Factors affecting post-transfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients

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ABSTRACT

A variety of patient and product related factors influenced the outcome of 6,379 transfusions given to 533 patients in the Trial to Reduce Alloimmunization to Platelets (TRAP Trial).(1) Responses measured were platelet increments, interval between platelet transfusions, and platelet refractoriness.

Patient factors that improved platelet responses were splenectomy and increasing patient age. In contrast, ≥2 prior pregnancies, male gender, splenomegaly, bleeding, fever, infection, DIC, increasing height and weight, lymphocytotoxic antibody positivity, an increasing number of platelet transfusions or receiving heparin or amphotericin were associated with decreased post-transfusion platelet responses.

Platelet factors that were associated with improved platelet responses were giving ABO-compatible platelets, platelets stored for ≤48 hours, and giving large doses of platelets while UV-B or gamma irradiation decreased platelet responses. However, in alloimmunized lymphocytotoxic antibody positive patients, the immediate increment to UV-B irradiated platelets was well maintained while all other products showed substantial reductions.

Refractoriness to platelet transfusions developed in 27% of the patients. Platelet refractoriness was associated with lymphocytotoxic antibody positivity, heparin administration, fever, bleeding, increasing number of platelet transfusions, increasing weight, ≥2 pregnancies, and male gender. The only factors that reduced platelet refractoriness rates were increasing the dose of platelets transfused or transfusing filtered apheresis platelets.

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INTRODUCTION

The TRAP Trial was a large, multi-institutional platelet transfusion trial to determine the relative effectiveness of leukocyte reduction, UV-B irradiation, and single donor apheresis platelets as methods of preventing alloimmune platelet refractoriness.\(^{(1)}\) This trial demonstrated that both UV-B irradiation and leukocyte reduction were equally effective in preventing both the development of lymphocytotoxic antibodies and platelet refractoriness when it was due to alloimmunization. However, other non-immune causes of platelet refractoriness were not analyzed in previous publications from the TRAP Trial.

As part of this transfusion trial, patients had pre-transfusion and serial post-transfusion platelet counts and time to next platelet transfusion measurements recorded to evaluate transfusion responses of platelet increment, days to next transfusion and platelet refractoriness. Certain clinical conditions of the patient at the time of the transfusion and characteristics of the transfused platelets were also monitored. Thus, the TRAP Trial data base represents an opportunity to evaluate patient and product-related characteristics that might influence post-transfusion platelet responses in the largest data set available for a relatively homogenous patient population. This data may also permit hypothesis generation as to why certain factors affect platelet transfusion responses.

METHODS

**Patient Population.**

Previously untreated patients with acute myelogenous leukemia (AML) scheduled to receive induction chemotherapy were eligible for study entry with the following exceptions: <15 years of age; patients who were to receive no or low dose chemotherapy or corticosteroids; recipients of multiple blood transfusions for a hematopoietic disorder >2 months before study en-
try; recipients of transfusions from more than 10 different donors between 2 weeks and 2 months before study entry; and those given chemotherapy or extensive radiation therapy within the past 2 years.

Institutional review boards approved this study at each trial site, and informed consent was obtained from each patient before enrollment in accordance with the Declaration of Helsinki.

**Preparation Of Platelets.**

Patients were randomly assigned to receive one of 4 types of platelet transfusions for 8 weeks after the first transfusion of study platelets: unmodified pooled random donor platelet concentrates (PC) (control); filtered, pooled random donor platelet concentrates (F-PC); ultraviolet B irradiated, pooled random donor platelet concentrates (UVB-PC); filtered random donor apheresis platelets (F-AP). Platelet pools were usually composed of 6 units of platelet concentrates prepared from whole blood by the platelet-rich plasma (PRP) method.\(^{(2)}\) Filtration with Pall PL-100 filters (Pall Biomedical, East Hills, New York) and UV-B irradiation at a dose of 1480 mJ/cm\(^2\) with a Haemonetics Irradiation Device (Haemonetics Corporation, Braintree, Mass.) were usually done shortly before transfusion. Apheresis platelets were collected with a Cobe Spectra Apheresis Machine (Cobe Laboratories, Lakewood, Colorado) with Version 2.6 or 3.6 software.

Cell counts of the platelet products were performed by automated counters after all processing was completed. Gamma (\(\gamma\)) irradiation was performed with Cesium irradiators at doses of 2500-3000 cGy. Volume reduction of platelet products was done by centrifugation. Platelets were considered ABO-compatible if the recipient had no antibodies incompatible with the donors red cell type.
Indications For Platelet Transfusions.

Most patients received prophylactic platelet transfusions for platelet counts of $\leq 20,000/\mu l$, or at higher levels for particular clinical indications; e.g., active bleeding or pre-surgery.

Response To Platelet Transfusions.

The post-transfusion platelet count is affected by the quality as well as the number of platelets transfused and also by the dilution of platelets in the patient’s blood volume. Calculations such as the corrected count increment (CCI) and the percent platelet recovery (PPR), which adjust for the number of platelets transfused and the patient’s blood volume, have been presumed to give a more precise comparison of the post-transfusion platelet responses between platelet preparations or between patients. Both calculations use ratios in which the platelet count increment is multiplied by an estimate of the patient’s blood volume and divided by the number of platelets transfused. A change in the CCI or PPR can occur with platelet products that have the same dose but different quality. The separate effects of dose and quality cannot be discriminated by ratio measures such as CCI or PPR, but regression analysis can provide a method of analysis that permits discrimination of these effects as well as other properties of the platelet product related to the preparation technique. Thus, the post-transfusion platelet increment was used as the primary method of assessing transfusion responses in this report, and longitudinal linear regression analyses were used to identify the effects of patient- and platelet-related factors including dose on transfusion responses. Most blood centers and hospitals do not perform platelet counts of the products transfused so calculations of PRPs or CCIs are not possible. This makes data analyses based on platelet increments much more relevant for clinicians as this data is routinely available.
In the original analysis of the TRAP Trial data, patients were considered to be platelet refractory if they had two serial 1-hour post-transfusion CCI’s of <5,000. For the current data analysis, patients were considered to be refractory if they had two sequential 1-hour post-transfusion platelet increments of <11,000/µl. The cut-off of 11,000 platelets/µl is the increment that would give a CCI of 5,000 for the average TRAP Trial patient, whose body surface area (BSA) was 1.91 kg/m² and whose average transfusion contained 4.08 x 10¹¹ platelets.

