The assessment of platelet function by thromboelastometry as a point-of-care test to guide Intercept-treated platelet support in hemato-oncological patients and hematopoietic stem cell transplantation recipients

Gerda C. Leitner[1], *Markus Ho*[1], *Alexander Tolios*[1], *Georg Hopfinger*[2], *Werner Rabitsch*[2], *and Philipp Wohlfarth*[2]

BACKGROUND: Pathogen inactivation (PI) techniques for platelet concentrates (PCs) are one of the latest innovations to improve blood safety and reduce the risk of transfusion-transmitted infections (TTIs). An impaired function and in vivo recovery of platelets as well as an increased PC demand are concerns regarding these techniques. The intent of this study was to evaluate the hemostatic effect of PCs treated with the Intercept™ System by thromboelastometry (TEM) and to assess the clinical validity of its results in comparison to post-transfusion increase (PTI) and corrected count increment (CCI).

STUDY-DESIGN AND METHODS: This prospective-observational study included 47 patients (m:f = 25:22; median age: 54 years [21-70]) of our Bone Marrow Transplantation unit with hemato-oncological malignancies transfused with Intercept™-treated PCs. Serial TEM measurements were performed just before and 1 hour after PC transfusion and were analyzed for their correlation with PTI and CCI as well as for clinical variables.

RESULTS: The majority of our patients had received a hematopoietic stem cell transplantation (HSCT) (n = 41; 87%). In median 9 (1-50) PCs were transfused. Serial TEM, PTI, and CCI measurements were available for 150 transfusion episodes. The median platelet dose transfused was 2.65×10^{11}/unit (1.8-6). The median CCI was 9.250 (0-28.000). We observed a significant improvement in TEM parameters ($p < 0.05$) after transfusion of PI PCs, which did not mandatory correlate with the 1-hour PTI and CCI.

CONCLUSION: Serial TEM measurements indicate the hemostatic effect of Intercept™-treated PCs. The 1-hour PTI and CCI may not appropriately reflect the in vivo function of platelets after PI PC transfusion.

Bacterial contamination is considered the most relevant risk factor for transfusion-transmitted infections (TTIs) following the administration of platelet concentrates (PCs).[1–5] Over recent decades, big efforts were made to increase blood safety and reduce the risk for TTIs. Various methods are currently in practice to achieve these goals, ranging from donor exclusion to pathogen reduction methods and pathogen inactivation (PI) techniques, the latter of which can be considered one of the most recent advances in the field. To date, two PI systems are available in clinical routine, the Mirasol® System (TerumBCT) using riboflavin and the Intercept™ System (Cerus) using amotosalen HCL as an active agent, respectively. Another system using only UVC light for PI (TheraflexUV-platelets) has just recently been developed.[6–8]

Several studies have demonstrated the safety and efficacy of PI methods and concluded that PI-treated platelets are non-inferior to conventional PCs in terms of bleeding prevention and other clinical outcomes.[6,9–12] However, the post-transfusion increment of platelet counts was

From the [1]Department of Blood Group Serology and Transfusion Medicine and [2]Stem Cell Transplantation Unit, Department of Medicine I, Medical University of Vienna, Vienna, Austria.

Address reprint requests to: Gerda C. Leitner, MD, University Clinic of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria; e-mail: gerda.leitner@meduniwien.ac.at

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significantly lower after transfusion of PI platelets in several of these studies, leading to a higher transfusion frequency.[10,11,13] Hence, concerns about the function, the in vivo recovery and an increased demand of PCs when using PI-treated PCs have arisen.

Thromboelastometry (TEM) is a point-of-care testing for platelet function and its use is advocated by the European Society of Anesthesiology (ESA) and others to tailor the need for platelet support in the surgical setting.[14,15] TEM measures viscoelastic changes of the entire clotting process and has been shown to reflect the hemostatic potential of patients' blood more accurately than conventional parameters such as platelet counts or clotting times.[16–18] Thus, we conducted a prospective observational study to assess the in vivo function of transfused Intercept™-treated platelets by TEM before and 1 hour after transfusion of PI platelets. Furthermore, we correlated these findings with standard parameters used to assess transfusion success, such as the post-transfusion increase (PTI) and the corrected count increment (CCI), as well as with other transfusion-related and clinical variables.

