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TRANSFUSION AND APHERESIS

Transfusion immunomodulation or TRIM: What does it mean clinically?

M. A. BLAJCHMAN

McMaster University, Departments of Pathology and Medicine and Canadian Blood Services Hamilton, Ontario, Canada

Abstract
Evidence from a variety of sources indicate that allogeneic blood transfusions can induce clinically significant immunosuppression, as well as other effects, in recipients. This clinical syndrome is generally referred to in the Transfusion Medicine literature as transfusion-associated immunomodulation, or TRIM. TRIM has been linked to an improved clinical outcome in the setting of renal allograft transplantation. Possible deleterious TRIM-associated effects include an increased rate of cancer recurrence and of post-operative bacterial infection. The recognition that TRIM can increase morbidity and mortality in allogeneically transfused individuals has become a major concern for those involved in Transfusion Medicine. However, based on available randomized controlled trials, whether TRIM predisposes recipients to increased risk for cancer recurrence and/or bacterial infection is still unproven. In contrast, data from experimental animal studies suggest that TRIM is an immunologically mediated biological effect, associated with the transfusion of allogeneic leukocytes; an effect, which can be completely ameliorated by the pre-storage leukoreduction of blood products. Relevantly, several (n = 5) recent large observational trials have provided important evidence for the existence of deleterious TRIM and related effects (mortality and organ dysfunction) of leukocyte-containing allogeneic cellular blood products. These latter data suggest that allogeneic blood product transfusions, containing leukocytes, are associated with an increased risk both for mortality, and organ dysfunction in recipients.

Introduction

The transfusion of allogeneic blood products results in the recipients being exposed to large amounts of foreign antigens (alloantigens) in both the soluble and the cell-associated form. The presence of these alloantigens in the circulation can create conditions for a variety of possible immunological responses, which include both alloimmunization and the down-regulation of immune responses. The latter effect generally has been referred to in the literature as transfusion-associated immunomodulation, or TRIM. TRIM has been associated with alterations in immune function in allogeneic transfusion recipients, including: decreased helper to suppressor T-lymphocyte ratio; decreased NK cell function; defective antigen presentation; and reduction in cell mediated immunity [1–4].

Clinical evidence for the existence of TRIM was initially reported in 1973. In their seminal study, Opelz et al. provided evidence, counter-intuitive at the time, that recipients of allogeneic blood transfusions had improved renal allograft survival [5]. Subsequent clinical studies, as well as data from experimental animals studies corroborated these findings. In fact, in the early 1980s, allogeneic blood transfusions were often administered deliberately to renal allograft recipients in order to try to delay, or prevent, the rejection of the renal allograft [6].

It is particularly noteworthy that although the TRIM effect was widely accepted to improve renal allograft survival in renal transplant recipients in the early 1980s, the practice of using allogeneic blood transfusions as a therapeutic modality in renal transplant patients has generally not seen widespread use. This was both because of concern that allogeneic blood products might be associated with the transmission of viral infections (i.e. HIV, HCV etc.) and the availability of increasingly effective immunosuppressive agents; the latter potentially mitigating the need for the TRIM effect.

Nonetheless, Opelz et al. have reported a clear-cut beneficial effect of allogeneic blood transfusion in

Correspondence: Dr. M. A. Blajchman, Departments of Pathology and Medicine, McMaster University Medical Centre, 1200 Main Street West, HSC 2N34, Hamilton, Ontario, Canada, L8N 3Z5, Tel: (905) 521-2100 x76274. Fax: (905) 527-4866. E-mail: blajchma@mcmaster.ca

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renal allograft recipients receiving contemporary immunosuppressive therapy [7]. In a collaborative study involving 14 renal transplant centers in Europe and North America, prospective renal allograft recipients of cadaveric allografts (n = 423) were randomized to receive either three unmodified allogeneic red blood cell (RBC) transfusions, or no transfusions. The one-year renal allograft survival rate was 90% in the recipients of the allogeneic RBCs vs. 82% in those renal allograft recipients who did not receive any allogeneic transfusions ($P = 0.02$). At 5 years, the corresponding renal allograft survival rates were 79% vs. 70% ($P = 0.025$) [7].