The pre-transfusion platelet count was routinely the morning count, and this count was used for ordering platelets. In general, a platelet count of ≤20,000/µl was used as the transfusion trigger. Post-transfusion platelet counts were drawn within 10 to 60 minutes after each transfusion, and repeat platelet counts were drawn the next morning and then daily until a subsequent platelet transfusion was given. For each transfusion, the post-transfusion platelet increments (post-transfusion platelet count minus pre-transfusion platelet count) at both 1 hour and 18-24-hours post-transfusion were calculated, as well as the days until the next platelet transfusion was given; i.e., the interval between transfusions.

**Antibody Testing.**

Sera were obtained at baseline and weekly thereafter for eight weeks. Sera were tested blindly in central laboratories after completion of the study for lymphocytotoxic antibodies against a panel of 30-60 HLA-typed frozen lymphocytes with an antiglobulin-augmented, complement-dependent assay.⁶,⁷ Samples were considered lymphocytotoxic antibody-positive if they reproducibly caused at least 60% cytotoxicity with one or more panel cells or at least 40% cytotoxicity with two or more cells. Although some baseline antibody-positive patients were randomized, they were excluded from all of the analyses reported here.
Patients And Transfusions Analyzed.

Of the 603 patients randomized in the TRAP Trial, 70 were excluded from the analyses reported here either because they were antibody-positive or had unknown antibody status at baseline (n=65), had no transfusions (n=4), or had no post-transfusion platelet counts (n=1). The remaining 533 patients received 7,672 transfusions. Of these, 531 transfusions were excluded because they were given after an interval between platelet transfusions of more than ten days. Since this interval is longer than the expected lifespan of transfused platelets in thrombocytopenic patients,\(^8\) it was assumed that autologous platelet recovery had occurred and that these transfusions were given during a second course of chemotherapy-induced thrombocytopenia. Transfusions were further restricted to the first 25 platelet transfusions a patient received so that heavily transfused patients would not unduely influence the results. Eight additional transfusions were omitted because they were extreme outliers with post-transfusion platelet counts above 129,000/µl (range 129,000/µl to 263,000/µl). In each case, the transfusion was given for bleeding and was the last the patient received, presumably after autologous platelet recovery had occurred. One other transfusion was omitted that had a pre-count of 450,000/µl and a post-count of 515,000/µl and was the patient’s first transfusion. Thus, the data analyses were limited to a total of 6,379 transfusions given to 533 patients. The mean number of transfusions per patient was 12.0 ± 7.1 (S.D.). Thirty-two percent of the patients had \(\leq 7\) or fewer transfusions, and 25% had \(\geq 17\) transfusions.

Clinical Conditions.

Certain clinical conditions that might influence a patient’s response to a platelet transfusion were recorded for all study patients. A clinical condition occurring during a 24-hour time period from midnight of one day to midnight of the next day was considered to have influenced
any platelets transfused in that time interval. Moderate to severe bleeding was defined as bleeding requiring a red blood cell transfusion or any evidence of CNS hemorrhage. Fever was defined as a maximum daily temperature of $\geq 101^\circ F$ or $38.4^\circ C$. Minor to moderate infection was defined as cellulitis, gingivitis, Hickman catheter infection, localized rectal abscess, dental abscess, etc. Severe infection was defined as pneumonia or bacteremia (positive blood cultures within 24 hours). Disseminated intravascular coagulation (DIC) was defined as a fibrinogen of $<100$ mg/dl with a fibrinogen degradation product assay above the normal range. Moderate to severe transfusion reactions were characterized by the following findings during or within 1 hour after a transfusion: 1) increase in temperature $\geq 3^\circ F$ ($2^\circ C$); 2) chills with rigors; 3) extensive urticarial eruption; 4) moderate to severe pulmonary symptoms (dyspnea, bronchospasm, or cyanosis); and 5) anaphylaxis. Medications recorded in association with a transfusion (given within 24 hours either before or after a transfusion) were amphotericin B, therapeutic heparin, and I.V. $\gamma$ globulin.

**Statistical Analysis.**

Risk factors contributing to platelet count increments within 1 hour and between 18-24 hours post-transfusion and to the interval between transfusions were analyzed by longitudinal linear regression using a random effects model derived by generalized estimating equations.$^{(9)}$ This model accounts for the correlation among transfusions given to the same patient.

Baseline patient factors considered were age, gender, history of pregnancy or previous transfusion, height, weight, and previous splenectomy. Patient characteristics evaluated for each transfusion were: administration of amphotericin, heparin or $\gamma$-globulin; lymphocytotoxic antibody status of the closest sample prior to the transfusion; palpable spleen; and the presence of bleeding, fever, infection, transfusion reaction, or DIC. The characteristics of the transfused
platelets that were analyzed were: transfusion sequence number; the product platelet count; ABO compatibility; actual preparation method of the platelet product (not necessarily the assigned product); and whether the platelet product was γ-irradiated, volume-reduced, or fresh (transfused within 48 hours of collection). Covariates with p>0.05 were eliminated by backwards stepwise selection. Interactions with platelet preparation method were added to the reduced model and the backwards stepwise elimination process was repeated. All patients with complete data for at least one transfusion were included in the analyses. For the multivariate analyses, the sample sizes were 5,778 transfusions in 530 patients for 1 hour count increments and 5,103 transfusions in 528 patients for 18-24 hour count increments. Analysis of transfusion intervals (5,423 transfusions in 525 patients) excluded patients who had only one transfusion and excluded the last transfusion for each patient.

Refractory status was analyzed by Cox regression models in a similar step-wise fashion. However, these analyses were patient-based by the patient’s randomization assignment rather than by the platelet product actually transfused. Five patients were excluded from this analysis as they had only one transfusion.

RESULTS

Patient Variables.