METHODS

Study design

This was a prospective observational study conducted at the Medical University of Vienna after prior approval of the local ethics committee (protocol 1948/2015). The primary aim of this study was to investigate the hemostatic effects of PI platelets treated with the Intercept™ Blood System/Cerus Europe B.V. using TEM as a surrogate marker for in vivo coagulation properties. As secondary objectives, the results obtained by TEM were correlated with the CCI and PTI as well as with transfusion-related and clinical variables. All consecutive inpatients with a hematological or oncological diagnosis treated at the Stem Cell Transplantation Unit of our university and having required a platelet transfusion were asked for participation in this study. All subjects provided a written informed consent prior to study inclusion. The individual observational period was restricted to the patients' in-hospital stay.

We recorded baseline variables regarding demographics, the underlying disease and its treatment, as well as on age and number of transfused platelets, and the amount of PCs administered during the hospital stay. For patients following hematopoietic stem cell transplantation (HSCT), we additionally collected procedure-related data including blood group compatibility between donor and recipient, and post-transplant complications. Furthermore, all patients were asked to fill in a bleeding diary.

TEM measurements were performed just before platelet transfusions and 1 hour thereafter in all included patients. In total, 177 transfusion episodes were analyzed. Serial measurements and a complete dataset were available in 150 of these episodes. All the other presented laboratory data were assessed in the routine setting.

TABLE 1. Demographic data of included patients

Patients	N = 47		
Male/female	25/22		
Age yrs median/ range	52	(21-70)	
Diagnosis	n	Male/ female	Age
AML	22	13/9	54 (36-66)
MM	6	4/2	64 (53-70)
Hodgkin disease	3	1/2	33 (32-54)
NHL	4	2/2	55 (29-56)
MDS	3	1/2	38 (38-59)
ALL	6	3/3	40 (21-56)
SAA/n.mammae/n. testis	1/1/1	1/2	31 (21-49)
Stem cell transplantation			
MUD	21	15/6	54 (29-66)
PBSCT related	4	1/3	48 (43-56)
Cord blood	5	1/4	31 (21-50)
Autologous PBSCT	11	5/6	55.5 (21-70)

ALL = acute lymphatic leukemia; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; MM = multiple myeloma; MUD = matched unrelated donor; NHL = non–Hodgkin's lymphoma; PBSCT = peripheral blood stem cell transplantation; SAA = severe aplastic anemia; yrs = years.

Patients

Forty-seven patients (m:f = 25:22; median age: 54 [range: 21-70] years) were included in this study. The most frequent underlying disease was acute myeloid leukemia (AML) (n = 22), followed by multiple myeloma (MM) and acute lymphoblastic leukemia (ALL) (n = 6, each). The remaining patients had non–Hodgkin's lymphoma (NHL) (n = 4), Hodgkin's lymphoma (n = 3), myelodysplastic syndrome (MDS) (n = 3), testicular cancer (n = 1), breast cancer (n = 1) and severe aplastic anemia (SAA) (n = 1), respectively. Forty-one (87%) of the patients were included during or after recent HSCT (autologous, n = 11; allogeneic, n = 30). Two patients died of multiorgan failure caused by sepsis during their conditioning regimen. In three patients, stem cell transplantation was performed 1 to 3 years before. They were inpatients due to transplant-related morbidity or relapse. One patient was never a transplant candidate (breast cancer). She received medical treatment for her underlying disease at the Stem Cell Transplantation Unit. Detailed demographic data are given in Tables 1 and 2.

HSCT

Conditioning regimens for autologous HSCT included the BEAM protocol (lymphoma) and high-dose melphalan (myeloma). In allogeneic HSCT recipients, myeloablative conditioning (n = 21) consisted of cyclophosphamide in combination with total body irradiation ≥8 Gray (fludarabine added in cases of cord blood as stem cell source), whereas the FLAMSA protocol was used for

TABLE 2. Blood group compatibility in allogeneic transplanted patients

Patients	n = 30				
Male/female	13/17				
Age/years (median/range)	52 (21-66)				
Stem cell source		Major	Minor	Bidirectional	Identical
MUD	21	6		2	13
PBSCT related	4		1		3
Cord blood	5	4			1

reduced-intensity conditioning (n = 9). Donors for allogeneic HSCT were mostly HLA-matched unrelated (n = 21) or sibling (n = 4) donors. Peripheral blood stem cells (PBSCs) (n = 25) were the most commonly used graft source followed by cord blood in the allogeneic setting (n = 5).