On the basis of the TRIM effect observed in renal allograft recipients, Gantt raised the intriguing question, in 1981, as to whether the TRIM effect might also be associated with an increased risk of cancer recurrence in patients undergoing surgery for resection of a malignancy [8]. Gantt's hypothesis was based on the premise that, if allogeneic blood transfusion down-regulated the host's immune surveillance mechanisms that might target malignant cells, the TRIM effect could thus enhance tumor growth in patients with a malignancy. A corollary of Gantt's hypothesis is that if allogeneic blood transfusions do indeed cause immunosuppression in a transfusion recipient, then such recipients could be at increased risk also for various infections, particularly post-operative bacterial infections.

Since 1980, more than 150 studies have examined the potential association between peri-operative allogeneic blood transfusions and either cancer recurrence and/or post-operative bacterial infections. Most of these studies are observational cohort studies comparing patients who received allogeneic transfusions with those that were not transfused [9,10]. In addition, 7 randomized control trials (RCTs) have compared the risk of cancer recurrence and/or post-operative infection in recipients of allogeneic blood transfusions compared to control subjects who did not [11].

Allogeneic blood transfusions and tumor growth

Studies in humans

As indicated above, most of the available data relating TRIM to tumor growth promotion are from non-randomized studies. These have been summarized elsewhere [4,9,11]. Of the available reports, approximately 50% of the non-randomized, mostly retrospective, studies indicate that allogeneic blood transfusions have an adverse affect on tumor-related prognosis. However, in the remaining studies no effect was observed [4,9].

The available observational studies usually compared the incidence of cancer recurrence, death due to cancer recurrence, and/or overall mortality between patients undergoing cancer resection or who did or did not receive an allogeneic transfusion [9,12–14]. These studies indicate that patients having allogeneic transfusions (compared with those not having such a transfusion) had a higher incidence of cancer recurrence, or death due to cancer recurrence; as well as a shorter overall survival after the cancer resection operation. These also indicate that patients receiving allogeneic transfusions generally differed from those not receiving such transfusions. These differences included several potentially important prognostic features, including: clinical stage of the malignancy; size, histological grade, and type of tumor; patient age; preoperative hemoglobin; duration and extent of surgery; amount of peri-operative blood loss; and the frequency of chronic systemic illness, such as congestive heart failure, lung disease, liver disease, kidney failure, or diabetes mellitus [9,10,15].

The latter caveats have led various investigators to different interpretations. Some investigators still concluded that peri-operative allogenic blood transfusions had a direct deleterious effect on allogeneic transfusion recipients [13]. Other investigators concluded that the allogeneic blood transfusions were simply a surrogate marker for a variety of adverse prognostic factors, as well as other variables that necessitated the need for peri-operative allogeneic transfusions in the first instance [10].

In some of the reported observational studies, the reporting authors used multivariant regression analysis to try to adjust for the effects of possible confounding factors. However, for most of the published observational studies, important potential confounding factors were not adequately dealt with by the investigators [11]. Thus, the TRIM effects reported as being "independent" by many teams of investigators may not be free of the effects of known confounding factors. These caveats notwithstanding, allogeneic blood transfusions often emerged in these studies as the leading predictor of cancer recurrence and cancer associated mortality in patients with a malignancy [11].

There have been three RCTs that compared the incidence of cancer recurrence in recipients of buffy-coat-reduced allogeneic RBCs with that of recipients of control blood [16–18]. All three studies enrolled patients undergoing colorectal cancer resection. The proportion of patients having allogeneic transfusions varied from 58% to 64% amongst the studies. The proportion of patients developing recurrent cancer varied from 23% to 25.5%. The findings of these 3 RCTs were combined in two meta-analyses [19,20] and the summary odds ratio (OR) of cancer recurrence in the allogeneic transfusion group compared to the control group, across the three studies, was 1.04 (95% CI, 0.81 to 1.35; $P > 0.05$) in one study [19]. In the other, the summary OR of death due to cancer recurrence was 0.98 (95% CI, 0.76 to 1.26; $P > 0.05$) [20].