The baseline characteristics of the 533 patients were as follows: 45% were females, and of the total population, 37% had a previous pregnancy, 80% had previous transfusion and 1% had a splenectomy. The average age of study participants was 52 ± 17 years, height was 170 ± 10 cm, and weight was 80 ± 18 kg (1 SD). The pre-selected set of clinical conditions and medications that were monitored during the trial, and the incidence of these factors concurrent with a platelet transfusion were: infection (minor to severe) 48%; fever 32%, palpable spleen 17%;
moderate to severe bleeding 12%; lymphocytotoxic antibody positive 5%; moderate to severe transfusion reaction 2%; DIC 1%; amphotericin 48%; therapeutic heparin 4%; and IV gamma globulin 0.4%.

**Characteristics Of The Transfused Platelets.**

There were 6254 platelet transfusions which had a known platelet count and were prepared by only one method. Platelet counts of the control (n=1495) and UVB-PC (n=1603) averaged $4.52 \pm 1.12$ and $4.39 \pm 1.16 \times 10^{11}$ respectively, compared to platelet counts of $3.70 \pm 1.07$ and $3.68 \pm 1.34$ for the F-PC (n=1658) and F-AP (n=1498), respectively ($\pm 1$ S.D.). The platelet counts were significantly less for the filtered platelet products compared to the non-filtered platelets ($p<0.001$). Overall, 97% of the transfused platelets were ABO-compatible, 59% were $\gamma$-irradiated, 29% were stored for $\leq 48$ hours, and 4% were volume reduced. There were no differences among the platelet preparation methods for any of these platelet product parameters.

**Response To Platelet Transfusions.**

Pre- and post-transfusion platelet counts, platelet increments, and days to next transfusion for the control and treated platelets are given in Table 1. Overall, the mean 1-hour platelet increments averaged $24,900 \pm 17,000$ platelets/µl, the 18-24 hour increments averaged $12,000 \pm 15,000$/µl, and the days to next transfusion averaged $1.75 \pm 1.26$.

There was a progressive decrease in post-transfusion platelet increments at both 1 and 18-24 hours post-transfusion and in days to next transfusion from the 1st to the 25th transfusion (Figure 1A). Results were similar when patients who became lymphocytotoxic antibody positive during the course of the study were removed from this analysis (Figure 1B).
Platelet Increments

Longitudinal regression analyses of patient and platelet-related variables demonstrated that a large number of factors were associated with either a statistically significant increase or decrease in the 1-hour and/or the 18-24-hour post-transfusion platelet increments (Table 2). Significant increases in post-transfusion platelet increments were associated with prior splenectomy at both 1 and 18-24 hours post-transfusion. Older patient age was also associated with increased platelet increments but only at 1-hour post-transfusion.

In contrast, patient-related factors that were associated with significant reductions in post-transfusion platelet increments at both 1 hour and 18-24 hours post-transfusion were ≥2 pregnancies (71% of females), male gender, palpable spleen, amphotericin, bleeding, fever, infection, and increasing weight and number of transfusions. Although having ≥2 pregnancies were associated with decreased platelet increments, the decrease was not progressive with higher numbers of pregnancies. Increasing height was associated with significantly reduced post-transfusion increments only at 1 hour post-transfusion, and heparin was associated with significantly decreased platelet increments only at 18-24-hours post-transfusion. Patient-related factors that were not associated with changes in post-transfusion platelet increments were transfusions prior to study entry, gamma globulin, transfusion reactions, or DIC.

When the characteristics of the transfused platelets were added to the linear regression analyses, significant increases in platelet increments were associated with ABO-compatible platelets and platelets stored for ≤48 hours at both post-transfusion time points. Gamma irradiation was associated with significantly decreased platelet increments only at 1 hour post-transfusion and varied depending on the product transfused; i.e., γ-irradiated platelets reduced the 1 hour increment, compared to controls by 3,000 platelets/µl (p=0.002), by 7,300 platelets/µl for
F-LR (p=0.0001), by 4,500 platelets/µl for UV-B (p=0.001), but there was no difference for F—AP (-600 platelets/µl, p=0.59). Volume reduction was not associated with changes in platelet increments.

The effect of the platelet count of the concentrate (dose) on the 1 hour platelet increment was influenced by the preparation method. Although the increment increased with dose for all preparations, for UVB-PC, there was a constant reduction in increment of 4,200 platelets/µl at all doses compared to control PC (p<0.001, Figure 2A and 2B). The increment for F-PC was reduced at lower doses compared to control PC, but increased at higher doses (interaction p=0.01, Figure 2C). The dose preparation interaction was even stronger for F-AP (interaction p<0.001, Figure 2D).

The 1 hour platelet increments for both lymphocytoxic antibody negative and positive patients at the time of transfusion are given in Table 3. The increments associated with each preparation as estimated by the regression model are given in Table 3 for the mean dose as observed for each preparation method and also for hypothetical equal doses for each preparation method. At the actual observed mean doses for lymphocytoxic antibody negative patients, the control platelets gave the largest estimated increment; however, at equal doses, F-AP gave the largest estimated increment. At 18-24 hours post-transfusion, the increments for UVB-PC and F-PC were not significantly different from control PC, regardless of dose (p=0.13). However, similar to the 1 hour increments, at 18-24 hours post-transfusion, F-AP showed a significant dose preparation interaction (p<0.001). For the observed mean F-AP dose of 3.68 x 10^{11} platelets, the increase in increment estimated by regression was 400 platelets/µl above the control, while the increase was estimated to be 4,500 platelets/µl for hypothetical equal doses.
Patients who were lymphocytotoxic antibody-positive at the time of transfusion had lower platelet count increments than patients who were lymphocytotoxic antibody-negative; however, the effect was much smaller for UVB-PC. The reduction for antibody-positive patients at 1 hour estimated from the regression analysis was 9,300 platelets/µl for the control, F-PC and F-AP, but was only 750 platelets/µl for UVB-PC. At 18-24 hours, the estimated reduction for antibody-positive patients was 4,000 platelets/µl for all four preparations (95% confidence interval 2,000 to 6,000 platelets/µl).

**Platelet Refractoriness**

Of the 528 patients analyzed, 143 (27%) became platelet refractory. Adverse factors that were significantly associated with an increased risk of becoming platelet refractory were: lymphocytotoxic antibody-positivity, ≥2 pregnancies, male gender, heparin, fever, bleeding, increasing number of platelet transfusions, and increasing weight (Table 4). There was a trend for a palpable spleen to increase platelet refractory rates (p=0.08). Other patient-related factors that did not affect the development of platelet refractoriness were: patient age, prior transfusions, splenectomy, height, amphotericin, transfusion reaction, and infection.

