PLATELET TRANSFUSION EFFICACY FOLLOWING PATHOGEN REDUCTION TREATMENT: AN ITALIAN RANDOMIZED CONTROLLED TRIAL

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A recent publication in TRANSFUSION (http://onlinelibrary.wiley.com/doi/10.1111/trf.14042/full) reported results from a randomized controlled trial (RCT) conducted in Italy that compared the transfusion of INTERCEPT™-treated platelets (Cerus) and Mirasol®-treated platelets (TerumoBCT) to untreated platelets.[1]

The Italian Platelet Technology Assessment Study was conducted as two parallel, non-inferiority randomized controlled trials (RCT) in six hospitals in Italy. The purpose was to assess the effectiveness and safety of pathogen reduced (PR) platelets versus non-PR platelets. Each trial was identical in design except that Mirasol was used in three centers and INTERCEPT in three other centers.

The primary endpoint for each trial was the percentage of patients who experienced World Health Organization Grade 2 or greater bleeding. A noninferiority margin of 11% was chosen based on an expected Grade 2 or greater bleeding in 20% of control patients. The study was terminated for economic considerations before reaching the planned sample size of 828 patients. The intention-to-treat (ITT) analysis was conducted on 424 evaluable patients.

The study enrolled patients 18 years or older with a hematological cancer who were anticipated to need two or more platelet transfusions during one of remission induction or consolidation chemotherapy or during allogeneic hematopoietic stem cell transplantation. Platelets were prepared in one of two ways: 1. from whole blood by the buffy-coat method or 2. were by apheresis, resuspended in approximately 30% plasma and 70% platelet additive solution. They were stored for up to 5 days at 20 to 24C. Hospitals that employed INTERCEPT technology used buffy coat–derived platelets in approximately 97% of transfusions, and hospitals that employed the Mirasol technology used buffy coat-derived platelets in approximately 50% of transfusions.

Patients were observed beginning on the first day of platelet transfusion and observation continued for 28 days or fewer if the patient did not receive any platelet transfusions for 7 consecutive days, was discharged, or died. Bleeding assessments were performed daily by a local physician who was blinded to the treatment allocation.

Assessment occurred between October 20, 2010 and June 30, 2014. In the INTERCEPT trial 360 patients were assessed for eligibility, and 118 were randomized to the PR arm and 119 were randomized to the standard platelets arm. In the Mirasol trial, 246 patients were assessed for eligibility and 102 patients were randomized to receive PR platelets and 99 were randomized to receive standard platelets

Adverse events to transfusion, complete remission in chemotherapy recipients, and frequency and causes of death between treated and control patients were not statistically significant for either PR technology.

In the Intercept arms, mean platelet unit use was 54% higher (95% CI, 36%-74%) and mean RBC use was 23% higher (95% CI, 8%-39%) compared to controls. In the Mirasol arms, mean platelet unit use was 34% higher (95% CI, 16%-54%) and mean RBC use was 32% higher (95% CI, 10%-57%) compared to

controls. In the Intercept arms, patients used 2.07 (95% CI, 0.82-3.51) more platelet units and 0.87 more RBC units. In the Mirasol arms, patients used 1.17 (95% CI, 0.27-2.07) more platelet units and 0.69 more RBC units.

In both INTERCEPT and Mirasol platelet recipients, the 1-hour and 24-hour posttransfusion absolute platelet count increments and also the corrected count increments (CCI) were decreased compared to the increments in controls. Differences between the treated and control arms were statistically significant with the exception of 1-hour CCIs in the INTERCEPT trial and 1-hour count increments in the Mirasol trial. Both results showed strong trends (see Tables 1 and 2.).

Table 1

INTERCEPT VERSUS CONTROL	*Increase or Decrease vs Control*	*P*
No. of days on platelet support: D	*+1.88 (+0.04; +3.72)*	*0.0452*
No. of platelet units transfused: R	*1.54 (1.36; 1.74)*	*<0.0001*
No. of platelet units transfused: D	*+2.07 (+1.49; +2.64)*	*<0.0001*
No. of platelets transfused, x 109/L: D	*+556 (+172; +941)*	*0.0047*
No. of RBC units transfused: R	*1.23 (1.08; 1.39)*	*0.0015*
No. of RBC units transfused: D	*+0.87 (+0.34; +1.41)*	*0.0014*
1-Hour posttransfusion platelet count increment, x 109/L: D	*-4.42 (-7.80; -1.04)*	*0.0105*
24-Hour posttransfusion platelet count increment, x 109/L: D	*-7.06 (-10.37; -3.75)*	*<0.0001*
1-Hour posttransfusion corrected platelet count increment: D	*-2004 (-4045; +38)*	*0.0543*
24-Hour posttransfusion corrected platelet count increment: D	*-3066 (-4926; -1206)*	*0.0014*

