Ann Hematol (2011) 90:1457–1465
DOI 10.1007/s00277-011-1222-3

ORIGINAL ARTICLE

Safety and clinical efficacy of platelet components prepared with pathogen inactivation in routine use for thrombocytopenic patients

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Received: 15 November 2010 / Accepted: 21 March 2011 / Published online: 19 April 2011
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Abstract This study was conducted to evaluate the safety and efficacy of platelet concentrates (PC) after photochemical treatment (PCT) with the INTERCEPT Blood System™ and transfused in routine use in a population of patients suffering from a variety of hematological diseases. This was an observational, single-arm, open-label study of pooled buffy-coat PC (n=298) or apheresis PC (n=262) treated with INTERCEPT™ and transfused to 51 thrombocytopenic hematology patients. PCT replaced CMV screening and gamma irradiation, and made optional bacterial testing obsolete. The primary study endpoint was the incidence of acute transfusion reactions (ATR). Secondary endpoints included bleeding assessment, platelet count increments, and adverse events (AE). For the 553 transfusions, a total of 55 AE were observed regardless of relationship to platelet transfusion. Ten AE associated with nine transfusions met the criteria for ATR (1.6%). All ATRs were grade 1. Twelve serious AE were reported in 10 patients, none was related to platelet transfusion. Mean 24-h CI and CCI were 10.9×10^9 and 6.6×10^3/L, respectively. No bleeding complications were attributable to the INTERCEPT-treated PC. This study confirms safety and efficacy of pathogen inactivated PC for support of thrombocytopenia and demonstrated that INTERCEPT technology can easily be implemented in routine operations.

Keywords Platelets · Amotosalen · Thrombocytopenia · Pathogen inactivation

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Introduction

Although great improvements in blood safety have been made in recent years, mostly as a result of pre-transfusion donor screening and testing, labile blood components still carry a significant risk of transfusion-transmitted infections (TTI). Firstly and of highest concern is currently the contamination with bacteria. However, the value of bacterial detection as a means for

prevention of transfusion-related sepsis has been controversially discussed and according to recent findings may be insufficient [1, 2]. Secondly, viruses for which no tests are available to date or such viruses not routinely tested for have to be addressed [3, 4]. New and emerging pathogens represent another threat for which the development of test systems can take up to several years [5]. Lastly, there are also logistical and economical limitations to the number of tests which can be added reasonable in routine use.

Another risk is the induction of transfusion-associated graft versus host disease (TA-GVHD) as the result of a co-transfusion of contaminating donor leukocytes. To date the gold standard for the inactivation of all leukocyte subsets is the gamma irradiation [6, 7]. This procedure is only effective when patients at risk for TA-GVHD are recognized and the appropriate component can be provided. The photochemical treatment (PCT) with the INTERCEPT Blood System is based on amotosalen and UVA light that specifically modifies nucleic acids to inhibit DNA and RNA replication and transcription. It has been demonstrated to be effective for both the inactivation of a broad range of pathogens including bacteria, viruses, and protozoa [8–11] as well as leukocytes [12–14]. So, gamma irradiation becomes unnecessary for platelet concentrates (PC).

Previous clinical trials and post-marketing hemovigilance studies have evaluated the safety and efficacy of PCT platelets [15–19]. For the first time in Germany, we have evaluated the clinical safety and efficacy of routinely used INTERCEPT-treated PC in the support of severely thrombocytopenic hematology patients in part with autologous stem cell transplantation.

Materials and methods

Study design This was an open-label, single-arm, single-center study to evaluate the safety and efficacy of PC prepared with pathogen inactivation using INTERCEPT technology in routine use for thrombocytopenic patients. All components were prepared and transfused at the University Hospital Schleswig-Holstein Campus Luebeck, Germany. All transfusions, independent of outcome, were reported on case report forms (CRF). Although this was an observational study, all CRF were monitored and checked against source document for accuracy.

To detect the occurrence of any unexpected deterioration of the patients' health (adverse events, AE) or symptoms of a possible acute transfusion reaction (ATR), all patients were monitored for a period of 24 h after each transfusion. Patients were also followed for 7 days after each transfusion for occurrence of serious AE regardless of relationship to PCT platelets. The primary endpoint was the incidence of ATR after administration of the PC. This was based upon the total number of transfusions administered. The secondary endpoints included the frequency of specific ATR. The observation of bleedings according to WHO criteria was an additional secondary endpoint. Also, the net increase in platelet count 16–24 h after transfusion (count increment, CI) and the platelet increase after transfusion corrected for dose and body surface area (corrected count increment, CCI) were additional secondary endpoints.

