Associations between red blood cell and platelet transfusions and the development of idiopathic pneumonia syndrome

Lisa K. Vande Vusse

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Masters of Science

University of Washington

2013

Reading Committee:

Noel S. Weiss, MD, DrPH, Chair

Timothy R. Watkins, MD

Program Authorized to Offer Degree:
School of Public Health; Department of Epidemiology

University of Washington

Abstract

Associations between red blood cell and platelet transfusions
and the development of idiopathic pneumonia syndrome

Lisa K. Vande Vusse

Chair of the Supervisory Committee:
Professor Noel S. Weiss, MD, DrPH
Department of Epidemiology

Objective: Blood transfusions are common during hematopoietic stem cell transplant (HSCT) and may contribute to lung injury. We examined the associations between receipt of red blood cell (RBC) and platelet (PLT) transfusions and the occurrence of Idiopathic Pneumonia Syndrome (IPS). ***Design***: Retrospective case-control study. ***Setting:*** Fred Hutchinson Cancer Research Center, 1997 – 2001. ***Patients***: 914 individuals hospitalized for allogeneic HSCT after myeloablative conditioning and transfused allogeneic blood components at their physicians' discretion. ***Measurements***: Each IPS case was matched to 2 controls on days-from-transplant. We estimated associations between RBC and PLT transfusions and IPS by post-transplant day 120 using conditional logistic regression models adjusted for IPS risk factors (age, disease indicating transplant, and dose of TBI) and a composite sum of "other" blood components transfused. Timing of transfusions relative to myeloid engraftment and PLT ABO-blood group (match vs. mismatch) were included as potential interaction terms. ***Main Results:*** The 77 IPS cases (8.4%) received a median of 2 RBC and 4 PLT units in the week prior to IPS onset, compared to 0 and 1 unit, respectively, among controls. In adjusted analyses, each additional PLT unit transfused in the prior week was associated with 33% higher IPS risk (odds ratio 1.33, 95% confidence interval 1.14 – 1.55, $p<0.001$). Recent transfusions of RBCs and PLTs were each statistically associated with greater risk of IPS when examined without the other; only PLTs retained this significance when both exposures were included in the model. The RBC and PLT associations were similar for subjects developing IPS before or after engraftment and the PLT association was unaffected by ABO-mismatch. ***Conclusions:*** PLT transfusions, and possibly RBC transfusions, are associated with an increased risk of IPS in the first 120 days after myeloablative HSCT.

ACKNOWLEDGMENTS

The author would like to recognize the biostatistical and editorial assistance of Katherine Guthrie, PhD and data management contributions of Gary Schoch, both of the Fred Hutchinson Cancer Research Center, Clinical Research Division, as well as the scientific content and editorial advising provided by Noel S. Weiss, MD, DrPH and Timothy R. Watkins, MD, MSc of University of Washington.

INTRODUCTION

Red blood cell (RBC) and platelet (PLT) transfusions are among the most common therapies administered to hematopoietic stem cell transplant (HSCT) recipients.[1,2] While lifesaving in some settings, transfusions are also associated with adverse outcomes in critically ill patients including death,[3-6] nosocomial infections,[3,7] and acute lung injury (ALI).[8,9] After receipt of HSCT, the development of ALI of noninfectious origin is termed Idiopathic Pneumonia Syndrome (IPS). IPS is defined as widespread noninfectious alveolar injury leading to abnormal pulmonary physiology that is not due to cardiac or renal dysfunction.[10] IPS typically occurs within 120 days of HSCT and is associated with 60-80% mortality.[11-14] Recognized clinical risk factors for IPS include myeloablative conditioning, age over 40 years at time of transplant, severe (grade III-IV) acute graft-versus-host-disease (GVHD), high dose total body irradiation (TBI; greater than 12 Gray), and acute leukemia or myelodysplastic syndrome as indication for transplant.[10-18] Although blood component transfusion is an established risk factor for ALI in critically ill and injured patients,[5,6,9,19-21] the association between blood component transfusions and development of IPS after HSCT has not previously been examined.

In this study, we examined the associations between receipt of RBC and PLT transfusions and subsequent development of IPS after HSCT. We also investigated whether the associations between transfusions and IPS were modified by the timing of transfusion relative to neutrophil engraftment, or by receipt of ABO blood group major- or minor-mismatched PLT units.

METHODS

Cohort description, eligibility, and definitions

We performed a study of patients who underwent myeloablative allogeneic HSCT at the Fred Hutchinson Cancer Research Center (FHCRC) between December 1997 and 2001. The cohort of 1100 myeloablative and nonmyeloablative HSCT recipients was previously studied to identify risk factors for IPS;[13] however, blood component transfusions were not specifically examined. The present analysis was restricted to the subgroup of 917 individuals receiving myeloablative conditioning regimens, from which 95% of IPS cases were identified, in order to compare patients with more homogeneous baseline IPS risk factors and transfusion needs. Patients were observed until post-transplant day 120, during which time it was expected that the large majority of IPS cases would be ascertained.[12,15] Three patients were excluded due to withdrawal of consent or imprisonment, leaving 914 available for analysis. All required data elements for this study were present within a rigorously validated research database, including the type, timing, and ABO blood type of all blood component transfusions.[13] This study was approved by the FHCRC Institutional Review Board.

We defined ABO blood group mismatch according to the Puget Sound Blood Center protocol (Seattle, WA), considering a transfused unit to be a match only if identical to both HSCT recipient and stem cell donor blood type.[22-24] A minor mismatch was defined as possible isoagluttinin (anti-ABO) antibody in the transfused product against the HSCT donor or recipient cells. A major mismatch represents possible isoagluttinin antibody in the transfusion recipient against the transfused cells. Actual isoagluttinin antibody titers were not available. We defined the time of myeloid engraftment as the first of three consecutive days on which the patient had an absolute neutrophil count greater than 500 per cubic millimeter.[25]

Exposures

Patients were transfused blood products at their medical providers' discretion. All blood components transfused to cohort members prior to transplant were prepared by the Puget Sound Blood Center according to Food and Drug Administration regulations. RBC components were prepared using U.S. standard centrifugation while PLT units could be prepared via single-donor apheresis or by pooling 4-6 donors' whole blood-derived PLT-rich plasma concentrates.

