Table 1. Differences between Chapare virus and its closest relative, Sabiá, are similar to differences between other distinct species of arenavirus

Virus	Nucleotide[a]		Amino Acid[b]			
	S segment	L segment	GPC	NP	L	Z
Chapare to Sabiá	26	30	22	15	26	28
Machupo to Junín	25–27	31	25–27	11–14	25	18–20
Machupo to Tacaribe	31–32	33	32–33	19–20	27–28	21
Amapari to Guanarito	27	32	29	14	28	28–32
Paraná to Flexal	29	n/a[c]	17	21	n/a	n/a

[a]Complete nucleotide segments only
[b]Complete amino acid sequences only
[c]Complete segment or gene sequence is not available for one or both viruses
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Table 2. Differences among strains of the same species of arenavirus

Virus	Nucleotide[a]		Amino Acid[b]			
	S segment	L segment	GPC	NP	L	Z
Allpahuayo	14	n/a[c]	2	2	n/a	n/a
Bear Canyon	3	3	2	1	2	0
Catarina	9	n/a	5	2	n/a	n/a
Flexal	0.1	n/a	0	0	n/a	n/a
Guanarito	2	n/a	1	0	n/a	11
Junín	7	3	2	4	2	1
Machupo	13	10	5	3	5	6
Pichindé	11	n/a	5	3	n/a	n/a
Whitewater Arroyo	0.4	n/a	0	1	n/a	n/a

[a]Complete nucleotide segments only
[b]Complete amino acid sequences only
[c]Complete segment or gene sequence is not available for more than one strain
doi:10.1371/journal.ppat.1000047.t002

were designed for the L polymerase gene on the L segment (L4160F, GCA GAR TTY AAA TCI AGA TT; L4393R, CCR TYI ASC CAR TCT ITI ACA TC; L4292F, GAT CAT TCI RTY GCI AAT GG; L4841R, CAI AII CCT ATA AAI CCW GAT G) [19] and the glycoprotein gene on the S segment (GP878+, GAC RTG CCW GGI GGI TAY TG; GP1126-, TAC CAA AAT TTG TGT ART TRC ART AIG G; GP1153+, CCT TAY TGY AAY TAC ACI AAA TTT TGG T; GP1396-, ATG TGY CTR TGI GTI GGI AW).

Reverse Transcription (RT) was done using 2.5 µL of RNA in a 25 µL total reaction volume and AMV RT (Promega Biosciences, San Luis Obispo, CA) at 42°C for 1 hr. Subsequent PCR amplification using FastStart Taq DNA Polymerase with GC-rich solution (Roche) was performed using 5 µL of the completed RT reaction in a 25 µL reaction volume with the following cycling conditions: 2 min at 95°C, (36 cycles of 1 min at 95°C, 1 min at 45°C, 2 min at 72°C), and a final elongation of 10 min at 72°C. Resulting DNA products were visualized and purified using a 1% agarose gel, and the Qiagen Gel Extraction Kit (Qiagen, Valencia, CA). PCR products were sequenced directly (without cloning) using the corresponding primers in a BigDye Terminator v3.1 reaction on a 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). Sequence was further analyzed using Sequencher (Gene Codes Corporation, Ann Arbor, MI).

Complete Genome Amplification & Analysis

To obtain full length sequence for each segment, alignments of all New World arenavirus complete genomes were used to design primers for the conserved regions (available upon request). The full length S segment was generated following the Thermoscript RT-PCR system's directions (Invitrogen, Carlsbad, CA) and using the 19C primer [10]. Reverse transcription was conducted at 55°C, while the PCR profile was the same as stated above with an increased extension time of 4 minutes.

