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*Marcus Picard-Maureau, Marek Z. Paśka

Platelet transfusion associated risks and improvement of platelet transfusion safety with Amotosalen/UVA pathogen inactivation technology

Ryzyka związane z transfuzją płytek krwi i sposoby podniesienia bezpieczeństwa przy użyciu technologii inaktywacji patogenów z wykorzystaniem Amotosalenu i światła UVA

Cerus Europe B.V., Stationsstraat 79-D, 3811 MH Amersfoort, The Netherlands

Summary

Despite the introduction of multiple measures to minimize the risk of transfusion-transmitted infections, there is still a residual risk of platelet transfusions, especially but not only for bacterial sepsis. Recently, the importance of a reliable hemovigilance system has been underlined and an up to 10-fold difference in the reporting of bacterial transmissions between active and passive reporting has been demonstrated. Another reason for a misjudging of the blood safety may derive from the fact that some pathogens cause obvious damage to critically ill and/or immunocompromised patients only and asymptomatic infections in immuno-competent recipients and thus are not being reported. Pathogen inactivation for platelets, a proactive approach not only broadly inactivating pathogens, but also white blood cells, could minimize the risk of transfusion transmitted infections and graft versus host disease due to residual leukocytes. Only the INTERCEPT technology has received approvals from the regulatory agencies in France, Germany and Switzerland, United States and Canada. That technology utilizes photoactive methods to modify nucleic acids. Long-term routine clinical experience, also with children and neonates, shows the safety and efficacy of INTERCEPT platelet transfusions. The national hemovigilance data of Switzerland, France and Belgium as well as single-center routine use studies show an improved clinical outcome in the acute as well as in the prophylactic setting with a significant decrease in septic and other non-hemolytic transfusion reactions, as well as prevention of graft-versus-host disease.

Keywords

platelet transfusion, transfusion-transmitted infection, pathogen-inactivation, transfusion reaction, sepsis

Platelet transfusion safety

Despite multiple improvements in the last decades like enhanced disinfection of the donor's venipuncture site, leukoreduction, and the introduction of new donor screening tests there is a residual risk of pathogen transmission by transfusion of platelets. There are 77 transfusion-transmissible infectious pathogens currently known, and the number is growing constantly (1). The highest platelet transfusion-associated risk is still the bacterial contamination, with an average rate of 1:1000-1:2000 platelet concentrates being contaminated as shown by bacterial culture testing with no significant difference between apheresis and whole-blood-derived platelet units (2-4). The source of platelet contamination is in the majority of cases trace amounts of bacteria from the donors' skin, but cases of contamination from transient donor bacteremia due to translocation from gut, small wounds or other sources cannot be excluded. In platelet units, many bacteria species find ideal growth conditions during storage which is performed at room temperature. Bacterial culture screening post production fails to detect large numbers of bacterially infected units and does not provide protection against septic transfusion reactions (STR) (5, 6). A recent active surveillance study from an American tertiary care academic hospital showed an average rate of transfused contaminated platelet concentrates of 1:2572 (20 of 51.440) despite negative initial bacterial culture testing post production (6). In multiple cases the patients showed signs of STR (retrospective analysis of patient

charts), which were not recognized/reported by the treating physicians. There is evidence pointing towards a significant underreporting of STR (6, 7). Hemovigilance data from France, Belgium and Switzerland for the years 2005-2016 showed that the rate of septic transfusion reactions may be completely abolished by the implementation of pathogen inactivation (Amotosalen/UVA) (7). This approach holds more promise than the continuous implementation of new tests for newly emerging pathogens or the attempts to improve for example the performance of the existing tests for bacteria.