All patients received Cytomegalovirus (CMV)-safe transfusions prior to transplant, while only CMV-seronegative patients received CMV-safe units after transplant. One hundred milliliters of plasma was removed from all ABO-mismatched PLT units at the time they were ordered for a specific patient. For all analyses, blood transfusions were grouped as RBC, PLT, and "other" which included cryoprecipitate, plasma, and rarely, whole blood or granulocytes. We considered only RBC and PLT units administered before the first day of IPS development as units of exposure because the temporal relationship of transfusion relative to IPS onset was unknown for units administered on the day a patient developed IPS. Transfusion requirements varied throughout the post-transplant period. Based on prior data suggesting that immunomodulatory pathways linking transfusion to lung injury may result in delayed onset,[26,27] we defined primary exposures *a priori* as blood transfusions received in the 7 days prior to IPS onset among cases, and the 7 corresponding days post-transplant among controls.

Outcome

As previously described by Fukuda *et al*, each patient's IPS status was determined via abstraction of clinical, radiographic, microbiologic, and histopathologic reports.[13] Two physicians, blinded to the number and timing of blood component transfusions, assigned IPS determinations using standard IPS definitions. IPS was defined using the 1993 National Heart, Lung, and Blood Institute workshop criteria which include multi-lobar infiltrates on chest imaging, signs or symptoms of pneumonia, abnormal pulmonary physiology characterized by increased alveolar-arterial oxygen difference or new/increased restrictive ventilatory abnormality, and absence of active lower respiratory tract infection by bronchoscopic lavage, lung biopsy, or autopsy.[28] IPS was excluded if lavage cultures grew 10^4 or more colony-forming units of bacteria per milliliter, grew a lung pathogen in the setting of compatible radiographic findings, or met European Organization for Research and Treatment of Cancer and Mycoses Study Group criteria for fungal pneumonia.[29,30] Patients with non-diagnostic lavage who responded to antimicrobial therapy and those with suspected fluid overload responsive to diuretics were not considered to have IPS. The date of IPS onset is the first day on which both abnormal chest imaging and pulmonary physiology were noted.

Statistical Analysis

Each IPS case was matched on days-from-transplant to two controls sampled from the set of patients under study at the time of IPS occurrence. To describe levels of exposure among cases and controls, RBC transfusions were categorized as zero, 1-2, or more than 2 units transfused during the seven days prior to the matched day. As PLT transfusion is more common after HSCT, they were categorized as 0, 1-2, 3-4, or >4 transfusions in the prior seven days. Because transfusion dependence varies throughout the transplant process, with the majority of transfusions received prior to myeloid engraftment, it was hypothesized that rates of IPS would vary both by time-from-transplant and transfusion amounts. We therefore determined crude incidence rates of IPS for the entire cohort by strata jointly defined by transfusion amount and time-since-transplant. Time was divided into weekly intervals for the first three weeks, 3 week intervals through weeks 4-12, then all remaining time (36 days) beyond week 12 was included in one interval. Incidence rates for IPS were then adjusted for time-from-transplant by indirect standardization:[31] (1) we first determined the expected number of IPS cases for each transfusion stratum if the corresponding person-time observed was divided equally over each day from 0 to 120; (2) we then calculated adjusted stratum-specific incidence rates as the number of expected events divided by observed person-time for each joint category of transfusion amount and time interval.

For the case-control analysis, crude and adjusted Mantel-Haenszel odds ratios with 95% confidence intervals were calculated separately for each RBC and PLT category. A score test tested the null hypothesis of no linear trend between transfusion levels and IPS risk. RBC and PLT sums for the week of interest were then modeled as separate continuous linear exposures in a conditional logistic regression model adjusted linearly for sums of other components transfused that week and identified confounders.[32] Based on prior studies, the following factors were included as potential confounders: age at transplant (≤40 years versus >40), TBI dose (0, 12, or >12 Gray), original disease (chronic myelogeneous leukemia/nonmalignant disease, acute leukemia/myelodysplastic syndrome, or other malignancy), stem cell source (bone marrow or peripheral blood), and the weekly transfusion total of any non-RBC and non-PLT blood component.[10-18,33-35] We considered presence of grade III-IV acute GVHD as a possible mediator of transfusion-related lung injury[10,12,36] and therefore did not adjust for it; in sensitivity analysis, adjustment for grade III-IV acute GVHD did not change our results. Three primary conditional logistic regression models were examined: one including only the number of RBC transfusions administered as the main exposure, a second examining only the number of PLT transfusions administered as the main exposure, and a third model including both RBCs and PLTs as exposures.

Two factors were considered as potential multiplicative-scale interaction terms in conditional logistic regression models. First, it is hypothesized that transplanted stem cell engraftment stimulates endothelial inflammation.[37,38] Engraftment may prime neutrophils to induce lung injury once exposed to one or more blood transfusions. As a result, we examined whether the associations between PLT and RBC transfusions and IPS varied by myeloid engraftment status. Forty patients were missing an engraftment day and thus we assumed did not engraft before death. Second, limited inventories commonly necessitate transfusing HSCT recipients with minor, major, or bidirectionally ABO-mismatched PLTs. As prior studies demonstrate decreased survival and more frequent acute GVHD in individuals receiving ABO-mismatched HSCT,[39,40] we also examined whether the association between PLT transfusion and IPS varied by receipt of major- or minor-mismatched PLT transfusions. A patient's weekly transfusion total was classified as mismatched if at least one of the units received was mismatched. Fifty-five patients lacked ABO blood group records, resulting in 859 patients available for the interaction term analysis.

Reported p-values are two-sided and based on the Wald statistic unless otherwise stated. Statistical analyses were performed using Stata 12 (StataCorp LP, College Station, TX) statistical software.

RESULTS

Baseline characteristics

Patients in the full cohort were predominantly male and self-reported as Caucasian (Table 1). Fifty-six percent were transplanted for acute leukemia or myelodysplastic syndrome, 39% for chronic leukemia or nonmalignant indication, and 5% for other malignancies such as multiple myeloma. Approximately two-thirds of HSCT recipients were given grafts from bone marrow source, the remainder from peripheral blood stem cells. Conditioning therapy included TBI for 58% of patients. One quarter developed severe acute GVHD. Of the 914 patients at risk, 77 (8.4%) developed IPS.   IPS onset occurred between days 4 and 106, with half of all cases occurring by day 22 and 70% of cases in the first 30 days after transplant (Figure 1).

