Comparison of the Hemostatic Efficacy of Pathogen-Reduced Platelets vs Untreated Platelets in Patients With Thrombocytopenia and Malignant Hematologic Diseases
A Randomized Clinical Trial

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IMPORTANCE Pathogen reduction of platelet concentrates may reduce transfusion-transmitted infections but is associated with qualitative impairment, which could have clinical significance with regard to platelet hemostatic capacity.

OBJECTIVE To compare the effectiveness of platelets in additive solution treated with amotosalen–UV-A vs untreated platelets in plasma or in additive solution in patients with thrombocytopenia and hematologic malignancies.

DESIGN, SETTING, AND PARTICIPANTS The Evaluation of the Efficacy of Platelets Treated With Pathogen Reduction Process (EFFIPAP) study was a randomized, noninferiority, 3-arm clinical trial performed from May 16, 2013, through January 21, 2016, at 13 French tertiary university hospitals. Clinical signs of bleeding were assessed daily until the end of aplasia, transfer to another department, need for a specific platelet product, or 30 days after enrollment. Consecutive adult patients with bone marrow aplasia, expected hospital stay of more than 10 days, and expected need of platelet transfusions were included.

INTERVENTIONS At least 1 transfusion of platelets in additive solution with amotosalen–UV-A treatment, in plasma, or in additive solution.

MAIN OUTCOMES AND MEASURES The proportion of patients with grade 2 or higher bleeding as defined by World Health Organization criteria.

RESULTS Among 790 evaluable patients (mean [SD] age, 55 [13.4] years; 458 men [58.0%]), the primary end point was observed in 126 receiving pathogen-reduced platelets in additive solution (47.9%; 95% CI, 41.9%-54.0%), 114 receiving platelets in plasma (43.5%; 95% CI, 37.5%-49.5%), and 120 receiving platelets in additive solution (45.3%; 95% CI, 39.3%-51.3%). With a per-protocol population with a prespecified margin of 12.5%, noninferiority was not achieved when pathogen-reduced platelets in additive solution were compared with platelets in plasma (4.4%; 95% CI, −4.1% to 12.9%) but was achieved when the pathogen-reduced platelets were compared with platelets in additive solution (2.6%; 95% CI, −5.9% to 11.1%). The proportion of patients with grade 3 or 4 bleeding was not different among treatment arms.

CONCLUSIONS AND RELEVANCE Although the hemostatic efficacy of pathogen-reduced platelets in thrombocytopenic patients with hematologic malignancies was noninferior to platelets in additive solution, such noninferiority was not achieved when comparing pathogen-reduced platelets with platelets in plasma.

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Platelet transfusion to prevent or treat bleeding due to thrombocytopenia is standard therapy worldwide. In recent years, the risk of transfusion-transmitted infections (TTIs) has been greatly reduced. However, infectious agent transmission—in particular, bacteria—remains a significant risk associated with platelet transfusion. One solution to further reduce the risk of TTIs is photochemical pathogen reduction (PR), a process by which pathogens are significantly depleted in number, albeit with some exceptions. However, PR technologies, such as amotosalen-UV-A treatment, induce functional platelet alterations. Previous clinical studies have raised concerns about the clinical effectiveness of pathogen-reduced platelets compared with standard untreated platelets. A 2013 Cochrane meta-analysis of published clinical trials reported a non-statistically significant relative risk of 1.06 (95% CI, 0.93-1.21; P = .39) with regard to grade 2 or higher bleeding associated with pathogen-reduced platelets and concluded that not enough evidence was available to be sure that such platelets work as effectively as standard platelets to prevent bleeding. A recently updated analysis reported a 1.10 (95% CI, 0.97-1.25; P = .15) relative risk of grade 2 or higher bleeding associated with pathogen-reduced platelets.

We conducted a randomized clinical trial to test the hypothesis that amotosalen-UV-A-treated platelets in additive solution (P-PR/PAS) are noninferior to untreated platelets in plasma (P-P) or to untreated platelets in additive solution (P-PAS) with regard to hemostatic efficacy in minimally selected patients with thrombocytopenia and malignant hematologic diseases. Introducing both P-P and P-PAS as reference treatments was deemed to be important because treatment with platelets in plasma remains the criterion standard with regard to platelet transfusion.

Methods

Study Oversight

The trial was performed according to the Declaration of Helsinki and the principles of good clinical practice. The trial protocol (Supplement 1) was approved by the Comité de Protection des Personnes Sud-Est and the Agence Nationale de Sécurité du Médicament. Before enrollment, patients were required to give written informed consent. All patient data were deidentified.