Patients Exclusively, adult patients with hematological diseases with thrombocytopenia requiring platelet transfusion support were enrolled ($n=52$). There were no additional patient inclusion or exclusion criteria. The study was approved by the local institutional ethics committee at the University of Luebeck, and all patients gave informed consent to participate. Platelet transfusions were ordered by primary care physicians according to the institutional operating procedure, and patients were managed according to standard clinical practice. Prophylactic platelet transfusions were given when the platelet count reached a threshold of $10–20\times10^9$/L or therapeutically at higher counts for active bleeding or in preparation for an invasive procedure.

Transfusion complications and haemostasis AE were defined as all events occurring after the transfusion regardless of the cause. An ATR was defined as any AE after transfusion with causal relationship to transfusion equal to "possibly related," "probably related," or "related." CRF for ATR were completed for each INTERCEPT platelet transfusion. All severe adverse events (SAE) occurring during the study were recorded on SAE-CRF regardless of the relationship to INTERCEPT and reported within 24 h of occurrence.

Bleeding assessments were performed prior to transfusion for each patient. In case bleeding was present prior to transfusion, posttransfusion bleeding status was also assessed. The respective clinical bleeding status was graded according to the WHO grading system (0, 1, 2, 3, 4; with grade 0, no bleeding) [16] and documented in accordance with WHO hemostatic assessments.

Platelet collection and pathogen inactivation The PC were either derived from pooled random-donor buffy coat (BC) or apheresis platelets suspended in 32–47% plasma and 53–68% platelet additive solution (InterSol™; Cerus B.V., Amersfoort, The Netherlands). For the preparation of apheresis PC (A-PC), the Amicus Cell Separator™

(Fenwal, La Chartre, France) was used and the additive solution was added automatically. The PC was in-process leukoreduced. The BC (volume range 47–67 mL) was prepared according to standard procedures using the Optipress System (Fenwal). Five BC were pooled with 280 mL of InterSol. After a low-speed centrifugation to separate the RBCs, platelet concentrates were leukoreduced with the integrated Sepacell PLX 5 filter.

For pathogen inactivation with the INTERCEPT Blood System for platelets (Cerus B.V.), the bags containing the PC were connected to the INTERCEPT disposable set by sterile tubing welding with the Terumo TSCD device (Terumo, Eschborn, Germany). The addition of 15 mL (for apheresis) or 17.5 mL (for BC) of 3 mM of amotosalen hydrochloride as first step in the integrated INTERCEPT tubing set was followed by illumination at 3 J/cm^2 UVA treatment in the INT 100 Illumination device (Cerus B.V.). Residual amotosalen was reduced in the integrated compound adsorption device (CAD) for 10–16 h at RT (20–24°C) on a shaker.

After the CAD phase, the INTERCEPT-PC were transferred into an integral 1.3-L PL2410 plastic container and stored at RT with agitation for up to 5 days (Fig. 1). During the study, platelet quality was assessed by in-process (100%) or monthly quality controls. Besides measurement of the pH value, the WBC and RBC counts, the residual concentration of amotosalen was quantified by HPLC according to published methods [20] at Focus Laboratory (Neuss, Germany) to ensure a residual amotosalen concentration of <2 μM as specified by the German authorities. In accordance with the marketing authorization of the University of Luebeck granted by the Paul-Ehrlich-Institut in 2007, INTERCEPT treatment replaced gamma irradiation for all PC used in this study. In addition, there was neither bacterial screening conducted nor CMV serology testing results were considered prior to release for patient administration.

Platelet count increment Pre- and posttransfusion platelet counts were performed for each PC. The net and corrected increase in platelet count (CI and CCI) 16–24 h after transfusion was calculated as follows:

$$\mathrm{CCI}\left(10^3\right) = \frac{\frac{\text{Platelet count increment} \times 10^9/\mathrm{L}}{10^6/\mathrm{L}}}{\text{Platelet count} \times 10^{11}/\mathrm{L} \times \text{Platelet volume}(\mathrm{L}) \times 10^{-11}/\mathrm{L}}$$

where

- Platelet CI = post-transfusion count (10^9/L) − pre-transfusion count (10^9/L),
- $\mathrm{BSA}(\mathrm{m}^2) = \mathrm{Wt}(\mathrm{kg})^{0.425} \times \mathrm{Ht}(\mathrm{cm})^{0.725} \times 0.007184$ (per *DuBois and DuBois*),
- The platelet count (10^{11}/L) = Platelet count/100 × (10^9/L), and
- L = liter.

In addition, the mean 16–24 h CI and CCI for the first eight transfusions per patient were determined. An evaluation of these endpoints, stratified to the mean of the first eight transfusions, was also conducted to assess the impact on transfusion response in patients receiving highly variable numbers of transfusions over prolonged periods of platelet support as described by the TRAP and the EuroSprite study groups [15, 21].

