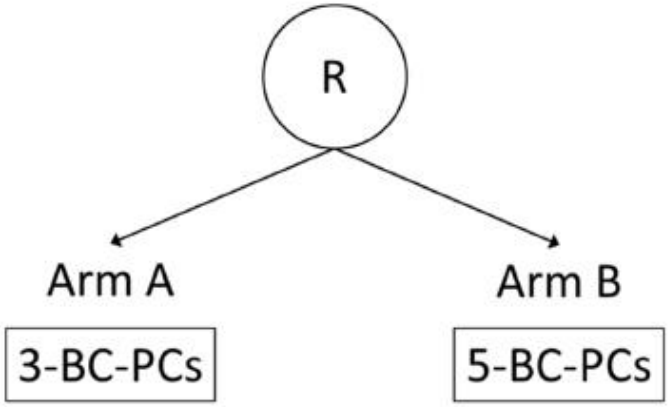
HagaZiekenhuis van Den Haag

Clinical effectiveness of 3 buffy coat-derived platelet concentrates as compared to the standard 5 buffy coat-derived platelet concentrates in hemato-oncology patients

The Alphabet study (Assessment of Buffy-Coat-Dosage)



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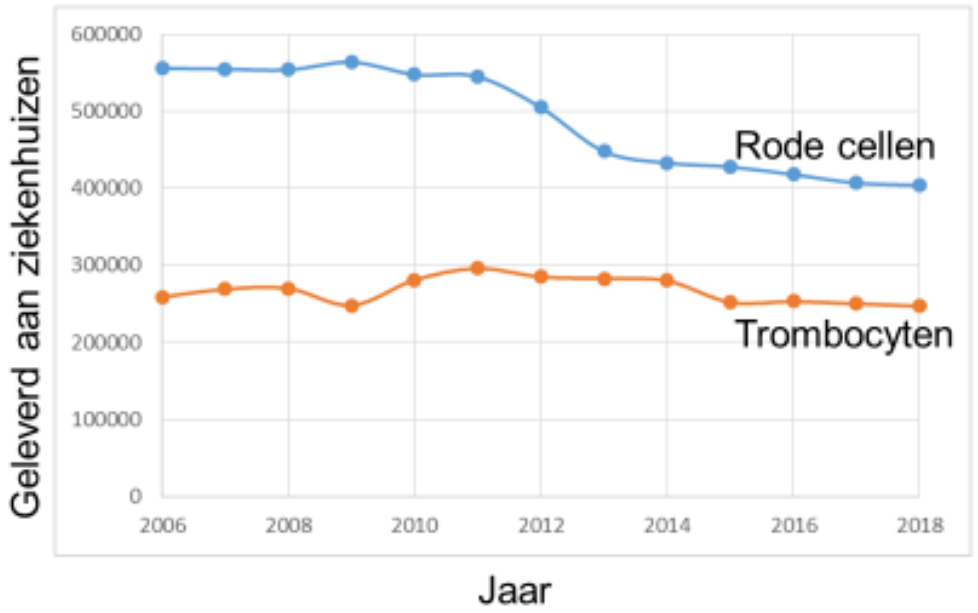
Disclosures

Sponsoring t.b.v. uitvoeren studies:

- Sanquin
- Terumo BCT
- Sanofi

Bloedverbruik



Minder beschikbare BC’s

Rationale

- Studies with apheresis platelets have shown that hemato-oncologic patients with hypoproliferative thrombocytopenia can be supported with lower platelet doses than the current standard.
- Overall platelet dose and donor exposure were lower. This is potentially beneficial as this may prevent antibody formation leading to platelet refractoriness.
- In Europe, platelet concentrates are derived from pooling buffy coat from multiple blood donations. The current standard is a pool from five buffy coats (5-BC-PCS).
- We aim to investigate the clinical effectiveness of a pool of three buffy coats (3-BC-PCs). For these pooled products, we want to demonstrate that lower doses do not result in more bleeding. Further, we aim to explore whether alloimmunization and refractoriness when using a pooled platelet product is lower when three rather than five buffy coats are used.

Even voorstellen: Het studie product

Samenstelling 3-BC-TCs

Dag 1	n=12
Volume, ml	208±6
Trombocyten, 10^9	217±33
Concentratie, $x10^9$/mL	1,04±0,15

Study design

- A prospective, randomized, open blinded endpoint, multicenter study.

- To demonstrate non-inferiority of 3-BC-PCs versus 5-BC-PCs with grade 1b+2 bleeding according to the Bleeding Severity Measurement Scale (BSMS) as primary endpoint.

Bleeding Severity Measurement Scale (BSMS)

TABLE 3. The BSMS*

Bleeding grade and classification		Description of bleeding
0. No bleeding		No bleeding.
1. Not clinically significant bleeding	1(a) Trace bleeding	Minimal bleeding or bleeding detectable by laboratory measures only. Bleeding does not have any impact on patient or on the level of care provided to the patient.
	1(b) Mild bleeding	Non–clinically significant bleeding. Bleeding does not have any impact on patient or level of care provided to the patient.
2. Clinically significant bleeding	2(a) Serious bleeding	Bleeding directly resulting in one or more of the following: • Significant pain (requiring medical treatment or intervention) • Need for interventions (including transfusion, surgery, invasive procedures, administration of medication, etc.) • Need for invasive investigations or increased monitoring
	2(b) Serious bleeding causing significant morbidity	Any bleeding meeting one or more of the following criteria: • All central nervous system bleeding • Resulting in hemodynamic instability: – Tachycardia (increase in resting heart rate by at least 20 bpm) *or* – Hypotension (decrease in systolic and/or diastolic BP by at least 20 mmHg) • Resulting in vision loss • Resulting in significant morbidity
	2(c) Fatal bleeding	Any bleeding directly contributing to patient's death