Laboratory parameters

Peripheral blood counts were measured with a CellDyn Ruby 3500 blood analyzer (Abbott Diagnositcs, Core Laboratory) before and 1 hour after platelet transfusion. We calculated the 1-hour PTI as well as CCI using the following formula: [(post-transfusion count - pre-transfusion count) × body surface area (m^2)]/platelet dose × 10^{-11}).[19,20] CCI values ≤5.000 were defined as low and reflected refractoriness, 5.000-7.500 as medium (satisfactory transfusion success), and >7.500 as successful platelet transfusion result.[19] Coagulation parameters (fibrinogen, Quick test, and aPTT) were analyzed with the STA-R Max® (STAGO group).

TEM

The ROTEM® (Pentapharm GmbH) is a point-of-care analyzer which uses citrated whole blood samples and analyzes the viscoelastic properties of the blood as it clots. In our department only the NATEM test was performed. In this test, clot formation is initiated through activation of coagulation by contact. For the purpose of the analysis, 3 mL of citrated blood was collected before and 1 hour after platelet transfusion. The clot formation time (CFT) and the maximal clot firmness (MCF) were regarded as the primary variables of interest, as both are mainly influenced by the number and the function of platelets.[21,22] The CFT is defined as the time from clotting start until the clot firmness reaches the 20 mm mark. The MCF is the greatest vertical amplitude of the typical trace and reflects the absolute strength of the fibrin and platelet clot.

Bleeding events and diary

Bleeding events and directed interventions were documented and graded according the WHO bleeding scale by the study team.[23] To detect all bleeding events, patients were additionally asked to fill in a diary and to record all events subjectively deemed as "bleeding." In case of an event, the duration, localization, and severity (minor, moderate, or severe according to the patient's opinion) of bleeding should be recorded.

Transfusion policy and history

Prophylactic transfusion of platelets was performed at a threshold of <20,000 platelets/μL; packed red blood cells (PRBCs) were routinely administered to achieve hemoglobin levels ≥8 g/dL. The number of PCs as well as number of PRBCs was recorded for each individual patient. Age, number of platelets transfused, and transfusion intervals were additionally documented for PCs.

Pathogen inactivation (PI) of platelets

Our institution produces solely single-donor platelets by apheresis. We have been using the Intercept™ system for PI of PCs since March 2012. This system has been shown to effectively inactivate contamination of PCs with a broad spectrum of viruses, bacteria, and parasites as well as donor leukocytes. Our national authorities allow a 7-day storage for 100% PI PCs, which has therefore been implemented as maximum storage time at our institution.

The Intercept™ system uses amotosalen HCl (a photoactive compound) and long-wavelength ultraviolet (UVA) illumination for ex vivo PI of PCs. Residual amotosalen and free photoproducts are reduced to low levels by exposure to a compound adsorption device (CAD) before transfer of the treated platelets to a storage container for release. Treatment of platelet components with the Intercept™ Blood System does not cause substantial differences in pH, lactate concentration, platelet count, morphology score, glucose concentration, aggregation, secretory and total adenosine triphosphate concentration, extent of shape change, or platelet hypotonic shock response compared to untreated platelet components.[6,24]

Statistical analysis

Results are shown as mean and standard deviation (SD) or median and range for descriptive purposes in the text. All statistical comparisons were made by non-parametric tests due to the non-normal distribution of the data. Differences between the pre- and post-transfusion CFT and MCF parameters as well as the pre- and post-transfusion peripheral blood counts were analyzed using the Wilcoxon paired signed rank test for dependent samples. Spearman ANOVA

was applied for correlation analyses. A p value <0.05 was considered statistically significant.

RESULTS

Patients

The median duration of in-hospital stay of the patients was 28 (range: 4-76) days. In total, 9 of 47 (19%) patients died in hospital either due to post-transplant complications (multi-organ failure, n = 2; sepsis, n = 1; veno-occlusive disease, n = 1; transplant-associated microangiopathy (TAM), n = 1; respiratory failure, n = 1; acute graft versus host disease, n = 1) or during the conditioning phase prior to stem cell infusion (sepsis, n = 1; multiorgan failure, n = 1). In the surviving patients, neutrophil engraftment occurred after a median of 14 (range: 9-40) days and platelet engraftment after a median of 11 (range: 8-30) days, respectively.