Interestingly, new Human-Immunodeficiency-Virus (HIV) and Hepatitis-B-Virus (HBV) variants have been ranked as high perceived risk for blood safety (position 2 and 10 of 77 respectively) during an international panel of experts rating (8). Indeed there are multiple cases of HIV and HBV transmission by blood transfusion described, which occurred despite serological and nucleic acid testing (NAT), likely because of viral variants and/or low viral loads below the limit of detection (9-11). A Polish study questions the effectiveness of the current donor deferral policy to reduce the risk of blood donations from donors carrying viruses in the early phase of infection (window period) when viral detection by standard blood screening measures often fails (12). The authors revealed that donor questionnaires about their risk behavior prior to donation were often not answered correctly. Besides these "classical" threats to transfusion, Hepatitis E is now one of the pathogens in the focus of the discussions. The seroprevalence for Hepatitis-E-Virus (HEV) is relatively high in Poland, and a recent study identified one of 2109 donors as HEV-positive by NAT, extrapolating 267 potential cases of transfusion-transmitted HEV annually (13). However, the clinical significance of such transmissions is questionable. A British study showed that only one of 43 patients which were infected by HEV during transfusion developed mild symptoms of hepatitis (14), and a German study showed that 6 patients which were infected by HEV during transfusion did not develop any symptoms (15). HEV is usually transmitted fecal-orally; the virus in blood is morphologically different from the virus found in feces and less infectious (16). HEV transmission by blood donation may still be a risk for immunosuppressed patients requiring multiple transfusions, which could potentially develop chronic infection (17). Outbreaks and spread of emerging arboviruses like Dengue Virus (DENV), Chikungunya Virus (CHIKV), West Nile Virus (WNV), Zika Virus (ZIKV) or Yellow Fever Virus (YFV) are an increasing threat for blood safety. The vector mosquitos capable of transmitting such pathogens are spreading through Europe from south to North, already endemic at the Mediterranean coast (Spain, France, Italy, Croatia, Greece) and south-east Europe (Bulgaria, West-Turkey) and introduced in Austria, Germany and even the Netherlands (18). WNV is currently endemic (2017 season) in Austria, Turkey, Northern Italy, Hungary, Croatia, Bulgaria, Greece and Spain (18). Since approx. 80% of virus-carriers are asymptomatic and may donate blood (19), there is a high risk for blood safety. Chikungunya outbreaks have been reported in France and Italy; recently an outbreak in the Lazio region (Rome) was confirmed in September 2017 (18) and led to a halt in platelet production for many blood banks. In the years 2010-2014, 1510 confirmed DENV infection cases have been reported in the European Union (18). Since this infection proceeds asymptomatic in approx. 80% of carriers (20), they represent a high potential risk as donors, and also a significant underreporting in the recipients is expected.

Especially in the field of hemato-oncology, recipients of blood transfusions have an impaired health, and are often immunocompromised. Pathogens which would lead to no or mild symptoms in healthy individuals may impact that patient group severely. Taking a significant underreporting of such infections due to non-detection and non-recognition into account (6, 7), additional layers of safety would be beneficial. Pathogen inactivation technology is a proactive approach to inactivate bacteria, viruses and parasites in blood components, further reducing the risk of STR.

Amotosalen/UVA pathogen inactivation technology

When considering the implementation of pathogen-inactivation and thus the use of such treated components in the clinics, the most important factor is the effective inactivation of all pathogens and white blood cells. But at least as important is the question of the clinical, i.e. hemostatic efficacy of such products. Therefore, clinical and routine evidence for the quality and safety of the treated platelets is favorable. The INTERCEPT Blood System (Cerus Europe BV, Amersfoort, Netherlands) uses a photoactive compound (Amotosalen, a modified natural psoralen) and UVA light to form adducts and crosslink nucleic acids irreversibly (21), a targeted process leading to inhibition of transcription, translation and replication, and finally pathogen inactivation. The INTERCEPT Blood System uses low-energy UVA light outside the absorption spectrum of proteins minimizing collateral damage of platelets. The mechanism of action (MOA) for INTERCEPT has been described in great detail on the molecular level (22) and is highly controlled also because it is independent of the generation of Reactive Oxygen Species (ROS) which are the integral part of the MOAs for the other technologies (23, 24). Extensive toxicological studies (25, 26) have been performed according to the ICH (international conference of harmonization); also for neonates (27), and hemovigilance studies (7,28) showed a high level of safety. The INTERCEPT Blood System inactivates a broad range of gram-negative and gram-positive bacteria (also high bacterial titers (29)), viruses (HIV, HBV, HCV, CMV and others) and parasites (Plasmodium, Trypanosoma), effectively (22, 30), also newly emerging arboviruses like DENV, WNV, ZIKA , CHIKV and YFV (31-33), but shows some weaknesses with non-enveloped viruses, which are usually not blood borne, but transmitted by the fecal-oral route (31). It inactivates white blood cells more effectively than gamma-irradiation (34), thus officially being the alternative to gamma-irradiation of platelets for the prevention of graft-versus-host disease (35). It is the only pathogen inactivation technology for platelets approved in the U.S.A., Canada, France, Switzerland and Germany, widely used in Europe (also in Poland), the Middle East, Russia, Kazakhstan

and the Americas. A series of clinical studies have been performed with INTERCEPT-treated platelets which were in several randomized controlled trials (RCT) compared to conventional platelets. All these studies were successful and reached their endpoints. Some studies revealed a loss in INTERCEPT-platelet recovery (assessed by corrected count increment (CCI)). This lower value in CCI had no statistically significant effect on the platelet function, i.e. the hemostatic function of the platelet concentrates, INTERCEPT platelets were functionally not inferior compared to untreated control platelets (36, 37).