Statistics Basic patient information was collected only for descriptive statistical purposes or in case of a SAE requiring more detailed investigations. The primary endpoint was the percentage of transfusions with at least one ACR in relation to the total number of transfusions performed. Transfusions were considered as stochastically independent investigational units. A 95% confidence interval required 542 transfusions with an expected ATR of 6% when the bounds should not extend more than ±2% from the observed rate. A total of 560 transfusions were investigated.

Results

A total of 52 subjects (28 males and 24 females) with a mean age of 57.3 years (range 22–78 years) were enrolled in the study (Table 1). The patients had a spectrum of hematological diseases with acute myelogenous leukemia (AML) representing the majority of cases (40.4%). One third (32.7%) of all patients underwent stem cell transplantation with autologous peripheral blood stem cells in addition to high-dose chemotherapy. One patient with AML, treated with chemotherapy did not receive any PC.

Characteristics of INTERCEPT platelet concentrates Of the 560 PC transfused, 262 units were collected by apheresis and 298 were pooled from BC. Prior to INTERCEPT treatment, the platelet doses of all PC units were within 2.5–6.0 × 10^{11} platelets per unit. The RBC

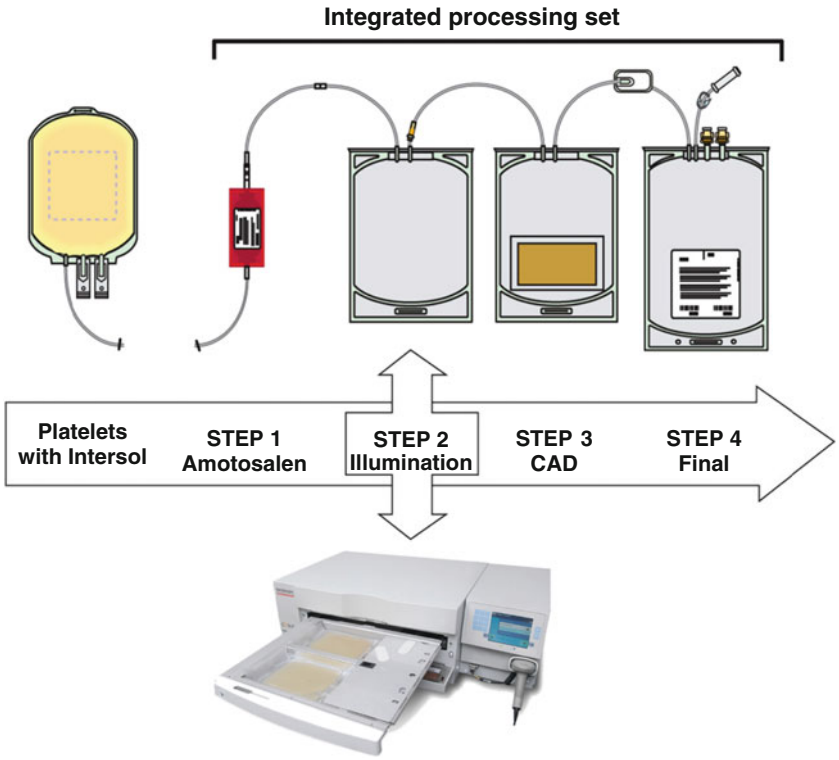

Fig. 1 The INTERCEPT Blood System consists of a UVA illumination device and an integral disposable set. Two units of platelets can be illuminated in parallel per cycle. The processing steps are described in detail in the "Materials and methods" section

contamination was $<4\times10^6$/mL and the WBC content below 1×10^6 per unit meeting QC requirements. After INTERCEPT treatment, the average dose per unit of buffy-coat PC (BC-PC) was $3.4\pm0.5\times10^{11}$ platelets (range 1.9–6.0×10^{11}) in 334.4±10 mL (range 298–361 mL). The average dose per unit of A-PC was $2.8\pm0.3\times10^{11}$ platelets (range 1.8–4.2×10^{11}) in 263.4±9.1 mL (range 212–299 mL) (Table 2). The pH value was within the range of 6.5–7.4 (mean 6.8±0.1) for the A-PC and 6.9–7.1 (mean 7.0±0.1) for the BC-PC. For these parameters more than 90% of all PC met the criteria of product quality which is in accordance with national requirements. For both types of PC, the residual amotosalen concentration after CAD was 0.15 μM (0.125–0.327 μM). These values are significantly

Table 1 Patient demographics: diagnosis and treatment regimen

	Male (*N*=28)[a]	Female (*N*=24)	Total (*N*=52)
	28 (100%)	24 (100%)	52 (100%)
Type of hematological malignancy			
ALL	4 (14.3%)	2 (8.3%)	6 (11.5%)
AML	8 (28.6%)	13 (54.2%)	21 (40.4%)
CLL	1 (3.6%)	0 (0%)	1 (1.9%)
NHL	6 (21.4%)	2 (83.3%)	8 (15.4%)
Other	9 (32.1%)	7 (29.2%)	16 (30.8%)
Current therapy			
Chemotherapy without stem cells	18 (64.3%)	16 (66.7%)	34 (65.4%)
Stem cell transplant with chemotherapy and/or radiotherapy	9 (32.1%)	8 (33.3%)	17 (32.7%)
No therapy	1 (3.6%)	0 (0%)	1 (1.9%)
Source of stem cells			
Autologous	9 (100%)	8 (100%)	17 (100%)
Type of stem cell graft			
PBSC	9 (100%)	8 (100%)	17 (100%)