Distribution of RBC, PLT, and other transfusions

Approximately one third of PLTs transfused to the total cohort were collected from the donor via apheresis and two-thirds from whole blood with multi-donor pooling. The median number of transfusions each individual received was 9 PLT units (interquartile range (IQR) 4-19) and 10 RBC units (IQR 5-18). The probability of having received at least one RBC unit by day 30 was 88%, and at least one PLT unit was 99%. Fifty percent of all RBC transfusions were administered by post-transplant day 24, and 75% by day 67. On average, patients were transfused RBC on 5 separate days (range 0-34 days). The median weekly sum of RBC transfusions was 2 units between days 9-20 post transplant and was zero during other times. In comparison, fifty percent of all PLT transfusions were administered by day 19 post-HSCT, and 75% by day 56. On average, each patient received PLT transfusions on 8 days (range 0-85 days). The median weekly sum of PLT transfusions ranged from 1 to 3 units between days 5-24 after transplant, and was zero at other times. The correlation between mean weekly sum of RBC and PLT transfusions started at 0.40 in the first week and increased steadily through 0.75 the final observation week (Figure 2).

Throughout the observation period, 17 patients received granulocyte infusions and 6 received whole blood, representing 0.48% and 0.07% of all transfusions, respectively. Each of these patients also received RBC and PLT transfusions and none subsequently developed IPS. Fresh frozen plasma was transfused to 178 total recipients, 5 of whom subsequently developed IPS. Only 1 of these 5 received no RBC or PLT in the week prior to IPS onset. In total, 4 units of cryoprecipitate were transfused to 3 patients, 2 of whom developed IPS after also receiving RBC and PLT transfusions in the prior 7 days. Among the 859 patients with complete blood donor ABO data, 403 (47%) received at least one minor-mismatched unit and 480 (56%) received at least one major-mismatched unit while at risk for IPS.

Idiopathic Pneumonia Syndrome incidence rates

The full cohort was observed for a total of 94,373 person-days. The overall incidence rate was 8.16 IPS cases per 10,000 person-days of observation, starting low in the first week, peaking in weeks 2 and 3, then trending downwards thereafter (Table 2A). Within any one time interval, crude incidence rates generally trended upwards across increasing strata of RBC and PLT transfusions (Tables 2A and 2B, respectively), a trend that persisted after adjustment for time-since-transplant (Table 3).

Results from the case control study

The 77 patients who developed IPS received a median of 2 RBC units, 4 PLT units, and zero "other" units in the week prior to IPS onset (Table 4). By comparison, patients selected as controls received a median of 0 RBC units, 1 PLT unit, and 0 "other" units during the corresponding week. The percentage of cases who were transfused RBC, PLT, either RBC or PLT, and other components during the week was 77%, 78%, 90%, and 14%, respectively, in contrast to 46%, 58%, 65%, and 1%, respectively, of controls. Crude and adjusted odds ratios tended to increase as the number of transfusions received in the prior week increased (score test for trend: crude RBC p=0.0001, PLT p<0.0001; adjusted RBC p=0.004, PLT p=0.002) (Table 5).

The multivariable conditional logistic regression analysis adjusted for confounders and weekly sum of non-PLT transfusions estimated that odds of IPS were 33% greater per additional PLT unit transfused in the prior 7 days (OR 1.33, 95% confidence interval (CI) 1.14-1.55, p<0.001) (Table 6). The association between each unit of RBCs transfused and the development of IPS adjusted for non-PLT blood transfusions and identified confounders (OR 1.22, 95% CI 1.06-1.40, p=0.006) decreased when also adjusted for weekly sum of PLT transfusions (OR 1.04, 95% CI 0.88-1.22, p=0.7).

While the likelihood ratio p-value for the interaction term of RBC transfusions given before versus after engraftment was statistically significant (p=0.008), neither RBC given before nor after engraftment were found to be associated with IPS outcome in adjusted models (Table 7). The timing of transfusion relative to neutrophil engraftment was not observed to modify the association between PLT transfusion and IPS development (p-value for interaction term 0.3). Likewise, receipt of out-of-group PLT transfusions, represented as both minor and major ABO-mismatch, did not modify the association between PLT transfusion and IPS (p-values 0.98 and 0.95, respectively).

DISCUSSION

The purpose of our study was to determine the degree to which RBC and PLT transfusions predispose patients receiving an allogeneic HSCT after myeloablative conditioning to IPS. We found both RBC and PLT transfusion to be extremely common, with 96% and 99% of patients transfused with these respective blood components within 120 days after HSCT. After adjusting for confounders, receipt of RBC and PLT components were associated with an estimated 22% and 30% higher IPS risk, respectively, per additional unit transfused in the prior week. The collinear relationship between RBC and PLT transfusions made it difficult to examine their independent effects on IPS development while controlling for one another, but there was a suggestion that PLT transfusions may be more determinative of IPS risk.

There are several hypothesized mechanisms linking transfusion to lung injury.[26,41-43] One theory postulates that passively transferred donor antibodies interact with the recipient's human leukocyte antigen (HLA I, II) or human neutrophil antigen (HNA) resulting in immune activation and subsequent lung injury.[43-52] However, while passive transfusion of cognate anti-leukocyte antibody alone can cause lung injury,[53] it is not always sufficient.[54-56] The proposed "two hit" hypothesis suggests that biologically active substances that accumulate in stored blood components,[57-59] which could include anti-leukocyte antibodies,[60] prime neutrophils and produce lung injury in the setting of an underlying inflammatory insult.[35,61,62] Conceivably, patients treated with HSCT may enter an inflammatory state due to the toxic effects of conditioning regimens, engraftment, and/or other immune factors, making them susceptible to transfusion-mediated lung injury.

Engraftment syndrome comprises tissue injury and endothelial inflammation occurring as transplanted cells engraft and may, like IPS, be mediated by systemic inflammation.[37,38] We hypothesized that due to the presence of circulating neutrophils and systemic inflammation, transfusing blood components after engraftment would result in greater IPS risk. In our case-control study, the association between RBC/PLT transfusion and IPS did not meaningfully differ by engraftment status of the transfusion recipient. These findings may imply that transfusion of bioactive substances is sufficient to result in lung injury in the absence of primed lymphocytes.