Thirty-four of38 surviving transplant patients were discharged and all four non-transplant left the ward after their disease-related problem was resolved. Seven of 38 experienced fever >38.5°C without further symptoms and were classified as fever of unknown origin (FUO). Acute graft-versus-host disease (GvHD) occurred in eight patients (gut and skin). Three developed Grade 1 GvHD, five Grade 2, and no Grade 3 GvHD was observed in this cohort of patients. In none of these patients an impairment of plasmatic coagulation was recorded.

Bleeding events and diary

In total, one or more bleeding events occurred in 19 (40%) patients, which were mainly Grade 1 and 2. Regarding risk factors for bleeding, these patients had GvHD (n = 8), sepsis (n = 4), or FUO (n = 7), respectively. Only one patient experienced a Grade 3 CNS bleeding without symptoms (diagnosed by imaging only) in the course of sepsis with *Klebsiella pneumoniae*. He required no red cell transfusions but 22 platelet transfusions during his inpatient stay. He fully recovered. A minority (n = 10) of patients filled in the bleeding diary. In four of them bleeding events were documented and recorded as petechial or mucosal bleeding. They were graded by the patients as minor (Grade 1 as assessed by the study team).

Transfusion requirements

A median of 2 (0-24) PRBCs and a median of 9 (range: 1-50) PCs were transfused during the inpatient stay. In total, 146 PRBCs and 512 PCs were transfused. The need for blood products according to HSCT characteristics and survival of patients is shown in Table 3.

Platelet support and TEM results

A total of 177 of 512 (35%) PC transfusion episodes were analyzed. In the remaining episodes, full data regarding the used PC were not available, additional venipuncture and blood draw was not feasible or agreed to by the patient, or TEM could not be performed (e.g., during weekends). Complete TEM measurements (directly before and 1 hr after transfusion) with conclusive results were available in 150 of 177 (85%) of these transfusion episodes. According to the duration of the respective inpatient hospital stay and the PC transfusion demands, the number of tested blood samples per patient ranged between 1 and 18 samples. The transfused platelets were a median of 4 (range: 1-7) days old with a median platelet content of 2.65×10^{11} (range: 1.8-6.0). The median 1-hour PTI was 13×10^3 (range: $0\text{-}48 \times 10^3$) /μL, which was 34% (0-110) of the calculated increase. The median CCI was 9.250 (range: 0-28.000) (Table 4).

In 114 of 177 (65%) PC transfusions in 30 patients, the CCI was >7.500; in 32 (18%) PC transfusions in 5 patients the CCI was ≤5.000. However, we found a significant reduction (mean 45%, SD 31; $p < 0.05$) in CFT and a significant increase (mean 27%, SD 26; $p < 0.05$) in MCF after PI PC transfusion (Table 4) in the majority of our patients, irrespective of the PTI or CCI values (Fig. 1A and B). Twenty-two of our patients reached a normal MCF (52-72 mm) value in 72 (48%) of tested transfusion events (Table 4). No marked improvement in TEM values (increase in MCF <10%) was observed in 16 of 150 (11%) measurements in five patients. In two cases each, acute GvHD and fever >38.5°C were present, two patients only had fever >38.5°C and one patient had sepsis, respectively. All of these five patients had satisfactory PTI (mean: 34%; SD: 8.6%) and CCI (mean: 7.500; SD 3.900), but suffered from bleeding events Grade 1 or 2.

We could not identify an association between the underlying disease, HSCT characteristics or blood group compatibility, and TEM parameters ($p > 0.5$).

TABLE 3. Platelet and red cell transfusions in total AND clinical status related in all patients' inclusive survival rate during observation period

Blood component	In total	Median (range)	
PRBCs	146	2 (0-24)	
PCs	512	9 (1-50)	
Status of treatment	n PRBCs median (range)	n PCs median (range)	BMT unit survival rate
MUD (21)	2 (0-18)	10 (1-50)	17/21
PBSCT related (4)	5 (2-24)	6 (3-45)	3/4
Cord blood (5)	11 (8-18)	37 (12-44)	3/5
aut PBSCT (11)	2 (0-24)	3 (1-47)	11/11
Non-transplanted patients*	4 (0-4)	8 (3-13)	4/6

*One patient was not a transplant candidate, she was diagnosed with n. mammae.
*Three patients had PBSCT years ago.
They are not included in this table.
The amounts of transfused blood products were recorded solely during the stay on the BMT unit and stopped in the outpatient setting or in case of transfer to an intensive care unit.
PCs = platelet concentrates; PRBCs = packed red blood cells.

