VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2015) **109**, 343–352

ORIGINAL PAPER

ISBT Science Series published by John Wiley & Sons Ltd on behalf of International Society of Blood Transfusion
DOI: 10.1111/vox.12287

A prospective, active haemovigilance study with combined cohort analysis of 19 175 transfusions of platelet components prepared with amotosalen–UVA photochemical treatment

F. Knutson,[1] J. Osselaer,[2] L. Pierelli,[3] M. Lozano,[4] J. Cid,[4] R. Tardivel,[5] O. Garraud,[6] T. Hervig,[7] D. Domanovic,[8] M. Cukjati,[8] S. Gudmundson,[9] I. B. Hjalmarsdottir,[9] A. Castrillo,[10] R. Gonzalez,[10] D. Brihante,[11] M. Santos,[11] P. Schlenke,[12] A. Elliott,[13] J.-S. Lin,[13] D. Tappe,[13] A. Stassinopoulos,[13] J. Green[13] & L. Corash[13]

[1]*Department of Immunology, Genetics, and Pathology, Uppsala University, Uppsala, Sweden*
[2]*Cliniques Universitaires de Mont Godinne, Universite Catholique de Louvain, Yvoir, Belgium*
[3]*Department of Experimental Medicine, Sapienza University of Roma, Rome, Italy*
[4]*Department of Hemotherapy and Hemostasis, CDB, IDIBAPS, Hospital Clinic, Barcelona, Spain*
[5]*EFS Bretagne, Rennes, France*
[6]*EFS Auvergne Loire, St. Etienne, France*
[7]*Department of Immunology and Transfusion Medicine, University of Bergen, Bergen, Norway*
[8]*Blood Transfusion Centre of Slovenia, Ljubljana, Slovenia*
[9]*Blood Bank, National University Hospital, Reykjavik, Iceland*
[10]*Transfusion Centre of Galicia, Santiago de Compostela, Spain*
[11]*Servico de Imuno-Hemoterapia, Instituto Portugues de Oncologia de Lisboa, Lisbon, Portugal*
[12]*Department of Blood Group Serology and Transfusion Medicine, Medical University of Graz, Graz, Austria*
[13]*Cerus Corporation, Concord, CA, USA*

Vox Sanguinis

Background and Objectives A photochemical treatment process (PCT) utilizing amotosalen and UVA light (INTERCEPT™ Blood System) has been developed for inactivation of viruses, bacteria, parasites and leucocytes that can contaminate blood components intended for transfusion. The objective of this study was to further characterize the safety profile of INTERCEPT-treated platelet components (PCT-PLT) administered across a broad patient population.

Materials and Methods This open-label, observational haemovigilance programme of PCT-PLT transfusions was conducted in 21 centres in 11 countries. All transfusions were monitored for adverse events within 24 h post-transfusion and for serious adverse events (SAEs) up to 7 days post-transfusion. All adverse events were assessed for severity (Grade 0–4), and causal relationship to PCT-PLT transfusion.

Results Over the course of 7 years in the study centres, 4067 patients received 19 175 PCT-PLT transfusions. Adverse events were infrequent, and most were of Grade 1 severity. On a per-transfusion basis, 123 (0·6%) were classified an acute transfusion reaction (ATR) defined as an adverse event related to the transfusion. Among these ATRs, the most common were chills (77, 0·4%) and urticaria (41, 0·2%). Fourteen SAEs were reported, of which 2 were attributed to platelet transfusion (<0·1%). No case of transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, transfusion-transmitted infection or death was attributed to the transfusion of PCT-PLT.

Received: 26 December 2014, revised 24 March 2015, accepted 27 March 2015, published online 15 May 2015

Correspondence: Jennifer M. Green, PhD Cerus Corporation 2550 Stanwell Drive Concord, CA 94520 USA
E-mail: jgreen@cerus.com

Conclusion This longitudinal haemovigilance safety programme to monitor PCT-PLT transfusions demonstrated a low rate of ATRs, and a safety profile consistent with that previously reported for conventional platelet components.

Key words: amotosalen, haemovigilance, INTERCEPT, pathogen inactivation, platelets, safety.

Introduction

Since 2002, the INTERCEPT™ Blood System for platelets (Cerus Corporation BV, Amersfoort, the Netherlands), a PCT process that inactivates viruses, bacteria, protozoa and leucocytes potentially contaminating PLT components with amotosalen and low-energy UVA, has been approved for use in Europe through CE Mark registration. Blood centres in Belgium, Italy, Norway and Spain implemented routine production of PCT-PLT in 2003. Adoption of PCT-PLT components has expanded since then and is currently in routine clinical use in more than 100 blood centres in 20 countries. As of September 2014, over 1·23 million PCT-PLTs have been produced for transfusion to patients.