Of the product-related factors, γ-irradiation was associated with a significant increase in platelet refractory rates (Table 4) while refractory rates were the same regardless of the type of platelets transfused (Figure 3). However, increasing the number of platelets transfused or giving equal doses of F-AP, compared to control PC, were both associated with significant decreases in platelet refractory rates; i.e., for equal platelet doses, F-AP had a significantly lower platelet refractory rate than control platelets (p=0.01). In contrast, for an average dose of 4.5 x 10^{11} control platelets compared to an average dose of 3.7 x 10^{11} apheresis platelets, the refractory rates for apheresis and control platelets were very similar with an estimated hazard ratio of 1.01 (Figure
3). As we defined refractoriness based on platelet increments rather than CCI, increasing the
dose of platelets transfused when the dose is not used as a denominator - as in the CCI calcula-
tion - would be expected to increase platelet increments and thereby, reduce refractory rates.
Neither ABO compatibility, fresh platelets, nor volume reduction had any effect on platelet re-
fractory rates.

There was also no apparent “cut-off” value for percent lymphocytotoxic panel reactivity
that showed a substantial relationship with the development of platelet refractoriness. For exam-
ple, using a cut-off of >0% panel reactivity, the sensitivity was at its highest value of 0.39 but
specificity was at its lowest of only 0.78. Using 10% increments in panel reactivity, the corre-
spanding values for sensitivity and specificity, respectively, were ≥10% (0.37, 0.81), ≥20% (0.30,
0.87), ≥30% (0.25, 0.90), ≥40% (0.22, 0.94), ≥50% (0.20, 0.95), ≥60% (0.19, 0.96), ≥70% (0.15,
0.97), ≥80% (0.13, 0.98), and ≥90% (0.09, 0.99). Sensitivity is the proportion refractory patients
classified (correctly) as positive; i.e., \[
\text{True positive} \quad \] 
\[
\text{True positive + False negative}
\]

while specificity is the pro-
portion of non-refractory patients classified (correctly) as negative; i.e., 
\[
\text{True negative} \quad \] 
\[
\text{True negative + False positive}
\]

**Interval Between Platelet Transfusions**

Significantly shorter transfusion intervals were associated with ≥2 pregnancies, male
gender, DIC, heparin, lymphocytotoxic antibody positivity, bleeding, amphotericin, fever, palpable spleen, infection, and increasing number of platelet transfusions and weight (Table 5). Plate-
let-related variables that were associated with significantly longer transfusion intervals were
platelets stored ≤48 hours, and increasing platelet dose, while UV-B irradiation was associated
with significantly shorter transfusion intervals.
Patient-related factors that did not influence days to next transfusion were: age, height, prior splenectomy or transfusions, γ-globulin, and a transfusion reaction. Similarly, platelet factors that had no influence on transfusion intervals were: ABO compatibility, γ-irradiation, volume reduction, control platelets, F-PC, or F-AP. There were no significant interactions with treatment and platelet dose or with treatment and lymphocytotoxic antibodies and days to next platelet transfusion.

**DISCUSSION**

Data collected during the TRAP trial provides a very large base of platelet transfusion related information.\(^\text{(1)}\) Reported here are the results of 6,379 transfusions given to 533 adult patients undergoing induction chemotherapy for acute myelogenous leukemia. Certain patient-related clinical factors and medications or platelet product-related factors that prior studies had suggested might influence platelet transfusion responses were recorded during the trial to distinguish between adverse post-transfusion platelet responses related to these factors rather than to the development of alloimmune platelet refractoriness. Some of the data reported here thus confirm prior studies documenting factors that may either adversely or beneficially affect platelet transfusion responses. In addition, other patient and product-related factors were identified that have not previously been recognized as influencing post-transfusion platelet responses. However, the large size of the data base sometimes gave statistically significant differences, but the actual change in platelet responses would not necessarily be considered clinically-relevant. The data were analyzed for 1 hour and 18-24 hour post-transfusion platelet increments, platelet refractory rates, and days to next transfusion; only significant differences are discussed here. Most prior studies have evaluated only immediate post-transfusion platelet responses.
linear regression analyses were used to identify independent effects of variables as well as potential interactions.

The biggest factor affecting post-transfusion platelet increments was the status of the spleen. Splenectomized patients (1% of the population) had post-transfusion platelet increments that averaged 24,800/µl and 12,400/µl greater than patients with normal sized spleens at 1 and 18-24 hours post-transfusion, respectively. Conversely, patients with a palpable spleen (17% of the population) had not only a decrease in their average platelet increments of 3,500 and 4,400 platelets/µl at the two time points, respectively, but also a decrease of 0.23 days in time to their next transfusion. The influence of the spleen on platelet increments has been previously documented, but prior data had not indicated that an enlarged spleen also reduced platelet transfusion intervals.[10,11]

There were several other baseline patient characteristics that also influenced platelet responses. Both females with ≥2 pregnancies and males had substantially decreased post-transfusion platelet increments of 8,900/µl and 5,700/µl at 1 and 18-24 hours post-transfusion, respectively, and time to next transfusion was reduced by 0.40 days, compared to females with ≤1 pregnancy. The affect of gender and prior pregnancies on platelet increments has been previously noted.[12] Surprisingly, there was no association of prior transfusions with response to platelet therapy, but this may reflect the restrictions on number and timing of prior transfusions that determined study eligibility. Increasing weight and height with corresponding increases in blood volume were associated with decreased post-transfusion platelet increments, and increasing weight also was associated with decreased platelet transfusion intervals. These effects were independent of gender. Increasing patient age was associated with improved platelet increments,
but only at 1-hour post-transfusion with no effect on 18-24 hour platelet increments or platelet transfusion intervals.

