Tamiami (AF485263), and Whitewater Arroyo (AF485264). The Genbank accession numbers used for the L segment analysis include: Allpahuayo (NC_010249), Amapari (AY924389), Bear Canyon (AY924390), Chapare (EU260464), Cupixi (NC_010252), Guanarito (NC_005082), Junín (NC_005080, AY819707, AY619640), Machupo (AY624354, NC_005079, AY619644), Oliveros (NC_010250), Pichindé (NC_006439), Pirital (NC_005897), Sabiá (NC_006313), Tacaribe (NC_004292), Tamiami (AY924393), and Whitewater Arroyo (AY924395).
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医薬品 研究報告 調査報告書

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研究報告の概要

○アモトサレンと紫外線A波で光化学処理した血小板輸血7437件の安全性プロファイルを示す能動的血液安全監視プログラム
背景:アモトサレンと紫外線A波で光化学処理した血小板(PCT-PLT)の輸血に関連する有害事象を調べるために能動的血液安全監視プログラムを実施した。輸血5106件の結果がすでに報告されている。我々はさらに7437件のPCT-PLTの結果を報告する。
方法:現行の血液安全監視プログラムの焦点は、PCT-PLT輸血に関連付けられるすべての有害事象を記録することである。有害事象データとして収集したデータは次の通り:輸血開始後の事象発現時間、臨床記述、バイタルサイン、放射線学的検査および細菌培養の結果、事象重症度(グレード0～4)、PCT-PLT輸血との因果関係。
結果:患者1400名(平均年齢60歳、範囲1～96歳)にPCT-PLTが輸血された。患者の大部分(53.4%)は、造血器腫瘍疾患を有し、従来の化学療法(44.8%)または幹細胞移植(8.6%)を要した。PCT-PLT 輸血68件が有害事象と関連付けられた。急性輸血反応(ATR)、PCT-PLT輸血との因果関係が「可能性あり」「可能性高」「確実」に分類された有害事象は発現頻度が低く(n=55, 55/7437=0.7%)、ほとんどがグレード1(即時／長期的な生命の危険なし)であった。患者39名(39/1400=2.8%)が何らかのATRを生じた。最も多く報告された自他覚症状は、悪寒、発熱、蕁麻疹、呼吸困難、悪心、嘔吐であった。5件の有害事象が重症(グレード2以上)であったが、PCT-PLT輸血との因果関係は認められなかった。PCT-PLTの複数回曝露は、ATR発現の確率を増加させなかった。輸血関連急性肺障害と死亡は報告されなかった。
結論:PCT-PLT輸血に関連したATRは発現頻度が低く、ほとんどが軽度であった。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
アモトサレンと紫外線A波で光化学処理した血小板の輸血は、副作用は発現頻度が低く、ほとんどが軽度であったとの報告である。	日本赤十字社では8項目の安全対策の一つとして、不活化技術の導入について、各不活化技術の効果、血液成分への影響、製造作業への影響などについて評価検討を行っている。外国での不活化実施状況や効果、新たな技術、副作用等の情報収集も含め総合的に評価し、導入について関係機関と協議しているところである。

(8)

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ORIGINAL PAPER

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An active haemovigilance programme characterizing the safety profile of 7437 platelet transfusions prepared with amotosalen photochemical treatment

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Vox Sanguinis

Background An active haemovigilance programme was implemented to survey adverse events (AE) associated with transfusion of platelets photochemically treated with amotosalen and ultraviolet A (PCT-PLT). The results of 5106 transfusions have already been reported. Here we report the results of an additional 7437 PCT-PLT transfusions.

Methods The focus of this ongoing haemovigilance programme is to document all AEs associated with PCT-PLT transfusion. Data collected for AEs include: time of event after starting transfusion, clinical descriptions, vital signs, results from radiographs and bacterial cultures, event severity (Grade 0–4) and causal relationship to PCT-PLT transfusion.

Results One thousand four hundred patients (mean 60 years, range 1–96) received PCT-PLT transfusions. The majority of the patients (53·4%) had haematology–oncology diseases and required conventional chemotherapy (44·8%) or stem cell transplantation (8·6%). Sixty-eight PCT-PLT transfusions were associated with AE. Acute transfusion reactions (ATR), classified as an AE possibly related, probably related, or related to PCT-PLT transfusions were infrequent (n = 55, 55/7437 = 0·7%) and most were of Grade 1 severity. Thirty-nine patients (39/1400 = 2·8%) experienced one or more ATRs. The most frequently reported signs/symptoms were chills, fever, urticaria, dyspnoea, nausea and vomiting. Five AEs were considered severe (≥ Grade 2); however, no causal relationship to PCT-PLT transfusion was found. Repeated exposure to PCT-PLT did not increase the likelihood of an ATR. No cases of transfusion-related acute lung injury and no deaths due to PCT-PLT transfusions were reported.