Postmarketing haemovigilance (HV) programmes that monitor adverse events during routine clinical use extend the safety characterization of new products or technologies. HV studies include a greater number and wider demographic spectrum of patients than are feasible in randomized controlled trials [1–3] and provide additional data about the safety profile of these products. The World Health Organization has issued a recommendation for HV programmes specifically in the field of blood transfusion safety to 'identify and prevent occurrence or recurrence of transfusion-related unwanted events' [4]. The European Haemovigilance Network also recommends surveillance for AEs after transfusion of labile blood components [5–7].

After centres began routine production of PCT-PLT, Cerus implemented an Internet-based, active HV programme to prospectively collect additional safety information. In this study, each PCT-PLT transfusion was reported and documented regardless of whether an AE occurred or not. This HV system was largely modelled after the French HV system for documentation of recipient transfusion incidents [8]. The PCT-PLT HV experience has been partially reported previously in two interim reports [9, 10]. This account provides an aggregate analysis of all 19 175 PCT-PLT transfusions occurring under the HV programme to date and includes data for 6632 additional transfusions.

Materials and methods

Study design

This was a prospective, non-randomized, one-arm, observational, HV study documenting all transfused PCT-PLT components (Table 1) in participating centres. Data presented here represent the total HV experience from three studies: HV1 [10], HV2 [9] and HV3 from inception in October 2003 to December 2010. The objective of the study was to determine the proportion of transfusions associated with an acute transfusion reaction (ATR) following administration of PCT-PLT. There were no randomization requirements, no inclusion criteria other than the need for PLT transfusion and no exclusion criteria of patients.

The study was conducted in accordance with the European regulations governing clinical investigations of medical devices and the International Conference on Harmonization Guideline for Good Clinical Practice E6 (CPMP/ICH/135/95). No ethical committee approval or patient consent was required as the system is a CE-marked Class III medical device approved for sale in the European Union, and the study was conducted under existing HV programmes in compliance with country law to monitor the impact of new technologies on blood transfusion practice. Patients received transfusions of PCT-PLT components according to the standard institutional practice. Patient confidentiality was preserved through assignment of a centre-specific study number, and sponsor did not have access to any patient files.

Study report forms

Participating centres used a standardized data capture form to record patient characteristics, primary diagnosis, indication for transfusion and clinical observations of AEs [10]. The data collection form was designed based on HV report forms already in use in Europe [11]. A data and safety monitoring board (DSMB) approved the HV report form before utilization and provided oversight of the study. Trained HV personnel from the blood centres recorded patient characteristics and demographics,

Table 1 INTERCEPT haemovigilance study centres

Country	Transfusion centre	Number of platelet transfusions
Belgium	Mont Godinne	7551
Belgium	Erasme	899
Belgium	Brugge	440
Czech Republic	Prague	4
Germany	Lübeck	77
France	Strasbourg	2048
France	St Etienne	854
France	Rennes	501
France	La Reunion	1950
Iceland	Reykjavik	354
Italy	Pescara	2
Italy	Rome	794
Norway	Bergen	634
Norway	Trondheim	139
Portugal	Lisbon	102
Slovenia	Ljubljana	540
Spain	Madrid RC	382
Spain	Leon	381
Spain	Barcelona	356
Spain	Santiago de Compostela	163
Sweden	Uppsala	1004

platelet component characteristics, transfusion events and AE documentation following the transfusion.

A checklist format was used to capture clinical AE symptoms and signs for each transfusion. The checklist documented the presence of fever, chills, cardiac arrhythmia, hypotension, pruritus, urticaria, skin rash, jaundice, pulmonary oedema, bronchospasm, dyspnoea, tachycardia, respiratory distress, nausea, vomiting, lower back pain, chest pain, abdominal pain and shock. AEs not listed on the checklist, such as refractoriness to platelet transfusion, hypertension, cephalea, pain in the leg, flush, malaise, cyanosis, oxygen desaturation, volume overload and transfusion-related acute lung injury (TRALI), were also recorded. Standardized criteria were used to define transfusion-related sepsis, TRALI [12], transfusion-associated circulatory overload (TACO) and transfusion-associated graft-versus-host disease (TA-GVHD).

Safety monitoring

Patients who received PCT-PLT were monitored for any AE with each transfusion. All AEs within the first 24 h and all serious adverse events (SAEs) within 7 days following each transfusion were recorded.

If an AE occurred after transfusion, additional clinical and biological information was collected to allow diagnosis and assessment of causality and severity. AEs were graded using a 0–4 numerical scale from least to most severe [13]: Grade 0: isolated dysfunction without clinical or biological manifestation; Grade 1: absence of immediate or long-term life-threatening effects; Grade 2: long-term life-threatening effects; Grade 3: immediate life-threatening effects; and Grade 4: death.

The clinical investigator at each site independently assessed the relationship of each AE to the preceding PCT-PLT transfusion. An ATR was defined as an AE possibly related, probably related or related to a PCT-PLT transfusion. SAEs (Grade 2–4 reactions) were reported in greater detail with a narrative for each event. All reported SAEs were reviewed by the appropriate national regulatory authority and by the Cerus Drug Safety Officer.