The relationship between receipt of ABO-mismatched blood component transfusion and IPS has not been previously investigated. Approximately one third of HSCT recipients are given a minor, major, or bidirectionally ABO-mismatched transplant,[63] which has been associated with shorter survival in some studies.[39,40] We hypothesized *a priori* that IPS would be more likely among transfused patients receiving ABO blood group mismatched PLT. Out-of-group PLT transfusions were frequently administered to our population of HSCT recipients; however, the association between PLT transfusion and IPS development did not significantly differ according to PLT major- or minor-ABO mismatch status. At FHCRC, ABO-mismatched PLT transfusions are routinely plasma volume-reduced before transfusion. It is possible that either ABO-mismatched PLT transfusions do not contribute importantly to IPS risk, or that the related risk is abrogated by reducing plasma-suspended inflammatory mediators. To optimize allocation of limited blood supplies, it will be important to validate this finding while considering anti-ABO antibody titers and component plasma volume, which were not available for this analysis.

Our study has noteworthy limitations. First, the cohort was transplanted 10-15 years ago at a single institution. It is possible that conditioning and treatment strategies during HSCT have changed since 2001 in a way that blood component exposure is now more or less important. For example, in 2006 the American Association of Blood Banks recommended instituting specific strategies to reduce Transfusion-related acute lung injury (TRALI),[64] which is defined as ALI occurring within 6 hours of a transfusion.[26] Unfortunately, our data did not allow us to determine the timing of blood component transfusion relative to IPS onset when both occurred the same day. Therefore it is not known how often IPS represents TRALI and unclear how our results would be impacted by current mitigation techniques.

Another potential limitation relates to research involving clinical syndromes like IPS. By definition, IPS encompasses a heterogeneous mix of clinical diagnoses (i.e. drug-induced pneumonitis, engraftment syndrome, diffuse alveolar hemorrhage) and histopathologic correlates (i.e. interstitial pneumonitis, diffuse alveolar damage).[10] Blood component transfusions might differentially modify mechanistic pathways specific to each lung injury phenotype. Our analyses were insensitive to phenotype-specific associations, which may diminish our ability to detect interactions and limit the generalizability of our findings. Finally, given the observational nature of the data, the results could be biased by residual confounding-our findings could be consistent with the conclusion that transfusions contribute directly to IPS pathogenesis, or alternatively that transfusions act as a marker of severe illness and are indirectly correlated with IPS. Adjusting for the known IPS clinical risk factors accounts for some portion of this indication bias, but possibly not all of it.

In conclusion, PLT transfusions were associated with greater risk of IPS in the first 120 days after myeloablative allogeneic HSCT. RBCs may also contribute, but collinearity between these frequent exposures did not allow an unequivocal assessment of their independent effects. Future work should seek to confirm these results using updated IPS criteria in the current era of transplant and transfusion practices and identify potentially modifiable blood donor and blood component processing characteristics (such as donor gender and component storage time) that contribute to IPS risk.

REFERENCES

1. Bernstein SH, Nadamanee AP, Vose JM, Tricot G, Fay JW, Negrin RS, DiPersio J, Rondon G, Champlin R, Barnett MJ, Cornetta K, Herzig GP, Giles G Jr, Keating A, Messner H, Wolff SN, Miller KB, Linker C, Cairo M, Hellmann S, Ashby M, Stryker S, Nash RA. A multicenter study of platelet recovery and utilization in patients after myeloablative therapy and hematopoietic stem cell transplantation. Blood 1998;91:3509-17.
2. Radia R, Pamphilon D. Transfusion strategies in patients undergoing stem-cell transplantation. Expert Rev Hematol 2011;4:213-20.
3. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 2008;36:2667-774.
4. Hebert PC, Wells G, Blajchmann MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409-17.
5. Netzer G, Shah CV, Iwashyna TJ, Lanken PN, Finkel B, Fuchs B, Guo W, Christie JD. Association of RBC transfusion with mortality in patients with acute lung injury. Chest 2007;132:1116-23.
6. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med 2005;33:1191-8.
7. Shorr AF, Jackson WL, Kelly KM, Fu M, Kollef MH. Transfusion practice and blood stream infections in critically ill patients. Chest 2005;127:1722-8.
8. Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB, O'Byrne MM, Evenson LK, malinchoc M, DeGoey SR, Afessa B, Hubmayr RD, Moore SB. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. Amer J Respir Crit Care Med 2007;176:886-91.
9. Iscimen R, Cartin-Ceba R, Yilmaz M, Khan H, Hubmayr RD, Afessa B, Gajic O. Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. Crit Care Med 2008;36:1518-22.
10. Panoskaltsis-Mortari A, Griese M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. Amer J Respir Crit Care Med 2011;183:1262-79.
11. Crawford SW, Hackman RC. Clinical course of idiopathic pneumonia after bone marrow transplantation. Am Rev Respir Dis 1993;147:1393-400.
12. Wingard JR, Mellits ED, Sostrin MD, Chen DY, Burns WH, Santos GW, Vriesendorp HM, Beschomer WE, Saral R. Interstitial pneumonitis after allogeneic bone marrow transplantation: nine-year experience at a single institution. Medicine (Baltimore) 1988;67:175-86.
13. Fukuda T, Hackman RC, Guthrie KA, Sandmaier BM, Boeckh M, Maris MB, Maloney DG, Deeg HJ, Martin PJ, Storb RF, Madtes DK. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. Blood 2003;102:2777-85.
14. Kantrow SP, Hackman RC, Boeckh M, Myerson D, Crawford SW. Idiopathic pneumonia syndrome: changing spectrum of lung injury after marrow transplantation. Transplantation 1997;63:1079-86.
15. Meyers JD, Gluornoy N, Thomas ED. Nonbacterial pneumonia after allogeneic marrow transplantation: a review of ten years' experience. Rev Infect Dis 1982;4:1119-32.

16. Weiner RS, Bortin MM, Gale RP, Gluckman E, Kay HE, Kolb HJ, Hartz AJ, Rimm AA. Interstitial pneumonitis after bone marrow transplantation: assessment of risk factors. Ann Intern Med 1986;104:168-75.

17. Sampath S, Schultheiss TE, Wong J. Dose response and factors related to interstitial pneumonitis after bone marrow transplant. Int J Radiat Oncol Biol Phys 2005;63:876-84.

18. Zhu KE, Hu JY, Zhang T, Chen J, Zhong J, Lu YH. Incidence, risks, and outcome of idiopathic pneumonia syndrome early after allogeneic hematopoietic stem cell transplantation. Eur J Haematol 2008;81:461-6.

