Analysis of reasons for not implementing pathogen inactivation for platelet concentrates

Analyse des raisons de ne pas mettre en place l’inactivation des pathogènes dans les concentrés plaquettaires

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Available online 12 April 2013

Abstract

In the last 10 years three technologies capable of inactivating pathogens in platelet concentrates have been authorized in Europe although only one based on the addition of amotosalen and illumination with ultraviolet A (UVA) light, has been approved by the National Agency for the Safety of Medicines and Health Products (ANSM). An intense debate exists about the implementation of pathogen inactivation technologies for labile blood components in general and for platelet concentrates in particular. In this review, we will analyze some of the most frequently argued reasons for not implementing pathogen inactivation for platelet components, i.e.: current platelet components are safe enough; pathogen inactivation technologies might be toxic for the recipient; and pathogen inactivation technologies affect platelet function and increase the risk of bleeding. The analysis and discussion of the evidence currently available to answer those reservations will be limited to the pathogen inactivation technology based on amotosalen and UVA.

Keywords: Pathogen inactivation; Platelets; Amotosalen; UVA

Résumé

Au cours des dix dernières années, trois technologies capables d’inacter des agents pathogènes dans les concentrés plaquettaires ont été autorisées en Europe, bien que seule celle basée sur l’addition d’amotosalen et illumination avec lumière ultraviolette A, ait été approuvée en France par l’Agence nationale pour la sécurité des médicaments et des produits de santé (ANSM). Un débat intense existe au sujet de la mise en œuvre des techniques d’inactivation des agents pathogènes pour les composants sanguins labiles en général et pour les concentrés de plaquettes en particulier. Dans cette revue, nous allons analyser quelques-unes des raisons les plus fréquemment mises en avant pour ne pas mettre en œuvre l’inactivation des agents pathogènes dans les concentrés plaquettaires, à savoir: les concentrés plaquettaires sont assez sûrs; les technologies d’inactivation des pathogènes pourraient être toxiques pour le receveur; les technologies d’inactivation des pathogènes modifient les fonctions plaquettaires et augmentent le risque de saignement. L’analyse et la discussion des preuves actuellement disponibles pour répondre à ces réserves seront limitées à la technologie basée sur l’inactivation des pathogènes par amotosalen et UVA.

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Mots clés : Inactivation des pathogènes ; Plaquettes ; Amotosalen ; UVA

1. Introduction

In the early 1980s, the recognition of the transmission of viral hepatitis and human immunodeficiency virus (HIV) infection to patients treated with coagulation factor concentrates, which were obtained from pooled human plasma, led to the introduction of measures by the manufacturer to inactivate the viruses potentially present in those products. The implementation of such measures was not immediate, and the first technology described in Germany, based on the heating, in solution, of the purified product, provoked concern that the heating pro-
cess might reduce the concentration the active component of the product. In fact, strong opposition was even expressed about this approach by a major hemophilia patient organization at that time [1].

A similar situation exists today for the world of labile blood components, where an intense debate exists about the implementation of pathogen inactivation technologies. The debate is possible because in the last 20 years several technologies have been developed, first for plasma and later for platelet concentrates, which can be applied to blood components. Currently, there are three different technologies approved in Europe (CE marked) to be applied to platelet concentrates: one is based in the addition of amotosalen and illumination with ultraviolet A (UVA) light (A-L, Intercept® Blood System, Cerus Europe BV, Amersfoort, the Netherlands), a second one combines the addition of riboflavin (vitamin B2) and illumination with UV light (range from 265 to 370 nm) (R-L, Mirasol®), TerumoBCT, Lakewood, USA) and the third applies only UV C (below 280 nM) under loose strong agitation (Theraflex UV, MacoPharma, Mouvaux, France). However in France only A-L has been approved by the National Agency for the Safety of Medicines and Health Products (formerly AFSSAPS, now ANSM) in 2003. In this review we will analyze the reservations more often argued for not implementing PI technologies, specifically A-L, the only one approved in France, for platelet concentrates.