Study Design and Outcomes

In this noninferiority trial, patients with malignant hematologic disorders who required platelet transfusion were enrolled in 13 tertiary university hospitals and randomized (1:1:1) to 1 of 3 platelet transfusion arms: P-PR/PAS (Intersol, Fresenius Kabi AG, and Intercept Blood System, Cerus Europe BV), P-P, or P-PAS (Intersol). The primary outcome was the proportion of patients with 1 or more moderate to severe bleeding events (World Health Organization [WHO] grade ≥2) up to 30 days after randomization.

The secondary end points included the proportion of patients with grade 3 or 4 bleeding events, the number of days with grade 2 or higher bleeding events, the 24-hour corrected count increment (CCI) after the first transfusion, the interval between the first and second transfusions, the number of platelet units and the total number of platelets transfused per patient, and platelet transfusion refractoriness (treatment failure) defined by a 24-hour CCI inferior to 4.5.

Eligibility Criteria

The main eligibility criterion was adult patients with bone marrow aplasia (platelet count <10 × 10^9/μL [to convert to 10^9/L, multiply by 1]), an expected hospital stay of more than 10 days, and an expected need of at least 2 platelet transfusions. Patient eligibility criteria included postchemotherapy aplasia, autologous and allogeneic stem cell transplantation, and other causes of prolonged aplasia (aplastic anemia, myelodysplastic syndrome requiring chemotherapy). Patients with documented refractoriness to platelet transfusion who required a specific platelet product potentially unavailable in a timely fashion (cytomegalovirus antibody negative, HLA compatible, or washed platelets) or anticoagulant treatment at enrollment were not included.

Data Collection

Bleeding events were monitored daily until the end of aplasia, transfer to another hospital department, the need for a specific platelet product (eg, HLA-matched product), or up to 30 days after enrollment. Data collected were recorded in a centralized electronic case report form managed by an independent clinical research organization (Clininfo).

Randomization

Randomization was centralized with stratification per center. The computerized randomization list was drawn up by the independent clinical research organization and the patient’s randomization number accessed through a secure site by a member of the site study team. Randomization was performed within 48 hours before the first platelet transfusion after enrollment.

Key Points

**Question** Are pathogen-reduced platelets in additive solution noninferior to untreated platelets for the prevention of World Health Organization grade 2 or higher bleeding?

**Findings** In this multicenter, 3-arm randomized clinical trial that analyzed 790 patients with thrombocytopenia and malignant hematologic diseases, bleeding of grade 2 or higher occurred in 47.9% of patients receiving pathogen-reduced platelets in additive solution, 43.5% of patients receiving platelets in plasma, and 45.3% of patients receiving platelets in additive solution. With a prespecified margin of 12.5%, noninferiority of pathogen-reduced platelets was not achieved when compared with untreated platelets in plasma but was achieved when compared with untreated platelets in additive solution.

**Meaning** Pathogen-reduced platelets in additive solution might be associated with reduced hemostatic efficacy compared with untreated platelets in plasma while being noninferior to untreated platelets in additive solution.
Platelet Transfusions
Criteria for prophylactic platelet transfusion were in accordance with current French guidelines17 and randomized clinical trials that involved platelet transfusion18-20; a platelet count less than 10 × 103/μL or more in case of fever, splenomegaly, anticoagulation, disseminated intravascular coagulation, or invasive medical procedures. Criteria for therapeutic platelet transfusion included severe hemorrhage and bleeding during surgery. Transfusion criteria were identical in all the study centers.

Patients received apheresis or pooled whole blood-derived platelets. All trial platelet products are authorized for routine use in France and were similarly prepared in accordance with current regulatory requirements, including prestorage leukodepletion (eMethods in Supplement 2). Both P-PAS and P-P were γ-irradiated, whereas P-PR/PAS was not. Platelet dose per transfusion followed the current French guidelines of 0.5 to 0.7 × 1010 platelets per kilogram. Trial blood product supply was ensured continuously by the Etablissement Français du Sang. The 24-hour CCI was calculated as previously described.12,21

Bleeding Assessment
Bleeding was assessed daily by research staff using patient interview, physical examination, and any relevant medical results, as previously described,18 with the exception of blood in feces, which was assessed using colorimetry and microscopic hematuria using dipsticks, with both performed at study center discretion. A daily bleeding grade was assigned centrally using WHO criteria by a member of the site study team masked to the study arm. All research staff had received web-based bleeding evaluation training. In addition, each patient’s anonymized bleeding score was adjudicated vis-à-vis the anonymized hospital medical report by an independent committee of clinical hematologists to determine the final maximum bleeding score.