If an AE was reported, temperature, blood pressure and heart rate were recorded. Abnormal clinical laboratory values, results of diagnostic procedures (chest radiograph) and bacterial cultures from patients and blood component sources were documented on the report form when considered by the physician to be associated with an ATR.

Preparation of test materials

PLTs were collected by apheresis or prepared from whole-blood-derived buffy-coat concentrates according to each centre's standard operating procedures. Briefly, volunteer donors were screened and tested for transfusion-transmitted pathogens according to each centre's procedures, and in compliance with relevant national regulations. All components were leucocyte reduced,

either by filtration (Sepacell™ PLS-5A; Asahi Biomedical, Tokyo, Japan; LRP6; Pall Medical, Portsmouth, UK) or process leucodepletion (Amicus Cell Separator, Fenwal, La Chatre, France, Haemonetics MCS+, Haemonetics, Braintree, MA, USA, or Trima, Terumo BCT, Lakewood, CO, USA). Collections containing $2{\cdot}5–6{\cdot}0 \times 10^{11}$ PLTs were suspended in approximately 35% plasma and 65% Inter-Sol™ (Fenwal, Fresenius-Kabi, Lake Zurich, IL, USA) and treated with amotosalen (nominal final concentration 150 μM) and 3 J/cm^2 UVA (320–400 nm) according to manufacturer's instructions for use. After treatment, PCT-PLTs were stored up to 5 or 7 days under temperature-controlled conditions (22 ± 2°C) before release for transfusion. For HV1, PCT-PLTs were transfused before the expiration period of 5 days. For HV2 and HV3, PCT-PLTs were transfused prior to 5 or 7 day storage depending upon regulations of each country.

Statistical analyses

Data were summarized descriptively by mean, standard deviation, median and range (minimum, maximum) for continuous data or by frequencies and percentages for categorical data, using SAS® version 9.3 (SAS Institute, Cary, NC, USA). All PCT-PLT transfusions administered to a patient were included in the full analysis population, and data were summarized on a per-transfusion basis and a per-patient basis. *P* values for ATR and SAE rates were calculated utilizing the two-sided Fisher's exact test.

The primary assessment of safety was the proportion of PCT-PLT transfusions associated with an ATR. Additionally, patient demographics, primary indication for transfusion, the number of PCT-PLT transfusions received, the characteristics of the PCT-PLT transfused, the AEs reported and the time to first reaction were summarized to characterize the safety profile of PCT-PLT. Among patients with at least one AE reported, the number of transfusions received before the first occurrence was also summarized.

Results

The study population from the culmination of three active HV programmes conducted from October 2003 to December 2010 provided a cohort of 4067 patients transfused with 19 175 PCT-PLT components. Of those, 2016 patients receiving 6632 PCT-PLT transfusions have not been previously reported. The geographic distribution of transfusions is presented (Table 1).

Patient characteristics

The majority of the patient population was male (60%; Table 2). The mean age of the combined cohort was 56·7 years of age (range <1–96) with 94% of patients greater than 18 years of age. The diagnostic indication for platelet transfusion was a haematology disorder (50·1%), or intra- or peri-operative support during surgery (17·5%). Diagnoses other than these accounted for 32% of patients. Of patients being treated for a haematology disorder, 42·4% were receiving conventional chemotherapy and 11·8% received a hematopoietic stem cell transplant (HSCT). The diagnosis was not specified for 19 patients (0·5%).

In the study population, 61·8% had received a blood product prior to the first PCT-PLT transfusion. Among these patients, 5·1% had a history of a transfusion reaction. PCT-PLT transfusions occurred mainly in non-intensive care, inpatient hospital settings. The remaining transfusions were administered in the intensive care unit or in outpatient clinics (Table 2).

Platelet component characteristics

There was a shift over time in the PLT production method used in the participating centres from apheresis collections to whole-blood buffy-coat extraction (Table 3). The majority of centres (97%) elected to use PCT-PLT without γ-irradiation for patients at risk of TA-GVHD based on reported data showing that INTERCEPT effectively inactivates T cells [14]. Additionally, only 1·9% of the units were human leucocyte antigen (HLA) matched (Table 3).

Number of transfusions per-patient

Approximately 56% of patients received multiple transfusions of PCT-PLT during the study. The mean number of transfusions received for each patient for the entire cohort was 4·7 (range 1–156) (Table 4). Of the 4067 patients, 44·1% received only one PCT-PLT transfusion, 27·9% patients received two to three transfusions, and 28·1% patients received four or more transfusions. Platelet usage was greater for patients diagnosed with haematologic disease where the mean number of transfusions per patient was 7·0 (Table 4).