It is important to note that, for ethical reasons, it is impossible to perform an RCT in which patients are randomly allocated not to receive an allogeneic blood transfusion or always to receive an allogeneic blood transfusion. However, it would be possible to randomize prospectively patients, who are required to receive allogeneic blood products, to receive different allogeneic blood products (i.e. leukoreduced vs. non-leukoreduced); at least in those countries that have not yet introduced universal leukoreduction.

It is important to note that the three RCTs mentioned above were all done in Western Europe [16–18]. The standard issue (since the early 1990s) of allogeneic RBCs in Western Europe has been as buffy-coat-reduced products. Buffy-coat-reduced cellular blood products have 70–80% of the allogeneic donor leukocytes removed. Thus, in two of these studies, the investigators compared outcomes of autologous blood to that seen in recipients of buffy-coat-reduced allogeneic RBCs. In the third study, the effect of buffy-coat-reduced allogeneic blood was compared with that seen in buffy-coat-reduced autologous blood.

Animal studies

The tumor growth promoting effect of allogeneic blood transfusions has also been studied in various experimental animal models [21]. Data from both inbred and outbred experimental animal models indicate that the tumor growth-promoting effect of allogeneic blood transfusions is an immunologically mediated biological phenomenon that is related to the presence of allogeneic donor leukocytes in the transfused blood product [21–23]. Moreover, these studies show that the tumor growth-promoting effect can be ameliorated by the pre-storage leukoreduction of the transfused allogeneic blood. Post-storage leukoreduction of the allogeneic blood was *not* as effective in ameliorating this effect [23].

To examine for the possible role of buffy-coat reduction on the allogeneic tumor growth-promoting effect of allogeneic blood, studies were done in the author's laboratory, in experimental animals, which examined this effect. In these studies, the tumor-growth promoting effect of non-buffy-coat reduced allogeneic whole blood was compared with that seen with allogeneic blood, which was buffy-coat poor. A significant reduction in the median number of pulmonary nodules was seen in rabbits that had received buffy-coat poor allogeneic blood, compared to that seen in recipients of unmodified allogeneic whole blood (34.0 vs. 74.0; $P < 0.0001$) [4]. However, the ameliorative effect of buffy-coat reduction was not complete, in that the median number of pulmonary nodules seen with buffy-coat-depleted whole blood was greater than that seen in animals that received 3 $\log_{10}$ pre-storage leukoreduced allogeneic whole blood, or those that did not receive any allogeneic whole blood (34.0 vs. 23.5 vs. 21.5) [4]. These data therefore indicate that the buffy-coat reduction of allogeneic blood has a significant ameliorating effect on tumor growth in allogeneic transfusion recipients, at least in rabbits.

Allogeneic blood transfusions and the risk of bacterial infection

The association between peri-operative allogeneic blood transfusion and the possibility of increased risk of post-operative bacterial infection following surgery has been reported in many observational studies. The available studies have been summarized elsewhere and indicate a possible association between allogeneic blood transfusion and post-operative infection [11].

Until recently, the various observational studies reporting an association between allogeneic blood transfusions and increased risk for post-operative infection were not adjusted for the effects of severity of illness and/or for the various risk factors for post-operative infection at specific sites. Some investigators partially accounted for the effects of confounding variables by excluding certain types of infection, such as urinary tract infections from the definition of post-operative infection. However, adjustments for the effects of all the possible confounding factors, in combination, has rarely been presented in the literature [11].