Conclusions Routine transfusion of PCT-PLT is well-tolerated in a wide range of patients. ATRs related to PCT-PLT transfusion were infrequent and most were of mild severity.

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Introduction

INTERCEPT Blood System™ uses a photochemical treatment methodology [PCT: amotosalen plus ultraviolet A (UVA) light] to inactivate viruses, bacteria, protozoa, and leucocytes in platelet (PLT) and plasma components. The PLT system received CE Mark registration in Europe in 2002. Several centres in Belgium, Spain, Norway and Italy began routine production of PCT-PLT in 2003. An active haemovigilance programme was immediately implemented to prospectively collect information on PCT-PLT transfusions administered to patients in routine clinical settings. Prior to CE Mark registration, the safety data of PCT-PLT were primarily obtained from controlled clinical trials with a limited number of patients and predetermined clinical and safety end-points [1–3]. The postmarketing haemovigilance programme provided a means to extend the characterization of the safety profile of PCT-PLT in routine use and in a broad patient population. The results of the first 5106 PCT-PLT transfusions have already been reported [4]. With additional centres in Belgium, Spain and France starting with the routine production of PCT-PLT, the database of this haemovigilance programme has been expanded [5].

In March 2007, the Canadian Blood Services and Héma-Québec organized a consensus conference to provide recommendations and guide decision-making about new pathogen inactivation technologies [6]. The panel, consists of nine healthcare professionals and members of the public, stressed the importance of postmarketing surveillance studies in the introduction of new technologies for blood safety. The panel recommended that specific studies should be mandated by the regulatory authorities and supported by the manufacturers and/or the blood suppliers. Postmarketing surveillance for adverse reactions to pathogen inactivation products should be linked to the national haemovigilance systems if possible. Depending on the new pathogen inactivation technologies implemented, specific additional surveillance outcomes may be identified. The panel also suggested that chronically transfused patients might serve as an ideal surveillance population to identify long-term toxicities of pathogen-inactivated products.

The active haemovigilance programme described in this study is in concordance with these recommendations. Although this programme is not directly linked to a specific country haemovigilance system nor designed to replace any existing haemovigilance system, the format of data collection is modelled after the data collection format of the French haemovigilance system for documentation of transfusion incidents [7]. The focus of the current programme is on all adverse events (AE), serious or non-serious, occurring after the start of PCT-PLT transfusion. Following the recent report of 5106 PCT-PLT transfusions [4], here we report the results of an additional 7437 transfusions of PCT-PLT.

Materials and methods

General study design

This was a prospective observational active haemovigilance study. The objective of this study was to document the transfusion safety profile for approximately 7500 PCT-PLT components prepared with the INTERCEPT Blood System™ for platelets (Cerus Europe BV, Leusden, the Netherlands). These components were prepared in three centres in Belgium (CTS UCL Mont Godinne, CTS Brabant-Hainaut and AZ Sint Jan AV), three centres in France (EFS-Alsace, EFS-Auvergne-Loire and EFS-Bretagne), and one centre in Spain (CHEMCYL Valladolid) and administered to thrombocytopenic patients under standard clinical practice in hospitals. There were no randomization requirements, no inclusion criteria and no exclusion criteria of patients other than the need to receive a platelet transfusion. Baseline demographical information was collected on all study participants. Patients were assigned a centre-specific study number to preserve anonymity.

Patients who received transfusions of PCT-PLT were monitored for any AEs after the start of each platelet transfusion, which is consistent with European Haemovigilance Network recommendations for surveillance of AE to transfusion of labile blood components, and with those of national transfusion services [7,8]. However, in this study, reporting was obligatory for all PCT-PLT transfusions in each participating clinical site. A transfusion report was required for each PLT transfusion regardless of whether or not an AE occurred. In case of occurrence of an AE, additional clinical and biological information was collected to allow diagnosis and assessment of causality and severity. The data in the final database were anonymous and were reported on a per-transfusion basis as well as on a per-patient basis. Transfusions associated with serious AEs were reported in greater detail.