AEs and ATRs following PCT-PLT transfusion

On a per-patient basis, the proportion of patients who experienced any AE, regardless of the grade or cause, was 3·1% (126/4067 patients; Table 5). Of these, 94 patients (2·3% of study population) were classified with an ATR possibly related, probably related or related to PCT-PLT transfusion. Only 13 patients (0·3%) were classified with a SAE; however, all but 2 were judged as unrelated to PCT-PLT and assigned alternative causes for the signs and symptoms by the investigators. No cases of TRALI,

Table 2 Patient and transfusion demographics

	Per-patient basis (N = 4067)	Per-transfusion basis (N = 19 175)
Sex		
Male	2441 (60·0%)	11 467 (59·8%)
Female	1622 (39·9%)	7703 (40·2%)
Unknown	4 (0·1%)	5 (<0·1%)
Age (years)		
Mean (SD)	56·7 (19·9)	
Median	61	
Minimum–Maximum	0–96	
Location of transfusion		
Intensive care unit		2835 (14·8%)
Outpatient		1164 (6·1%)
Regular ward		15 170 (79·1%)
Unknown		6 (<0·1%)
Haematology–Oncology patients	2038 (50·1%)	14 349 (74·8%)
Conventional chemotherapy	1725 (42·4%)	11 898 (62·0%)
Stem cell Transplant	478 (11·8%)	3231 (16·9%)
Surgery patients	710 (17·5%)	1317 (6·9%)
Cardiovascular surgery	593 (14·6%)	1025 (5·3%)
Solid organ transplantation	79 (1·9%)	192 (1·0%)
Other diagnosis	1300 (32·0%)	2856 (14·9%)
Missing diagnosis	19 (0·5%)	653 (3·4%)
History of a previous transfusion		
Yes	2512 (61·8%)	12 771 (66·6%)
No	1176 (28·9%)	5308 (27·7%)
Unknown	378 (9·3%)	1095 (5·7%)
Missing	1 (<0·1%)	1 (<0·1%)
If history of previous transfusion – did they experience an ATR?		
Yes	127 (5·1%)	1338 (10·5%)
No	2272 (90·4%)	11 078 (86·7%)
Unknown	112 (4·5%)	352 (2·8%)
Missing	1 (<0·1%)	3 (<0·1%)

Table 3 PCT-PLT component characteristics

HV study	Patients	Transfusion episodes	% Buffy coat	% Apheresis	% γ-Irradiated	% HLA matched
HV1 [10]	651	5106	8·0	92·0	2·7	3·1
HV2 [9]	1400	7437	35·2	64·8	1·1	2·5
HV3	2016	6632	58·8	41·2	5·3	0·3
Total	4067	19 175	36·1	63·9	3·0	1·9

HLA, human leucocyte antigen; HV, haemovigilance.

TA-GVHD and no deaths due to PCT-PLT transfusions were reported. Additionally, consistent with the rationale for pathogen reduction, no transfusion-transmitted infection occurred.

On a per-transfusion basis, 167 of 19 175 transfusions resulted in an AE (0·9%). Of those, 123 transfusions (0·6%) were classified as ATRs. Only 14 transfusions (0·1%) resulted in SAEs, of which 2 (<0·1%) were classified as ATRs attributed to PCT-PLTs.

Patients with primary haematological disease (n = 2038) demonstrated a greater probability of ATRs (4·3%, $P < 0·001$) than found for the rest of the cohort. However, the rate of SAE experienced by this population was the same (0·3%). Interestingly, cardiovascular surgery

Table 4 Number of transfusion episodes per-patient group[a]

Number of transfusions	Per-patient basis
Total patient population (n = 4067)	
Mean (SD)	4·7 (9·9)
Median	2
Minimum–Maximum	1–156
1	1794 (44·1%)
2	804 (19·8%)
3	328 (8·1%)
≥4	1141 (28·1%)
Paediatric patients (n = 242)	
Mean (SD)	4·6 (8·4%)
Median	2
Minimum–Maximum	1–66
1	109 (45·0%)
2	49 (20·2%)
3	16 (6·6%)
≥4	68 (28·1%)
Neonate patients (n = 46)	
Mean (SD)	2·0 (2·0)
Median	1
Minimum–Maximum	1–9
1	31 (67·4%)
2	8 (17·4%)
≥4	7 (15·2%)
Haematology–Oncology patients (n = 2038)	
Mean (SD)	7·0 (13·1)
Median	3
Minimum–Maximum	1–156
1	649 (31·8%)
2	346 (17·0%)
3	190 (9·3%)
≥4	853 (41·9%)
Cardiovascular patients (n = 593)	
Mean (SD)	1·7 (1·7)
Median	1
Minimum–Maximum	1–24
1	391 (65·9%)
2	116 (19·6%)
3	34 (5·7%)
≥4	52 (8·8%)

[a]One transfusion episode is equivalent to one PCT-PLT component.

patients (n = 593) experienced a lower ATR rate (0·3%, $P < 0·001$) and a similar SAE rate (0·5%, $P = 0·421$) compared to the rest of the patient population.