2. Platelet concentrates are safe enough

Currently, thanks to the measures adopted to increase the safety of transfusions (donor selection, screening tests), the viral infectious risks associated with a platelet transfusion is very low but with wide variation among different countries depending on the epidemiologic characteristics and donor selection criteria used. Table 1 shows the estimated residual risk of transfusion-transmitted infections by donations screened by nucleic acid testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV in four European countries [2,3]. As can be seen, HBV virus risk varies between countries by as much as 15 times and for HIV by as much as 10 times.

And there is another consideration that should be emphasized and is the fact that the recipient of a platelet transfusion prepared from whole blood donations is exposed during a single transfusion to, in general, five donors. As a result, the risk for HBV in Italy is 1 in 14,388 or for HIV the risk in Spain is 1 in 110,000 per platelet transfusion and in average a patient suffering from a hematologic malignancy will receive about six transfusions per cycle of treatment, making the risk per patient much higher [4].

But actually the most important infectious thread for the recipient of a platelet transfusion is not in viral area but in the bacteria. Since the early days of blood transfusion, bacteria have been a frequent contaminant of the components and causing sepsis in the recipients [5]. The rate of confirmed positive by bacterial culture with sampling on day 0 to 1 varies between 1 in 1036 and 1 in 4329 platelets concentrates depending on volume tested, delay in sampling and type of platelets tested [6]. However, not all the contaminated provokes a septic reaction in the recipient; only between 1 in 4 and 1 in 35 of the contaminated units will provoke a septic reaction in the recipient [6].

Several reasons might explain the difference between the rate of bacterial contamination in the product and the incidence of septic reactions in the recipient of a platelet transfusion. One might be that platelet transfusions are frequently administered to patients suffering from hemato-oncology diseases that are, often, already receiving broad-spectrum antibiotics. But another explanation is that treating physicians do not recognize a transfusion reaction as a septic reaction. For instance, Walther-Wenke et al. followed 113 potentially or confirmed positive units that were already transfused at the time of the first positive signal in BacT/ALERT screening cultures. They found six febrile reactions to culture positive platelet concentrates not classified even as a transfusion reaction by physicians [7].

Several countries have implemented bacterial detection for preventing bacterial sepsis in the recipient of a platelet transfusion. Two methods of screening are currently available bacterial culture (Bact-ALERT, bioMerieux) with separated culture bottles for aerobic and anaerobic bacteria and the eBDS system (Pall Corporation), which relies on oxygen consumption by bacteria and thus can detect only aerobic bacteria. However, the cumulative experience has shown that bacterial screening even with the more sensitive system, unfortunately, does not eliminate completely bacterial sepsis from platelet transfusion. For example, in USA, AABB introduced in the 22nd edition of its Standards for Blood Banks and Transfusion Services in 2003 the requirement, effective March 1 2004, that “methods to limit and to detect” bacteria in all platelet components must be in place [8]. Eder et al. reported the experience of the American Red Cross after implementing bacterial detection using BacT-Alert in platelet concentrated prepared by apheresis. Between 2004 and 2008, apheresis donations with negative culture provoked 26 septic reactions in the recipient of the transfusion (1 in 68,697 donations) and four deaths due to bacterial sepsis (1 in 446,535) [9]. In comparison to the figures observed before implementation of bacterial culture testing, those figures represent approximately a 50% decrease in reported sepsis and fatalities.

Due to the remaining risk of bacterial sepsis in units that have undergone bacterial culture, a new test for detecting contaminated units at the time of issue has been developed [10]. Another strategy that has been implemented is reduce the shelf life of platelet concentrates since most of the septic reactions are seen when platelet concentrates are stored for 4 to 5 days when bacterial growth inside the product reaches its maximum.
Germany limited the shelf life of platelet concentrates to 4 days since June 2008 and in Japan the shelf life of platelet concentrates is 3 days [11]. The shortening in the shelf life of platelet concentrates will probably provoke an increase in the outdating of units.