D=DIFFERENCE R=RATIO

Table 2

MIRASOL VERSUS CONTROL	*Increase or Decrease vs Control*	*P*
No. of days on platelet support: D	*+1.45 (+0.11; +2.80)*	*0.0342*
No. of platelet units transfused: R	*1.34 (1.16; 1.54)*	*<0.0001*
No. of platelet units transfused: D	*+1.17 (+0.61; +1.73)*	*<0.0001*
No. of platelets transfused, x 10^9/L: D	*+399 (+118; +681)*	*0.0057*
No. of RBC units transfused: R	*1.32 (1.10; 1.57)*	*0.0024*
No. of RBC units transfused: D	*+0.69 (+0.25; +1.14)*	*0.0023*
1-Hour posttransfusion platelet count increment, x 10^9/L: D	*-8.91 (-18.94; +1.11)*	*0.0810*
24-Hour posttransfusion platelet count increment, x 10^9/L: D	*-4.28 (-7.47; -1.08)*	*0.0090*
1-Hour posttransfusion corrected platelet count increment: D	*-5282 (-10,436; -128)*	*0.0446*
24-Hour posttransfusion corrected platelet count increment: D	*-2554 (-4212; -896)*	*0.0027*

D=DIFFERENCE R=RATIO

The authors noted their results confirmed the findings of other studies that lower post-transfusion platelet count increments are found in PR platelet recipients compared to recipients of control platelets. They suggested that the reduced increments were a possible cause of the modest reduction of the platelet transfusion interval. This could explain the finding of a mean of one or two more platelet units given to PR platelet recipients compared to recipients of untreated platelets. Although this absolute mean increment per patient was small, it corresponded to 54% and 34% greater platelet transfusion in the recipients of INTERCEPT-treated and Mirasol-treated platelets, respectively.

The authors were not certain why the RBC use was increased in the recipients of INTERCEPT and Mirasol platelets compared to controls. They conjectured that the increase in bleeding observed in PR platelet recipients, while clinically minor, may have cumulatively led to greater RBC transfusion in some patients.

The authors noted that they were not able to draw conclusions regarding noninferiority for the primary endpoint owing to the low statistical power of both the INTERCEPT and Mirasol trials. In this regard, the percentage of patients with Grade 2 or greater bleeding in the INTERCEPT arm was +6.1% (UCL, +19.2%) p=0.1648 and in the Mirasol arm was +4.1% (UCL +18.5% p=0.2489). The number of days with Grade 2 or greater bleeding were also not significantly different in either the INTERCEPT or Mirasol arms.

Despite methodological differences, all INTERCEPT trials show comparable reductions of mean posttransfusion CCIs with PR platelets compared to untreated platelets. In this regard, mean 24-hour CCIs with INTERCEPT platelets were 33.5% lower in this study and 30.2%[2], 33.7%[3], 29.8%[4], 31.9%[5], and 30.0%[6] lower compared to control platelet CCIs in other published trials. The authors state, "This finding, which also was confirmed in our study using relatively fresher platelets, may be clinically and economically relevant, because lower posttransfusion platelet counts detected on the day after transfusion may cause increased platelet use."

The authors also reiterate that the lower post-transfusion platelet count increments in INTERCEPT PR platelets were associated with 54% more platelet transfusions in this trial. This is in accord with higher mean numbers of platelet transfusions per patient in other INTERCEPT trials: 36%[2], 35%[3], and 12%[5].

The authors note that there is less extensive published information available on the clinical effectiveness of platelets prepared with the Mirasol technology. One French RCT randomized 118 patients to receive Mirasol-treated or standard platelets.[7] The primary outcome was 1-hour posttransfusion CCIs, which were 11,725 and 16,939 in recipients of PR platelets and standard platelets, respectively. This corresponded to a 30.8% reduction in Mirasol platelet recipients. This result is quite similar to the 30% reduction in mean 1-hour CCI with Mirasol-treated platelets found in this trial. The French study also found a 50% higher median number of on-protocol platelet transfusions in Mirasol compared to standard platelet recipients in the 28-day treatment period (4.5 vs. 3.0, respectively).

The authors conclude that their data provides strong evidence of lower post-transfusion platelet count increments with PR platelets compared with standard platelets and that this decrement was observed while testing both technologies with relatively fresher platelets compared with the other published RCTs. They further observe that while the risk and type of bleeding and frequency and type of AEs did not appear to differ between PR and standard platelets, any PR reduction in infectious risk

should be balanced against increased component utilization and its economic impact. "Considering the economic restrictions that affect health systems in many jurisdictions, the increased margin of microbiological and immunological safety of PR platelets must be balanced with the cost of the procedures and with the possibility that lower post-transfusion platelet count increments generate increased blood component utilization." Beyond the authors' conclusions, the significant increase in the number of RBC units transfused in both the INTERCEPT and Mirasol arms is a novel and noteworthy finding with patient safety and economic implications.

Septic reactions from platelet transfusions continue to occur.[8] The Verax Biomedical Platelet PGD test is FDA-cleared to detect bacteria in leukocyte reduced apheresis platelets (LRAP) suspended in plasma, LRAP suspended in Platelet Additive Solution C and plasma, and pre-storage pools of up to six leukocyte reduced whole blood derived platelets suspended in plasma, within 24 hours prior to platelet transfusion as a safety measure following testing with a growth-based quality control test cleared by the FDA for platelet components and is also cleared for pools of up to six units of leukocyte reduced and non-leukocyte reduced whole blood derived (WBD) platelets suspended in plasma that are pooled within four hours of transfusion. In addition, seven-day expiration is available for apheresis platelets in plasma collected with the Amicus and Trima devices. The PGD test is the only technology available in the US to extend platelet expiration to seven days and can effectively detect bacterially contaminated platelets prior to transfusion without altering platelet quantity or quality.

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