19. Silverboard H, Aisiku I, Martin GS, Adams M, Tozycki G, Moss M. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma 2005;59:717-23.

20. Pereboom IT, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ. Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury. Anesth Analg 2009;108:1083-91.

21. Rubenfeld GD, Herridge M. Epidemiology and outcomes of acute lung injury. Chest 2007;131:554-62.

22. Fung MK, Downes KA, Shulman IA. Transfusion of platelets containing ABO-incompatible plasma. Arch Pathol Lab Med 2007;121:909-16.

23. Lasky LC, Warkentin PI, Kersey HJ, Ramsay NK, McGlave PB, McCullough J. Hemotherapy in patients undergoing blood group incompatible bone marrow transplantation. Transfusion 1983;23:277-85.

24. O'Donghaile D, Kelley W, Klein HG, Flegel WA. Recommendations for transfusion in ABO-incompatible hematopoietic stem cell transplantation. Transfusion 2012;52:456-8.

25. Rihn C, Cilley J, Naik P, Pedicano AV, Mehta J. Definition of myeloid engraftment after allogeneic stem cell transplantation. Haematologica 2004;89:763-4.

26. Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, Meade M, Morrison D, Pinsent T, Robillard P, Slinger P. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44:1774-89.

27. Marik PE, Corwin HL. Acute lung injury following blood transfusion: expanding the definition. Crit Care Med 2008;36:3080-4.

28. Clark JG, Hansen JA, Hertz MI, Parkman R, Jensen L, Peavy HH. NHLBI workshop summary. Idiopathic Pneumonia Syndrome after bone marrow transplantation. Am Rev Respir Dis 1993;147:1601-6.

29. de Jaeger A, Litalien C, Lacroix J, Guertin MC, Infante RC. Protected specimen brush or bronchoalveolar lavage to diagnose bacterial nosocomial pneumonia in ventilated adults: a meta-analysis. Crit Care Med 1999;27(11):2548-60.

30. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Corokaert F, Denning DW, Donnely JP, Edwards JE, Erjavec Z, Fiere D, Lorholary O, Maertens J, Meis JF, Patterson TF, Ritter J, Selleslag D, Shah PM, Stevens A, Walsh TJ. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7-14.

31. Koepsell TD, Weiss NS. Epidemiologic Methods: Studying the occurrence of illness. New York, New York: Oxford University Press, Inc.; 2003.

32. Breslow NE, Day, NE. Statistical Methods in Cancer Research, Volume 1: The Analysis of Case-Control Studies. Lyon, France: IARC Scientific Publications; 1980.

33. Ho VT, Weller E, Lee SJ, Alyea EP, Antin JH, Soiffer RJ. Prognostic factors for early severe pulmonary complications after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2001;7:233-9.

34. Sachs UJ, Bux J. TRALI after the transfusion of cross-match-positive granulocytes. Transfusion 2003;43:1683-6.
35. Silliman CC, Boshkov LK, Mehdizadehkaahi Z, Elzi DF, Dickey WO, Podlosky L, Clarke G, Ambruso DR. Transfusion-related acute lung injury: epidemiology and prospective analysis of etiologic factors. Blood 2003;101:454-62.
36. Crawford SW, Longton G, Storb R. Acute graft-versus-host disease and the risks for idiopathic pneumonia after marrow transplantation for severe aplastic anemia. Bone Marrow Transplant 1993;12:225-31.
37. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. Bone Marrow Transplant 2011;46:1495-502.
38. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. Bone Marrow Transplant 2001;27:893-8.
39. Kanda J, Ichinohe T, Matsuo K, Benjamin RJ, Klumpp TR, Rozman P, Blumber N, Mehta J, Sohn SK, Uchiyama T. Impact of ABO mismatching on the outcomes of allogeneic related and unrelated blood and marrow stem cell transplantations for hematologic malignancies: IPD-based meta-analysis of cohort studies. Transfusion 2009;49:624-35.
40. Ozkurt ZN, Yegin ZA, Yenicesu I, Aki SZ, Yagci M, Sucak GT. Impact of ABO-incompatible donor on early and late outcome of hematopoietic stem cell transplantation. Transplantation Proc 2009;41:3851-8.
41. Toy P, Gajic O, Bacchetti P, Looney MR, Gropper MA, Hubmayr R, Lowell CA, Norris PJ, Murphy EL, Weiskopf RB, Wilson G, Koenigsberg M, Lee D, Sculler R, Wu P, Grimes B, Gandhi MJ, Winters JL, Mair D, Hirschler N, Sanchez Rosen R, Matthay MA: TRALI study group. Transfusion-related acute lung injury: incidence and risk factors. Blood 2012;119:1757-67.
42. Ganguly S, Carrum G, Nizzi F, Heslop HE, Popat U. Transfusion-related acute lung injury (TRALI) following allogeneic stem cell transplant for acute myeloid leukemia. Am J Hematol 2004;75:48-51.
43. Bux J, Sachs UJH. The pathogenesis of transfusion-related acute lung injury (TRALI). Br J Haematol 2007;136:788-99.
44. Davoren A, Curtis BR, Shulman IA, Mohrbacker AF, Bux J, Kwiatkowska BJ, McFarland JG, Aster RH. TRALI due to granulocyte-agglutinating human neutrophil antigen-3a (5b) alloantibodies in donor plasma: a report of 2 fatalities. Transfusion 2003;43:641-5.
45. Chapman CE, Stainsby D, Jones H, Love E, Massey E, Navarrete C, Lucas G, Soni N, Morgan C, Choo L, Cohen H, Williamson LM. Ten years of haemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion 2009;49(3):440-52.
46. Reil A, Keller-Stanislawski B, Guenay S, Bux J. Specificities of leukocyte alloantibodies in transfusion-related acute lung injury and results of leukocyte antibody screening of blood donors. Vox Sang 2008;95:313-7.
47. Sachs UJ, Wasel W, Bayat B, Bohle M, Hattar K, Berghofer H, Reil A, Bux J, Bein G, Santoso S, Weissmann N. Mechanism of transfusion-related acute lung injury induced by HLA class II antibodies. Blood 2011;2011:669-77.
48. Kopko PM, Popovsky MA, MacKenzie MR, Paglierone TG, Muto KN, Holland PV. HLA class II antibodies in transfusion-related acute lung injury. Transfusion 2001;41:1244-8.
49. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 1985:573-7.
50. Bux J, Becker F, Seeger W, Kilpatrick D, Chapman J, Waters A. Transfusion-related acute lung injury due to HLA-A2-specific antibodies in recipient and NB1-specific antibodies in donor blood. Br J Haematol 1996;93:707-13.