Study Masking
All persons involved in monitoring and evaluating bleeding were masked to the study arm and differed from those preparing and administering the study products. Platelet bags were all similarly labeled as being part of the study protocol. The P-P product differed slightly from the 2 other platelets by regard to product color, and P-PR/PAS bags were stamped with a small transparent identification, with both differences discernable if a deliberate effort was made.

Adverse Events
All adverse events were recorded and reviewed by the Evaluation of the Efficacy of Platelets Treated With Pathogen Reduction Process (EFFIPAP) Safety Committee.

Sample Size Calculation
This noninferiority study was designed with a statistical power of 80% to detect an absolute difference of at least 12.5% (Δ for noninferiority) for the primary outcome between the P-PR/PAS arm and each of the 2 control arms, assuming a 60% incidence rate of bleeding grade 2 or higher.18 With use of nQuery Advisor, version 7.0 (Statistical Solutions), the required sample size was 810 patients, with 270 per arm. After analyzing initial recruitment, the targeted sample size was increased by 30 patients to take into account that some randomized patients might not require transfusion as expected at the time of enrollment.

Statistical Analysis
Analyses are reported for the per-protocol population. All randomized patients who received at least 1 platelet concentrate that conformed to the assigned treatment arm were included in the per-protocol analysis. These were patients who had received products as planned in the protocol, with a few rare exceptions in which 1 or more off-protocol platelet concentrates were transfused in addition to the assigned study product. Statistical analyses were performed using Stata, version 13.1 (StataCorp). The detailed statistical analysis plan is available in Appendix F in Supplement 1. Nominal data are expressed as number (percentage) and continuous data as mean (SD) except when the distribution was not normal, in which case median (interquartile range [IQR]) is used. For the primary outcome, a 1-sided test22,23 with a prespecified noninferiority margin of 12.5% was used in accordance with previous12,24 and ongoing studies.25 Because of multiple comparisons, a first-order risk Bonferroni correction was applied, resulting in a .025 significance threshold, with Wald 95% CIs calculated using binomial distribution. For the primary outcome, center effects were tested using Logit regression.

For secondary end points, superiority comparisons, an analysis of variance, or Kruskal-Wallis test, depending on normality, was used for continuous data and a χ2 test for nominal data. A 2-sided P < .025 significance level was used. When a difference was significant, a post hoc Scheffé, Wilcoxon, or χ2 test was used. The 95% CIs are given for proportions of bleeding events using binomial distribution. When daily bleeding assessments were missing, a multiple imputation method using the mean of data before and after the missing data26 was applied as predefined in the protocol.

Results
Study Population and Platelet Products
From May 16, 2013, through December 24, 2015, a total of 859 consecutive patients were screened and 842 enrolled and randomized (Figure). Of these, 790 patients were evaluable (mean [SD] age, 55 [13.4] years; 458 men [58.0%]). The number of patients included per center varied (median, 56; range, 17-126). However, patients were evenly distributed among the 3 study arms in all 13 centers (eFigure 1 in Supplement 2). A total of 4983 platelet products were transfused. Of these, 90 transfusions (1.8%) were not in accordance with the study arm (off-protocol platelet transfusions), mainly because of nonavailability of the assigned product. All 790 evaluable patients received at least one on-protocol platelet transfusion. Of them, 734 (92.9%) received exclusively on-protocol platelets, whereas only 7 (0.9%) received less than 50% of on-protocol platelets. The distribution among the study arms of off-protocol platelet transfusions is given in eTable 1 in Supplement 2. In view of the small proportion of off-protocol transfusions, the per-protocol popul-
lation and intention-to-treat populations were considered to be identical. No substantial differences were found in patient characteristics among the study arms (Table 1). Test results for center effect were negative. The median follow-up duration was 18 days (IQR, 12-25 days) in all 3 arms. Three patients died during the study period of causes unrelated to study treatment.

Mean platelet dose per transfusion was 4.5 × 10^11 (0.6 × 10^11) but differed among the treatment arms (Table 2). Platelet characteristics (ratio between apheresis platelets and pooled whole blood-derived platelets, mean platelet storage age, and ABO incompatibility) exhibited moderate to no imbalance among the treatment arms (eTable 2 in Supplement 2).