TABLE 4. Completed measurements

n = 150
Platelets transfused $\times 10^{11}$: 2.65 (1.96-6.0)
Platelet age (days): 4 (1-7)
Number of transfused platelets: 9 (1-50)
Transfusion interval (days): 3.1 (1.16-9)

Plt pre 10^9/L	Plt post 10^9/L	% of calculated increase	CCI	CFT sec pre	CFT sec post	MCF mm pre	MCF mm post
10 (1-33)	24 (2-63)	34 (0-110)	9.250 (0-28.000)	404 (145-2054)	227* (97-1090)	41 (4-69)	51* (31-77)

All values are given as mean and range, asterisks* indicate statistical significance ($p < 0.05$).
CCI = corrected count increment; CFT = clot formation time; MCF = maximal clot firmness; mm = millimeter; Plt = platelet; sec = seconds.
CFT normal value: 35 sec-160 sec.
MCF normal value: 52 mm-72 mm.

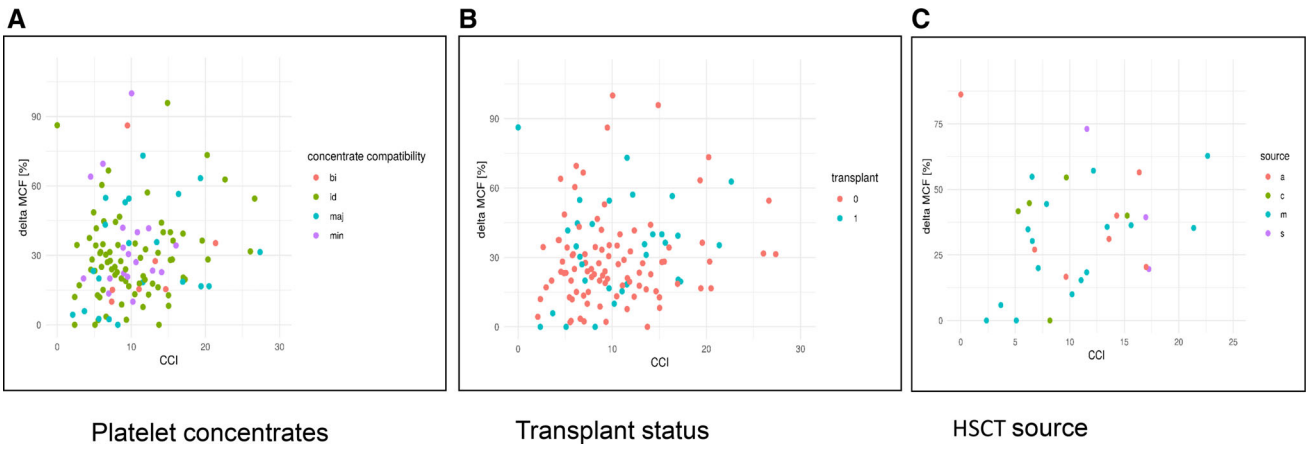

Fig. 1. TEM results showed no correlation between PC-blood group compatibility HSCT status and HSCT source. A shows no association and correlation between improvement of MCF (y-axis), CCI (x-axis), and blood group compatibility between recipient and donor of platelet concentrates (PCs) (colored dots); p > 0.5. B shows no association and correlation between improvement of MCF, CCI, and transplant status (0 = no TX, 1 = TX); p > 0.5. C shows no association and correlation between improvement of MCF, CCI, and source of stem cell graft (a = autologous, c = cord blood, m = matched unrelated donor, s = sibling); p > 0.5. Statistical calculations were done using the Spearman Anova Test, p value <0.5 was considered significant. [Color figure can be viewed at wileyonlinelibrary.com]

(Fig. 1A-C). Also GvHD, fever, or severity of bleeding events did not correlate with TEM measurement results in the overall cohort ($p > 0.05$) (Figs. 2A, B and 3A, B).

DISCUSSION

The aim of the study was to assess the hemostatic effects of PCs treated with the Intercept™ system for PI in a cohort of hemato-oncological patients predominantly during or after HSCT. We further aimed to evaluate whether TEM could be a useful point-of-care test to optimize patients' transfusion management with respect to platelet support.

At our institution, 70% of the about 6,000 annually distributed PCs are given to patients with hemato-oncological disorders in the prophylactic setting. For clinical routine, others and we rely on the PTI and the CCI to assess platelet substitution success in the non-bleeding patient.[25,26] Inadequate PTI often leads clinicians to administer additional PCs even without overt signs of bleeding.