Recently there have been three large observational studies reported in which the authors attempted to adjust for many of the potential confounding variables. Thus, Carson et al. conducted a retrospective cohort study of 9,598 consecutive patients with hip fractures, who underwent surgical repair between 1983 and 1993, at twenty hospitals across the US. The primary outcome variable was serious bacterial infection defined as bacteremia, pneumonia, deep wound infection, or septic arthritis/osteomyelitis. The adjusted relative risk of serious post-operative infection associated with allogeneic transfusions was calculated to be 1.43 (95% CI, 1.16 to 1.78; $P = 0.001$) [24].

Similarly, Chang et al. analyzed a database of 1,349 patients, undergoing elective colorectal surgery for various diseases of the colon or rectum at 11 Canadian University hospitals. Ten prognostic variables were found to be associated with both transfusion and post-operative wound infection, with the final regression model adjusting for four of these confounders. In this study, allogeneic blood transfusions were found to be a significant independent predictor of post-operative wound infection (OR = 1.18; 95% CI, 1.05 to 1.33; $P = 0.007$) [25].

Finally, Vamvakas and Carven reported a retrospective cohort study of 416 consecutive patients admitted to one hospital for coronary artery bypass surgery [26]. The outcome variable was limited to

post-operative wound infection, or pneumonia, and adjustment was made for the effects of chronic systemic illness and specific risk factors for wound infection and/or pneumonia. In this latter study the adjusted risk of post-operative infection or pneumonia increased by 6% per unit of allogeneic RBCs and/or platelets transfused ($P=0.0284$), or by 43% per patient receiving a mean transfusion dose of 7.2 units of RBCs and/or platelets [26].

There have been 7 RCTs reported that have compared the incidence of post-operative infection between recipients of buffy-coat-reduced RBCs, standard allogeneic RBCs, or whole blood; with recipients of autologous, WBC-reduced buffy-coat-reduced allogeneic RBCs, or whole blood [11]. These seven studies are statistically very heterogeneous. Thus, when all seven studies were considered together, to be included in a potential meta-analysis, the probability that the disagreements about the findings might have arisen by chance was smaller than 1 per 10,000 [11]. Two studies [27,28] reported a significant ($P<0.05$) TRIM effect, two studies [29,20] reported a marginally significant ($P<0.10$) TRIM effect and three studies did not detect any TRIM effect. More importantly, the variation in the results of these 7 RCTs range from a 7.3-fold increase in the risk of post-operative infection to no effect. The various characteristics of these seven studies are extensively examined elsewhere and the final conclusion is that these seven studies do not show unanimity of a TRIM effect and thus cannot be combined in a meta-analysis [11,31,32].

To try to explain the disagreements among the 7 RCTs, Blajchman [31] & Vamvakas and Blajchman [32] proposed a meta-analysis of the 7 RCTs using individual patient data (IPD). Such an analysis, usually is referred to as an IPD-meta-analysis, would require the re-coding of the raw data prospectively by the authors of the 7 RCTs, using a common patient data form; as well as the collection of additional data through a retrospective review of the medical records of all the patients who were enrolled in the original seven studies. The additional information would be required in order to try to explain and redeem possible disagreements amongst the various studies. Such information would probably highlight differences in severity of illness, or application of diagnostic criteria for post-operative infection, between the treatment and the control arms of the various studies; thus allowing the meta-analysts to assess the possible effects of bias and confounding. Such an IPD-meta analysis is yet to be done.

Post-operative mortality and organ dysfunction following allogeneic transfusions

In addition to showing a possible association between allogeneic blood transfusion and post-operative infection, the study of van de Watering et al. from Leiden detected an unexpected association between WBC containing allogeneic blood transfusion and post-operative mortality (This was not the primary end-point) [30]. Twenty-four of 306 cardiac surgery patients (7.8%) having allogeneic blood transfusions consisting of buffy-coat-reduced RBCs died, compared with 11 of 305 patients (3.6%) receiving buffy-coat-reduced RBCs that were also WBC-reduced (by filtration) before storage. The mortality was 10 out of 303 (3.3%) in a third arm receiving buffy-coat-reduced RBCs that were WBC reduced after storage. This overall difference in 60-day mortality was due to a highly significant ($P=0.001$) difference amongst the three arms.