[a] One male patient with AML, treated with chemotherapy without stem cell transplantation, did not receive any platelet transfusion but was included in the demographic summary

Table 2 Platelet dose and volume by product type

	INTERCEPT apheresis platelets	INTERCEPT buffy-coat platelets	Total
Platelets per unit (10^{11})			
Mean±SD	2.8±0.3	3.4±0.5	3.1±0.5
Median	2.9	3.4	3.1
Min–max	1.8–4.2	1.9–6.0	1.8–6.0
N	259	298	557
Volume per unit (mL)			
Mean±SD	263.4±9.1	334.4±10.0	301.2±36.7
Median	263	335	319
Min–max	212–299	298–361	212–361
N	262	298	560

below the upper limit of 2 μM specified in marketing authorization granted by the Paul-Ehrlich-Institut and the manufacturing license by the local authorities (State of Schleswig-Holstein).

Safety and adverse events A total of 560 INTERCEPT-treated PC were transfused according to standard local practices at the University of Luebeck; of those, 553 transfusions could be analyzed subsequently. Seven transfusions could not be followed as the patients were transferred off the unit and could not be followed. These transfusions were listed but they were not included in the AE or ATR analysis. Fifty-two subjects were enrolled, of which 51 subjects received at least one INTERCEPT platelet transfusion. Information on transfusions per subject is given in Table 3 with the range being 1–71 (average of 11 transfusions) and a median exposure of 6 transfusions per subject.

Of the 553 transfusions analyzed, 55 (9.9%) were associated with at least one AE. A total of 59 AE were reported for the 55 transfusions, that means 4 transfusions were associated with 2 AE. Ten AE were classified as possibly related, probably related, or related to INTERCEPT-PC and considered as an ATR. These 10 ATR were associated with nine transfusions giving the overall rate of ATR on a per transfusion basis of 1.63% (9/553, 95% confidence interval 0.75–3.07%; Table 4). All ATR were of grade 1 (absence of immediate or long-term life-threatening medical conditions). The most frequent signs and symptoms were chills (0.9%), followed by skin rash (0.4%), dyspnea (0.4%), itching (0.2%), and urticaria (0.2%, Table 4). All other signs and symptoms including weakness, elevation of temperature, and lid/brow edema summed up to 0.5%. On a per patient basis, 43% (22/51) of the patients experienced one or more AE regardless of relationship to INTERCEPT-treated PC. The 10 ATR were reported in only 4 of the 51 patients giving an overall rate of ATR on a per patient basis of 7.8% (Table 4).

Table 3 Number of platelet transfusions per patient

Number of INTERCEPT-PC transfusions	Number of patients (%)
Received at least one INTERCEPT-PC	51 (100%)
1 transfusion	6 (11.8%)
>1 transfusion	45 (88.2%)
2–10 transfusions	27 (52.9%)
>11 transfusions	18 (35.3%)
Number of transfusions per patient	
Mean±SD	11±12.5
Min–max	1–71
Median	6.0

A total of 12 SAE occurred in 10 patients during the study period. These events were attributed to progression of underlying illness and were considered unrelated to the transfusion of INTERCEPT-PC by the investigator, with the exception of one patient where the investigator was unable to assess causality accurately.

The most frequent SAE reported were infections (9/51 or 17.6% of patients) and among those, sepsis was reported in 11.8% (or 6/51 of patients, Table 5). One patient experienced an SAE of infection of unknown origin. The second most frequent SAE reported were vascular disorders (4/51 or 7.8% of patients). Five of the 51 patients (9.8%) transfused with INTERCEPT-PC died while on study (Table 6). These patients all showed progression of their hematological disease accompanied by severe neutropenia due to either primary disease or treatment. None of the deaths were classified as related to the transfusion of INTERCEPT-PC.

Platelet count increments The primary efficacy variables were the mean 16–24 h CI and CCI following each transfusion. The mean pre-transfusion platelet count was 14.6×10^9/L; the mean posttransfusion count was 25.5×10^9/L. The mean net increase (CI) of 9.7×10^9/L (apheresis PC) was statistically significant when compared to 12.01×10^9/L (BC-derived PC; p value <0.01, Wilcoxon rank sum test).