Paediatric patients (n = 242) experienced a similar ATR rate (3·7%, $P = 0·179$) and SAE rate (0·4%, $P = 0·550$) when compared with adults. No paediatric patient experienced an SAE judged to be related to PCT-PLT. Additionally, the number of PLT transfusions per patient received by paediatric patients was similar to the total study population (Table 4). No AEs occurred in neonate patients under 28 days old (n = 46).

Characteristic of clinical signs and symptoms associated with ATRs

The most common clinical characteristics of ATRs per-patient were chills (1·5%) and urticaria (0·9%) (Table 5). The other reported ATRs were reported in 0·6% or less of patients for each symptom (Table 5). The symptoms observed, their frequencies and the clinical severities were similar in this study as to those reported for conventional PLT [15–23]. Most ATRs were described by investigators as Grade 1 in severity.

On a per-transfusion basis, the most frequently observed ATR symptom was chills reported for 77 of 19 175 transfusions (0·4%). Urticaria was observed after 0·2% of transfusions. Additional signs and symptoms were present with 0·1% or less of transfusions (Table 5).

Cardiac and respiratory events

The subset of AEs specific to the system order class for cardiac disorders and respiratory, thoracic and mediastinal disorders were summarized (Table 5). There were 10 transfusion recipients with cardiac disorder AEs: seven were tachycardia (0·2%) and three were cardiac arrhythmia (<0·1%). The majority of these events were Grade 1 in severity, and consistent with reported observations in transfusion recipients. Adverse events in the respiratory, thoracic and mediastinal disorders categories were present in 22 patients (0·5%) and were most frequently due to dyspnoea (19 patients) (Table 5). Respiratory distress was observed in three patients (<0·1%), and there was 1 case (<0·1%) of bronchospasm. No cases of TRALI or anaphylaxis were reported for haematology–oncology patients within the period of observation despite repeated exposure to PCT-PLT.

Further analysis of the reported AEs in the cardiac and respiratory system organ class revealed classification of six cardiac events (0·1% of patients) and 13 respiratory events (0·3% of patients) as ATRs, the majority of which were Grade 1 (Table 5). Of these, 5 were cases of tachycardia, 1 was a case of arrhythmia, 12 were cases of dyspnoea, and one was a case of bronchospasm.

SAE following platelet transfusion

During the course of the programmes, a total of 13 patients (0·3%) experienced AEs classified as SAEs. Eleven of the 13 SAEs were assessed to be 'unrelated or probably unrelated' to the PCT-PLT transfusion and were attributed to the progression of underlying disease. The remaining 2 SAE were described by the investigator as 'possibly related' to the PCT-PLT transfusion.

Table 5 Clinical characteristics of AE and transfusion reactions

	Per-transfusion basis (n = 19 175)				Per-patient basis (n = 4067)			
	Any AEs	AE attributed to platelets (ATR)	SAE	SAE attributed to platelets	Any AEs	AE attributed to platelets (ATR)	SAE	SAE attributed to platelets
Transfusions with at least one event Signs/Symptoms[a]	167 (0·9%)	123 (0·6%)	14 (0·1%)	2 (<0·1%)	126 (3·1%)	94 (2·3%)	13 (0·3%)	2 (<0·1%)
Fever	40 (0·2%)	26 (0·1%)	3 (<0·1%)	0	36 (0·9%)	23 (0·6%)	3 (0·1%)	0
Chills	99 (0·5%)	77 (0·4%)	4 (<0·1%)	0	76 (1·9%)	59 (1·5%)	3 (0·1%)	0
Pruritus	17 (0·1%)	16 (0·1%)	0	0	15 (0·4%)	14 (0·3%)	0	0
Hypotension	9 (<0·1%)	4 (<0·1%)	6 (<0·1%)	1 (<0·1%)	9 (0·2%)	4 (0·1%)	6 (0·1%)	1 (<0·1%)
Cardiac arrhythmia	3 (<0·1%)	1 (<0·1%)	1 (<0·1%)	0	3 (0·1%)	1 (<0·1%)	1 (<0·1%)	0
Urticaria	43 (0·2%)	41 (0·2%)	1 (<0·1%)	1 (<0·1%)	37 (0·9%)	35 (0·9%)	1 (<0·1%)	1 (<0·1%)
Skin rash	12 (0·1%)	12 (0·1%)	0	0	11 (0·3%)	11 (0·3%)	0	0
Dyspnoea	19 (0·1%)	12 (0·1%)	3 (<0·1%)	0	19 (0·5%)	12 (0·3%)	3 (0·1%)	0
Respiratory distress	3 (<0·1%)	0	3 (<0·1%)	0	3 (0·1%)	0	3 (0·1%)	0
Nausea/vomiting	14 (0·1%)	8 (<0·1%)	3 (<0·1%)	0	11 (0·3%)	6 (0·1%)	2 (<0·1%)	0
Lower back pain	6 (<0·1%)	1 (<0·1%)	0	0	2 (<0·1%)	1 (<0·1%)	0	0
Chest/abdominal pain	3 (<0·1%)	2 (<0·1%)	1 (<0·1%)	1 (<0·1%)	3 (0·1%)	2 (<0·1%)	1 (<0·1%)	1 (<0·1%)
Shock	9 (<0·1%)	1 (<0·1%)	9 (<0·1%)	1 (<0·1%)	8 (0·2%)	1 (<0·1%)	8 (0·2%)	1 (<0·1%)
Bronchospasm	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)	1 (<0·1%)
Tachycardia	8 (<0·1%)	6 (<0·1%)	1 (<0·1%)	0	7 (0·2%)	5 (0·1%)	1 (<0·1%)	0
Platelet refractoriness	2 (<0·1%)	2 (<0·1%)	0	0	2 (<0·1%)	2 (<0·1%)	0	0
Other	27 (0·1%)	15 (0·1%)	6 (<0·1%)	0	25 (0·6%)	14 (0·3%)	6 (0·1%)	0