Study report forms

The report form used for this haemovigilance programme was developed on the basis of haemovigilance report forms already in use. Information was collected in several broad categories: patient demographic/diagnosis data, platelet component characteristics, transfusion events and documentation of all AEs following transfusion. An acute transfusion reaction (ATR) was defined as an AE possibly related, probably related, or related to a PCT-PLT transfusion.

AEs were graded for clinical severity within the following categories: 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. For each transfusion, the following

signs, symptoms and specific clinical syndromes were evaluated: fever, chills, cardiac arrhythmia, hypotension, itching, urticaria, skin rash, jaundice, pulmonary oedema, bronchospasm, dyspnoea, respiratory distress, nausea, vomiting, lower back pain, chest pain, abdominal pain, and shock. Any other findings could be entered as free text including refractoriness to platelet transfusion and transfusion-related acute lung injury. The following available clinical signs were recorded before and after each transfusion: temperature, blood pressure and heart rate. Abnormal clinical laboratory values, results of diagnostic procedures (chest X-ray) and bacterial cultures from patient and blood component sources were recorded when associated with an AE following a PCT-PLT transfusion.

Preparation of platelet components

Platelet components were collected by apheresis or from whole blood-derived buffy-coat procedures according to each centre's standard operating procedures. Volunteer donors were screened and tested for transfusion-transmitted pathogens according to each centre's standard operating procedures in compliance with respective national regulations. All components were leucocyte reduced, either by filtration (Sepacell PLS-5A, Asahi Biomedical, Tokyo, Japan) or process leucodepletion (Amicus Cell Separator, Fenwal, La Chatre, France; Haemonetics MCS+, Haemonetics, Braintree, MA, USA). Platelet components containing 2·5 to 6·0 × 10^{11} platelets were suspended in approximately 35% plasma and 65% InterSol™ (Fenwal) and prepared with amotosalen (nominal final concentration 150 μM) and a 3 J/cm^2 UVA light treatment (320–400 nm) according to the manufacturer's instructions for use (Cerus Europe BV). After treatment, PCT-PLTs were stored up to either 5 or 7 days under temperature-controlled conditions (22 ± 2 °C) before release for transfusion depending on country-specific regulations. PCT-PLTs were transfused before the expiration period of 5 days in France and Spain or 7 days in Belgium. PCT-PLTs were not cultured for bacterial contamination prior to release, and PCT was used in place of γ-irradiation for prevention of transfusion-associated graft-versus-host disease in all sites except EFS-Bretagne and EFS-Auvergne-Loire.

Platelet transfusion

PCT-PLT components for transfusion were ordered according to standard indications within each institution. The investigator was requested to report all AEs occurring after starting transfusion without time limitation. The severity of each AE (Grade 0 to 4) and the relationship of each AEs to the preceding platelet transfusion were assessed by the investigator. Serious adverse events were reported in greater detail with a narrative for each event.

Statistical analyses

All statistical analyses, summary tables and data listings were generated using SAS® version 8·2. The primary assessment of safety was the proportion of ATR for the transfusions reported. The safety profile of PCT-PLT transfusions included information on: the number of PCT-PLT transfusions by patient; the patient population profile; the characteristics of the PCT-PLT transfused, and the characteristics of the AE following platelet transfusion.

Data were analysed on a per-transfusion basis as well as on a per-patient basis. All PCT-PLT transfusions administered to a patient were included in the full analysis population, whether or not an AE was observed. Data were summarized for each parameter using descriptive statistics (mean, standard deviation, median, and range).

Statistical tests were performed for the exploration of risk factors only (multivariate logistic regression at 10% significant level). The variables included in the analysis are patient gender, age, previous transfusion history, type of platelet concentrate, γ-irradiation, antigen-matching and primary diagnosis. Variables with descriptive statistics were tested for *P* values and odds ratio. The number and proportion (%) of transfusions with one or more AEs were summarized overall, by seriousness and by relationship to platelet transfusion. Corresponding 95% confidence intervals (CIs) were calculated.

The non-survival analysis method is a univariate analysis of the number of transfusions received before the first occurrence of an AE. Only patients with at least one AE were considered in this analysis.