Nonetheless, because this study had not been designed *a priori* to investigate post-operative mortality as a primary, or even as a secondary outcome; this group of investigators performed a second study–an RCT that *specifically* tested the hypothesis that WBC-reduction by pre-storage leukocyte filtration reduces post-operative mortality and/or post-operative multi-organ failure. Thus, between 1999 and 2001, 496 complex cardiac surgery patients were randomized to receive either buffy-coat-reduced RBCs, or WBC-leukoreduced (by filtration) buffy-coat-reduced RBCs. The primary end-point of this study was mortality at 90 days. Secondary endpoints included in-hospital mortality, multiple organ dysfunction, infections and hospital stay. The difference in mortality at 90 days was not statistically significant (12.7% vs. 8.4%; odds ratio 1.52; 95% confidence intervals were 0.84 to 2.73). Recipients of buffy-coat reduced RBCs were found to be twice as likely ($P=0.05$) to die within 60 days of their cardiac operation compared to recipients of WBC reduced RBCs (10.1% vs. 5.5%) [33]. Interestingly, there was no difference in hospital length of stay (13.8 vs. 13.3 days) between the two arms of this study.

It is noteworthy that a recent double blind RCT from the US has been reported, also in patients undergoing elective cardiac surgery. 562 patients undergoing cardiopulmonary bypass surgery in 3 hospitals were randomized to receive either prestorage leukoreduced RBCs or standard not leukoreduced RBCs. The leukoreduced RBC cohort ($n=304$) showed a lower 60-day mortality (the primary end-point) than that seen in the standard RBC cohort ($n=258$) (4.9% vs. 9.7%; $P=0.029$). This data has only thus far been reported in an abstract, [24] but is similar to that reported in the two Dutch studies [30,33].

Recently, the results of two before/after studies which were done in Canada where universal leukoreduction (ULR) was introduced in 1999, have been reported [35,36]. Both studies show a beneficial effect of leukoreduction on recipient mortality and/or evidence of organ dysfunction. In one of these studies,

14,786 adult patients were evaluated, who received leukoreduced RBC transfusions following cardiac surgery, repair of a hip fracture, or required intensive care following a surgical intervention [35]. Those patients who received leukoreduced RBCs (n = 7804) had a lower mortality rate (6.19% vs. 7.03%; $P = 0.04$) than those who received non-leukoreduced RBCs (n = 6982). However, serious nosocomial infections were not shown to be lower in the leukoreduced cohort ($P = 0.63$) [35]. It should be noted that the relative difference in mortality between the two groups in this study is 13.6%.

In the second study, [36] in 515 premature low birth weight neonates weighing less than 1250 grams, the leukoreduced cohort (n = 246) was shown to be associated with a lower risk for bacteremia (OR = 0.59; 95% CI: 0.34–1.01), bronchopulmonary dysplasia (OR = 0.42; 95% CI: 0.25–0.70), retinopathy of prematurity (OR = 0.56; 95% CI: 0.33–0.93), necrotizing enterocolitis (OR = 0.39; 95% CI: 0.17–090), and intraventricular brain hemorrhage (OR = 0.65; 95% CI: 0.35–119). In this latter study both the crude and the adjusted rates for these outcomes indicate that leukoreduction is associated with improved clinical outcome and reduced neonatal ICU length of stay [36].

Relevantly, a meta-analysis was recently undertaken to examine whether an association exists between allogeneic blood transfusions and mortality [37]. An association between allogeneic transfusions and mortality was not detected across all clinical settings; however, subgroup analysis suggested that there was an association between WBC-containing allogeneic blood transfusions and short-term mortality in cardiac patients undergoing open-heart surgery [37]. Whether such results justify the institution of ULR of all blood products for all allogeneic blood recipients still remains open to debate.