Some authors have proposed that pathogen inactivation of platelet concentrates would be the solution for preventing the transmission of bacterial infections and many other pathogens [12]. Hemovigilance data seems to confirm this view. Cazenave et al. looked at hemovigilance data regarding transfusion-transmitted bacterial infections associated with platelet transfusion in Alsace where pathogen inactivation for platelet concentrates with A-L has been in place since 2006 and the rest of France. Between 2006 and 2011, 115,648 inactivated platelet concentrates have been transfused in Alsace with no case of bacterial sepsis reported. In contrast in the rest of France 37 bacterial sepsis have been reported (1 in 43,283 transfused units) with seven cases leading to the death of the recipient of the contaminated platelet concentrate (1 in 228,782).

Another point to consider is the issue of the risk of emerging pathogens [13]. The current reactive paradigm which basically involves the implementation of a new set of interventions in response to each new, or potential, transfusion-transmitted infection agent identified implies a delay between the identification of the agent and the implementation of the preventing measures, which leads to the transmission by transfusion of a certain number of cases [14]. The last example of emerging pathogen transmitted by transfusion in USA was the West Nile virus that after being identified in 2002, lead to the development of a screening test applicable in Blood Transfusion Centers in July 2003, a remarkable short period of time [15]. However by then, mathematical models suggested that hundreds of transfusion transmissions had already occurred [16]. Only in 2002, 23 cases of transfusion-transmitted cases of WNV were reported, leading to the death of the recipient in nine of them (39%) [17].

In recent years, France has experienced several outbreaks of emerging pathogens in its overseas departments, Chikungunya virus in the île de la Réunion in 2006 and 2007, and Dengue virus and Trypanosoma Cruzi in Martinique and Guadeloupe-Guyane. In both cases it lead to the introduction of A-L inactivation technology for platelet concentrates [18].

In conclusion, in spite of all the efforts, there is still a by no means negligible risk of transfusion transmission of infection associated to platelet transfusion therapy, mainly bacterial. Bacterial detection methods, even with the more sensitive ones, at the moment of preparation are able to decrease, just 50% of the cases of bacterial sepsis associated to platelet transfusion. And the potential existence of emerging and re-emerging pathogens should not be neglected when evaluating the infectious risks of platelet transfusion.

3. Pathogen inactivation technique might be toxic for the recipient

Amotosalen, like all the psoralens, is a tricyclic molecule but with an added amine side chain that converts the molecule in highly water soluble and less lipophilic than other psoralens. It can thus quickly pass cellular membranes, bacterial walls or viral envelopes and readily interact with nucleic acids without interacting with proteins or cellular lipids. It readily intercalates into double-helical structures of DNA or RNA where covalent bonds between its reactive groups and pyrimidine bases are formed upon UVA illumination. Even intrastrand reactions are possible so single-stranded nucleic acids also serve as targets. The formation of the cross-links between the strands of the nucleic acids prevents replication of the genome and this reaction can only occur in the presence of UVA light. After UVA exposure, residual amotosalen and free photoproducts generate are absorbed in a compound adsorption device (CAD), before the platelet concentrate is ready for transfusion [19]. As a result of this CAD phase the residual amotosalen decreases from 150 μmol/L to approximately 0.5 μmol/L. This represents that a patient would receive with a platelet component inactivated with A-L, approximately 1 μg/kg of amotosalen [20]. Interestingly, in humans the clearance of amotosalen is biphasic, the early clearance is very rapid (half-life of 40 minutes), with a slower terminal phase (median terminal half-life is 6.5 hours) with not amotosalen detectable at 24 hours after transfusion [21]. Measurements of amotosalen in patients under platelet transfusion support for up to 28 days with inactivated components showed no accumulation.