Results

Distribution of transfusions

A total of 7437 PCT-PLT transfusions were documented between May 2005 and January 2007 and constitute the full analysis population. The distribution of transfusion reports were: 3057 (41·1%) from CTS UCL Mont Godinne, 2048 (27·5%) from EFS-Alsace, 899 (12·1%) from CTS Brabant-Hainaut, 572 (7·7%) from EFS-Auvergne-Loire, 440 (5·9%) from AZ Sint Jan AV, 381 (5·1%) from CHEMCYL, and 40 (0·5%) from EFS-Bretagne.

Patient demographics

A total of 1400 patients underwent transfusion (Table 1). The majority of the patients were male (61·3%) and the mean age was 60 years (range < 1–96 years). Haematology–oncology diseases treated by chemotherapy (44·8%) and stem cell transplantation (8·6%) constituted 53·4% of the primary diagnoses and therapies among the transfused population. A significant number of patients receiving platelet transfusion (17·2%)

Table 1 Patient and transfusion demographics

	Patient characteristics (n = 1400)	Transfusion characteristics (n = 7437)
Gender (n, %)		
Male	858 (61·3%)	4354 (58·5%)
Female	542 (38·7%)	3082 (41·4%)
Unknown		1 (< 0·1%)
Age (years)		
Mean ± SD	60·0 ± 17·8	
Median	63	
(minimum–maximum)	(<1–96)	
Location of transfusion		
Intensive care unit		1145 (15·4%)
Outpatient		382 (5·1%)
Regular ward		5908 (79·4%)
Unknown		2 (< 0·1%)
Haematology–oncology patients	748 (53·4%)	5463 (73·5%)
Conventional chemotherapy	627 (44·8%)	4481 (60·3%)
Stem cell transplant	121 (8·6%)	982 (13·2%)
Surgery patients	241 (17·2%)	480 (6·5%)
Cardiovascular surgery	209 (14·9%)	349 (4·7%)
Solid organ transplantation	32 (2·3%)	131 (1·8%)
Other diagnoses	397 (28·4%)	859 (11·6%)
Missing diagnosis	14 (1·0%)	635 (8·5%)
History of a previous transfusion		
Yes	837 (59·8%)	5029 (67·6%)
No	398 (28·4%)	1927 (25·9%)
Unknown	165 (11·8%)	481 (6·5%)
If 'Yes' – did they experience a transfusion-related adverse event?[a]		
Yes	53 (6·3%)	382 (7·6%)
No	779 (93·0%)	4639 (92·2%)
Unknown	5 (0·6%)	8 (0·2%)

[a]For per-patient basis, the denominator is 837; for per-transfusion basis, the denominator is 5029.

were undergoing cardiovascular surgery or solid organ transplantation. Other diagnoses included haematology–oncology diseases not treated by chemotherapy and/or stem cell transplantation and surgery other than cardiovascular surgery and solid organ transplantation.

Of all patients, 837 patients (59·8%) had already received another blood product before the first PCT-PLT transfusion (Table 1). Among these patients, 53 patients (6·3% of 837) had a history of a transfusion reaction of some type in the past.

Platelet component demographics

Most of the PCT-PLT units were manufactured from apheresis platforms (4822, 64·8% vs. 2615, 35·2% for buffy-coat products). The majority of the PCT-PLTs (7357, 98·9%) were not treated with γ-irradiation [9]. Among the 7437 PCT-PLTs transfused, only 2·5% (189 units) of platelet units were human leucocyte antigen-matched products.

A large proportion of the PCT-PLT components (5908, 79·4%) were transfused in non-intensive care hospital wards (Table 1). Intensive care units and day-hospital units were the location for 15·4 and 5·1% of the PCT-PLT transfusions (1145 and 382 units, respectively). While most of the PCT-PLT components (5463, 73·5%) were administered to haematology–oncology patients, only 480 PCT-PLT components (6·5%) were administered to surgery patients.

The majority of the PCT-PLT components (5029, 67·6%) were administered to patients who had already received another blood component before the first PCT-PLT transfusion (Table 1). Among these transfusions, 382 (7·6% of 5029) PCT-PLT components were transfused to patients reported to have experienced at least one transfusion reaction in the past.

Number of transfusions per patient

The range of PCT-PLT transfusions per patient was 1 to 129, with an average of 5·3 ± 10·8 (median: 2) transfusions per patient. Of the 1400 patients who received PCT-PLT transfusions, 529 patients (37·8%) received only one PCT-PLT transfusion during this study period, 418 patients (29·9%) received two to three transfusions, and 453 patients (32·4%) received more than four PCT-PLT transfusions during the study. The majority of patients who received multiple transfusions had a primary diagnosis of haematology–oncology diseases treated by chemotherapy and/or stem cell transplantation.