ATR, acute transfusion reaction; SAE, serious adverse event; AE, adverse event.

[a]Number of signs/symptoms can exceed number of AE due to multiple observed signs/symptoms per AE.

ISBT Science Series published by John Wiley & Sons Ltd on behalf of International Society of Blood Transfusion
Vox Sanguinis (2015) **109**, 343–352

Patient 01-464 developed a haemorrhage during mitral valve surgery and was treated with PCT-PLT and methylene blue-treated fresh frozen plasma. He experienced hypotension after the second study transfusion. One day later, the patient experienced a second hypotensive event after receiving a red blood cell transfusion. The investigator attributed the event as an allergic adverse event related to the PLT transfusion. The patient recovered and was released.

Patient 1868 had a history of aortic valve replacement and bypass. The patient experienced urticaria, bronchospasm, hypotension and chest/abdominal pain after a single transfusion of PCT-PLT and required mechanical ventilation. The patient recovered the same day, and the bacterial culture of the platelet container was negative. No device malfunctions were reported during the preparation of the PLTs, and the patient did not receive any additional transfusions. The investigator considered the events 'possibly related' to the PCT-PLT transfusion.

Number of transfusions prior to the first AE

Among the 126 patients who experienced at least one AE, repeated exposure to PCT-PLT did not appear to increase the likelihood of a transfusion reaction (Table 6). The mean number of transfusions before first AE occurrence was 8·3.

Table 6 Number of PCT-PLT transfusions per patient prior to the first AE

Number of transfusions before first AE	Per-patient basis
Total patient population (n = 4067, 126 AE)	
1	37 (0·91%)
2	16 (0·39%)
3	8 (0·20%)
4	9 (0·22%)
5	5 (0·12%)
6–10	22 (0·54%)
11–19	15 (0·37%)
≥20	14 (0·34%)
Mean (SD)	8·3 (14·6)
Median	4
Minimum–Maximum	1–139
Paediatric patients (n = 242, 13 AE)	
1	3 (1·24%)
2	1 (0·41%)
4	1 (0·41%)
6–10	4 (1·65%)
11–19	2 (0·83%)
≥20	2 (0·83%)
Mean (SD)	9·8 (10·1)
Median	6
Minimum–Maximum	1–30
Haematology–Oncology patients (n = 2038, 111 AE)	
1	26 (1·28%)
2	14 (0·69%)
3	8 (0·39%)
4	9 (0·44%)
5	5 (0·25%)
6–10	20 (0·98%)
11–19	15 (0·74%)
≥20	14 (0·69%)
Mean (SD)	9·2 (15·3)
Median	4
Minimum–Maximum	1–139
Cardiovascular patients (n = 593, 3 AE)	
1	2 (0·34%)
6–10	1 (0·17%)
Mean (SD)	2·7 (2·9)
Median	1
Minimum–Maximum	1–6

AE, adverse event.

Discussion

This active HV programme prospectively monitored routine transfusions of 19 175 PCT-PLT components into 4067 recipients. Only 94 patients (2·3%) experienced an ATR during the study (Table 5). On a per-transfusion basis, 123 transfusions (0·6%) were associated with ATRs (Table 5). The active design of this HV programme stipulated that all transfusions were evaluated, allowing for a greater amount of clinical data to be collected for a large patient population. This approach facilitates the detection of unexpected or low-grade AEs.

There are several published reports on the frequency of ATRs for conventional PLTs that can be used as a comparison to determine whether use of PCT-PLTs is associated with an increased risk. Concurrent to this PCT-PLT HV programme, independent national HV programmes in France and Switzerland documented their experience with PLT transfusions [24]. The Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS), later renamed Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM), has published results from an independent, active HV programme which monitors the routine use of blood components in France. Between 2009 and 2012, approximately 250 000 conventional PLT products were transfused each year. ATR frequency was reported to be 102·88 per 20 000 units (0·5%), 527·9 per 100 000 units (0·5%), 443·2 per 100 000 units (0·4%) and 406·1 per 100 000 units (0·4%) for each year, respectively [17–20].