Of the patient-related factors during the trial, administration of amphotericin (48% of the patients), as previously reported,\(^{13,14}\) was associated with decreased post-transfusion increments of 2,700 and 2,500 platelets/µl at 1 and 18-24 hours post-transfusion, respectively, and also with a decrease in time to next transfusion of 0.28 days. Heparin administration (4% of the patients) decreased platelet increments by 3,800 platelets/µl at 18-24 hours post-transfusion, reduced the platelet transfusion interval by 0.37 days, but there was no effect at one hour post-transfusion. However, whether this is really a heparin-specific effect or due to the underlying condition for which the heparin was being given cannot be determined from the data. As previously noted,\(^{12-18}\) fever, bleeding, and infection may alter platelet responses. These three factors were all associated with modest reductions in post-transfusion platelet increments of 1,500 to 1,700 platelets/µl at 1 hour post-transfusion and of 1,800 to 3,100 platelets/µl at 18-24 hours post-transfusion, and reduced the transfusion interval by 0.18 to 0.33 days.

A previously unrecognized finding was the observation that the more platelet transfusions a patient received, the lower were their post-transfusion platelet increments at both 1 and 18-24 hours post-transfusion, and the shorter was the time to their next platelet transfusion (Figure 1A and 1B). This effect was seen regardless of the product transfused and was not related to the presence of lymphocytotoxic antibodies. There appeared to be a logarithmic decrease in platelet responses with the most pronounced effect occurring with the earliest transfusions. The explanation for this phenomenon is not immediately apparent particularly since it occurred so early in their transfusion course. As a patient’s clinical condition becomes progressively worse following their chemotherapy with fever, infections, administration of multiple antibiotics, etc. poorer
platelet responses might be anticipated later in their course. However, many of these potentially adverse factors were included in our longitudinal linear regression analyses and platelet sequence number produced effects independent of these factors. Alternatively, the poor platelet responses may be related to endothelial damage resulting from the patient’s chemotherapy program with increased platelet adherence to the damaged endothelium and thereby more rapid platelet loss from circulation. This hypothesis needs further evaluation.

The presence of DIC did not affect either the 1-hour or 24-hour post-transfusion platelet increments but did decrease the time to next platelet transfusion by 0.42 days. DIC has been previously shown to be associated with poor responses to transfused platelets.\(^{(12-18)}\)

Concerning product-related variables both the transfusion of ABO-compatible platelets, as well as platelets stored for <48 hours were associated with substantially improved platelet increments at both 1-hour post-transfusion by 4,600 and 1,900 platelets/µl, respectively and at 18-24 hours post-transfusion by 6,300 and 2,000 platelets/µl, respectively. It has previously been reported that ABO-compatibility improves post-transfusion platelet responses but does not improve platelet survivals consistent with our observations.\(^{(19)}\) Transfusion of platelets ≤48 hours compared to >48 hours old was also associated with an increase in the transfusion interval of 0.19 days. Longer platelet storage times have been reported to decrease post-transfusion platelet viability.\(^{(20-23)}\) However, some investigators have suggested that storage adversely affects only platelet concentrates rather than apheresis platelets.\(^{(24)}\) In our study, an equal benefit of platelets stored for ≤48 hours was seen for all the types of platelets transfused. Gamma irradiation of the platelets prior to transfusion decreased 1-hour post-transfusion increments by 2,800 platelets/µl but had no effect on 18-24 hour post-transfusion platelet increments or platelet transfusion intervals. Other studies have shown that \(\gamma\)-irradiation in the doses used in this study did not affect
post-transfusion platelet increments, \(^{(25,26)}\) while higher doses have been known to adversely affect platelet responses.\(^{(27)}\)

It is also not surprising that a relationship between increased platelet increments and prolonged transfusion intervals was observed, as it is known that, at platelet counts of \(\leq 70,000/\mu l\), there is a direct relationship between platelet count and platelet survival.\(^{(8)}\) This platelet count versus survival relationship may explain why those factors that improved platelet increments usually resulted in longer transfusion intervals while reduced increments shortened transfusion intervals.

There were significant interactions between platelet dose, the type of platelets transfused, and lymphocytotoxic antibodies that influenced post-transfusion platelet responses. For any given dose, the 1 hour post-transfusion increment for UVB-PC compared to control PC was less by a constant amount of 4,200 platelets/\(\mu l\). This data suggests that, following UV-B irradiation, a fixed fraction of platelets are damaged and do not circulate. In contrast, for the filtered platelet products, 1-hour platelet increments were less at low doses and increased at high doses compared to control PC. It may be that filtration also damages platelets but when higher doses of platelets are filtered, there may be less potential for individual platelet interaction with the filter. Thus, filter damaged platelets would represent a smaller fraction of the transfused platelets at higher doses. In addition, it may be that the filter preferentially removes older platelets resulting in an improved response for the platelets that pass the filter. However, for filtered platelets, the effect of dose on platelet count increment was the same for platelets stored for \(\leq 48\) hours or \(>48\) hours.

The presence of lymphocytotoxic antibodies substantially reduced 1-hour post-transfusion platelet increments for all products by at least 9,300 platelets/\(\mu l\) except those that were UV-B irradiated, where the reduction was only 750 platelets/\(\mu l\). Interestingly, the benefit of UV-B irra-
Radiation was not observed at 24 hours post-transfusion, as the increment was less by at least 4,000 platelets/µl for all products at this time interval. It is known that UV-B irradiation reduces the expression of some antigens on the surface of lymphocytes, and it may also reduce antigen expression on the surface of platelets as a possible explanation for these observations. However, we are unaware of studies that have measured antigen expression on platelets pre- and post-UV-B irradiation. There have been some studies suggesting that acid elution, which is known to remove a significant amount of the HLA antigens from the surface of platelets, may improve post-transfusion platelet increments in some patients who are alloimmunized. However, acid elution is a cumbersome process that may substantially damage the platelets. Our data may suggest that, for alloimmunized patients, the transfusion of UV-B irradiated platelets might provide better immediate platelet increments and, thereby, improved platelet hemostasis compared to that achieved with either filtered or control platelet transfusions. Unfortunately, UV-B irradiated platelets are not yet commercially available.

