Supplementary Online Content


eMethods. Platelet Product Production

eFigure 1. Detailed Patient Flowchart

eFigure 2. Differences in Frequency of Bleeding WHO Grade 2 or Higher Among Study Arms: Noninferiority Assessment

eTable 1. Off-protocol Platelet Transfusions

eTable 2. Platelet Product Characteristics

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Platelet Product Production

All blood products used in the trial are approved for routine use in France and were prepared by the branches of the “Etablissement Français du Sang” (EFS) according to identical protocols and as specified by the manufacturer’s instructions and in accordance with French regulations.

Platelets concentrates (PC) were produced either by apheresis collection (APCs) or by the buffy coat method from whole blood (pooled PC [PPC]). The type of PC (APL or PPC) provided to study patients depended on current transfusion practices in each of the 13 clinical centers involved in the study.

To obtain PPC, whole blood was collected with a bottom-and-top pack and stored overnight at room temperature before buffy coat separation by centrifugation. Five buffy coats with the same ABO group together with 1 unit of platelet additive solution (PAS) (Intersol®, Fresenius Kabi AG, Bad Homburg, Germany) or one unit of plasma from one of the donors were pooled through a sterile connection into an automated separation device (TACSI, Terumo BCT, Lakewood, CO). A low-speed differential centrifugation separated the platelet-rich supernatant from erythrocytes followed by leukoreduction by filtration to achieve <1*10^6 white blood cells/PC. Single donor APC were collected using Trima Accel (Terumo BCT Lakewood, CO) MCS+ (Haemonetics, Braintree, MA) or Amicus (Fenwal, Fresenius Kabi, Lake Zurich, IL) blood cell separators. For APC in PAS, PAS addition (55 to 70% PAS / 30 to 45% plasma) was made during the process. Leukoreduction to < 1*10^6 white blood cells/PC was performed during the process, or subsequently by filtration.

For transfusion-related acute lung injury (TRALI) prevention, and per current practice in France, apheresis donors were male, female without children or female with children and tested for the absence of anti-HLA (class I and II) antibodies. For PPC in PAS (55 to 70% PAS / 30 to 45% plasma), with or without pathogen reduction (PR), no more than 2 of 5 of the buffy-coat donors could be women with children and untested for anti-HLA antibodies. Identical rules applied for PPC in plasma with the exception that in the presence of (no more than 2) female donors with children and untested for anti-HLA antibodies the plasma from these donors was not used to resuspend the platelet pool.

For the preparation of PR-treated PC, both APC and PPC underwent amotosalen UV-A photochemical treatment (Intercept®, Cerus Europe BV, Amersfoort, Netherlands) according to the manufacturer’s instructions. Residual amotosalen and photoproducts were removed after 4 to 8 hours of incubation using a compound adsorption device. Untreated PCs were gamma-irradiated with 25 to 40 Gy, while PR-treated PC were not, per current French regulations. Platelet concentrates were stored for up to 5 days with reciprocal agitation at controlled temperature (20-24°C) before transfusion.

ABO identical platelets were preferably transfused. If unavailable, ABO compatible platelets from donors with a low anti-A or anti-B IgG Ab titer, or in a limited number of cases, ABO incompatible platelets provided by donors with a low anti-A or anti-B IgG Ab titer, were transfused (eTable 2).
**eFigure 1. Detailed Patient Flowchart**

Eligible population (n=859) → Excluded (n=17) → Randomized (n=842) →

- Allocated to P-PR/PAS (n=280)
- Received ≥1 P-PR/PAS transfusions (n=266)
- Patients per center:
  - Center 1 (n=43)
  - Center 2 (n=43)
  - Center 3 (n=27)
  - Center 4 (n=15)
  - Center 5 (n=28)
  - Center 6 (n=24)
  - Center 7 (n=11)
  - Center 8 (n=6)
  - Center 9 (n=19)
  - Center 10 (n=15)
  - Center 11 (n=10)
  - Center 12 (n=8)
  - Center 13 (n=17)

- Lost to follow-up:
  - Withdrew consent (n=3)

- Analyzed (n=263)

- Allocated to P-P (n=280)
- Received ≥1 P-P transfusions (n=263)
- Patients per center:
  - Center 1 (n=45)
  - Center 2 (n=40)
  - Center 3 (n=25)
  - Center 4 (n=16)
  - Center 5 (n=29)
  - Center 6 (n=24)
  - Center 7 (n=10)
  - Center 8 (n=6)