Table 4 Clinical characteristics of adverse events

	Transfusions with any events[a]	Transfusions with ATRs attributed to platelets[b]	Patients with any events[a]	Patients with ATRs attributed to platelets[b]
Number of transfusions with at least one event	55/553 (9.9%)	9/553 (1.6%)		
Number of patients with at least one event			22/51 (43.1%)	4/51 (7.8%)
Signs/Symptoms				
Fever	39 (7.0%)	0 (0%)	19 (37.3%)	0 (0%)
Chills	5 (0.9%)	5 (0.9%)	1 (2.0%)	1 (2.0%)
Hypotension	2 (0.4%)	0 (0%)	1 (2.0%)	0 (0%)
Itching	1 (0.2%)	1 (0.2%)	1 (2.0%)	1 (2.0%)
Urticaria	1 (0.2%)	1 (0.2%)	1 (2.0%)	1 (2.0%)
Skin rash	3 (0.5%)	2 (0.4%)	3 (5.9%)	2 (3.9%)
Dyspnea	5 (0.9%)	2 (0.4%)	4 (7.8%)	1 (2.0%)
Nausea/vomiting	1 (0.2%)	0 (0%)	1 (2.0%)	0 (0%)
Shock	1 (0.2%)	0 (0%)	1 (2.0%)	0 (0%)
Other	9 (1.6%)	3 (0.5%)	7 (13.7%)	2 (3.9%)
Acute renal failure	1 (0.2%)	0 (0%)	1 (2.0%)	0 (0%)

[a] Multiple adverse events were reported following some transfusions

[b] Causal relationship based on imputation of possibly related, probably related, or related to INTERCEPT platelet transfusion

However, no significant difference was noted in CCI following administration of either apheresis or BC-derived PC ($p=0.14$, Table 7). The 16–24 h CCI for all transfusions was 6.6×10^3 and 7.2×10^3 or 6.0×10^3 respectively for subset analysis (≤ or >8 PC transfusions). The difference in mean CCI was not statistically ($p=0.07$) significant, although there was a trend for lower CCI after more than eight transfusions (data not shown).

Haemostatic assessments The haemostatic efficacy of INTERCEPT-PC was assessed before and after each transfusion for 24 h. The clinical bleeding status did not change pre-and posttransfusion indicating that the INTERCEPT-PC were efficacious in support of haemostasis and prevention of bleeding. The maximum bleeding scores pre-and posttransfusion were similar. The maximum grade of bleeding occurred prior to transfusion in 393/560 (70.2%) transfusions. The most frequent bleeding score for all organ systems was grade 1. This was observed mostly in the mucocutaneous organ system with slightly lower posttransfusion values than pre-transfusion values. Across all organ systems, fewer patients had grade 1 bleeding posttransfusion than pre-transfusion. One grade 4 gastrointestinal event was observed before transfusion. Two grade 4

Table 5 Summary of patients with serious adverse events but not related to amotosalen or INTERCEPT treatment

Pattern	Primary disease	Neutrophils (/μL)	Suspected source	Contributory factors	Outcome
1	Acute leukemia	<100	Pneumonia	Therapy resistant AML, prolonged neutropenia	Died
2	Multiple myeloma	130	Enterocolitis	Diarrhea	Recovered
3	Acute leukemia	<20	Pulmonary aspergillosis	Relapsed acute leukemia	Died
4	Acute leukemia	<20	*Candida* pneumonia	CNS acute leukemia, pulmonary decompensation	Died
5	NH lymphoma	<100	Gram negative+blood culture	*Clostridium difficile*, diarrhea, acute renal failure	Died
6	MDS/leukemia	<100	Fungal pneumonia	Renal failure	Died
7	NH lymphoma	4,920	None	Blood culture negative, HSCT with engraftment	Recovered
8	Acute leukemia	<100	*Candida* in BAL	DIC, pulmonary infiltrates	Recovered
9	Acute leukemia	<40	*Escherichia coli*+blood culture	Aspiration pneumonia, peritonitis, ascites, colitis, *C. difficile*, pulmonary failure	Recovered

Table 6 Summary of deaths of patients

Patient	Primary disease	Transfusions (*n*)	Contributory factors	Probable cause of death
1	Acute leukemia	31	Severe neutropenia	Fungal pneumonia
2	Acute leukemia	71	Severe neutropenia	Aspergillosis, DIC
3	Acute leukemia	39	Severe neutropenia	Fungal pneumonia
4	NH lymphoma	20	Severe neutropenia	Gram (−) sepsis, ARDS
5	MDS/leukemia	34	Severe neutropenia	Fungal pneumonia

neurological events were observed, one before and one after a PC transfusion.