We implemented 100% PI for PCs with the Intercept™ system 7 years ago at our institution. Noteworthy, several studies have demonstrated that transfusion of Intercept™-treated platelets results in lower PTI and lower CCI compared to transfusion of conventional PCs.[27] However, none of these studies indicated higher frequencies of severe bleeding events (Grade 3 and 4 WHO).[27]

TEM investigates the hemostatic potential of whole blood samples and may thereby better reflect platelet transfusion success than PTI or CCI, as hemostatic effects of PCs may not only be mediated by the simple count increase. TEM is strongly recommended by the European Society of Anesthesiology (ESA) as a routine point-of-care test to evaluate hemostasis in the surgical setting.[28] TEM guided support of coagulation factors or PCs is cost-saving and effective.[29,30]

In our study, we observed that PTI and CCI did not correlate with CFT and MCF in TEM measurements (Table 4, Figs. 4A-D). A CCI of >7.500 reflecting successful

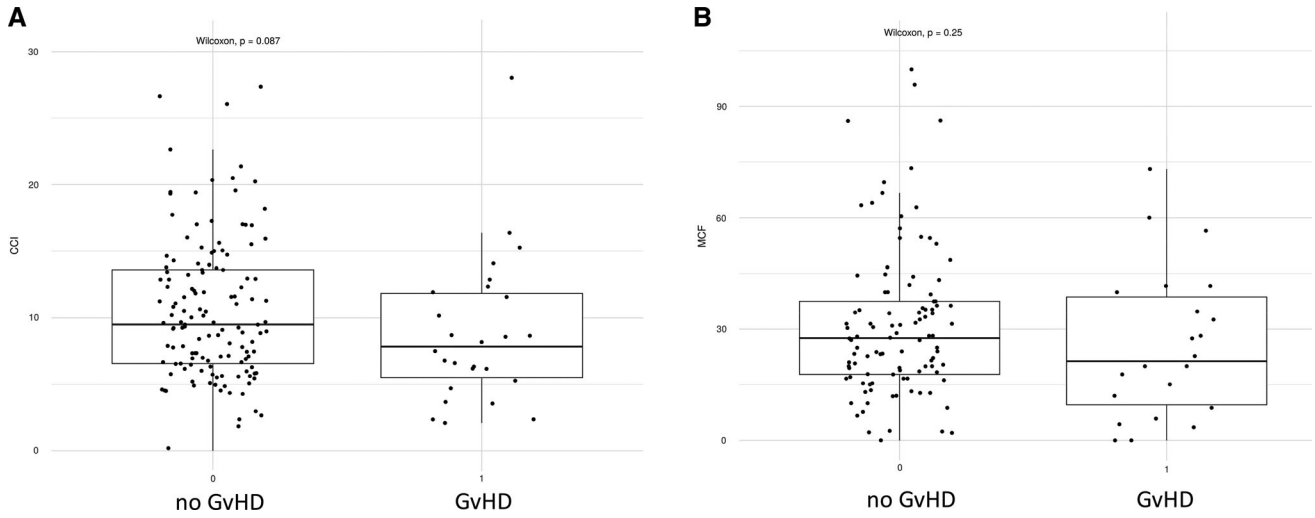

Fig. 2. Impact of the presence or the absence of acute GvHD on corrected count increment (CCI) values and increase in the TEM parameter "maximal clot firmness" (MCF) after platelet transfusion. A shows the influence of GvHD on the CCI (y -axis). CCI was lower in with GvHD but without significance (p = 0.08). B shows the influence of GvHD on increase of posttransfusional MCF which showed no difference (p = 0.28). For statistical analysis the Wilcoxon paired signed rank test applied.