Two patients from CTS UCL Mont Godinne received more than 100 transfusions analysed in this haemovigilance plan. One 56-year-old man (J01-636) who was treated by conventional chemotherapy for haematology–oncology disease received 129 PCT-PLT components within an 8-month period (from April 2006 to November 2006). One 72-year-old woman (J01-071) who was also treated by conventional chemotherapy for haematology–oncology disease received 107 PCT-PLT components within a 10-month period (from August 2005 to November 2006).

Adverse events following PCT-PLT transfusion

On a per-transfusion basis, 68 (0·9% of 7437 transfusions, 95% CI: 0·7–1·2%) transfusions were associated with an AE (Table 2). Of which, 55 (0·7% of 7437 transfusions, 95% CI: 0·6–1·0%) were classified as ATR possibly related, probably related, or related to PCT-PLT transfusion. Only five events were classified as serious AEs (0·07%, 95% CI: 0·0–0·2%), and were judged as probably unrelated to the PCT-PLT transfusion based on the observation of alternative causes for symptoms and no evidence of causal relationship to the platelet transfusion. No cases of transfusion-related acute lung injury and no deaths due to PCT-PLT transfusions were reported.

Table 2 Clinical characteristics of adverse events (AE)

	On a per-transfusion basis n (% = n × 100/7437)				On a per-patient basis n (% = n × 100/1400)			
	Any AEs	AE attributed to platelets (ATR)[b]	SAE[a]	SAE attributed to platelets[a,b]	Any AEs	AE attributed to platelets (ATR)[b]	SAEs[a]	SAE attributed to platelets[a,b]
Number with at least one event	68 (0·9%)	55 (0·7%)	5 (< 0·1%)	0 (0·0%)	45 (3·2%)	39 (2·8%)	4 (0·3%)	0 (0·0%)
Signs/Symptoms[c]								
Fever	8 (0·1%)	6 (< 0·1%)	0 (0%)	–	7 (0·5%)	5 (0·4%)	0 (0%)	–
Chills	45 (0·6%)	40 (0·5%)	2 (< 0·1%)	–	31 (2·2%)	28 (2·0%)	1 (< 0·1%)	–
Itching	2 (< 0·1%)	2 (< 0·1%)	0 (0%)	–	1 (< 0·1%)	1 (< 0·1%)	0 (0%)	–
Hypotension	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–
Urticaria	14 (0·2%)	14 (0·2%)	0 (0%)	–	13 (0·9%)	13 (0·9%)	0 (0%)	–
Skin rash	5 (< 0·1%)	5 (< 0·1%)	0 (0%)	–	4 (0·3%)	4 (0·3%)	0 (0%)	–
Dyspnoea	8 (0·1%)	6 (< 0·1%)	1 (< 0·1%)	–	8 (0·6%)	6 (0·4%)	1 (< 0·1%)	–
Respiratory distress	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–	1 (< 0·1%)	0 (0%)	1 (< 0·1%)	–
Nausea/vomiting	8 (0·1%)	5 (< 0·1%)	3 (< 0·1%)	–	5 (0·4%)	3 (0·2%)	2 (0·1%)	–
Lower back pain	6 (< 0·1%)	1 (< 0·1%)	0 (0%)	–	2 (0·1%)	1 (< 0·1%)	0 (0%)	–
Chest/abdominal pain	1 (< 0·1%)	1 (< 0·1%)	0 (0%)	–	1 (< 0·1%)	1 (< 0·1%)	0 (0%)	–
Shock	4 (< 0·1%)	0 (0%)	4 (< 0·1%)	–	3 (0·2%)	0 (0%)	3 (0·2%)	–
Tachycardia	4 (< 0·1%)	3 (< 0·1%)	1 (< 0·1%)	–	3 (0·2%)	2 (0·1%)	1 (< 0·1%)	–
Other	14 (0·2%)	11 (0·1%)	3 (< 0·1%)	–	12 (0·9%)	10 (0·7%)	3 (0·2%)	–

[a]Serious adverse event (SAE): long-term life threatening, immediate life threatening or death.

[b]Causal relationship that was possibly related, probably related, or related to PCT-PLT transfusion.