Discussion

Pathogen inactivation treatment of blood components intended for transfusion is becoming increasingly performed as a safety measure in Europe and some other countries worldwide. This might be in part the result of the conclusions from several international conferences [22] as well as of reports describing the shortcomings of bacterial detection as a means to improve transfusion safety [1, 2]. For platelets a pathogen inactivation technology has to demonstrate its efficacy in prevention of infectious disease transmission without compromising its clinical efficacy in terms of haemostasis. In addition it is crucial that the implementation is easy and does not lead to an increased usage or expiration and wastage of products. The INTERCEPT Blood System has been demonstrated to inactivate a broad range of pathogens in both platelets and plasma components utilizing the same device and applying the same active compound [8–11]. Previous clinical and preclinical studies have demonstrated the safety and efficacy of INTERCEPT-treated PC when given as prophylaxis for bleeding and to treat active bleeding. Indeed, and as demonstrated in the SPRINT trial conducted in the USA, when compared to patients treated with conventional PC, thrombocytopenic patients who received INTERCEPT-treated PC showed a similar rate of grade 2 bleedings [16].

Here, we analyzed the safety and therapeutic efficacy of INTERCEPT-treated PC in routine practice for the support of thrombocytopenic patients for the first time in Germany. All patients in this cohort had hematological diseases (e.g., AML, non-Hodgkin lymphoma) treated with high-dose chemotherapy and about one third received autologous peripheral blood stem cell transplantations. Due to their

Table 7 Count increments based on type of component

	Apheresis platelets	Buffy coat platelets	*P* values	Total
Platelet count pre-transfusion (10^9/L)				
Mean±SD	15.0±8.0	14.3±7.7	0.19	14.6±7.9
Median	15.2	14		7.9
Min–max	1–45	0–49		0–49
N	255	298		553
Platelet count posttransfusion (10^9/L)				
Mean±SD	24.6±14.8	26.3±12.2	0.02	25.5±13.5
Median	23.0	25		24
Min–max	1–81	0–77		0–81
N	253	283		536
24-h platelet count increment (10^9/L)				
Mean±SD	9.7±12.93	12.01±11.25	<0.01	10.92±12.12
Median	7.6	11.0		9.4
Min–max	−19.8 to 62	−19.5 to 57.7		−19.8 to 62
N	250	281		531
24-h platelet corrected count increment (10^3)				
Mean±SD	6.29±8.51	6.81±6.3	0.14	6.57±7.42
Median	5.3	3.4		5.8
Min–max	−15.4 to 35.6	−8.6 to 31.4		−15.4 to 35.6
N	247	281		528

very severe underlying diseases, the patients were at high risk for infection and bleeding complications as well as for development of TA-GVHD. In the course of this study, no case of TA-GVHD, CMV infection, or transfusion-related sepsis were reported, which is especially remarkable since the products were neither gamma irradiated nor additionally tested by bacterial detection measures and the results of CMV testing were not considered. The PC produced for this study were derived either from apheresis or pooled BC. To determine the ease of implementation in routine operation, the robustness of the system and the conformity of the INTERCEPT-treated PC with the local requirements were analyzed in detail. None of the products failed the requirements with respect to WBC or RBC content or residual amotosalen or pH value. In addition, greater than 90% of all PC met requirements for volume and platelet content after the manufacturing process was completed.

CI as well as CCI are still regarded as parameters predictive for the response to platelet transfusions and thus the success of a transfusion [21, 23, 24]. The CI and CCI are affected by both component characteristics and the disease and its treatment regimen. The impact of platelet dose on transfusion outcome is being determined at present in several studies including the PLADO study [25]. It is expected to have an impact on the number of platelets to be administered but we have to await the studies' final conclusions. We routinely determined the 16–24 h CI and CCI and found a statistically significant increase 24 h after transfusion. This increase was independent of type of PC transfused, i.e., pooled BC- or A-PC. A detailed analysis, in which we determined a possible effect of the number of transfusions on the CCI, as described in previous studies [15, 16, 21] by analyzing the CCI for the first eight transfusions did not show a statistically significant difference but a trend toward a reduction in CCI with increasing numbers of transfusions was detectable. The values for both the 24 h CI and the 24 h CCI are in accordance with values described in previous studies with INTERCEPT-treated PC [CCI 24 h=6.6×10^3 in our single-center (Luebeck) observational study versus 6.7×10^3 (SPRINT study)], but more importantly also in such studies analyzing these parameters for conventional, untreated PC. This demonstrates that INTERCEPT-treated PC indeed are comparable in their efficacy to conventional PC. This clinical observation is also in line with the observed in vivo recovery and life span of radio-labeled platelets treated with INTERCEPT after a 5-day storage period [26].