51. Sachs UJ, Hattar K, Weissmann N, Bohle RM, Weiss T, Sibelius U, Bux J. Antibody-induced neutrophil activation as a trigger for transfusion-related acute lung injury in an ex vivo rat lung model. Blood 2006;107(3):1217-9.
52. Saw CL, Hannach B, Petrazsko T, Nickerson P. Blood donors implicated in transfusion-related acute lung injury with patient-specific HLA antibodies are more broady sensitized to HLA antigens compared to other blood donors. Transfusion 2012;52:1-8.
53. Dooren MC, Ouwehand WH, Verhoeven AJ, von dem Borne AE, Kuijpers RW. Adult respiratory distress syndrome after experimental intravenous gamma-globulin concentrate and monocyte-reactive IgG antibodies. Lancet 1998;352:1601-2.
54. Toy P, Hollis-Perry KM, Jun J, Nakagawa M. Recipients of blood from a donor with multiple HLA antibodies: a lookback study of transfusion-related acute lung injury. Transfusion 2004;44:1683-8.
55. Kopko PM, Marshall CS, MacKenzie MR, Holland PV. Transfusion-related acute lung injury: report of a clinical look-back investigation. JAMA 2002;287:1968-71.
56. Maslanka K, Michur H, Zupanska B, Uhrynowska M, Nowak J. Leucocyte antibodies in blood donors and a look back on recipients of their blood components. Vox Sang 2007;92:247-9.
57. Silliman CC, Clay KL, Thurman GW, Johnson CA, Ambruso DR. Partial characterization of lipids that develop during the routine storage of blood and prime the neutrophil NADPH oxidase. J Lab Clin Med 1994;124:684-94.
58. Maslanka K, Smolensa-Sym G, Michur H, Wrobel A, Lachert E, Brojer E. Lysophosphatidylcholines: bioactive lipids generated during storage of blood components. Arch Immunol Ther Exp 2012;60:55-60.
59. Silliman CC, Moore EE, Kelher MR, Khan SY, Gellar L, Elzi DJ. Identification of lipids that accumulate during the routine storage of prestorage leukoreduced red blood cells and cause acute lung injury. Transfusion 2011;51:2549-54.
60. Van Buren NL, Stroncek DF, Clay ME, McCullough J, Dalmasso AP. Transfusion-related acute lung injury caused by an NB2 granulocyte-specific antibody in a patient with thrombotic thrombocytopenic purpura. Transfusion 1990;30:42-5.
61. Silliman CC, Bjornsen AJ, Wyman TH, Kelher MR, Allard J, Bieber S, Voelkel NF. Plasma and lipids from stored platelets cause acute lung injury in an animal model. Transfusion 2003;43:633-40.
62. Silliman CC, Paterson AJ, Dickey WO, Stroneck DF, Popovsky MA, Caldwell SA, Ambruso DR. The association of biologically active lipids with the development of transfusion-related acute lung injury: a retrospective study. Transfusion 1997;37:719-26.
63. Seebach JD, Stussi G, Passweg JR, Loberiza FR Jr, Gajewski JL, Keating A, Goemer M, Rowlings PA, Tiberghien P, Elfenbein GJ, Gale RP, van Rood JJ, Reddy V, Gluckman E, Bolwell BJ, Klumpp TR, Horowitz MM, Ringden O, Barrett AJ. ABO blood group barrier in allogeneic bone marrow transplantation revisited. Biol Blood Marrow Transplant 2005;11:1006-13.
64. American Association of Blood Banks Association Bulletin #06-07. 2006. (Accessed 2013, at http://www.aabb.org/resources/publications/bulletins/Pages/ab06-07.aspx.)

TABLES

Table 1. Characteristics of 914 myeloablative hematopoietic stem cell recipients and grafts

Patient characteristics	**Value**	
Age in years, median (IQR*)	41	(31 – 49)
Less than 40, n (%)	434	(47)
40 or older, n (%)	480	(53)
Male, n (%)	502	(55)
Race, in order of frequency, n (%)		
White	743	(82)
Asian/Pacific Islander	51	(6)
Hispanic	50	(6)
Black	13	(1)
Native American	13	(1)
Other	33	(4)
Cytomegalovirus seropositive, n (%)	442	(49)
Transplant characteristics		
Stem cell sources, n (%)		
Bone marrow	598	(65)
Peripheral blood	311	(34)
Both of the above	5	(1)
Second transplant, n (%)	21	(2)
Stem cell donor, n (%)		
Related, HLA matched	428	(47)
Related, HLA mismatched	55	(6)
Unrelated	431	(47)
Recipient CMV negative, donor positive, n (%)	134	(15)
Dose of total body irradiation, n (%)		
No irradiation	385	(42)
12 Gray	256	(28)
More than 12 Gray	273	(30)
Methotrexate used, n (%)	874	(96)
Acute graft-versus-host disease, n (%)		
None	145	(16)
Grade I-II	537	(59)
Grade III-IV	229	(25)
Days to engraftment, n = 879†, median (IQR)*	19	(16 – 23)

* IQR indicates interquartile range

† Data was missing for 1% or less of records unless noted

Table 2A. Incidence rates of Idiopathic Pneumonia Syndrome by red blood cell transfusion levels and time since transplant

	Number of red blood cell transfusions (prior 7 days)											
	Overall			0			1 - 2			>2		
Week	No.* cases	Time*	IR*	No. cases	Time	IR	No. cases	Time	IR	No. cases	Time	IR
1	1	6376	1.6	1	3811	2.6	0	1522	0	0	1043	0
2	21	6262	33.5	5	2403	20.8	9	2168	41.5	7	1691	41.4
3	15	6077	24.7	2	2342	8.5	6	2409	24.9	7	1326	52.8
4-6	20	17307	11.6	4	12881	3.1	10	3344	29.9	6	1082	55.5
7-9	10	16637	6	4	12807	3.1	3	3170	9.5	3	660	45.5
10-12	6	15918	3.8	2	11469	1.7	2	3673	5.5	2	776	25.8
>12	4	25796	1.6	0	21076	0	2	3922	5.1	2	798	25
TOTAL	77	94373	8.2	18	66789	2.7	32	20208	15.8	27	7376	36.6