- Lost to follow-up:
  - Withdrew consent (n=1)

- Analyzed (n=262)

- Allocated to P-PAS (n=282)
- Received ≥1 P-PAS transfusions (n=266)
- Patients per center:
  - Center 1 (n=38)
  - Center 2 (n=43)
  - Center 3 (n=27)
  - Center 4 (n=16)
  - Center 5 (n=29)
  - Center 6 (n=26)
  - Center 7 (n=10)
  - Center 8 (n=6)
  - Center 9 (n=20)
  - Center 10 (n=15)
  - Center 11 (n=10)
  - Center 12 (n=7)
  - Center 13 (n=19)

- Lost to follow-up:
  - Withdrew consent (n=1)

- Analyzed (n=265)
eFigure 2. Differences in Frequency of Bleeding WHO Grade 2 or Higher Among Study Arms: Noninferiority Assessment

a) p-value of .03. This p-value superior to .025 for the difference between P-PR/PAS and P-P, based on a non-inferiority test with a non-inferiority margin of 12.5%, indicates that non-inferiority between P-PR/PAS and P-P is not accepted.

b) p-value of .012. This p-value inferior to .025 for the difference between P-PR/PAS and P-PAS, based on a non-inferiority test with a non-inferiority margin of 12.5%, indicates that non-inferiority between P-PR/PAS and P-PAS is accepted.
Table 1. Off-protocol Platelet Transfusions

<table>
<thead>
<tr>
<th>% of off-protocol transfusions received per patient</th>
<th>P-PR/PAS (n=263)</th>
<th>P-P (n=262)</th>
<th>P-PAS (n=265)</th>
<th>Total (n=790)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>224 (85.2)</td>
<td>248 (94.7)</td>
<td>262 (98.9)</td>
<td>734 (92.9)</td>
</tr>
<tr>
<td>]0;25]</td>
<td>28 (10.7)</td>
<td>8 (3.1)</td>
<td>2 (.8)</td>
<td>38 (4.8)</td>
</tr>
<tr>
<td>]25;50]</td>
<td>7 (2.7)</td>
<td>3 (1.2)</td>
<td>1 (.4)</td>
<td>11 (1.4)</td>
</tr>
<tr>
<td>]50;75]</td>
<td>4 (1.5)</td>
<td>3 (1.2)</td>
<td>0 (0)</td>
<td>7 (.9)</td>
</tr>
</tbody>
</table>

Platelet transfusions

<table>
<thead>
<tr>
<th>No of transfusions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-protocol</td>
</tr>
<tr>
<td>Off-protocol*</td>
</tr>
</tbody>
</table>

* 6 of these transfusions concerned the first transfusion
**eTable 2. Platelet Product Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>P-PR/PAS (n=1761)</th>
<th>P-P (n=1396)</th>
<th>P-PAS (n=1722)</th>
<th>Total (n=4879)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. APC (%)</td>
<td>906 (51.5)</td>
<td>749 (53.6)</td>
<td>776 (45.1)</td>
<td>2431 (49.8)</td>
</tr>
<tr>
<td>No. PPC (%)</td>
<td>855 (48.5)</td>
<td>647 (46.4)</td>
<td>946 (54.9)</td>
<td>2448 (50.2)</td>
</tr>
<tr>
<td>Platelet product age in days, Mean (SD)</td>
<td>3 (1.0)</td>
<td>3.0 (1.0)</td>
<td>3.0 (1.0)</td>
<td>3.0 (1.0)</td>
</tr>
<tr>
<td><strong>Platelet-Recipient ABO matching</strong> *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. ABO identical (%)</td>
<td>1041 (72.3)</td>
<td>791 (71.8)</td>
<td>975 (77.0)</td>
<td>2807 (73.7)</td>
</tr>
<tr>
<td>No. ABO compatible but not identical (%)</td>
<td>299 (20.8)</td>
<td>202 (18.4)</td>
<td>180 (14.2)</td>
<td>681 (17.9)</td>
</tr>
<tr>
<td>No. ABO incompatible (%)</td>
<td>99 (6.9)</td>
<td>108 (9.8)</td>
<td>112 (8.8)</td>
<td>319 (8.4)</td>
</tr>
</tbody>
</table>

* excluding 1062 platelet products transfused to non-identical ABO hematopoietic stem cell graft recipients and 3 platelet products in a patient with missing blood type.

N=3807 transfusions: 1439 P-PR/PAS ; 1101 P-P ; 1267 P-PAS

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