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

On a per-patient basis, 45 patients (3·2% of 1400 patients) who received at least one transfusion of PCT-PLT experienced the 68 AEs following PCT-PLT transfusions (Table 2). Only 39 patients (2·8% of 1400 patients) experienced the 55 ATRs attributed to the PCT-PLT transfusion. Four patients experienced serious AEs following transfusion; however, no causal relationship to PCT-PLT transfusion could be established.

All AEs regardless of the relationship with the PCT-PLT transfusion occurred within 4 h after the start of the platelet transfusion (mean time: 0·3 ± 0·51 h, 0–3·3 h). The majority of AEs (64, or 94·1% of 68 AEs) occurred in patients who were not premedicated. The other four AEs occurred in patients who were premedicated with antipyretic or antihistaminic drugs, or corticosteroids.

Characteristics of clinical signs and symptoms associated with adverse event

On a per-transfusion basis, the most frequently observed symptoms/signs (≥ 0·1% of the total 7437 transfusions) were fever, chills, urticaria, dyspnoea, nausea and/or vomiting (Table 2). The individual incidence of each of the following signs/symptoms was < 0·1%: itching, hypotension, skin rash, respiratory distress, lower back pain, chest or abdominal pain, shock and tachycardia. All additional symptoms included in the category of other, such as refractoriness to platelet transfusion, hypertension, cephalea, pain in the leg, flush, malaise, cyanosis, oxygen desaturation and volume overload were also reported but with an individual incidence of less than 0·1%. Most of ATRs were described principally as Grade 1 chills and urticaria (Table 2).

On a per-patient basis, the most frequently observed symptoms/signs (≥ 0·5% of the total 1400 patients) were fever, chills, urticaria and dyspnoea (Table 2). Approximately 0·1–0·4% of the population (from 2 to 5/1400) experienced the following signs/symptoms: skin rash, nausea/vomiting, shock, lower back pain and tachycardia. Clinical refractoriness to transfusion, hypertension, headache and flushing were additional symptoms reported in the category of 'other'. Less than 0·1% of the study population (only 1/1400) experienced the following signs/symptoms such as hypotension, itching, respiratory distress and chest/abdominal pain. Symptoms such as pulse increase, leg pain, cyanosis, oxygen desaturation, malaise and/or volume overload were also reported in the category of 'other'. Most of the ATRs consisted of various combinations of fever (0·4%), chills (2·0%), urticaria (0·9%), skin rash (0·3%), dyspnoea (0·4%), nausea/vomiting (0·2%), tachycardia (0·1%) and others symptoms (0·7%) (Table 2).

Serious adverse events following platelet transfusion

During the course of this surveillance, five serious AEs were reported following transfusion of PCT-PLT (0·07%, 95% CI: 0·0–0·2). These serious AEs were assessed by the investigators as being 'unrelated or probably unrelated' to the PCT-PLT transfusions and were attributed to progression of underlying illness.

Patient B01-201 was admitted to hospital for a presumed pulmonary infection postchemotherapy. Additional co-morbidities at the time of admission were septic shock, acute renal insufficiency, neutropenia and thrombocytopenia. Intravenous (i.v.) antibiotic therapy was initiated and multiple transfusions of blood products (including PCT-PLT) were administered. One hour after administration of the second platelet unit, the patient complained of dyspnoea, respiratory distress was found to be hypotensive and tachycardic. Severe volume overload was determined to be the aetiology and treatment with oxygen, diuretics, and dialysis was initiated. The event was assessed by the investigator to be unrelated to the PCT-PLT transfusion.

Patient J01-382 experienced chills, nausea and sudden hypotension during transfusion with PCT-PLT. Prior to this, the patient had received at least four PCT-PLT transfusions with no AE. The transfusion was stopped and the patient was treated with i.v. fluids and recovered. Four days later, the patient experienced a second hypotensive episode after transfusion, which was spontaneously resolved. Subsequent to this, the patient received 19 additional PCT-PLT transfusions without any clinical sequelae. This patient did not receive any angiotensin-converting enzyme (ACE) inhibitors. Based on the patient's history and the lack of transfusion reaction with the subsequent transfusions, the investigator assessed both of these events as probably unrelated to PCT-PLT transfusion.

Patient J01-516 was admitted for ischaemic cardiomyopathy and underwent double vessel coronary artery bypass graft (CABG). The patient's postoperative recovery was complicated by a significant decrease in blood pressure, which occurred 10 min after start of transfusion of PCT-PLT. Despite vasopressor support and a 6-min period of circulatory arrest, the patient's condition continued to deteriorate and he died. Cause of death was attributed to an aortic dissection with major disseminated intravascular coagulopathy and mesenteric infarct and was assessed by the investigator as unrelated to the PCT-PLT transfusion.