An extensive program of pre clinical research has assessed the potential toxicity of amotosalen and its derivatives generated during UVA light illumination has been performed. These included animal studies on acute and chronic toxicology but also studies to assess long-term toxicology like genotoxicity, reproductive toxicology, neonatal and juvenile animal development and carcinogenicity. Safety margins for amotosalen in the various toxicology studies have been shown to be very large (> 350-fold in repeated-dose, reproductive, safety pharmacology studies; > 1000-fold in the carcinogenicity study) [22–24]. When compared to prescription pharmaceuticals, these safety margins appear more pronounced. Pharmaceuticals may have very low safety margins (< 1, anticancers) to safety margins of less than 10 for cardiovascular agents, antinfectives, and anti-inflammatory agents. Even a commonly used over-the-counter compound such as acetaminophen has a safety margin for hepatotoxicity of approximately 5-fold [23]. Also data exist suggesting the lack of neoantigen formation as a consequence of the inactivation process with A-L [25].

After introducing A-L treated platelet concentrates in routine in several countries, two studies have reported the safety profile of inactivated components in transfused patients. Active hemovigilance data for 5106 platelet components treated with A-L administered to 651 patients were collected in 5 different European countries. A total of 5,051 transfusion (98.9%) and 609 patients (93.5%) had no reported reactions. Adverse events occurred in 42 transfusions (0.8%) (possibly, probably or related to transfusion) and 42 patients (6.4%) but in only 32 patients (4.9%) was a causal relationship to platelet transfusion established. One reaction was serious and no deaths were related to platelet transfusion. Among the transfusion reactions, the most frequent clinical events in descending frequency were chills, fever, dermatologic reactions, dyspnea, nausea or vomiting and hypotension. The authors concluded that platelet concentrates
treated with A-L exhibited a safety profile similar to that previously reported for conventional platelet components [26].

A similar finding was reported in another group of 7,437 inactivated platelet components transfused in three European countries, 35.7% of them in France. An acute transfusion reaction classified as possibly related, probably related or related to A-L treated platelet component was recorded in 0.7% of the transfusions, most of them being mild (grade 1, absence of immediate or long-term life-threatening effects) [27]. Hemovigilance data collected during the Chikungunya virus epidemic on Île de La Réunion between 2006 and 2007 when universal A-L pathogen inactivation of platelet components was implemented has been also published [28]. In that period 1950 apheresis platelet concentrates were transfused to 335 adults (>18 years), 51 pediatrics (≥1 to <18 years) and 41 infants (<1 year). An acute transfusion reaction was found in the 1.6% of the transfusions to the pediatric patients and in the 0.1% of the adults, being the most frequent observed symptoms/sings, chills, itching and urticaria. In previous year the incidence of acute transfusion reaction with conventional components suspended in 100% plasma was 2.2 for 2004 and 5.4% for 2005 [28].

In summary, available data suggest that the levels of amotosalen to which the recipient of inactivated platelet components is exposed is cleared from the circulation in less than 24 hours and that the concentrations at which some toxicity is observed in animals and in vitro models are at least, two to three orders of magnitude higher to that observed in patients after transfusion. Hemovigilance data have not found an increase in the incidence of acute transfusion reactions in patients receiving A-L inactivated platelets.

4. Pathogen inactivation technology affects platelet function and increases the risk of bleeding

Several studies have looked at the effect of the A-L treatment on in vitro functions of the platelets during preparation and storage. In one of the studies, of the several in vitro parameters tested, statistically significant higher values were observed only in glucose consumption, lactate production, and CD62P expression of A-L platelet units compared to platelet units kept as a control, and differences were relatively small in most cases. The treatment also caused a loss in platelet concentration of approximately 6.5% [29,30]. In vitro studies performed under flow conditions suggested that platelets treated with A-L preserved adhesive and aggregating properties up to 7 days, similar to non-treated platelets [31]. Because the results of the in vitro studies showed that the characteristics of the platelets in the A-L units were acceptably preserved, the next step was to study the recovery and survival of treated platelets in healthy subjects using radiolabelling techniques. Such studies showed that A-L units, compared to control units, showed statistically significant lower rates of in vivo recovery (42.5% vs. 50.3%) and survival (4.8 days vs. 6.0 days) [32]. In vivo studies have shown that in spite of statistically significant lower posttransfusion corrected count increments (CCI) the correction of the prolonged bleeding time in thrombocytopenic patients observed with A-L inactivated platelets was similar to that observed with the unmanipulated product [33].

