

Transfusion-Induced Immunomodulation and Its Possible Role in Cancer Recurrence and Perioperative Bacterial Infection

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Over the last decade, it has become evident that homologous transfusions carry immunologic consequences beyond the well-understood ones of alloimmunization to blood cell antigens. Transfusions constitute temporary transplants of large amounts of allogeneic antigen given intravenously and cause down-regulation of many cellular immune functions. These changes may explain in part the association of transfusion with such clinically important events as (1) improved survival of renal allografts, (2) decreased recurrence rates for autoimmune disease, (3) increased frequency and earlier recurrences of solid tumors, (4) increased frequency of post-operative bacterial infection, and (5) increased severity of viral infection. Preliminary data suggest that, in animal models and clinical settings, syngeneic or autologous transfusions are not associated with such events. This finding supports the hypothesis that these associations are cause and effect and involve immunologic mechanisms.

INTRODUCTION

For some years it has been known that transfusion has generalized immunologic effects on recipients in addition to the well-known clinically significant effect of alloimmunization to various blood cell or plasma antigens [1]. The best characterized clinical effect due to transfusion-induced immunomodulation is improved survival of renal allografts in previously transfused patients [2]. The mechanism of this effect is still largely mysterious but is almost universally considered to involve down-regulation of the immune functions that lead to rejection of histoincompatible tissue [3]. During the 1980s extensive clinical investigation, largely phenomenologic, has yielded evidence that these transfusion-induced effects may not be restricted to the allograft setting. It has been hypothesized that transfusion may compromise host defenses against solid tumors [2-6], bacterial organisms [6,7], and viruses [8]. Most recently, transfusion has been implicated as favorably modifying the course of Crohn's disease (regional enteritis), a gastrointestinal disease of possible autoimmune etiology [9,10]. Transfusion in the clinical setting is implicated as a potential suppressor of immunologic effector cells and as a stimulator of immunologic suppressor cells. We will briefly review the evidence for these contentions, except for the renal allograft effect, which will be addressed by one of the other symposium participants.

TRANSFUSION AND IMMUNE FUNCTION

We have recently reviewed this subject elsewhere [1]. Transfusion in both animal models and clinical settings appears to increase the generation of host suppressive activity in the form of suppressor cells and anti-idiotypic antibodies. This result is most strikingly seen when the suppression is measured as donor-specific, after initial exposure to large amounts of donor antigen intravenously. Subsequent challenge with a donor allograft is frequently followed by extended survival of histoincompatible tissue as compared with its survival in animals or patients not previously exposed to donor blood. There also appear to be generalized, but poorly characterized decreases in recipient functions such as cytotoxic or natural killer cells, monocyte/macrophage migration to sites of infection, ability to respond to mitogens or skin test antigens, and so on. The components of transfused blood responsible for these effects, which have been frequently although not universally observed, are uncertain. Based upon the renal allograft setting, white blood cells are thought to be major contributors, but, in some animal model systems, plasma or red cells have been observed to cause qualitatively similar effects. In general, many studies of this sort would benefit from repetition using more highly purified blood components and more modern, sophisticated tests of immune function.

TRANSFUSION AND CANCER RECURRENCE

Perhaps the most controversial question is whether homologous transfusion is associated with earlier or increased numbers of recurrences of solid tumors [2-6]. While almost all studies demonstrate that transfused patients fare poorly in terms of time to or frequency of recurrence compared with non-transfused patients, these differences have not always reached statistical significance. In some instances, the difference in outcome between transfused and non-transfused patients has been significant and large, but multivariate analysis determined that, after variables such as tumor stage, complexity of surgery, and the like were accounted for, transfusion was no longer a statistically significant independent predictor of recurrence.

A number of factors probably contribute to the variability of results reported in such studies. First, all studies to date have been retrospective reviews of previously treated patients. This method inevitably involves loss to follow-up of many patients and variations in treatment practices over time in any given single institution. Second, transfusion is not a random variable. Transfused patients tend to be those who are having the longest operations and lowest hematocrits prior to surgery. Third, other variables may contribute to the degree of post-transfusion immunomodulation. Some anesthetic agents may be immunosuppressive, and variation in anesthesia practice may contribute to the extent of immunosuppression observed after operation and transfusion [11]. One can speculate that the same variation may apply to various other drugs or treatment modalities used perioperatively in oncologic patients. Fourth, some studies simply have an insufficient number of subjects to detect even large differences in outcome between transfused and non-transfused patients. These features, virtually the antithesis of a randomized controlled investigation, make it all the more remarkable that any pattern has emerged in studies of cancer recurrence and transfusion.

In spite of these difficulties, we believe the weight of evidence supports the contention that transfused patients are at significantly greater risk of recurrence than non-transfused patients in some clinical settings. In our own studies, patients receiving the larger amounts of plasma and white cell debris in whole blood were at greater risk of

recurrence than those receiving comparable amounts of red cell concentrates, which contain lesser amounts of these potentially immunosuppressive substances [12]. Even though pre-treatment anemia and duration of surgery were excellent predictors of who was eventually transfused, these factors were not significant predictors of recurrence of, or of death due to cancer [13]. Finally, tumor stage and transfusion appear to be independent and additive predictors of recurrence of, or of death due to cancer [14]. At least in our cohort of patients, the seemingly reasonable contention that transfusion is acting as a surrogate marker for extent of tumor, difficulty of tumor resection, or disease severity as measured by anemia, is not supported by a detailed analysis.