Swissmedic, the Swiss Agency for Therapeutic Products, also reported results from an independent HV surveillance programme on the frequency and severity of transfusion reactions. In 2008, 155 ATRs were observed after 27 669 transfusions (0·6%) [25]. Analysis of the

combined period from 2009 to 2011 documents 223 ATRs per 66 000 transfusions (0·3%) [23]. Based on the data above, there appears to be no increased risk of ATRs after transfusion of PCT-PLTs vs. conventional PLTs.

The French and Swiss programmes also published the results of their experience utilizing PCT-PLT components. The results reported are consistent with the frequency and type of AEs reported here. The French HV programme from 2009 to 2010 documents the rates of ATRs related to PCT-PLT transfusion to be steady at 0·2% (51 of 21 767 transfusions) and 0·2% (34 per 21 897 transfusions) for each year, respectively. Swissmedic also reported their HV experience for the years 2011–2013. The reported rate of ATRs that were related to PCT-PLT transfusion was 0·3% (251 per 95 515 transfusions) [23], again similar to the results described here.

When patient groups are subdivided by diagnosis, differences in ATR rates were observed. The higher ATR rate observed for patients with haematologic disease may be attributed to the increased number of transfusions this population received (Table 4). Similarly, the decreased ATR rate observed for cardiovascular surgery patients may be due to decreased platelet usage in these patients (Table 4). However, importantly the SAE rate for both these populations was not different than observed for the overall population.

Since country-specific HV programmes do not report on a per-patient basis, it is difficult to determine a baseline rate of transfusion reactions per recipient. Some available literature includes the Trial to Reduce Alloimmunization to Platelets (TRAP) study, which examined the incidence of moderate and severe ATRs in 598 patients with acute myeloid leukaemia receiving 8769 PLT transfusions [16]. The study found that 22% of patients experienced at least one ATR. For this programme, when ATRs were evaluated for only haematology–oncology patients, a significantly lower per-patient (4·3%) and per-transfusion (0·8%) ATR rate was observed. It is thought that the use of platelet additive solution (PAS) during the preparation of PCT-PLTs may partially account for the reduction in ATR incidence. The TRAP study did not utilize PAS during platelet preparation.

Consistent with the suggestion above, a study by Cazenave *et al*. [26] found that the AE rate was significantly less from transfusions of PLTs prepared with 65% T-Sol/35% plasma vs. 100% plasma (2·0% vs. 2·9%, $P = 0·0094$). The AE rate was reported to decrease to 1·7% for transfusions additionally treated with PCT ($P = 0·0214$). A recent study by Tobian *et al*. [27] also demonstrated that the ATR rate was lower for PLTs prepared in 65% PASIII/35% plasma than 100% plasma (1·0% vs. 1·8%, respectively). The 604 patients who received 3884 PLT transfusions suspended in 100% plasma experienced 72 ATR, while the 345 patients who received 1194 PLT transfusion containing PASIII experienced only 12 ATR. Therefore, the use of PASIII resulted in a 46% reduction in ATR.

The absence of reports of TRALI associated with platelet transfusion in this HV programme is important in the view of previous observations in the SPRINT trial of ALI in approximately 5% of HSCT patients [12]. The haematology–oncology patients enrolled in this HV programme were repeatedly transfused and observed for all AEs and SAEs following each transfusion (including respiratory symptoms) for 7 days. Under these conditions, it appears highly likely that probable cases of TRALI would be reported given the intensity of the medical intervention required to diagnose and treat TRALI. Additionally, a similar low frequency of TRALI associated with routine use of PLT components has been observed by the French HV system. From 2008 to 2011, only 2 (0·005%, $n = 82\,383$ transfusions) cases of TRALI occurred after PCT-PLT transfusion and 26 (0·003%, $n = 1\,022\,224$ transfusions) were associated with transfusion of conventional PLTs.

In conclusion, we report the combined 7-year results of an active HV programme designed to monitor all PCT-PLT transfusions at participating centres. Incidence of ATR associated with PCT-PLTs was consistent with the per-transfusion ATR rates of conventional PLTs and at the lower range of ATRs reported per-patient. The clinical experience of 4067 patients receiving 19 175 transfusions has demonstrated that PLT components treated with amotosalen and UV light for pathogen reduction were well tolerated in routine clinical practice.

Acknowledgements

F Knutson, J Osselaer, L Pierelli, M Lozano, J Cid, R Tardivel, O Garraud, T Hervig, D Domanovic, M Cukjati, S Gudmundson, IB Hjalmarsdottir, A Castrillo, R Gonzalez, D Brihante, M Santos, P Schlenke and L Corash contributed to study design and data acquisition. A Elliott, J Lin, D Tappe, A Stassinopoulos, J Green and L Corash contributed to the analysis and interpretation of the data. J Green drafted the manuscript. All authors critically evaluated and revised the manuscript and approved the submitted version. A Elliott, J Lin, D Tappe, A Stassinopoulos, J Green and L Corash are employees and own stock or stock options of Cerus Corporation. M Lozano received research grants from Cerus Corporation. J Osselaer and O Garraud have served on Cerus's European Scientific Advisory Board.