Unfortunately none of the in vitro tests available has shown a correlation with the clinical response to a platelet concentrate transfusion. Thus, the gold standard for definitively establishing the effect of a new technology on platelet concentrates continues to be a clinical trial with clinically relevant endpoints and a sufficient number of patients. Several clinical studies have looked at the effect of A-L treatment on platelet concentrates in patients. The first clinical study published was the euroSPRITE study, a multicenter, randomized, controlled, double-blinded trial in thrombocytopenic patients requiring repeated platelet transfusions conducted in Europe to evaluate the therapeutic efficacy and safety of platelet concentrates prepared using the buffy coat method and treated with A-L. For euroSPRITE, 103 patients were randomized to receive A-L platelets (311 transfusions) or control platelets (256 transfusions). The mean 1-hour posttransfusion count increment for up to the first eight transfusions was lower in the patients receiving the A-L platelets compared to controls (27.5 vs. 35.8; \(P = 0.03\)). When the 1-hour count increment was adjusted for differences in platelet dose using the CCI, the mean 1-hour CCI was not statistically significantly different between treatment groups (13,100 vs. 14,900; \(P = 0.11\)). The mean 24-hour posttransfusion CCI was less (\(P = 0.02\)) for the test group (7400 ± 5500) than for the control group (10,600 ± 7100). Clinical hemostasis, hemorrhagic AE, and overall AE were not different between treatment groups [34].

One year later, the results of SPRINT trial was published. In this case the primary endpoint was the proportion of patients with World Health Organization (WHO) Grade 2 or higher bleeding during the period of platelet support. A total of 645 patients (318 in the A-L arm and 327 patient in the control arm) were evaluated after receiving 4719 platelet transfusions (2678 A-L; 2041 control). The primary endpoint, the incidence of Grade 2 or higher bleeding (58.5\% A-L platelets vs. 57.5\% controls), and the secondary endpoint, the incidence of Grade 3- or 4 bleeding (4.1\% A-L vs. 6.1\% controls), were equivalent between the two groups (\(P = 0.001\) by non-inferiority). The mean 1-hour posttransfusion platelet CCI (11,100 A-L vs. 16,000 controls), average number of days to next platelet transfusion (1.9 A-L vs. 2.4 controls), and number of platelet transfusions (8.4 A-L vs. 6.2 controls) were statistically significant different (\(P < 0.001\)). Transfusion reactions were fewer following A-L platelets (3.0\% vs. 4.4\%; \(P = 0.02\)) [35]. Later, a publication reported and extended analysis of the adverse events found during the SPRINT trial [36]. The study found that petechiae was more frequently reported in the group of patients receiving A-L treated platelet components (39\%) than in the group receiving unmanipulated platelets (29\%, \(P < 0.01\)). Also fecal occult blood positive test was more frequently reported in the group transfused with A-L platelets (33\%) than in the control (25\%, \(P = 0.03\)). There was no differences between the two groups regarding epistaxis, hematuria or oral mucosal petechiae [36]. An apparent increase in lung toxicity found during SPRINT trial [35], disappeared after blind re-analysis of the patient data [35–37]. However in spite of these data, lung toxicity seems to be a cause of major concern for Food and Drug Administration in United States [38].
Interestingly a randomized controlled trial with 43 patients performed with an optimized integrated set for the treatment of platelet concentrates for A-L which minimized the loss of platelets during treatment in Europe, the 1- and 24-hour CCI was not statistically significant different between the A-L and the control group. Number, frequency and dose of platelet transfusions, acute transfusion reactions and adverse effects were similar between the two groups [39].