Platelet refractoriness was defined as two sequential 1-hour post-transfusion platelet increments of <11,000 platelets/µl, and 27% of patients developed platelet refractoriness. Patient related factors that were associated with increased rates of platelet refractoriness were lymphocytotoxic antibody-positivity, ≥2 pregnancies, male gender, heparin, fever, bleeding, and increasing number of transfusions and weight. Interestingly, although lymphocytotoxic antibody positivity was associated with increased rates of platelet refractoriness, there was no “cut-off” level of antibody positivity with panel lymphocytes that predicted a high rate of platelet refractoriness. The only platelet-related variable that increased the rates of platelet refractoriness was γ-irradiation while giving high doses of platelets, or F-AP platelets at equivalent doses to control platelets decreased platelet refractory rates. In the original report of the TRAP Trial refractori-
ness was based on CCI measurements rather than on platelet increments as in the current analysis. The overall refractoriness rate, including both immune and non-immune causes, using CCI measurements, was much lower at 10% compared to 27% based on platelet increment. Using CCI as a measure of refractoriness, only F-PC gave a statistically significant decrease in refractory rates compared to control PC (8% versus 16%, respectively, p=0.03) while refractory rates for UVB-PC and F-AP did not differ from control PC.

In summary, as previously stated, the size of the data base and the number of analyses performed may have resulted in statistically significant differences that may not necessarily be clinically relevant. Therefore, to put the data into a more clinically relevant context, we have somewhat arbitrarily defined a difference in post-transfusion platelet increments and days-to-next transfusion of ≥20% from the overall transfusion results (i.e., a change in 1-hour and 24-hour post-transfusion increments of ≥5,000/µl and ≥2,400 platelets/µl, respectively, and days-to-next transfusion of ≥0.35 days) or an increase in the hazard ratio of ≥2.0 for measurements of platelet refractoriness as clinically important. In Table 6, we have included information on only those factors that meet these criteria. Some factors were found to positively or negatively affect multiple platelet response measurements while others affected only one.

Some factors could not be analyzed in this way because they represented continuous variables; i.e., transfusion number, height, weight, and patient age. However, for the other factors, only two factors improved the clinical response to platelets; i.e., prior splenectomy, which had an enormous affect on improving platelet increments, and ABO compatibility had an important but lesser affect on increments. The most adverse factors - in order of severity - were: lymphocytotoxic antibody positivity; females with ≥2 pregnancies or males; heparin administration;
bleeding; palpable spleen; fever; amphotericin; and DIC. All other factors discussed as statistically-significant would not be considered to have a major clinical impact on the transfusion support of thrombocytopenic patients.
ACKNOWLEDGMENTS

The authors recognize the contributions of: Ginny Knight for excellent administrative and secretarial assistance; and, most importantly, the clinical coordinators at each trial site as, without their incredible diligence and dedication, this study would not have been possible: Alice Fuller, Johns Hopkins University; Lonnie Kagen, Blood Center of Southeastern Wisconsin; Shari Lennon and Mary Clay, University of Minnesota; Mary Meisch and Pat Nordsij, University of Wisconsin; Dottie Norris, University of Maryland Cancer Center; Dee Townsend-McCall, Puget Sound Blood Center; and Anne Waldman-Sloane, University of Florida.
REFERENCES


Table 1. Platelet transfusion responses

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>UVB-PC</th>
<th>F-PC</th>
<th>F-AP</th>
<th>Transfusions*</th>
<th>Platelet Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Transfusion Platelet Count</td>
<td>21,800 ± 13,200</td>
<td>21,800 ± 12,500</td>
<td>21,100 ± 12,700</td>
<td>20,700 ± 13,100</td>
<td>6,237</td>
<td>21,400 ± 12,900</td>
</tr>
<tr>
<td>1-Hour Post-Transfusion Platelet Count/µl</td>
<td>48,700 ± 21,600</td>
<td>45,600 ± 18,900</td>
<td>43,400 ± 18,800</td>
<td>47,600 ± 24,600</td>
<td>6,223</td>
<td>46,200 ± 21,100</td>
</tr>
<tr>
<td>1-Hour Platelet Increment/µl</td>
<td>26,900 ± 17,100</td>
<td>23,800 ± 14,900</td>
<td>22,300 ± 15,400</td>
<td>26,800 ± 19,900</td>
<td>6,209</td>
<td>24,900 ± 17,000</td>
</tr>
<tr>
<td>18-24 Hour Post-Transfusion Platelet Count/µl</td>
<td>34,500 ± 19,000</td>
<td>33,400 ± 17,100</td>
<td>31,600 ± 16,000</td>
<td>34,500 ± 19,700</td>
<td>5,469</td>
<td>33,500 ± 18,000</td>
</tr>
<tr>
<td>18-24 Hour Platelet Increment/µl</td>
<td>12,500 ± 15,800</td>
<td>11,400 ± 14,200</td>
<td>10,700 ± 13,800</td>
<td>13,400 ± 16,500</td>
<td>5,455</td>
<td>12,000 ± 15,000</td>
</tr>
<tr>
<td>Days To Next Transfusion</td>
<td>1.81 ± 1.30</td>
<td>1.67 ± 1.18</td>
<td>1.72 ± 1.25</td>
<td>1.81 ± 1.31</td>
<td>5,848</td>
<td>1.75 ± 1.26</td>
</tr>
</tbody>
</table>

Data are given as average ±1 S.D. based on method used to prepare the platelets.

*Total platelet transfusions for which data were available.
Table 2. Longitudinal linear regression analyses of patient and platelet related variables affecting post-transfusion platelet increments