Furthermore, of the almost 20 studies performed on colorectal cancer recurrence and transfusion, those which concluded that transfusion was a significant predictor of outcome generally involved larger numbers of patients (by about 40 percent) than the negative studies. Thus they were less likely to be afflicted by a type II or beta error. Moreover, the studies finding a significant association between transfusion and recurrence almost invariably included multivariate analysis of other potentially important predictors of outcome. We suspect that the failure to find a significant association between transfusion and colorectal cancer recurrence in many of the negative studies is in large part due to smaller patient numbers, differences in patient selection (e.g., omission of patients with certain types of resections or tumors), and choice of methodologies for data analysis. Of note is the fact that of almost 50 studies performed to date on a variety of tumors, transfusion has yet to be found to be statistically significantly associated with a favorable influence on tumor recurrence. This result is surprising given purely stochastic considerations; at least two or three studies might be expected to have found such a result if transfusion is an irrelevant variable. More important, some animal data suggest that transfusion might protect against tumor spread or recurrence; no clinical data exist to support this possibility.

The hypothesis that stored plasma (i.e., whole blood) and its contents (e.g., white cell debris, soluble histocompatibility antigens, immunoglobulins) may be particularly likely to mediate post-transfusion immunosuppression is supported by results in the renal transplant setting. Whole blood appears to be a more potent promoter of graft tolerance than red cells alone [15]. Furthermore, while two recent studies of the effect of whole blood transfusion on cancer recurrence failed to achieve statistical significance, in both studies, recipients of whole blood did in fact have poorer outcomes than did recipients of red cells [16,17]. In one of these studies, the authors found that those transfused patients who had received fresh frozen plasma fared the worst by far [16].

We believe that carefully performed, controlled, randomized studies, with a sufficient number of patients, in which standard blood components are compared with leukocyte- and plasma-depleted components, are warranted from the current data. We do not, however, think the data are sufficient to argue for changes in how oncology patients are currently transfused. There is no evidence that use of washed or frozen-deglycerolized red cells will materially benefit cancer patients in terms of the course of their disease. On the other hand, pre-operative deposit of autologous blood for cancer surgery perhaps deserves more consideration, for a variety of reasons, than has heretofore been given.

TRANSFUSION AND POST-OPERATIVE INFECTION

Whereas the possible association between transfusion and cancer recurrence remains in considerable doubt, the relationship between perioperative transfusion and

an increased incidence of bacterial infections appears fairly certain from both animal and clinical studies. With a few exceptions, animal studies have demonstrated that transfusion of allogeneic blood, as compared with saline or syngeneic blood, is associated with greater morbidity or mortality after experimental infection [18]. Furthermore, of 12 clinical studies in which the association between transfusion and infection could be determined, 11 found that transfusion was significantly and independently associated with an increased risk of bacterial infection [19]. In most of these studies, even after accounting for factors such as shock, degree of wound contamination, duration of surgery, and type or extent of injury or surgery, transfusion remained a statistically significant predictor of infection. Indeed, in most of these studies, transfusion was the single most significant predictor of infection post-operatively.

In addition to the dramatic association between transfusion and post-operative infection clinically, there are experimental animal data to demonstrate impaired monocyte/macrophage function after allogeneic transfusion [20]. Finally, we recently reported preliminary data that in patients undergoing hip replacement surgery, patients who received autologous blood only had a much reduced incidence of post-operative infection compared with a similar group of patients who received equivalent amounts of homologous blood [21]. Especially convincing is the fact that the infections in these studies are predominately away from the wound site itself, suggesting a generalized reduction in host resistance to infection. There are virtually no data suggesting that transfusion is acting as a surrogate marker or covariate for one or more other variables that might be expected to predict infection. Even if transfusion were acting as a surrogate for such variables, one would expect the increase in infection rate to involve predominately the wound or operative site, which is not the case.

If these data can be extended and confirmed, it appears that post-operative bacterial infection could be the single most common significant complication associated with homologous transfusion. Clinical studies have consistently shown a post-operative infection rate of about 25 to 30 percent in homologously transfused patients, as compared with a rate of perhaps 5 to 10 percent in non-transfused or autologously transfused patients in similar clinical settings.

Bacterial infections may not be the only ones potentiated by transfusion. We reported that patients with post-transfusion AIDS seemed to be disproportionately those who had received very large amounts of blood [8]. This finding has recently been confirmed, suggesting that the severity of post-transfusion immunosuppression after infection may be a contributing factor in determining which patients develop severe HIV-1 infection early in their course [22]. Similar preliminary data exist for cytomegalovirus infection [23].

SUMMARY

The bulk of experimental and clinical data support the theory that homologous transfusion causes down-regulation of immunologic functions in many settings. These changes in immune function may account for the favorable association of transfusion with increased renal allograft survival and decreased recurrence in Crohn's disease. Conversely, these transfusion-induced effects may be causal in the unfavorable association with increased cancer recurrence and increased post-transfusion bacterial and viral infection rates. Host defenses against malignancy and infection may in some instances be severely compromised by transfusions of homologous blood, but the circumstances under which this condition occurs remain uncertain. Likewise, the hypothesis that modification of blood components to contain fewer leukocytes or less

plasma might ameliorate these effects is attractive, but little or no data exist to support or refute it.

Perhaps the clearest lesson to be taken from this developing area of research is one already learned during the 1980s: the safest transfusion is an autologous one, or one not given, preferably due to a clinical assessment that there is a marginal likelihood of benefit as compared to the risk.

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