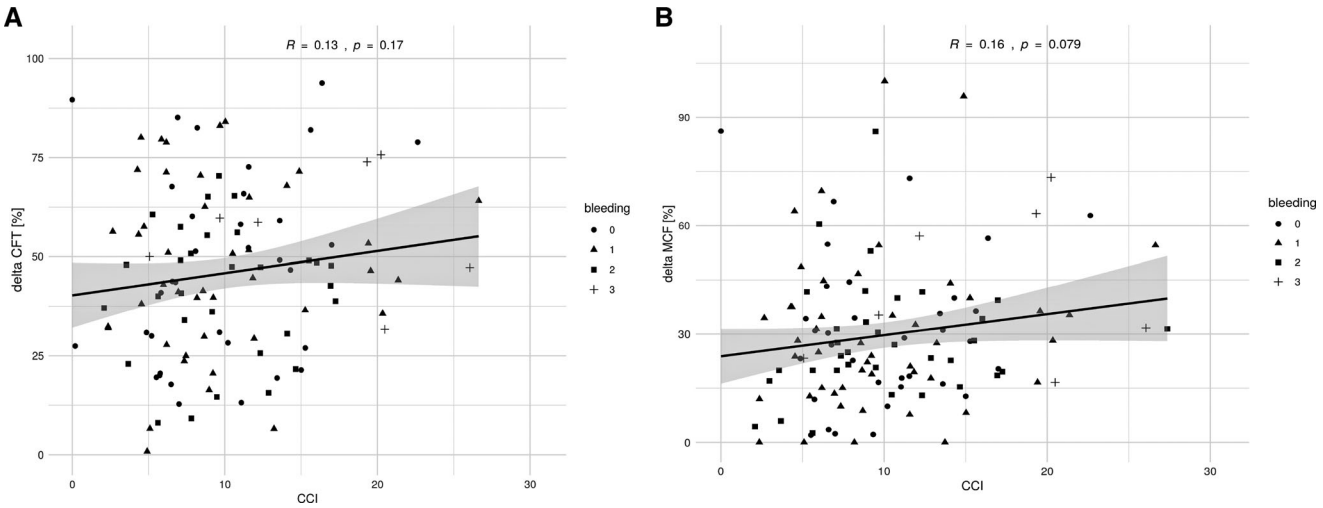

Fig. 3. Post transfusion changes in CFT and MCF (150 transfusions in 47 patients). A shows the shortening of clot formation time (CFT-y axis) following platelet transfusion in patients with and without bleeding in correlation with the corrected count increment (CCI - x axis). Shortening of CFT was observed after almost all platelet transfusions. No correlation between reduction of CFT and CCI could be detected (R = 0.13, p = 0.17) irrespective the bleeding status of patients. Statistical calculations were done using the Spearman Anova Test. B shows the increase of maximal clot firmness (MCF-y axis) following platelet transfusion in patient with and without bleeding in correlation with the corrected count increment (CCI - x axis). Increase of MCF was observed after almost all platelet transfusions. No correlation between reduction of MCF and CCI could be detected (R = 0.16, p = 0.079) irrespective the bleeding status of patients. Statistical calculations were done using the Spearman Anova Test.

platelet transfusion was achieved in 114 of 177 cases (64%). However, a respective significant ($p < 0.05$) decrease of CFT and increase of MCF were observed in 134 (89%) of 150 PC transfusion episodes. This fact may have indicated improved hemostasis in the transfused patients irrespective peripheral platelet counts and the calculated transfusion results.

Previously, the hypothesis was generated that transfused platelets may be not visible in the circulation due to their migration to damaged tissues.[25] This may explain why low post-transfusion platelet values do not necessarily result in an increased risk of bleeding. More recently, investigations on "new platelet production procedures" like PI treatments found that a possible functional platelet impairment