Primary End Point

Grade 2 or higher bleeding occurred in 126 patients in the P-PR/PAS group (47.9%; 95% CI, 41.9%-54.0%), 114 patients in the P-P group (43.5%; 95% CI, 37.5%-49.5%), and 120 patients in the P-PAS group (45.3%; 95% CI, 39.3%-51.3%) (Table 2). Thus, considering a prespecified 12.5% margin, noninferiority was not achieved when comparing P-PR/PAS and P-P, whereas
noninferiority was achieved when comparing P-PR/PAS and P-PAS (eFigure 2 in Supplement 2). The absolute risk difference for grade 2 or higher bleeding was 4.4% (95% CI, −4.1% to 12.9%) when comparing P-PR/PAS and P-P (relative increase of 10.1%; 95% CI, −8.7% to 32.7%) and 2.6% (95% CI, −5.9% to 11.1%) when comparing P-PR/PAS and P-P (relative increase of 5.7%; 95% CI, −11.9% to 27.0%).

Secondary End Points
All secondary end point results are given in Table 2. Severe bleeding events of WHO grade 3 or 4 occurred in 82 patients (10.4%; 95% CI, 8.2%-12.5%), with no significant difference between treatment arms (P = .68). The number of days with grade 2 or higher bleeding was not significantly different among the treatment arms when considering all patients or patients experiencing at least 1 day with grade 2 or higher bleeding.

The median number of platelet transfusions per patient was 5 (IQR, 3-8). Patients in the P-PR/PAS group received significantly more transfusions (median, 6; IQR, 4-9) compared with patients in the P-P group (median, 5; IQR, 2-7; P < .001) but not compared with the patients in the P-PAS group (median, 5; IQR, 3-8; P = .17). Patients in the P-PR/PAS group were significantly more likely to receive a second platelet transfusion less than 2 days after the first transfusion (73 [31.6%] compared with patients in the other treatment arms (P-P: 29 [13.2%]; P-PAS: 35 [15.2%]; P < .001 for both tests). The median total amount of platelets received per patient was similar in the 3 arms (P-PR/PAS: median, 22.6; IQR, 14.5-36; P-P: median, 22.2; IQR, 11.5-34.3; P-PAS: median, 21.9; IQR, 13.2-37.8; P = .67). Red blood cell transfusions did not differ either (P-PR/PAS: median, 4; IQR, 2-7; P-P: median, 4; IQR, 2-8; P-PAS: median, 4; IQR, 2-6; P = .89). The mean (SD) 24-hour CCI after the first platelet transfusion was 7.9 (6.3) overall and significantly lower in the P-PR/PAS arm compared with the other 2 arms (P-PR/PAS: 5.0 [5.2]; P-P, 10.2 [6.4]; P-PAS: 8.2 [6.0]; P < .001 for both tests). Treatment failure occurred more frequently in the P-PR/PAS arm. In relation to such treatment failures, 8 patients in the P-P/PAS arm and 2 patients in the P-P arm received alternative nonstudy platelet products (ie, P-PAS) on request of the clinical team.

Adverse Events
Adverse events considered as probably or certainly linked to the platelet transfusion were scarce (Table 3). The frequency of allergic reactions differed between treatment groups, with a higher frequency in the P-P group. The frequency of pulmonary events did not differ among the treatment arms, and none were considered to be linked to platelet transfusion.

Discussion
In our study, noninferiority was not achieved when comparing P-PR/PAS and P-P, whereas noninferior was achieved when comparing P-PR/PAS and P-PAS (eFigure 2 in Supplement 2).
comparing P-PR/PAS and P-PAS with regard to grade 2 or higher bleeding in minimally selected patients with thrombocytopenia and hematologic diseases.

These findings were observed with a predefined 12.5% noninferiority margin considered as appropriate from a clinical perspective. Furthermore, an identical margin has been used in several prior or ongoing studies that assessed the hemostatic efficacy of platelets administered at different doses or having undergone PR. Platelet additive solution was introduced in Europe in the early 2000s and subsequently in North America to increase plasma for fractionation and to reduce plasma-related adverse reactions. Although reporting no significant differences regarding bleeding complications and transfusion interval, to our knowledge, the only published clinical trial that prospectively assessed PAS reported a significant reduction of 1- and 24-hour count increments and CCI with P-PAS compared with P-P. To assess a potential independent effect of PAS (in treated or untreated platelets) and a “creeping inferiority” risk with regard to platelet quality, we thought it appropriate to introduce both P-PAS and P-P as reference treatments.