References

1 van Rhenen D, Gulliksson H, Cazenave JP, *et al.*: Transfusion of pooled buffy coat platelet components prepared with photochemical pathogen inactivation treatment: the euroSPRITE trial. *Blood* 2003; **101**:2426–2433

2 McCullough J, Vesole DH, Benjamin RJ, *et al.*: Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial. *Blood* 2004; **10**:1534–1541

3 Janetzko K, Cazenave JP, Kluter H, *et al.*: Therapeutic efficacy and safety of photochemically treated apheresis platelets processed with an optimized integrated set. *Transfusion* 2005; **45**:1443–1452

4 http://www.who.int/bloodsafety/haemovigilance/en/ Accession date 10 April 2015.

5 de Vries RR, Faber JC, Strengers PF: Haemovigilance: an effective tool for improving transfusion practice. *Vox Sang* 2011; **100**:60–67

6 Faber JC: Work of the European Haemovigilance Network (EHN). *Transfus Clin Biol* 2004; **11**:2–10

7 Faber JC: Haemovigilance in Europe: the European Haemovigilance Network. *Transfus Clin Biol* 2001; **8**:285–290

8 Andreu G, Morel P, Forestier F, *et al.*: Hemovigilance network in France: organization and analysis of immediate transfusion incident reports from 1994-1998. *Transfusion* 2002; **42**:1356–1364

9 Osselaer JC, Cazenave JP, Lambermont M, *et al.*: An active haemovigilance programme characterizing the safety profile of 7437 platelet transfusions prepared with amotosalen photochemical treatment. *Vox Sang* 2008; **94**: 315–323

10 Osselaer JC, Messe N, Hervig T, *et al.*: A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment. *Transfusion* 2008; **48**:1061–1071

11 Willaert B, Vo Mai MP, Caldani C. French haemovigilance data on platelet transfusion. *Transfus Med Hemother* 2008; **35**:118–121

12 Corash L, Lin JS, Sherman CD, *et al.*: Determination of acute lung injury after repeated platelet transfusions. *Blood* 2011; **117**:1014–1020

13 Agence Francaise de Securite Sanitaire des Produits de Sante. *Rapport Annuel hemovigilance 2001*. Paris, Agence Francaise de Securite Sanitaire des Produits de Sante, 2001

14 Grass JA, Wafa T, Reames A, *et al.*: Prevention of transfusion-associated graft-versus-host disease by photochemical treatment. *Blood* 1999; **93**:3140–3147

15 Domen RE, Hoeltge GA: Allergic transfusion reactions: an evaluation of 273 consecutive reactions. *Arch Pathol Lab Med* 2003; **127**:316–320

16 Enright H, Davis K, Gernsheimer T, *et al.*: Factors influencing moderate to severe reactions to PLT transfusions: experience of the TRAP multicenter clinical trial. *Transfusion* 2003; **43**:1545–1552

17 Agence Francaise de Securite Sanitaire des Produits de Sante. *Rapport Annuel Hemovigilance 2009*. Paris, Agence Francaise de Securite Sanitaire des Produits de Sante, 2009

18 Agence Francaise de Securite Sanitaire des Produits de Sante. *Rapport Annuel Hemovigilance 2010*. Paris, Agence Francaise de Securite Sanitaire des Produits de Sante, 2010

19 Agence Nationale de Securite du Medicament et des Produits de Sante (2011). *Rapport Annuel Hemovigilance 2011*. Paris, Agence Nationale de Securite du Medicament et des Produits de Sante, 2011

20 Agence Nationale de Securite du Medicament et des Produits de Sante. *Rapport Annuel Hemovigilance 2012*. Paris, Agence Nationale de Securite du Medicament et des Produits de Sante, 2012

21 Swissmedic Haemovigilance Annual Report 2010, 2010

22 Swissmedic Haemovigilance Annual Report 2012, 2012

23 Swissmedic Haemovigilance Annual Report 2013, 2013

24 Cazenave JP, Waller C, Kientz D, *et al.*: An active hemovigilance program characterizing the safety profile of 7483 transfusions with plasma components prepared with amotosalen and UVA photochemical treatment. *Transfusion* 2010; **50**:1210–1219

25 Swissmedic Haemovigilance Annual Report 2008, 2008

26 Cazenave JP, Isola H, Waller C, *et al.*: Use of additive solutions and pathogen inactivation treatment of platelet components in a regional blood center: impact on patient outcomes and component utilization during a 3-year period. *Transfusion* 2011; **51**:622–629

27 Tobian AA, Fuller AK, Uglik K, *et al.* The impact of platelet additive solution apheresis platelets on allergic transfusion reactions and corrected count increment (CME). *Transfusion* 2014; **54**:1523–1529; quiz 1522