<table>
<thead>
<tr>
<th>Variable</th>
<th>1-HOUR POST-TRANSFUSION (n=5,778)</th>
<th>18-24 HOURS POST-TRANSFUSION (n=5,103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Platelet Increment*</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Patient Related:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase Platelet Increment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>24,800</td>
<td>15,300 to 34,300</td>
</tr>
<tr>
<td>Age†</td>
<td>100</td>
<td>50 to 150</td>
</tr>
<tr>
<td>Decrease Platelet Increment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females with ≥ 2 Pregnancies or Males</td>
<td>-8,900</td>
<td>-6,500 to -11,300</td>
</tr>
<tr>
<td>Palpable Spleen</td>
<td>-3,500</td>
<td>-1,300 to -5,800</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>-2,700</td>
<td>-1,900 to -3,600</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-1,700</td>
<td>-600 to -2,800</td>
</tr>
<tr>
<td>Fever</td>
<td>-1,600</td>
<td>-800 to -2,300</td>
</tr>
<tr>
<td>Infection</td>
<td>-1,500</td>
<td>-700 to -2,300</td>
</tr>
<tr>
<td>Heparin</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Weight‡</td>
<td>-190</td>
<td>-140 to -240</td>
</tr>
<tr>
<td>Height§</td>
<td>-140</td>
<td>-40 to -230</td>
</tr>
<tr>
<td>Transfusion Sequence Number¶</td>
<td>-200</td>
<td>-130 to -270</td>
</tr>
<tr>
<td>Platelet Related:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase Platelet Increment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO-Compatible</td>
<td>4,600</td>
<td>2,700 to 6,500</td>
</tr>
<tr>
<td>Stored ≤ 48 Hours</td>
<td>1,900</td>
<td>1,100 to 2,700</td>
</tr>
<tr>
<td>Decrease Platelet Increment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma Irradiated</td>
<td>-2,800</td>
<td>-1,300 to -4,300</td>
</tr>
</tbody>
</table>

Only variables with statistically significant effects are included in the table.

* Estimated change in platelet increment /µl at 1-hour or 18-24 hours post-transfusion.
† An increase in age of 1 year increases platelet increment by 100 /µl.
‡ An increase in weight of 1 kilogram decreases platelet increment by -190 or -150 /µl at 1 hour or 18-24 hours post-transfusion, respectively.
§ An increase in height of 1 centimeter decreases platelet increment by -140 /µl at 1 hour post-transfusion.
¶ An increase of 1 in the transfusion sequence number decreases platelet increment by -200 or -210/µl at 1 hour and 18-24 hours post-transfusion, respectively.
Table 3. Effect of the platelet count of the concentrate and the preparation method on one-hour post-transfusion platelet count increments

<table>
<thead>
<tr>
<th>Platelet</th>
<th>Observed Mean Dose x 10^{-11}</th>
<th>Estimated 1-Hour Increment*</th>
<th>Hypothetical Equal Dose x 10^{-11}</th>
<th>Estimated 1-Hour Increment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control PC</td>
<td>4.52</td>
<td>29.2 / 19.9</td>
<td>4.52</td>
<td>29.2 / 19.9</td>
</tr>
<tr>
<td>UVB-PC</td>
<td>4.39</td>
<td>24.5 / 23.7</td>
<td>4.52</td>
<td>25.0 / 24.3</td>
</tr>
<tr>
<td>F-PC</td>
<td>3.70</td>
<td>24.6 / 15.3</td>
<td>4.52</td>
<td>28.9 / 19.6</td>
</tr>
<tr>
<td>F-AP</td>
<td>3.68</td>
<td>27.9 / 18.6</td>
<td>4.52</td>
<td>34.0 / 24.7</td>
</tr>
</tbody>
</table>

*Estimates are given for patients who were either negative/positive for lymphocytotoxic antibodies at the time of transfusion.
Table 4. Longitudinal linear regression analyses of patient and platelet related factors affecting platelet refractory rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Related</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Increase Platelet Refractory Rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytotoxic Antibody Positive</td>
<td>3.48</td>
<td>1.71 to 7.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Females with ≥ 2 Pregnancies or Males</td>
<td>2.78</td>
<td>0.18 to 0.72</td>
<td>0.004</td>
</tr>
<tr>
<td>Heparin</td>
<td>2.43</td>
<td>1.33 to 4.44</td>
<td>0.004</td>
</tr>
<tr>
<td>Fever</td>
<td>2.12</td>
<td>1.51 to 2.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.00</td>
<td>1.22 to 3.17</td>
<td>0.006</td>
</tr>
<tr>
<td>Transfusion Sequence Number</td>
<td>1.15</td>
<td>1.09 to 1.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight</td>
<td>1.01</td>
<td>1.00 to 1.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Product Related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase Platelet Refractory Rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma Irradiation</td>
<td>1.45</td>
<td>1.01 to 2.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Decrease Platelet Refractory Rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Dose</td>
<td>0.53</td>
<td>0.44 to 0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>F-AP</td>
<td>0.58</td>
<td>0.38 to 0.89</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Platelet refractoriness was defined as two sequential transfusions with platelet increments of <11,000 platelets/µl at 1-hour post-transfusion.
Table 5. Longitudinal linear regression analyses of patient and platelet related variables affecting interval to next transfusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Days To Next Transfusion*</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease Days To Next Transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females with &gt; 2 Pregnancies or Males</td>
<td>-0.40</td>
<td>-0.21 to -0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DIC</td>
<td>-0.40</td>
<td>-0.05 to -0.75</td>
<td>0.03</td>
</tr>
<tr>
<td>Heparin</td>
<td>-0.37</td>
<td>-0.20 to -0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocytotoxic Antibody Positive</td>
<td>-0.36</td>
<td>-0.19 to -0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-0.33</td>
<td>-0.23 to -0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>-0.28</td>
<td>-0.20 to -0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>-0.25</td>
<td>-0.18 to -0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Palpable Spleen</td>
<td>-0.23</td>
<td>-0.05 to -0.42</td>
<td>0.01</td>
</tr>
<tr>
<td>Infection</td>
<td>-0.18</td>
<td>-0.11 to -0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfusion Sequence†</td>
<td>-0.02</td>
<td>-0.02 to -0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight‡</td>
<td>-0.01</td>
<td>0.00 to -0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Platelet Related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase Days To Next Transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets Stored &lt;48 hours</td>
<td>0.19</td>
<td>0.12 to 0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet Dose§</td>
<td>0.16</td>
<td>0.14 to 0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decrease Days To Next Transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UVB-PC</td>
<td>-0.21</td>
<td>-0.06 to -0.37</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Estimated change in days to next transfusion.
† An increase of 1 in the transfusion sequence number decreases the days to next transfusion by 0.02 days.
‡ An increase of 1 kilogram in weight decreases the days to next transfusion by 0.01 days.
§ An increase of $10^{11}$ platelets transfused increases the days to next transfusion by 0.16 days.
Table 6. Clinically important factors affecting transfusion outcomes