* "No." indicates number of cases; Time is measured in person-days; "IR" indicates incidence rate, per 10,000 person-days

Table 2B. Incidence rates of Idiopathic Pneumonia Syndrome by platelet transfusion levels and time since transplant

	Number of platelet transfusions (prior 7 days)														
	Overall			0			1 - 2			3 - 4			>4		
Week	No.* cases	Time*	IR*	No. cases	Time	IR	No. cases	Time	IR	No. cases	Time	IR	No. cases	Time	IR
1	1	6376	1.6	1	3457	2.9	0	2008	0	0	547	0	0	364	0
2	21	6262	33.5	2	307	65.2	3	2745	10.9	8	1970	40.6	8	1240	64.5
3	15	6077	24.7	0	1247	0	2	2084	9.6	4	1473	27.2	9	1273	70.7
4-6	20	17307	11.6	5	12322	4.1	3	2459	12.2	1	1125	8.9	11	1401	78.5
7-9	10	16637	6	5	13665	3.7	1	1686	5.9	2	662	30.2	2	624	32.1
10-12	6	15918	3.8	3	12466	2.4	1	1975	5.1	1	874	11.4	1	603	16.6
>12	4	25796	1.6	1	22254	0.5	1	2136	4.7	1	788	12.7	1	618	16.2
TOTAL	77	94373	8.2	17	65718	2.6	11	15093	7.3	17	7439	22.9	32	6123	52.3

* "No." indicates number of cases; Time is measured in person-days; "IR" indicates incidence rate, per 10,000 person-days

Table 3. Cumulative incidence* of Idiopathic Pneumonia Syndrome by levels of red blood cell and platelet transfusions, adjusted for time-from-transplant

Number of transfusions (prior 7 days)		Red blood cells		Platelets	
		Crude	Adjusted	Crude	Adjusted
0		2.70	3.26	2.59	5.88
1-2		15.84	13.27	7.29	9.26
>2	(RBC† only)	36.61	35.18	-NA-	-NA-
3-4	(PLT† only)			22.85	16.60
>4	(PLT only)			52.56	34.99

* Incidence rates, reported per 10,000 person-days
† RBC indicates red blood cells; PLT indicates platelets

Table 4. Sum of red blood cell, platelet, and other blood transfusions in the 7 days prior to Idiopathic Pneumonia Syndrome onset among 77 cases and 154 controls matched on days-from-transplant

Measure	Red blood cell		Platelet		Other components	
	Case	Control	Case	Control	Case	Control
Mean (SD)	2.7 (2.6)	1.6 (2.3)	4.5 (4.4)	2.1 (2.8)	1.2 (5.2)	0.1 (0.9)
Median (IQR)	2 (3)	0 (2)	4 (6)	1 (3)	0 (0)	0 (0)
Min - Max	0 - 12	0 - 12	0 - 20	0 - 21	0 - 40	0 - 9

Table 5. Percent of Idiopathic Pneumonia Syndrome cases and matched controls exposed to red blood cell or platelet transfusions in the prior 7 days

Exposure	Number of units	Cases (N=77)	Controls (N=154)	Crude OR* (95% CI)		Adjusted OR* (95% CI)	
Red blood cells	0	23.4	53.3	-Ref-		-Ref-	
	1-2	41.6	27.3	3.47	(1.69 – 7.11)	3.39	(1.53 – 7.52)
	>2	35.1	19.5	4.10	(1.90 – 8.85)	2.59	(1.12 – 6.00)
Platelets	0	22.1	40.9	-Ref-		-Ref-	
	1-2	14.3	23.4	1.13	(0.48 – 2.69)	1.22	(0.46 – 3.22)
	3-4	22.1	19.5	2.10	(0.93 – 4.74)	2.11	(0.83 – 5.35)
	>4	41.6	16.2	4.74	(2.12 – 10.61)	4.01	(1.62 – 9.91)

*Odds ratios adjusted for age, radiation dose, disease indicating transplant, and strata of "other" transfusions

†Score test for trend: red blood cells p = 0.0001, platelets p<0.0001 in crude analyses; red blood cells p = 0.0042, platelets p=0.0016 in adjusted analyses

Table 6. Multivariable conditional logistic regression estimates of Idiopathic Pneumonia Syndrome risk according to red blood cell and/or platelet transfusions received in the prior 7 days

	Separate Model*			Combined Model†		
Predictor	**OR‡**	**(95% CI‡)**	**p-value**	**OR‡**	**(95% CI‡)**	**p-value**
Red blood cell sum	1.22	(1.06 – 1.40)	0.006	1.04	(0.88 – 1.22)	0.669
Platelet sum	1.30	(1.16 – 1.47)	<0.001	1.33	(1.14 – 1.55)	<0.001

*Models adjusted for confounders and 7 day sum of non-platelet, non-red blood cell transfusions

†Models included confounders and 7 day sum of red blood cell, platelet, and other transfusions

‡OR indicates odds ratio; CI indicates confidence interval

Table 7. Conditional logistic regression estimates of transfusion-related Idiopathic Pneumonia Syndrome risk according to engraftment and ABO mismatch status

Transfusion type	Weekly sum of units	OR*†	(95% CI*)	p value‡§
Red blood cell†	Pre-engraftment	0.90	0.74 – 1.10	0.301
	Post-engraftment	0.54	0.10 – 2.84	0.471
Platelet†	Pre-engraftment	1.25	1.00 – 1.55	0.047
	Post-engraftment	1.54	0.30 – 7.81	0.602
	All plasma-matched	1.35	1.13 – 1.61	0.001
	1 or more minor mismatch	1.05	0.27 – 4.09	0.939
	All cell-matched	1.39	1.10 – 1.74	0.006
	1 or more major mismatch	1.03	0.30 – 3.58	0.961

*OR indicates odds ratio; CI indicates confidence interval

†Models adjusted for the sums of all other types of transfusions from the prior 7 days, as well as age, irradiation dose, and disease indicating transplant

‡Reported p-values are based on the Wald test

§Likelihood ratio test p-values for engraftment interaction terms: red blood cell 0.008, platelet 0.304