Routine use analysis showed that the usage of INTERCEPT platelets significantly reduced the incidence of transfusion reactions by elimination of white blood cells and pathogens, the incidence of platelet related transfusion reactions per 1000 transfusions dropped 48% in Strasbourg (38) and the incidence of high imputability grade 3 and 4 transfusion reactions dropped 66% in Switzerland (39) after introduction of INTERCEPT. Furthermore analyses of the potential impact of the introduction of INTERCEPT in the routine showed that there was no sign of increased component utilization neither when analyzing platelet nor red blood cell usage. Also no difference in the transfusion intervals for INTERCEPT platelets (38, 40), even in massively transfused patients (41) has been seen. These findings from routine clinical use however question some clinical trial results, which showed decreased transfusion intervals and increased transfusions per patient (36, 37). That discrepancy could be explained by the artificial, protocol regulated trial environment, which does not apply during routine use.

Pediatric use

INTERCEPT-treated blood components can be applied to patients without any age restrictions, also to children and neonates. The Cerus post-marketing hemovigilance studies provided an opportunity to obtain additional information regarding safety and efficacy of INTERCEPT-treated platelets in this specific population (28, 42, 43). In the hemovigilance (HV) program in the 244 pediatric patients treated with INTERCEPT platelet components no adverse events (AEs) or adverse transfusion reactions (ATRs) were reported in Study HV1 or Study HV2. In Study HV3, 13 children (age 1 to 18 years) and no infants (age < 1 year) experienced AEs; 9 children and no infants experienced ATRs. The most frequently reported ATRs were consistent with recognized signs and symptoms associated with transfusion of platelet components (pruritus, urticarial, chills, pyrexia) and were assessed as Grade 01. Only 1 child experienced a serious adverse event (SAE); a 10 year-old male experienced a convulsion, which was considered unrelated to the transfusion of an INTERCEPT platelet component. In a study at Belgium assessing the outcome of 472 transfusions of INTERCEPT platelets to 90 pediatric patients, therapeutic count increments were achieved and no unexpected transfusion reactions specifically to INTERCEPT platelets were observed (44). At a German university hospital 24 children with a mean age of 5.8 years (0-13) were transfused with 94 INTERCEPT platelet units. Also here the transfusions were well tolerated and no unexpected adverse events were recognized, the clinical effects of INTERCEPT platelets were not different from untreated controls (45). During the CHIKV epidemic in Ile de La Reunion, France, 51 pediatric, and 41 infant patients were transfused with INTERCEPT-treated platelet components. Eight ATRs occurred in 6 pediatric hematology-oncology patients. The relatively high frequency of these reactions was related to the increased exposure in these patients with hematologic malignancy resulting in repeated transfusion exposures. No ATRs were observed in infants (46). In summary literature search revealed published data from 450 pediatric patients safely and efficiently transfused with INTERCEPT platelets.

Conclusions

For INTERCEPT it has been shown that the treated platelets can be stored for up to 7 days and still show high degree of hemostatic efficacy and safety (47). The clinical benefits of introducing pathogen-inactivated components are the significant reduction of transfusion reactions, the prevention of septic transfusion reactions and non-hemolytic transfusion reactions, which is achieved by the inactivation of pathogens and white blood cells. Such effects have been shown by long-term hemovigilance data for INTERCEPT platelet components from national registries (7), recently the experience since the nationwide introduction of INTERCEPT platelets has been reported for a period of 6-7 years from Switzerland (36). The published clinical routine data from 450 pediatric patients showed safety and efficacy of INTERCEPT platelet transfusion to that patient group.

The patients benefitting most from such components are immunocompromised patients with multiple platelet transfusions, like bone-marrow transplant patients, patients under chemotherapy and leukemia patients, as well as solid-organ transplant patients. Generally, all patients benefit from reduced transfusion reactions and higher blood safety, especially considering the high underreporting of transfusion-transmitted infections. Currently sustainable health-economic studies are not available, since measuring the consequences for the general health budget (for example length of stay, length of stay at the intensive care unit, mortality, drug usage) and the blood center (for example replacement of some pathogen tests and bacterial testing, replacement of gamma irradiation) are region-specific and challenging to assess. However, single centers like Karolinska University Hospital Stockholm or Aarhus University Hospital showed positive cost-benefit analysis for INTERCEPT platelets at the blood center level at conference posters and presentations (ISBT 2016 Dubai, AABB 2017 San Diego, ISBT 2018 Toronto).

Conflict of interest

The authors are employees of Cerus Corporation, the manufacturer of the INTERCEPT Blood System.

Corresponding address

*Marcus Picard-Maureau
Cerus Europe B.V., Stationsstraat 79-D,
3811 MH Amersfoort, The Netherlands
Phone: +31 33-496-0600
mpicardm@cerus.com

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