In the course of this study, 560 transfusions of INTERCEPT-treated PC were administered to 51 patients. Data on the response to transfusion were documented for 553 transfusions. The AE being classified as related to transfusion of INTERCEPT-treated PC were infrequent and all of them of mild severity. The focus of our single-center study was on ATR rather than on AE though. The study enrolled an intensely transfused patient population representative of routine clinical practice. Still, the incidence of ATR was low (1.6% per transfusion) and all reported ATR were of mild severity. A positive effect after introduction of INTERCEPT treatment on the rate of ATR has been demonstrated before [17]. A low rate of ATR with mild severity is consistent with the reports on the active hemovigilance studies with INTERCEPT-treated PC. This hemovigilance program is ongoing with >35,000 transfusions being documented and analyzed to date [18, 19]. In the course of the study reported here, a total of 12 SAE occurred in 10 subjects. These events were all attributed to progression of underlying illness and were considered unrelated to INTERCEPT-treated PC.

The SPRINT study analyzed the safety and efficacy of INTERCEPT-treated PC in a large cohort of hemato-oncology patients [16]. The primary endpoint was the proportion of patients with grade 2 bleeding. Secondary endpoints included the proportion of patients with grade 3 and 4 bleedings, 1 h CCI, and 24 h CCI. INTERCEPT-treated PC were found to be equivalent to control PC for prevention of bleeding. This is even more remarkable because it was reported that the platelet dose in the test arm (INTERCEPT-treated PC) was lower than in the control arm as were the CI and CCI values. Our study shows that there was no change in the bleeding status, indicating that the INTERCEPT-treated PC were effective to support haemostasis and to prevent bleeding. Also, it was evident, based on organ system specific data, that most bleedings were determined as bleeding score 1 with the majority involving the mucocutaneous organ system. Fewer patients had bleedings after transfusion than prior to transfusion.

In conclusion, this study extends prior observations that pathogen inactivation with the INTERCEPT Blood System provides PC which are well tolerated in patients requiring intensive platelet transfusion support during high-dose chemotherapy and which seem to be therapeutically adequately effective. It demonstrates that INTERCEPT treatment of PC is safe in routine use even for such at risk patients who are severely immunocompromised and have undergone stem cell transplantation.

Acknowledgment The authors would like to thank Dr. Jocelyne Flament and Valentine Franck for their input into the study design and their role in initiating this study; Aimee Luck-Murphy, Vanessa Harris, Edgar Berger, and Margaret Rheinschmidt for their assistance in monitoring and verifying the entries of all CRFs; and Silke Andresen and Monika Bauhaus for their technical and logistical support of the study.

Financial disclosure This study was supported in part by Cerus Corporation. Four authors (JI, DS, LL, and LC) were affiliated with and held stock or stock options in Cerus Corporation during the conduct of this study. PS received an honorarium for oral presentation.