FIGURES

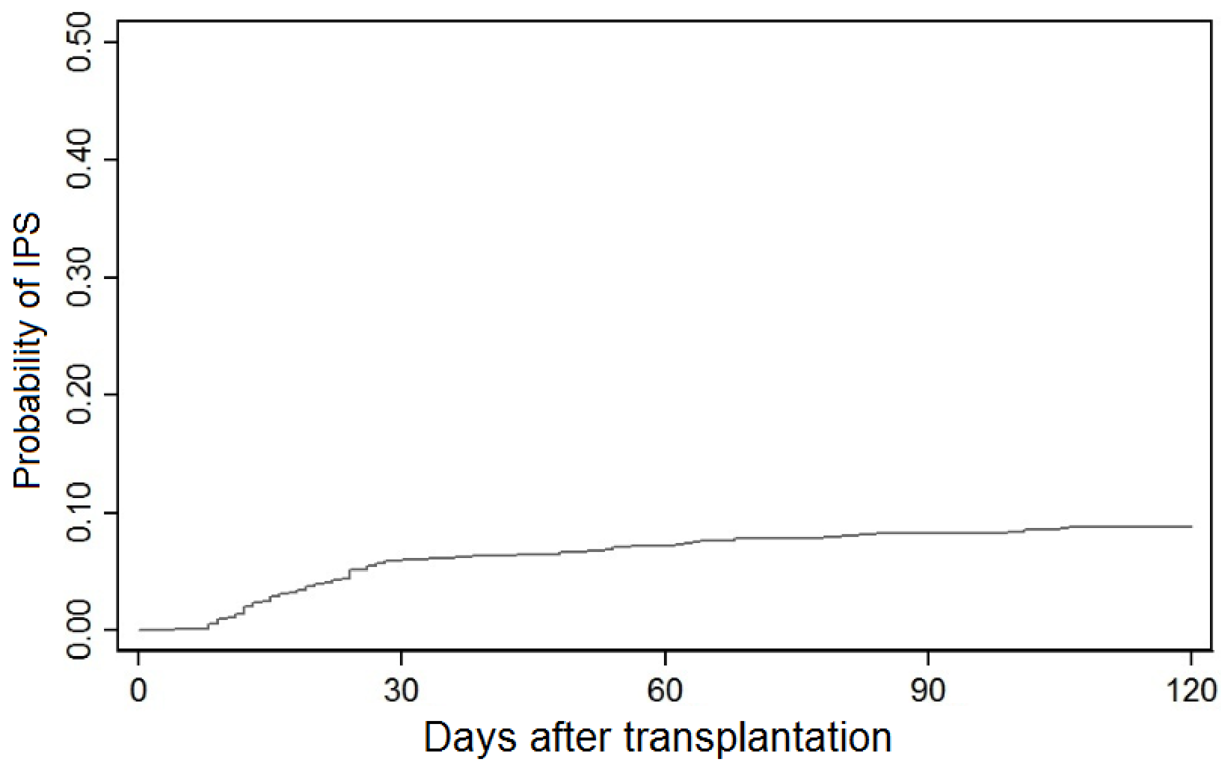

Figure 1. Cumulative incidence of Idiopathic Pneumonia Syndrome. Idiopathic Pneumonia Syndrome occurred within 120 days of transplant in 8.4% of 914 patients who underwent myeloablative allogeneic hematopoietic stem cell transplantation, 1997-2001.

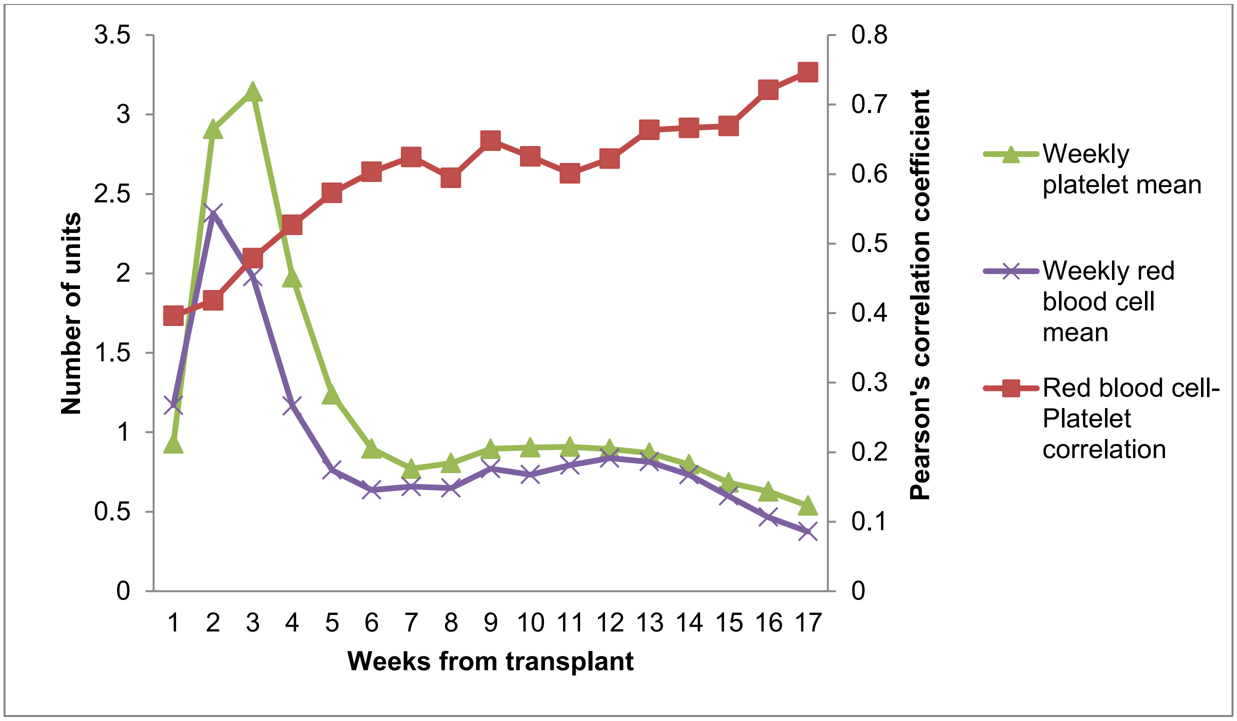

Figure 2. Mean weekly transfusion sums. Mean weekly sums of red blood cell and platelet transfusions were greatest early after hematopoietic stem cell transplantation with increasing correlation throughout observation (range 0.40 – 0.75).