Conclusions

A causal relationship between allogeneic blood transfusions and cancer recurrence and/or post-operative infections appear to be indicated by the observational studies reported between 1985 and 2000, *but* not by the available RCTs [9,11,31,32]. Specifically, the available RCTs (n = 3) provide no indication that peri-operative allogeneic blood transfusion causes an increase in cancer recurrence or death due to cancer recurrence, at least in patients with colorectal cancer [11].

With regard to the issue of possible TRIM associated post-operative infection, the available observational studies support the hypothesis of an increased risk of post-operative infection in recipients of allogeneic blood transfusions compared to patients who have not been transfused [11,24–26]. However, it is impossible to determine from the available data whether some of the increased risk of post-operative infection seen in association with allogeneic blood transfusions would persist if the effects of patient selection bias, observation bias, and/or the other clinically relevant confounding factors for bacterial infection were to be removed completely. In this regard it is important to note that the RCTs investigating the association between peri-operative allogeneic blood transfusion with post-operative infection were either unblinded or single-blinded. No double-blind RCTs addressing this question have been done! Moreover, because the diagnosis of nosocomial infections is often subjective, observation bias may be an important concern for several of these RCTs. Lastly, the available RCTs did not present sufficient information about severity of illness, or the distribution of risk factors for post-operative infection. In the absence of such information, the possible contributions of confounding factors and/or bias cannot be excluded from the available RCTs [11].

One possible explanation for the disagreements among the available RCTs investigating the possible impact of TRIM on infection may be that the TRIM effect is quite small (i.e. less than 10%) [11]. Such a small effect would not be detected consistently, particularly in small studies, and its detection would be highly dependent on both the size and the particular design of each individual study. Thus, to detect a 10% difference in the risk of a post-operative infection between treatment and control arms of equal size, 20,000 (10,000 per arm) patients would be required, if the overall infection rate were 20%, and if half of the enrolled patients did not receive any allogeneic transfusions. Therefore, the data from the available RCTs, which together comprise just over 3,000 patients, are likely insufficient for the determination of a small adverse TRIM effect. In fact, in this author's opinion, it is unlikely that an RCT of sufficient power, capable of detecting a TRIM effect of 10% or less, will ever be conducted! [11,31] It may be relevant, therefore, that the recently reported non-randomized observational before/after study of the institution of ULR which reported a 13.6% ($P = 0.04$) lower rate of mortality associated with the use of prestorage leukoreduced transfusions may be the largest data base available, in this regard [35]. In other words, this may be as close as we will ever get to a study of sufficient power to address this question.

Thus, the answer to the question as to whether ULR is effective in abrogating the TRIM effect is still unproven [38]. Moreover, the potential implementation of ULR will leave open the issue as to whether allogeneic blood transfusions are causally associated with TRIM. Thus, the issue whether ULR should be introduced now or await definitive double-blind RCTs of sufficient power, which examine both the existence of the deleterious TRIM effect and the efficacy of WBC reduction in abrogating these effects,

is still being debated [11,38]. Recently, Vamvakas and Blajchman presented pro and con arguments relating to the decision to implement ULR [38]. They indicated that on the one hand, it is possible to argue that the decision to implement ULR should be made on the basis of existing evidence, because better evidence is unlikely to be forthcoming soon. Alternatively, they indicated that one could argue that a policy decision should not be made until it is possible to make such a decision based on clear-cut evidence to warrant the introduction of ULR [38].

Relevantly, the United States Department of Health and Human Services (DHHS) Advisory Committee on Blood Safety and Availability (ACBSA) met on January 25 and 26, 2001 to discuss how the US Government should respond to the current debate in the US over the introduction of ULR [39,40]. ACBSA recommended, by a vote of 11 to 2, with 2 abstentions, that ULR should be implemented as soon as feasible. In separate recommendations, ACBSA also recommended that the DHHS should strive to minimize the impact of this recommendation on the supply of blood components, to ensure adequate funding for this effort, and to support continuing research in this area [39].