A Dutch-Belgian HOVON cooperative group has reported the results of a study where they look at the clinical effectiveness of buffy-coat derived leucoreduced platelet concentrates stored up to 7 days in plasma, in platelet additive solution with or without A-L treatment [40]. The authors reported that the primary endpoint of the study, 1-hour CCI was reduced a 31% for A-L treated group in comparison to platelet concentrates in plasma ($P < 0.0001$). In addition, 32% of patients had bleeding events (59% of them grade 1, i.e. petechiae, minimal or microscopic bleeding not requiring intervention) in the A-L arm, as compared to 19% (63% grade 1, $P = 0.045$) in the plasma arm. Due to these reasons the inclusion of patients in the A-L group was halted by the study Data Safety Monitoring Board. It is worthy of notice that the patients in the A-L arm had a mean pre transfusion platelet count significantly lower in comparison to patients receiving platelet products in plasma ($16 \pm 11$ vs. $18 \pm 13$, $P = 0.04$) and that the mean platelet content trans fused product was also significantly lower ($3.9 \pm 1.0 \times 10^{11}$ vs. $3.4 \pm 0.8 \times 10^{11}$, $P < 0.0001$). In theory CCI calculation controls for the platelet dose administered and the posttransfusion platelet count increment, but data suggests that lower pretransfusion counts and lower platelet content in the product produce lower CCI. In the PLADO study the group of patient receiving higher platelet dose had a posttransfusion CCI significantly higher (11 vs. 10, $P = 0.03$) in comparison to the group receiving medium dose [41].

The authors admitted that the number of off-protocol transfusions in the A-L arm (34%) was an important limitation of the study and that the open label aspect of the study might have biased the evaluation of bleeding [40]. Corash and Sherman, late challenged some other methodological aspects of the study [37]. Meanly that the bleeding was not evaluated by specified research personnel blinded to the treatment received by the patient using clearly defined methods. That might explain the difference in incidence of bleeding between the HOVON study and other big platelet transfusion study such as PLADO where grade 2 bleeding (gross, symptomatic bleeding and oropharyngeal bleeding or epistaxis for more than 30 minutes during a 24-hour period) was of 60% [41] as compared to HOVON where the incidence was 6% in the plasma arm.

The results of a 201-patient, multicenter, randomized, controlled, double-blinded clinical trial comparing a single transfusion of A-L platelets with control platelets stored 6 or 7 days (TESSI study) has been reported. The primary endpoint was the 1-hour CCI evaluated with a non-inferiority margin ratio of A-L treated/control greater than 0.70. The A-L: control platelet concentrates ratio of 1-hour CCI was 0.87 (95% confidence interval: 0.73–1.03), demonstrating non-inferiority of A-L platelets. The mean 1-hour CCI for A-L and control platelets were 8163 and 9383, respectively; the mean 1-hour count increments were not significantly different between the two groups. The 24-hour CCI was significantly lower for A-L platelets (4589 vs. 6549), as was the 24-hour count increment ($10^{12}$/L: 11.1 vs. 15.2). However, the median time to the next platelet transfusion after transfusion of study platelet concentrates was not significantly different between groups: (2.2–2.3 days; $P = 0.72$). The number of red blood cell concentrates (RBC) transfused 24 hours after study platelet concentrates and the maximal posttransfusion hemostatic scores were also not significantly different between groups. Acute transfusion reactions, hemorrhagic AE, overall AE, and serious AE were not significantly different between the A-L and non-treated groups [42].