Different fractions of the full-length L RNA were amplified using 2-step or 1-step RT-PCR protocols and following the manufacturer recommendations. Briefly, cDNA was synthesized in the first approach using 10 µl of purified RNA, specific primers, dNTPs and Superscript III (Invitrogen) in 20 µl reactions. Amplification reactions were done using 5 µl of cDNA, specific primers, dNTPs and Platinum Taq DNA polymerase High Fidelity (Invitrogen) in 50 ul reactions. Alternatively, 1-step RT-PCR were performed using 5 µl of RNA, dNTPs and the enzyme blend provided by the SuperScript III One-Step RT-PCR System with Platinum Taq High Fidelity (Invitrogen) in a 50 µl reactions. Amplification reactions were analyzed in TBE/agarose gels and DNA bands purified using QIAquick Gel Extraction Kit (Qiagen). Sequencing reactions were done as described above.

Phylogenetic Analysis

All full length S and L segment sequences available in Genbank were used to compute pairwise uncorrected genetic distances using PAUP 4.0b10 (Sinauer Associates) for the following viruses: Allpahuayo, Amapari, Chapare, Flexal, Guanarito, Junín, Machupo, Paraná, Pichindé, Pirital, Sabiá, Tacaribe, Tamiami, and Whitewater Arroyo.

A representative sub-set of full length sequences (omitting multiple near identical variants of the same virus) were included in a Bayesian phylogenetic analysis. Sequence alignments were done with ClustalX [20] with manual adjustments and phylogenetic analysis was done with MrBayes3.1.2 [21] using the GTR+I+G model in 2 runs of 500,000 generations using the sequence of Pichindé virus as the outgroup.

Supporting Information

Table S1 Amino acid distances for complete L and Z genes and nucleocapsid and glycoprotein genes of the New World arenaviruses
Found at: doi:10.1371/journal.ppat.1000047.s001 (0.34 MB PDF)

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Author Contributions

Conceived and designed the experiments: CA JO SN. Performed the experiments: BE CA JC. Analyzed the data: BE RA PB EV CA JV JC PR TK JO SN. Contributed reagents/materials/analysis tools: SD RA PB EV