General instructions:

1. In most instances, the scale is meant to document new or ongoing bleeding. For example, a bruise should be documented on its first occurrence. After initial documentation, it should only be documented if it is worsening in severity.
2. The highest scoring bleeding determines the patient's bleeding severity on that day.
3. Sources of information to help document bleeding include the patient (examination, history) and the hospital chart (medications prescribed, investigations ordered, physicians/nurses notes, etc.), and health care providers looking after the patient.
4. Note that an isolated decrease in Hb may not be considered sufficient evidence of a bleed.

* Grade 1 bleeding consists of trace bleeding and mild bleeding and is not clinically significant. Grade 2 bleeding consists of serious bleeding, serious bleeding causing significant morbidity, and fatal bleeding. Grade 2 bleeding is clinically significant.

From: Webert [Transfusion 2012;52:2466]

Prepares – re-adjudicated

		Control	Intervention
Transfusion episodes	*n*	279	277
ISTH			
ISTH CRNMB + major bleeding	*n*[1] *(%)*	23 (8)	17 (6)
Days CRNMB + major bleeding	*Median (IQR)*	0 (0-0)	0 (0-0)
Highest grade of bleeding	*n (%)*		
No or minor		256 (92)	260 (94)
CRNMB		14 (5)	7 (3)
Major		9 (3)	10 (4)
BSMS			
Webert grade 1b + 2	*n*[1] *(%)*	184 (66)	187 (68)
Webert grade 2	*n (%)*	22 (8)	17 (6)
Days with grade 1b + 2 bleeding	*Median (IQR)*	2 (0-5)	2 (0-5)
Days with grade 2 bleeding	*Median (IQR)*	0 (0-0)	0 (0-0)
Highest grade of bleeding	*n (%)*		
No		54 (19)	47 (17)
1a		41 (15)	43 (16)
1b		162 (58)	170 (61)
2		22 (8)	17(6)

[1]difference and 95% CI; WHO>=2: difference 3 percentage points 95% CI (-6 to 11); Webert>=1b: difference 2 percentage points 95% CI (-6 to 9); Webert>=2: difference -2 percentage points 95% CI (-6 to 2); ISTH CRNMB + major: difference -2 percentage points 95% CI (-6 to 2)

Power calculation

- To demonstrate non-inferiority of 3-BC-PCs versus 5-BC-PCs with percentage of days with grade 1b+2 bleeding according to the Bleeding Severity Measurement Scale (BSMS) as primary endpoint.

- Previous data from the PREPAReS trial [Van der Meer & Ypma et al 2018] showed that on 20% of the days during a transfusion episode, patients had a grade 1b or grade 2 bleed (BSMS).

- As upper boundary of the 95% confidence interval of the ratio of the mean bleeding percentages in both arms, we accept an 37.5% higher percentage of days with a 1b+2 bleed (so an increase in bleeding days from the expected 20% to at most 27.5%).

- With 80% power, 0.025 one sided alpha, and accounting for a cluster effect induced by patients who get randomized multiple times, per arm 260 patients are needed, which is 520 in total for the entire trial.

Inclusion criteria

- In order to be eligible to participate in this study, a subject must meet all of the following criteria:
  - Age ≥ 18 years.
  - Expected ≥ 2 platelet transfusion requirements during current hospitalization.
  - Signed informed consent.
  - Having a hemato-oncologic disease.

Exclusion criteria

- A potential subject who meets any of the following criteria will be excluded from participation in this study:

  - Known immunological refractoriness to platelet transfusions.
  - HLA- and/or HPA-alloimmunization and/or clinical relevant auto-antibodies.
  - Indications to use HLA-typed platelet concentrates.
  - Indications to use hyper-concentrated (plasma-reduced) platelet concentrates, for example patients with known severe allergic reactions or transfusion-associated circulatory overload (TACO).
  - Micro-angiopathic thrombocytopenia (TTP, HUS) and ITP.

Secondary objectives

To compare 3-BC-PCs versus 5-BC-PCs with respect to

- total number of platelets received
- total number of individual buffy coats received
- the 1 and 24 hour CI
- the 1 and 24 hour CCI
- percentage of patients with at least one bleeding grade 1b+2 according to the BSMS
- percentage of patients and percentage of days per patient with at least one ≥ clinically relevant minor bleeding grade according to the ISTH bleeding scale
- rate of HLA alloimmunization
- adverse transfusion reactions
- platelet transfusion interval
- total number of platelet transfusions
- total number of red cell and plasma transfusions
- association between albumin/creatinine in urine and/or CRP and clinically relevant bleeding grades according to the BSMS
- cost benefit analysis

Participerende centra

- We hebben nu toezeggingen van Haga, LUMC, UMCG en Zwolle.

- Uiteindelijk willen we 8 – 10 centra openen, we zijn nog met de HOVON in gesprek. Studie coördinatie en centraal Datamanagement zal door het HagaZiekenhuis worden verzorgd.