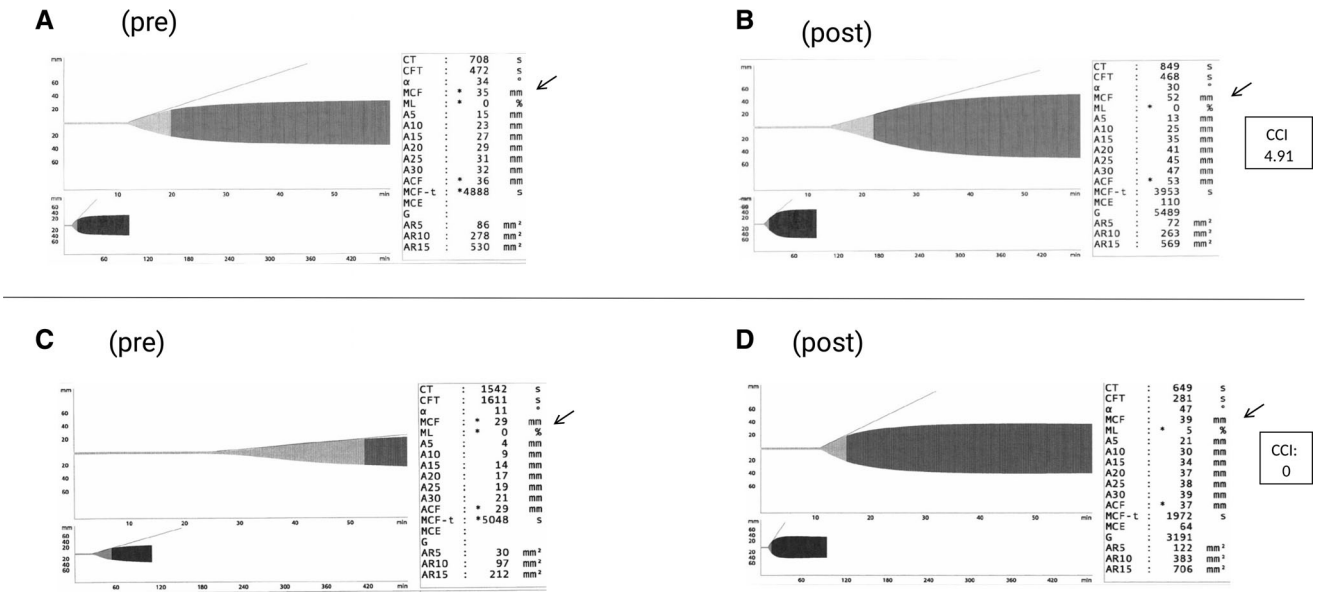

Fig. 4. TEM results post PC support exemplarily of two patients with low CCI values. A and B show a patient who had a normalized MCF after PC support although CCI was below 5000 which indicated possible refractory. C and D show another patient with a significant improved MCF ($p < 0.05$) after PC support although the CCI was 0 (zero), highly suspicious for platelet refractory.

may be compensated for by the formation of platelet-derived pro-coagulant microparticles in these products.[31] The same was shown for new storage conditions like platelet cold storage or cryopreservation.[32] These findings may also explain the discrepancy between standard efficiency parameters (i.e., PTI and CCI) and more functional tests like TEM. In our cohort, platelet-consuming conditions like GvHD or febrile status, sepsis etc. resulted in poor post-transfusion increase combined with poor CCI in five patients and 32 transfusion episodes, but was incoherent with an improvement in TEM parameters in these patients. Furthermore, none of these patients developed a bleeding complication, which both may support the above-mentioned hypothesis.

Importantly, 16 PC transfusions in five patients revealed low post-transfusion TEM results not predicted by CCI (mean 7.500 ± 3.900) or post-transfusion platelet increase (34%, SD 8.6). All five had bleeding events Grade 1 and 2. Regarding the overall cohort, WHO Grade 1 and 2 bleeding (clinically not relevant) occurred in 19 patients, and only one patient experienced a life-threatening WHO Grade 3 bleeding, which may occur in up to 4-9% of HSCT patients.[33]

In the surgical setting, especially in cardiac surgery, bleeding is mainly due to impaired platelet function caused by mechanical damage and/or anticoagulation treatment. In the hemato-oncologic setting bleedings are caused predominantly by low platelet numbers due to impaired production and increased turnover.[34] Twenty-thousand platelets in the peripheral blood were the defined trigger for prophylactic PC support in the non-bleeding patient in our cohort. Clinical conditions and comorbidities like GvHD or sepsis appeared to have had an impact on PTI and CCI ($p = 0.08$) but no negative effect on TEM results ($p = 0.25$) (Fig. 2A, B). One major problem of this study concerned the compliance of included patients with the study protocol, which was limited by the additional venipuncture required for the 1-hour measurements and the low adherence to the writing of the bleeding diary. Despite having given prior informed consent to participate in this study, many patients were not willing to have an additional venipuncture after each platelet transfusion or did not fill in their diary. Therefore, only 177 of 512 PCs could be analyzed. As a second limitation, we could not provide a control group to conduct a comparison between both conventional and PI PCs as all our products are PI-treated as a part of clinical routine at our institution.

In summary, PI-treated platelets using the Intercept™ system were efficient in avoiding severe bleeding complications in our patients. Furthermore, we were able to confirm that transfusion of PI platelets improves hemostasis as measured by TEM.[35] This is an important finding and might be helpful to re-define platelet refractoriness,[36] as PTI and CCI measurements are probably not adequate to define transfusion success when using PCs generated by "new platelet production procedures." In line with this, our findings support TEM measurements as an adjunctive tool for decision making concerning the need for a further prophylactic platelet transfusion in the non-bleeding patient.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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