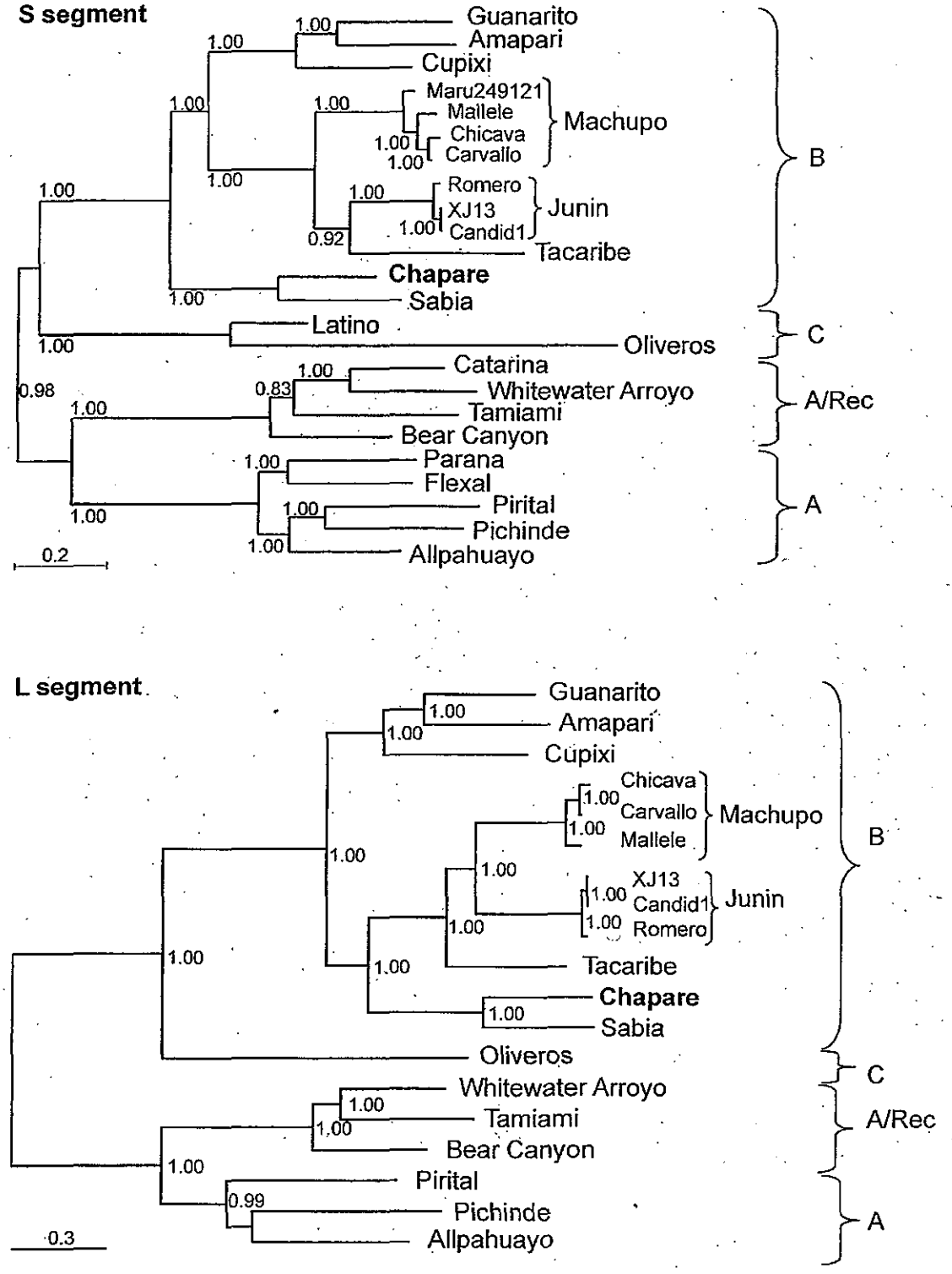

Figure 2. Phylogenetic analysis of the complete S and L RNA segments of New World arenaviruses. Complete S and L segments for New World arenaviruses were analyzed by Bayesian inference of phylogeny (MrBayes3.1.2) using the sequence of Pichindé virus as the outgroup. Multiple strains are grouped with small brackets and large brackets group the arenavirus Clades: A, A/Rec, B, and C. The Genbank accession numbers for the S segment analysis include: Allpahuayo (AY012686), Amapari (AF485256), Bear Canyon (AY924392), Catarina (DQ865245), Chapare (EU260463), Cupixi (AF512832), Flexal (AF485257), Guanarito (NC_005077), Junin (AY619641, NC_005081, AY746353), Latino (AF512830), Machupo (AY924208, AY619645, AY924202, NC_005078), Oliveros (U34248), Paraná (AF485261), Pichindé (NC_006447), Pirital (NC_005894), Sabiá (NC_006317), Tacaribe (NC_004293),

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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JV JC PR JO. Wrote the paper: BE SN. Initial clinician that reported the case, described the clinical course and provided specimens: SD. Clinicians involved in the case investigation: RA and EV. Participated in field investigation: PB. Participated in case investigation: JV. Edited the paper: TK. Led NMRCD investigation: JO.