Patient J01-780 experienced a hypotensive episode, cyanosis, oxygen desaturation and nausea approximately 30 min after receipt of PCT-PLT. The patient received oxygen therapy to treat the event and recovered. The patient had received two units of PCT-PLT before and one unit after this event with no adverse reactions. The patient had a history of hypotensive episodes, which occurred in the absence of transfusions. Based on the patient's history, the event was assessed by the investigator as probably unrelated to the PCT-PLT transfusion.

Risk factors associated with adverse event

The risk for AE was not correlated with the patient gender, age, or antigen-matching. The risk for AE for patients who already had been transfused before the first PCT-PLT transfusion appeared trending higher compared to patients who did not have any transfusion history; however, the difference did not reach statistical significance ($P = 0·0675$; odds ratio: 1·875; 95% CI: 0·956–3·648). Buffy-coat-derived platelets were associated with a lower risk for AE compared to apheresis products ($P = 0·0305$; odds ratio: 0·473; 95% CI: 0·240–0·932). Irradiated PCT-PLTs were of similar risk for AE compared to non-irradiated PCT-PLTs ($P = 0·0848$; odds ratio: 6·344; 95% CI: 0·776–51·862). No trending can be concluded because, of the total 7437 platelet transfusions, only 80 PCT-PLT components were γ-irradiated in EFS-Bretagne and EFS-Auvergne-Loire. Haematology-oncology patients treated with conventional chemotherapy were at a higher risk for AE compared to the other patients ($P \leq 0·0001$; odds ratio: 7·660; 95% CI: 3·014–19·467).

Number of transfusions prior to the first adverse event

Among the 45 patients who experienced at least one AE, repeated exposure to PCT-PLT did not appear to increase the likelihood of a transfusion reaction (Table 3). By using the non-survival analysis method (a subset analysis for patients with any AE only), the mean number of transfusions before first AE occurrence was 8·8 ± 10·1 (median = 4, minimum = 0 and maximum = 37).

Discussion

In accordance with the recommendations made by the panel of the Canadian Consensus Conference, an active haemovigilance programme has been implemented in Europe to document the occurrence of AE following transfusion of PCT-PLT [6]. To date, two reports have been prepared. The first report was on the transfusion of 5106 PCT-PLT components administered to patients in five European centres from October 2003 to December 2005 [4]. The second report as described here was on additional 7437 transfusions of PCT-PLT administered to patients in seven European centres between May 2005 and January 2007. This represents a total of 12 543 independent transfusions documented to date. There are no overlaps of PCT-PLT transfusions reported in this haemovigilance programme.

Overall, the incidence of ATR attributed to transfusion of PCT-PLT in both of the haemovigilance reporting periods was infrequent either on a per-transfusion basis (0·8% first period

Table 3 Number of PCT-PLT transfusions per patient prior to the first adverse event (AE)

Number of PCT-PLT transfusions per patient until first occurrence of AE	Full analysis population (n = 1400)
1	11 (0·79%)
2	6 (0·43%)
3	3 (0·21%)
4	3 (0·21%)
5	1 (0·07%)
6–10	9 (0·64%)
11–19	6 (0·43%)
≥ 20	6 (0·43%)
N (non survival analysis method)	45
Mean ± SD	8·8 ± 10·1
Median	4
Minimum–maximum	0–37

vs. 0·7% second period) or on a per-patient basis (4·9% first period vs. 2·8% second period). The slightly higher occurrence of ATR per patient in the first reporting period was not surprising, because the mean number of transfusions per patient (7·8 ± 16·2) [4] was greater than those observed in the second period (5·3 ± 10·8). All ATRs were mild in severity and of Grade 1 or lower. No serious AE from both study periods were attributed specifically to transfusion of PCT-PLT.

