	0.6
	Male	1.00			1.00			1.00		
Treatment plan	AlloHSCT/chemo	1.43	(1.19 to 1.72)	0.0001	-		-	1.57	(1.20 to 2.05)	0.002
	AutoHSCT	1.00			-		-	1.00		
Previous day platelet count and bleeding episode interaction	Count:0-20/Episode:1	9.77	(3.35 to 28.54)	0.0002	4.98	(1.74 to 14.28)	<0.0001	17.50	(1.98 to 154.35)	0.07
	Count:21-30/Episode:1	2.25	(0.67 to 7.61)		1.41	(0.43 to 4.67)		6.64	(0.69 to 63.63)	
	Count:31-40/Episode:1	2.74	(0.74 to 10.16)		1.73	(0.48 to 6.28)		5.26	(0.50 to 55.83)	
	Count:41-50/Episode:1	2.57	(0.56 to 11.77)		1.94	(0.43 to 8.83)		6.20	(0.48 to 80.40)	
	Count:51+/Episode:1	1.00			1.00			1.00		
	Count:0-20/Episode:2+	6.65	(3.41 to 12.99)		4.00	(1.95 to 8.21)		4.89	(2.14 to 11.19)	
	Count:21-30/Episode:2+	6.18	(3.08 to 12.37)		4.54	(2.15 to 9.60)		5.54	(2.32 to 13.24)	
	Count:31-40, Episode:2+	4.19	(1.99 to 8.83)		3.39	(1.52 to 7.56)		2.75	(0.95 to 7.99)	
	Count:41-50, Episode:2+	4.07	(1.80 to 9.20)		3.61	(1.52 to 8.57)		3.16	(1.10 to 9.31)	
	Count:51+, Episode:2+	1.00			1.00			1.00		

Parameter		Main model (n=598) (Analysis 2a)		Thrombocytopenia model (n=588) (Analysis 2b)			Fever model (n=469) (Analysis 2c)		
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)		P value	Hazard ratio (95% CI)		P value
No of days with plt count <10 & treatment plan interaction	0 days & Allo/chemo	-	-	1.00		0.0002	-		-
	1 day & Allo/chemo	-	-	2.08	(1.46 to 2.96)		-		-
	2 days & Allo/chemo	-	-	2.04	(1.33 to 3.13)		-		-
	3 days & Allo/chemo	-	-	3.71	(2.39 to 5.76)		-		-
	0 days & AutoHSCT	-	-	1.00			-		-
	1 day & AutoHSCT	-	-	1.45	(1.08 to 1.93)		-		-
	2 days & AutoHSCT	-	-	1.36	(0.96 to 1.94)		-		-
	3 days & AutoHSCT	-	-	1.24	(0.76 to 2.02)		-		-
Highest temp in previous 3 days (degrees Celsius)	<37.5	-	-	-		-	1.00		0.03
	37.5-<38	-	-	-		-	1.15	(0.81 to 1.62)	
	38-<38.5	-	-	-		-	1.27	(0.89 to 1.80)	
	>=38.5	-	-	-		-	1.73	(1.26 to 2.38)	

Additional information about the methods

Development and validation of the statistical methods

The statistical models were built iteratively using likelihood ratio tests to test for significance levels of each factor. At each iterative step, significance levels of 10% were considered for inclusion in the model and levels of 5% were considered for removal from the model. Final models were assessed using standard model checking methods.

The dataset used for developing each model was dependent on the completeness of the factors of interest. The baseline characteristics model (analysis 1) was based on 560 patients where baseline characteristics were reported and 30 day follow up was complete. A negative binomial model was selected for this analysis due to over dispersion in the data. A chi-square goodness of fit test implied a satisfactory fit.

The main recurrent event analysis (analysis 2a) was based on 589 patients where baseline data were complete and previous day platelet count was reported. The dataset excluded data from the first three study days to allow investigation of the effect on any one day of a red cell transfusion in the previous three days. Robust sandwich variance estimates were used for the confidence intervals for the recurrent event modeling due to non-independent events for each patient. Frailty modeling was considered but not used as the models failed to converge.

The following recurrent event models (analyses 2b and 2c) were based on the model from analysis 2a using subsets of the dataset where platelet count from the previous 3 days was complete (analysis 2b) or where fever data were reported (analysis 2c), fitting the new factor of interest.

Sensitivity analyses were performed for each model.

Sensitivity analyses

Sensitivity analyses consisted of repeating all analyses but excluding skin bleeds (as the most common type of bleed and often considered of lesser clinical significance) or vaginal bleeds (in view of the different results for sex) to explore whether these bleeding types were particularly influential on the models. Hazard ratios for analysis 2a were compared to those for the subsets used for subsequent analyses to ensure consistency across the datasets. Further sensitivity analyses were performed to check the different assumptions on skin bleed duration comparing counting just the first day of subsequent bleeding days to counting all days of subsequent bleeding.