References

1. Buchmeier MJ (2007) Arenaviridae. In: Knipe DMaH PM, ed. Fields Virology. 5th ed. Philadelphia: Lippincott, Williams and Wilkins. pp 1791–1828.
2. Gonzalez JP, Emonet S, de Lamballerie X, Charrel R (2007) Arenaviruses. Curr Top Microbiol Immunol 315: 253–288.
3. Bowen MD, Peters CJ, Nichol ST (1997) Phylogenetic analysis of the Arénaviridae: patterns of virus evolution and evidence for cospeciation between arenaviruses and their rodent hosts. Molecular Phylogenetics & Evolution 8: 301–316.
4. Archer AM, Rico-Hesse R (2002) High genetic divergence and recombination in Arenaviruses from the Americas. Virology 304: 274–281.
5. Charrel RN, Lemasson JJ, Garbutt M, Khelifa R, De Micco P, et al. (2003) New insights into the evolutionary relationships between arenaviruses provided by comparative analysis of small and large segment sequences. Virology 317: 191–196.
6. Salvato MS, Clegg JCS, Buchmeier MJ, Charrel RN, Gonzalez JP, Lukashevich IS, Peters CJ, Rico-Hesse R, Romanowski V (2005) Family *Arenaviridae*. In: Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball LA, eds. Virus Taxonomy: Eighth Report of the International Committee on Taxonomy of Viruses Elsevier Academic Press. pp 725–733.
7. Johnson KM, Kuns ML, Mackenzie RB, Webb PA, Yunker CE (1966) Isolation of Machupo virus from wild rodent Calomys callosus. Am J Trop Med Hyg 15: 103–106.
8. Murphy FA, Webb PA, Johnson KM, Whitfield SG, Chappell WA (1970) Arenoviruses in Vero cells: ultrastructural studies. J Virol 6: 507–518.
9. Salazar-Bravo J, Dragoo JW, Bowen MD, Peters CJ, Ksiazek TG, et al. (2002) Natural nidality in Bolivian hemorrhagic fever and the systematics of the reservoir species. Infection, Genetics & Evolution 1: 191–199.
10. Bowen MD, Peters CJ, Nichol ST (1996) The phylogeny of New World (Tacaribe complex) arenaviruses. Virology 219: 285–290.
11. Weaver SC, Salas RA, de Manzione N, Fulhorst CF, Duno G, et al. (2000) Guanarito virus (Arenaviridae) isolates from endemic and outlying localities in Venezuela: sequence comparisons among and within strains isolated from Venezuelan hemorrhagic fever patients and rodents. Virology 266: 189–195.
12. Cajimat MN, Fulhorst CF (2004) Phylogeny of the Venezuelan arenaviruses. Virus Research 102: 199–206.
13. Weaver SC, Salas RA, de Manzione N, Fulhorst CF, Travasos da Rosa AP, et al. (2001) Extreme genetic diversity among Pirital virus (Arenaviridae) isolates from western Venezuela. Virology 285: 110–118.
14. Cajimat MN, Milazzo ML, Hess BD, Rood MP, Fulhorst CF (2007) Principal host relationships and evolutionary history of the North American arenaviruses. Virology 367: 235–243.
15. Moncayo AC, Hice CL, Watts DM, Travassos de Rosa AP, Guzman H, et al. (2001) Allpahuayo virus: a newly recognized arenavirus (arenaviridae) from arboreal rice rats (oecomys bicolor and oecomys paricola) in northeastern peru. Virology 284: 277–286.
16. Flanagan ML, Oldenburg J, Reignier T, Holt N, Hamilton GA, et al. (2008) New world Clade B arenaviruses can use transferrin receptor 1 (TfR1)-dependent and -independent entry pathways, and glycoproteins from human pathogenic strains are associated with the use of TfR1. J Virol 82: 938–948.
17. Radoshitzky SR, Abraham J, Spiropoulou CF, Kuhn JH, Nguyen D, et al. (2007) Transferrin receptor 1 is a cellular receptor for New World haemorrhagic fever arenaviruses. Nature 446: 92–96.
18. Lisieux T, Coimbra M, Nassar ES, Burattini MN, de Souza LT, et al. (1994) New arenavirus isolated in Brazil. Lancet 343: 391–392.
19. Fischer SA, Graham MB, Kuehnert MJ, Kotton CN, Srinivasan A, et al. (2006) Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med 354: 2235–2249.
20. Thompson JD, Gibson TJ, Plewniak F, Jeanmougin F, Higgins DG (1997) The CLUSTAL_X windows interface: flexible strategies for multiple sequence alignment aided by quality analysis tools. Nucleic Acids Res 25: 4876–4882.
21. Ronquist F, Huelsenbeck JP (2003) MrBayes 3: Bayesian phylogenetic inference under mixed models. Bioinformatics 19: 1572–1574.

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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。

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。

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

Vox Sanguinis (2008) 94, 315–323

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.

Key words: PCT, platelets, haemovigilance, safety, INTERCEPT.

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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%)