Meta-analysis is a useful statistical tool, which allows the combination of different studies, in the hope of identifying among different study results patterns, source of disagreements or other relationship. So far, there are three meta-analysis published dealing with the results of clinical studies related to pathogen inactivation technologies. The first one published by Vamvakas in 2011 combined randomized controlled clinical studies published with A-L with the only clinical study published with riboflavin and light [43]. The author concluded that the application of pathogen inactivation to platelet component was associated with a significant ($P < 0.05$) reduction in 1-hour (summary mean difference 3,260) and 24-hour posttransfusion CCI (3,315) as well as a significant increase in all and in clinically significant bleeding complications although the frequency of severe bleeding complications did not differ. To note that for the CCI meta-analysis the results of the SPRINT trial were not included because the standard deviation of CCI was not reported in the publication.

One year later, Vamvakas published another meta-analysis with some methodological changes in comparison to the former one [44]. This time the focus was limited to randomized, controlled trials performed with A-L treated platelet components, and the SPRINT and TESSI trials were included in the analysis. For the meta-analysis of the bleeding complications were grouped as “severe” (grades 3 and 4) and “clinically significant” (grades 2 through 4). This time when the five studies were integrated there were no differences in all bleeding or clinically significant bleedings between patients transfused with A-L treated platelet components or controls. This finding changed depending on what kind of data was included in the meta-analysis. For instance, when the expanded safety analysis data instead of the initial report where the bleeding was collected by trained research personnel blinded to the type of platelet transfused, was integrated in the meta-analysis, then an increase in clinically significant bleeding complications is found.

The same year that Vamvakas published the second meta-analysis, Cid et al., published another one. The authors identified the same studies as Vamvakas but avoided any re-categorization of bleeding complications found in the clinical trials. Due to the homogeneity of data the posttransfusion 24-hours CCI could be analyzed and it was found that the transfusion of A-L platelet concentrates was associated to a statistically significant decrease (weighted mean difference [WMD], 3000, $P < 0.00001$). Using subgroup analysis in those trials that guaranteed the ABO
compatibility of platelet transfusion with the recipients, it was found that 1-hour CCI was significantly decreased if the group of patients receiving A-L treated platelets compared to control (WMD 1.400, \textit{P} = 0.03). The transfusion interval between consecutive platelet transfusions was increased in the group receiving A-L inactivated platelets between 0.28 to 0.5 days depending on the trials included in the subgroup analysis. When, due to the heterogeneity found, only double-blinded and high methodologic quality score randomized controlled trials were combined for studying the impact in bleeding complications reported, the use of A-L platelet concentrate was not associated with an increase in the bleeding when compared with the use of control [45].

There is also indirect evidence that suggest that the transfusion of A-L treated platelet concentrates is not associated to an increase in bleeding and is from the data of the use of RBC. In the SPRINT trial [35] and in the HOVON trial [40], the mean number of RBC transfusions was similar in patients receiving A-L treated platelet concentrates and in patients receiving control platelet components. In the Janetzko et al. study the number of RBC transfusions per day at risk was the same in both groups [39]. Similar finding has been reported by centers, which have implemented in routine A-L inactivation technology for platelet concentrates [46,47].

In summary evidence exist indicating that the inactivation of platelet concentrates with A-L provokes measurable effects on platelet in vitro tests although their adhering and aggregating capacities to damaged endothelium under flow conditions are preserved up to 7 days of storage. Data from in vivo studies using radiolabelling have shown that the recovery and survival of A-L inactivated platelets are decreased a 15.5% and a 20%, respectively, as compared to control. Data from randomized controlled trials suggest that 24-hour CCI is significantly reduced as compared to patients receiving non-inactivated products. However data from randomized controlled trials, meta-analysis and from its use in routine in some center suggest that hemostatic capacity of A-L treated platelets is maintained and bleeding is not increased.

Disclosure of interest

M.L. has received research grants from TerumoBCT and CerusCo and lecture fees from TerumoBCT and Cerus Co. J.C. received lecture fees in the past from TerumoBCT and Cerus Co.

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