This decision by ACBSA was taken despite the knowledge that if ULR were to be implemented in the US and elsewhere, the question as to whether deleterious allogeneic blood transfusion TRIM effects were clinically important would still be open. In fact, it appears that the DHHS ACBSA recommendation on ULR was based on the available data indicating clinical efficacy of ULR for some indications, partial clinical efficacy of ULR for others, and no clinical efficacy for others [38,40]. Thus, ACBSA indicated that if universal WBC reduction were to be introduced in the US, it would still be important to establish definitively the existence of adverse TRIM effects and to obtain additional scientific information about the clinical impact and mechanism of the TRIM phenomenon.

References

[1] Bordin JO, Heddle NM, Blajchman MA. The biologic effects of leukocytes present in transfused cellular blood products. Blood 1994;84:1703–1721.

[2] Blajchman MA, Bordin JO. Mechanisms of transfusion-related immuno-suppression. Curr Opin in Hemato 1994;1:457–461.

[3] Bordin JO, Blajchman MA. Immunosuppressive effects of allogeneic blood transfusions: Implications for the patient with a malignancy. Hematol/Oncol Clin of North Am 1995;9:205–218.

[4] Blajchman MA. Immunomodulatory effects of allogeneic blood transfusions: Clinical manifestations and mechanisms. Vox Sang 1998;74:315–319.

[5] Opelz G, Sengar DP, Mickey MR, et al. Effect of blood transfusions on subsequent kidney transplants. Transplant Proc 1973;5:253–259.

[6] Cicciarelli JC, Iwaki Y. Direct transfusion effects in organ transplantation. In: Singal DP, editor. Immunological effects of blood transfusion. Boca Raton, FL: CRC Press; 1994. pp 43–61.

[7] Opelz G, Vanrentergehm Y, Kirste G, et al. Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients. Transplantation 1997;63:964–967.

[8] Gantt CL. Red blood cells for cancer patients. Lancet 1981;2: 363.

[9] Brand A, Houbiers JGA. Clinical studies of blood transfusion and cancer. In: Vamvakas EC, Blajchman MA, editiors. Immunomodulatory effects of blood transfusion. Bethesda, MD: AABB Press; 1999. pp 145–190.

[10] Vamvakas EC, Moore SB. Blood transfusions and postoperative septic complications. Transfusion 1994;34:714–727.

[11] Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: Fact or fiction? Blood 2001;97:1180–1195.

[12] Francis DM. Relationship between blood transfusion and tumor behavior. Br J Surg 1991;78:1420–1428.

[13] Blumberg N, Heal JM. Effects of transfusion on immune function: Cancer recurrence and infection. Arch Pathol Lab Med 1994;118:371–379.

[14] Vamvakas E. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. Transfusion 1995; 35:760–768.

[15] Vamvakas EC, Carven JH, Hibberd PL. Blood transfusion and infection after colorectal cancer surgery. Transfusion 1996;36: 1000–1008.

[16] Heiss MN, Mempel W, Delanoff C, et al. Blood transfusion-modulated tumor recurrence: first results of a randomized study of autologous versus allogeneic blood transfusion in colorectal cancer surgery. J Clin Oncol 1994;12:1859–1867.

[17] Busch ORC, Hop WCJ, van Papendrecht MAWH, et al. Blood transfusions and prognosis in colorectal cancer. N Engl J Med 1993;328:1372–1376.

[18] Houbiers JGA, Brand A, van de Watering LMG, et al. Randomized controlled trial comparing transfusion of leukocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. Lancet 1994;344:573–578.

[19] Vamvakas E. Transfusion-associated cancer recurrence and infection: meta-analysis of the randomized controlled clinical trials. Transfusion 1996;36:175–186.