On a per-transfusion basis, the prevalence of ATR has been reported in the literature to range from 18 to 31%; however, these studies were conducted some years ago with variable methods of platelet preparation [10–13]. More recently, the incidence of moderate and severe ATR has been reported from the trial to reduce alloimmunization to platelets (TRAP) study, which examined 8769 platelet transfusions in 598 patients during induction therapy for acute leukaemia [14]. In the TRAP study, platelet components were prepared by four methods: unfiltered pooled whole blood-derived platelets in plasma; filtered pooled whole blood-derived platelets in plasma; unfiltered pooled whole blood-derived platelets in plasma treated with ultraviolet B illumination to reduce human leucocyte antigen sensitization; and filtered apheresis platelets in plasma. None of these components were prepared with additive solutions. The overall incidence of ATR was 2·2% of transfusions, and 22% of patients experienced at least one ATR. In comparison to the TRAP trial, the current study in which all grades of reactions were reported, both the proportion of transfusions associated with a reaction was lower (0·7%) as well as the proportion of patients (2·8%) experiencing at least one ATR. The use of 65% InterSol, a platelet additive solution, in the preparation of PCT-PLT may partially contribute to the reduction in the observed incidence of ATR [15].

The incidence of ATR in this study can be compared to data from the haemovigilance network in France [7]. In France, data were reported for transfusion reactions, with an incidence of four events per 1000 platelet components (0·4%), during 2 years in which the reporting system was first implemented. However, this may be an underestimate since each whole blood platelet concentrate in a pool was tabulated as an individual component transfusion. More recently, Kerkhoffs *et al.* [16] compared the incidence of transfusion reactions for leucoreduced pooled platelet components in plasma and plasma with additive solution in a study of 168 patients and 765 transfusions. They observed an incidence of 5·5% of transfusions with reactions for platelets in plasma vs. 2·4% of transfusions for platelets in a mixture of plasma and additive solution. On a per-patient basis, 9·5% of patients transfused with platelets in plasma plus additive solutions had reactions compared to 15·5% of patients supported with platelets suspended in plasma. These results further support the role of the platelet additive solution, InterSol, in the reduction of ATR observed in this study.

During the conduct of this study, an interim analysis of 2497 PCT-PLT transfusions administered to 606 patients in the three regions of France (EFS-Alsace, EFS-Auvergne-Loire and EFS-Bretagne) was performed [5]. Of the 606 patients, the predominant recipients of PCT-PLT were haematology-oncology patients (46·2%); 39·9% treated with chemotherapy and 6·3% treated with stem cell transplantation. These proportions were only slightly lower than those in the overall study population of 1400 patients, yet only four of the 606 patients (0·7%) reported an AE, including one serious AE of volume overload classified as unrelated to PCT-PLT transfusion. This low rate of AE observed in the French regions could contribute to the overall low incidence of ATR per patient in this study.

Premedication in patients did not play a role in the overall low incidence of ATR reported in this study. Information on premedication was only requested in case of AE occurrence. Of the 68 transfusions with occurrence of at least one AE, only two antipyretic, two antihistaminic and one corticosteroid were prescribed to patients. For the majority (64/68, or 94·1%) of these transfusions, patients were not premedicated.

The active haemovigilance programme described here is a prospective observational study, which was designed to assess the safety profile of PCT-PLT in routine clinical practice. The data from this programme represent the largest prospective experience to date for recording potential AE associated with platelet transfusions compared to prior studies of retrospective design and limited in size [10,16–18]. The present study was designed to be consistent with European haemovigilance practices in which reporting of all grades of transfusion-associated reactions has been emphasized [7,8]. In contrast to other haemovigilance studies, obligatory reporting for all platelet transfusions was required irrespective of whether or not an AE was observed. The current study focused on AE that could be linked to PCT-PLT transfusions after starting transfusion, but there were no specific limitations

on when adverse events could be reported following transfusion. Based on the patient population supported with platelet transfusion, the study was designed to capture repeated transfusions of PCT-PLT within patients to determine potential effects of repeated exposure to this new type of platelet component.

A limitation of the present study is the absence of a concurrent control group receiving conventional platelet components with which to determine a comparative baseline incidence of ATR. However, because reporting is obligatory, the expected outcomes of this active haemovigilance study are the increase in clinical experience with transfusion of PCT-PLT, the detection of unexpected AE following PCT-PLT transfusions in patient populations and for indications that were not studied previously in a formal clinical trial environment, and the establishment of a safety database for future reference.

In the current study, which was specifically designed to capture all grades of transfusion reactions, the prevalence of ATR per transfusion, was at the lower range of those reported in studies with conventional components. Prior exposure to PCT-PLT transfusions did not increase the likelihood of an ATR. The overall incidence of ATR was lower than that previously reported either on a per-transfusion or on a per-patient basis. Based on experience in a broad patient population, platelet components prepared with amotosalen photochemical treatment were well-tolerated in routine clinical practice.

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