Our finding that noninferiority was not achieved between P-PR/PAS and P-P differs from that of the sole sufficiently powered study of hemostatic efficacy: the SPRINT trial. That study, which had a similar 12.5% margin, reported noninferiority for grade 2 or higher bleeding frequencies when comparing P-PR/PAS and P-P. However, the mean number of days with grade 2 bleeding was greater in the P-PR/PAS arm.

We observed noninferiority between P-PR/PAS and P-PAS. This finding agrees with several small, European randomized clinical trials that examined bleeding occurrence as a secondary objective. In contrast, the Dutch-Belgium Hemato-Oncology Cooperative Group (HOVON) study reported significant differences in grade 2 or higher bleeding between P-PR/PAS and P-P (and between P-PR/PAS and P-P). More recently, the Italian Platelet Technology Assessment Study (IPTAS) reported an absolute grade 2 or more bleeding risk difference of 6.1% when comparing P-PR/PAS and P-PAS (22% vs 15.9%, a 37% relative increase). However, the reported differences did not reach significance, and conclusions on noninferiority could not be made because of premature termination and low statistical power.

In agreement with a review of prior studies, the frequency of severe bleeding (grade 3 and 4) was not different among the treatment arms. While reassuring, all reported studies, including ours, are insufficiently powered to adequately assess differences regarding such bleeding events.

The overall frequency of grade 2 or higher bleeding in our study was intermediate between that reported in several previous studies but similar to the frequencies observed in 2 large randomized clinical trials of platelet transfusion. The reported incidence of bleeding depends on factors that may differ among studies, such as assessment method and frequency, criteria used to grade bleeding, and patient population.

In accordance with previous studies, P-PR/PAS was also associated with a decreased interval between 2 transfusions and a lower 24-hour CCI. Treatment failure frequency was also increased. These later factors suggest impaired in vivo platelet viability and/or reduced circulation capacity. Reduced numbers of platelets in P-PR/PAS may have contributed to the reduced interval while not contributing to the reduced CCI.

Of note, for grade 2 or higher bleeding incidence and for 24-hour CCI and frequency of treatment failures, results with P-PAS were intermediate between P-PR/PAS and P-P. Such findings suggest that PAS might affect platelet quality in accordance with a recent in vitro study. Consequently, using P-PAS as sole control when evaluating test platelets may indeed not be appropriate. Untreated platelets in plasma, their natural environment, should remain the criterion standard for studies that evaluate in vivo efficacy of platelets undergoing treatment that may impair their function.

Transfusion-associated adverse events were infrequent, mainly low-grade allergies and fever, and in line with current French hemovigilance data. The higher frequency of allergies associated with P-P was expected. Evidence that supports increased pulmonary adverse events with P-PR/PAS, as possibly suggested in the SPRINT trial, was not found.

**Limitations**

Our study has some weaknesses. It was not sufficiently powered to allow for a third comparison between P-P and P-PAS, an issue that deserves further investigation. Furthermore, all efforts were made to maximize masking of study investigators, the medical team, and patients to treatment arm. However, with a deliberate effort, both P-P (as in all studies comparing P-P and P-PAS) and P-PR/PAS bags could be recognized as such. The low occurrence of TTI prevented the inclusion of a safety end point with regard to TTI risk reduction. Lastly, our results regarding prophylactic platelet transfusion in patients with thrombocytopenia and hematologic diseases cannot substitute for careful clinical assessment of similarly treated platelets in other clinical contexts, such as acute bleeding in the context of posttraumatic coagulopathy.

Our results highlight the difficulty in maintaining an optimal functional quality of blood products while ensuring maximum TTI prevention. We suggest that differing geographic and temporal infectious epidemiologic contexts, as well as the increased cost of providing platelet support, are additional issues that should also be considered.

**Table 3. Transfusion-Related Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. (%) of Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-PR/PAS (n = 1822)</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Other (not severe)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

**Abbreviations:** See Table 2.

a P = .02 for results from post hoc analyses comparing P-PR/PAS with P-P.

b P = .01 for results from post hoc analyses comparing P-PR/PAS with P-PAS.
Conclusions

In our study, P-PR/PAS was not inferior to P-PAS with regard to clinical hemostatic efficacy in a hematologic context. However, such noninferiority was not achieved when comparing P-PR/PAS and P-P. Furthermore, our CCI results suggest reduced in vivo platelet recirculation resulting from the use of PAS and PR. Pathogen reduction technology, in addition to platelet storage in PAS, could be associated with reduced hemostatic efficacy compared with untreated platelets stored in plasma.

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