[20] McAlister FA, Clark HD, Wells PS, Laupacis A. Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies. Br J Surg 1998;85:171–178.

[21] Bordin JO, Blajchman MA. Blood transfusion and tumor growth in animal models. In: Vamvakas EC, Blajchman MA, editors. Immunomodulatory Effects of Blood Transfusion. Bethesda, MD.: AABB Press; 1999. pp 29–42.

[22] Blajchman MA, Bardossy L, Carmen R, Sastry A, Singal DP. Allogeneic blood transfusion-induced enhancement of tumor growth: Two animal models showing amelioration by leukodepletion and passive transfer using spleen cells. Blood 1993; 81:1880–1882.

[23] Bordin JO, Bardossy L, Blajchman MA. Growth enhancement of established tumors by allogeneic blood transfusion in experimental animals and its amelioration by leukodepletion: The importance of the timing of the leukodepletion. Blood 1994;84:344–348.

[24] Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. Transfusion 1999;39: 694–700.

[25] Chang H, Hall GA, Geerts WH, et al. Allogeneic red blood cell transfusion is an independent risk factor for the development of postoperative bacterial infection. Vox Sang 2000;78: 13–18.

[26] Vamvakas EC, Carven JH. Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: effect of the length of storage of transfused red cells. Transfusion 1999; 39:701–710.
[27] Jensen LS, Andersen AJ, Christiansen PM, et al. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. Br J Surg 1992;79:513–516.
[28] Jensen LS, Kissmeyer-Nielsen P, Wolff B, et al. Randomized comparison of leukocyte-depleted versus buffy-coat-poor blood transfusion and complications after colorectal surgery. Lancet 1996;348:841–845.
[29] Heiss MM, Mempel W, Jausch K-W, et al. Beneficial effect of autologous blood transfusion on infectious complications after colorectal cancer surgery. Lancet 1993;342:1328–1333.
[30] Van de Watering LMG, Hermans J, Houbiers JGA, et al. Beneficial effect of leukocyte depletion of transfused blood on post-operative complications in patients undergoing cardiac surgery: A randomized clinical trial. Circulation 1998;97: 562–568.
[31] Blajchman MA. Allogeneic blood transfusions, immunomodulation and postoperative bacterial infection: Do we have the answers yet? Transfusion 1997;37:121–125.
[32] Vamvakas EC, Blajchman MA. A proposal for an individual patient data based meta-analysis of randomized controlled trials of allogeneic transfusion and postoperative bacterial infection. Transfus Med Rev 1997;11:180–194.
[33] Bilgin YM, van de Watering LMG, Eijsman L, et al. Double blind, randomized control trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. Circulation 2004;109:2755–2760.
[34] Boshkov LK, Furnary A, Morris C, et al, Prestorage leukoreduction of red cells in elective cardiac surgery: Results of a double blind randomized controlled trial. Blood 2004; 104: 112a (abstract).
[35] Hébert PC, Fergusson DA, Blajchman MA, Wells GA, Kmetic A, Coyle D, Heddle N, Germain M, Goldman M, Toye B. Clinical consequences of the Canadian universal leukoreduction program for red cells. JAMA 2003;289:1941–1949.
[36] Fergusson D, Hébert PC, Lee S, Walker CR, Barrington KJ, Lawrence J, Blajchman MA, Shapiro S. Effectiveness of universal leukoreduction of allogeneic blood transfusions in premature infants. JAMA 2003;289:1950–1956.
[37] Vamvakas EC. WBC-containing allogeneic blood transfusion and mortality: A meta-analysis of randomized controlled trials. Transfusion 2003;43:963–973.
[38] Vamvakas EC, Blajchman MA. Universal WBC reduction: The case for and against. Transfusion 2001;41:691–712.
[39] Nightingale SD. Conference Report: Universal WBC reduction. Transfusion 2001;41:1306–1309.
[40] Caplan AL. Editorial: Universal WBC reduction. Transfusion 2001;41:1190–1191.