References

1. Murphy WG, Foley M, Doherty C, Tierney G, Kinsella A, Salami A, Cadden E, Coakley P (2008) Screening platelet concentrates for bacterial contamination: low numbers of bacteria and slow growth in contaminated units mandate an alternative approach to product safety. Vox Sang 95:13–19
2. Schrezenmeier H, Walther-Wenke G, Müller T, Weinauer F, Younis A, Holland-Letz T, Geis G, Asmus J, Bauerfeind U, Burkhart J, Deitenbeck R, Förstemann E, Gebauer W, Höchsmann B, Karakassopoulos A, Liebscher U-M, Sänger W, Schmidt M, Schunter F, Sireis W, Seifried E (2007) Bacterial contamination of platelet concentrates: results of a prospective multicenter study comparing pooled whole blood-derived platelets and apheresis platelets. Transfusion 47:644–652
3. Dodd RY, Notari EP, Stramer SL (2002) Current prevalence and incidence of infectious disease markers and estimated window period risk in the American Red Cross blood donor population. Transfusion 42:975–979
4. Dodd RY, Leiby D (2004) Emerging infectious threats to the blood supply. Annu Rev Med 55:191–207
5. Allain JP, Bianco C, Blajchman MA, Brecher ME, Busch M, Leiby D, Lin L, Stramer S (2005) Protecting the blood supply from emerging pathogens: the role of pathogen inactivation. Transfus Med Rev 19(2):110–126
6. Corash L, Lin L (2004) Novel processes for inactivation of leukocytes to prevent transfusion-associated graft versus host disease. Bone Marrow Transplant 33:1–7
7. Schlenke P (2004) Protection against transfusion-associated graft versus host disease in blood transfusion: is gamma-irradiation the only answer? Transfus Med Hemother 31(suppl 1):24–31
8. Lin L, Dikeman R, Molini B et al (2004) Photochemical treatment of platelet concentrates with amotosalen and long-wavelength ultraviolet light inactivates a broad spectrum of pathogenic bacteria. Transfusion 44:1496–1504
9. Lin L, Hanson CV, Alter HJ et al (2005) Inactivation of viruses in platelet concentrates by photochemical treatment with amotosalen and long-wavelength ultraviolet light. Transfusion 45:580–590
10. Van Voorhis WC, Barrett LK, Eastman RT, Alfonso R, Dupuis K (2003) *Trypanosoma cruzi* inactivation in human platelet concentrates and plasma by a psoralen (amotosalen HCl) and long-wavelength UV. Antimicrob Agents Chemother 47:475–479
11. Eastman RT, Barrett LK, Dupuis K, Buckner FS, Van Voorhis WC (2005) Leishmania inactivation in human pheresis platelets by a psoralen (amotosalen HCl) and long-wavelength ultraviolet irradiation. Transfusion 45:1459–1463
12. Grass JA, Hei DJ, Metchette K, Cimino GD, Wiesehahn GP, Corash L, Lin L (1998) Inactivation of leukocytes in platelet concentrates by photochemical treatment with psoralen plus UVA. Blood 91:2180–2188
13. Grass JA, Wafa T, Reames A, Wages D, Corash L, Ferrera JLM, Lin L (1999) Prevention of transfusion-associated graft-versus host disease by photochemical treatment. Blood 93:3140–3147
14. Hei DJ, Grass JA, Lin L, Corash L, Cimino G (1999) Elimination of cytokine production in stored platelet concentrate aliquots by photochemical treatment with psoralen plus ultraviolet A light. Transfusion 39:239–248
15. van Rhenen D, Gulliksson H, Cazenave J-P, Pamphilon D, Ljungman P, Klueter H, Vermeij H, Kappers-Klune M, de Greef G, Laforet M, Lioure B, Davis K, Marblie S, Mayaudon V, Flament J, Conlan J, Conlan M, Lin L, Metzel P, Buchholz D, Corash L (2003) Transfusion of pooled buffy coat platelet components prepared with photochemical pathogen inactivation treatment: the euroSPRITE trial. Blood 101:2426–2433
16. McCullough J, Vesole D, Benjamin R, Slichter S, Pineda A, Snyder E, Stadtmauer E, Lopez-Plaza I, Coutre S, Strauss RG, Goodnough LT, Fridey JL, Raife T, Cable R, Murphy S, Howard IVF, Davis K, Lin JS, Metzel P, Corash L, Koutsoukos A, Lin L, Buchholz D, Conlan M (2004) Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT trial. Blood 104:1534–1541
17. Cazenave J-P, Waller C, Mendel I, Kientz D, Kandel G, Raidot J-P, Wiesel ML, Laforet M, Isola H (2008) Clinical experience with conventional versus INTERCEPT platelet concentrates transfused to all patients during two one-year periods: reduction of adverse events with equivalent use of blood products. Vox Sang 95(suppl 1):305–306
18. Osselaer J-C, Messe N, Hervig T, Bueno J, Castro E, Espinosa A, Accorsi P, Junge K, Jacques M, Flament J, Corash L (2008) A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment. Transfusion 48:1061–1071
19. Osselaer J-C, Cazenave J-P, Lambermont M, Garraud O, Hidajat M, Barbolla L, Tardivel R, Defoin L, Waller C, Mendel I, Raidot JP, Kandel G, De Meuter R, Fabrigli P, Dehenau D, Arroyo JL, Padron F, Gouezec H, Corral M, Jacquet M, Sundin D, Lin L, Corrash L (2008) An active haemovigilance programme characterizing the safety profile of 7437 platelet transfusions prepared with amotosalen photochemical treatment. Vox Sang 94:315–323
20. Lin L, Conlan M, Tessman J, Cimino G, Porter S (2005) Amotosalen interactions with platelet and plasma components: absence of neoantigen formation after photochemical treatment. Transfusion 45:1610–1620
21. Slichter S, Davis K, Enright H, Braine H, Gemsheimer T, Kao K-J, Kickler T, Lee E, McFarland J, McCullough J, Rodey G, Schiffer CA, Woodson R (2005) Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. Blood 105:4106–4114
22. Klein HG, Anderson D, Bernardi MJ, Cable R, Carey W, Hoch JS, Robitaille N, Sivilotti MLA, Smaill F (2007) Pathogen inactivation: making decisions about new technologies. Transfusion 47:2338–2347
23. Bishop JF, Matthews JP et al (1991) Factors influencing 20-hour increments after platelet transfusion. Transfusion 31:392–396
24. Ishida A, Handa M et al (1998) Clinical factors influencing posttransfusion platelet increment in patients undergoing hematopoietic progenitor cell transplantation—a prospective analysis. Transfusion 38:839–847
25. Slichter SJ, Kaufman RM, Assmann SF et al (2008) Effects of prophylactic platelet (plt) dose on transfusion (tx) outcomes (PLADO Trial). Blood 112(no.11):111
26. Snyder E, Raife T, Lin L, Cimino G, Metzel P, Rheinschmidt M, Baril L, Davis K, Buchholz DH, Corash L, Conlan MG (2004) Recovery and life-span of ^{111}indium-radiolabeled platelets treated with pathogen inactivation with amotosalen HCL(S-59) and ultraviolet A light. Transfusion 44:1732–1740