<table>
<thead>
<tr>
<th>Factor</th>
<th>1-Hour Platelet Increment/µl</th>
<th>18-24-Hour Platelet Increment/µl</th>
<th>Refractoriness (Hazard Ratio)</th>
<th>Days-To-Next Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>24,900</td>
<td>12,000</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>Clinically Important Change</td>
<td>≥5,000*</td>
<td>≥2,400*</td>
<td>≥2.0†</td>
<td>≥0.35*†</td>
</tr>
<tr>
<td>Improved Platelet Responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>+24,800 †</td>
<td>+12,400 †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO Compatible</td>
<td>+4,600 †</td>
<td>+6,300 †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Platelet Responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytotoxic Antibody Positive</td>
<td>-9,300 ‡§</td>
<td>-4,000 ‡</td>
<td>3.48 ‡</td>
<td>-0.36 ‡</td>
</tr>
<tr>
<td>Females with ≥2 Pregnancies and males</td>
<td>-8,900 †</td>
<td>-5,700 †</td>
<td>2.78 ‡</td>
<td>-0.40 ‡</td>
</tr>
<tr>
<td>Palpable Spleen</td>
<td>-3,500 †</td>
<td>-4,400 †</td>
<td></td>
<td>-0.23</td>
</tr>
<tr>
<td>Heparin</td>
<td>---</td>
<td>-3,800 †</td>
<td>2.43 ‡</td>
<td>-0.37 ‡</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-1,700 †</td>
<td>-3,100 †</td>
<td>2.00 ‡</td>
<td>-0.33</td>
</tr>
<tr>
<td>Fever</td>
<td>-1,600 †</td>
<td>-2,000 †</td>
<td>2.12 ‡</td>
<td>-0.25</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>-2,700 †</td>
<td>-2,500 †</td>
<td></td>
<td>-0.28</td>
</tr>
<tr>
<td>DIC</td>
<td>---</td>
<td>---</td>
<td></td>
<td>-0.40 †</td>
</tr>
</tbody>
</table>

* A clinically important change for 1-hour and 24-hour post-transfusion increments and days-to-next transfusion was considered to be a ≥20% difference from the overall responses observed in the trial.
† For the hazard ratio, an increase of ≥2.0 was considered clinically important.
‡ Value meets the criteria for a clinically important change. If a result is given but not noted with an ‡, it is statistically significantly different but does not meet the clinically important criterium. If no value is listed, there was neither a clinically important or statistically significant difference for the outcome measure.
§ The platelet increment was estimated to be 9,300 less at 1-hour post-transfusion for all study arms except UV-B (see text). The platelet increment was estimated to be 4,000 platelets/µl less at 18-24 hours post-transfusion for all arms.
FIGURE LEGENDS

FIGURE 1  Relationship Between Number Of Platelet Transfusions And Platelet Increments at 1 and 18-24 Hours Post-Transfusion And Days To Next Transfusion.

The mean 1-hour post-transfusion platelet increments are plotted for the first 25 transfusions given to all study patients. This data represents 6,334 transfusions given to 533 patients [(●)]. Similar data for the 18-24-hour post-transfusion platelet increments are shown for 5,555 transfusions given to 531 patients [(○)]. Data for days to next transfusion for 5,955 transfusions given to 530 patients [(▲)]. (Figure 1A).

When the same analyses are plotted for only lymphocytotoxic antibody negative patients the results are similar. One hour increments for 5,484 transfusions given to 477 patients (●), 18 – 24 hour increments for 4,833 transfusions given to 475 patients (○) and days to next transfusion for 5,144 transfusions given to 474 patients (▲). (Figure 1B)

FIGURE 2  Relationship Between 1-Hour Post-Transfusion Platelet Increment And Platelet Count Of The Transfused Platelet Concentrate for PC, UVB-PC, F-PC, and F-AP.

In each part of this figure, the 1-hour platelet increment is plotted versus the platelet count of the transfused platelet concentrate for control PC (Figure 2A), UVB-PC (Figure 2B), F-PC (Figure 2C), and F-AP (Figure 2D). The equations for the regression lines are control PC: 10.17 + 4.21 x dose x 10^{11}; UVB-PC: 5.98 + 4.21 x dose x 10^{11}; F-PC: 4.84 + 5.33 x dose x 10^{11}; and F-AP: 1.08 + 7.28 x dose x 10^{11}. The regression line for the control PC is plotted as a dotted line in each panel for comparison with the regression line for the treated platelets shown as the solid line in Figures 2B, 2C, and 2D.
FIGURE 3  Development Of Platelet Refractoriness.

The estimated percent of patients who will become platelet refractory is plotted against the time to become platelet refractory. Of the 528 patients analyzed, 143 (27%) became platelet refractory. By 17 days, 25% were estimated to become refractory, and this number would be projected to increase to 42% with continued platelet transfusions. There was no difference in the incidence of platelet refractoriness among the patients assigned to receive control PC, UVB-PC, F-PC, and F-AP. Refractoriness was defined as two serial platelet transfusions with 1-hour post-transfusion platelet increments of <11,000 platelets/μl.
Figure 1A

1A

1-Hour
18-24 Hour
Mean Days to Next Transfusion

Mean Platelet Increment ($\times 10^3/\mu l$)

Mean Days To Next Transfusion

Platelet Transfusion Number
Figure 1B

1B

Mean Platelet Increment (x 10^3/µl)

Platelet Transfusion Number

Mean Days To Next Transfusion

- 1-Hour
- 18-24 Hour
- Mean Days to Next Transfusion
Figure 2A

1 Hour Platelet Increment (x 10^3/µl) vs. Platelets Transfused (x 10^{11})

Control PC (------)

UVB-PC (———)

Control PC (------)

Figure 2B

1 Hour Platelet Increment (x 10^3/µl) vs. Platelets Transfused (x 10^{11})

UVB-PC (———)

Control PC (------)
Figure 3

The graph shows the percentage of platelet refractory over time from the first platelet transfusion for different conditions:

- **Control PC**
- **F-PC**
- **F-AP**
- **UVB-PC**

The x-axis represents the time from the first platelet transfusion in days, ranging from 0 to 42. The y-axis represents the platelet refractory percentage, ranging from 0 to 100. The graph indicates the trend over time for each condition.
Factors affecting post-transfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients

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