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Perspectives and Commentaries

Blood Transfusions for Surgical Cancer Patients: More Harm Than Good?

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(A COMMENT ON: Pastorino U, Valente M, Cataldo T *et al.* Perioperative blood transfusion and prognosis of resected stage Ia lung cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 1375–1378.)

BLOOD transfusions are widely used in major cancer surgery and have contributed greatly to the safety of extensive resections. Blood transfusions are, however, associated with certain risks which increase with the quantity of blood transfused. The potential harmful effects of blood transfusions include transfusion reactions because of incompatibility, and transmission of infectious disease due to the presence of bacterial, viral or protozoal organisms in the transfused blood. Transfusion of large quantities of blood may produce metabolic disturbances and coagulopathies. Blood transfusions can also produce clinically important changes in the immune response of the recipient.

There is convincing evidence that the immunomodulating effects of transfusions can be beneficial to some patients and considerable circumstantial evidence that the immunomodulating effects can be deleterious to other patients. On the beneficial side, the immunomodulating effects of transfusions have led to increased rates of success after renal allografting [1–3]. Moreover, there is a dose–response relationship between the number of transfusions and long term renal allograft function rates.

On the side of possible deleterious effects due to immunomodulation by transfusions have been reports of increased susceptibility to post-operative infection and increased recurrence and decreased survival after cancer surgery. The similarity between tumor antigens and histocompatibility antigens [4] has lead a number of investigators to question whether blood transfusions given to certain groups of cancer patients might favor tumor growth just as they favor preservation of the allograft. The issue is whether certain types of blood transfusions have an effect on the growth of residual micrometastases that may remain after surgical resections of a cancer.

A number of retrospective investigations of surgical cancer patients have lead to reports of an adverse association between perioperative blood transfusions and the recurrence rate and/or survival rate after resection of cancers that could not be related to confounding variables. While the majority of reports have suggested the possibility of an adverse effect of blood transfusions on the survival of patients following cancer surgery, a number of investigations have failed to demonstrate any such adverse relationship. I am not, however, aware of any report that has suggested a beneficial relationship between blood transfusions and long term survival of cancer patients, rather the investigations have noted either an adverse relationship or no differences in survival. The retrospective report on 283 surgically resected lung cancer patients by Pastorino *et al.* [5] is among those which have failed to confirm any adverse association with the administration of perioperative blood transfusions. Our own studies have identified an adverse association between blood transfusion and the survival of surgically resected lung cancer patients and colon cancer patients, but we have not identified an adverse relationship between survival and perioperative blood transfusions in patients undergoing resection of breast cancers or rectal cancers [6–8]. These apparently conflicting reports are reminiscent of the conflict-

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ing reports and controversy that went on in the 1970s relative to the possibility of a relationship between blood transfusions and renal allograft survival. The weight of data and prospective studies eventually provided incontrovertible evidence that blood transfusions could lead to improved renal allograft survival. The data on any cause-and-effect relationship between blood transfusions and adverse outcome for surgical cancer patients is as yet far from incontrovertible. Further retrospective studies will not likely resolve the issue. Prospective randomized trials are needed.

More needs to be learned about the immune changes in humans that occur after transfusion, but a recent review has summarized the currently available information [9]. Studies have shown that after blood transfusions there can be decreased lymphocyte reactivity to both antigenic and mitogenic stimuli. The plasma of transfused patients can develop suppressive effects that are associated with the α2-macroglobulin component. Increased suppressor cell activity may be responsible for some of the decreased lymphocyte responsiveness after transfusion. The effects of blood transfusions on immune responsiveness are probably multifactorial.

The components of transfused blood that are most strongly suspected of being responsible for the immunomodulation are the leukocytes and the platelets. Cotton wool filtered blood and blood that has been frozen are substantially leukocyte free; both of these preparations have a decreased ability to improve the survival of renal allografts. Pure red cells may not be totally free of immunomodulating effects as it has been shown that phagocytosis of blood cells by macrophages can lead to decreased reactivity of bystander lymphocytes. It is possible that the phagocytosis of effete red cells after transfusions might lead to some degree of immunosuppression.

Studies to prospectively investigate the relationship between blood transfusion and survival of surgical cancer patients might utilize the information derived from the studies on renal transplant patients. In a prospective randomized study, patients transfused with packed red blood cells could be compared to patients transfused with "leukocyte free" red cells specially prepared by either cotton wool filtration or by a multiple washing process such as that which is used in the preparation of frozen blood.

Despite the obvious benefits of blood transfusions in some circumstances, there are definite well-established risks associated with each transfusion (in addition to the potential adverse immunomodulating effects of transfusions) that make it necessary to carefully evaluate our criteria for administration of transfusions. In the past there was frequently a policy to attempt to replace blood loss ml for ml, particularly for children. Many surgical and anesthetic services have an arbitrary policy of transfusing when hematocrits are less than 30% or hemoglobin levels are less than some arbitrary figure such as 9.5 g/100 ml [10]. The critical issue is oxygen delivery to the peripheral tissues. Oxygen delivery is the product of blood flow (or cardiac output) and the arterial oxygen content. Hemoglobin is a principle determinant of the arterial oxygen content, and when hemoglobin content of the blood is decreased, most patients are capable of substantial cardiovascular compensation, leading to increased cardiac output and adequate oxygen delivery [11, 12]. When the blood volume is adequately maintained with crystalloid solutions, tissue oxygenation can frequently be well maintained at hematocrits of 20% and lower [13]. Higher hematocrits may be beneficial in a few patients to provide greater protection in the event of further blood loss or in the event the patient were to undergo transient oxygen deprivation. Even greater degrees of anemia may be well tolerated. It has been suggested that mixed venous pO_2 and oxygen extraction ratios are better indices of critical need for transfusion than hematocrit or hemoglobin [14]. In experimentally induced extreme anemia, instability begins to occur at hemoglobin less than 3.5 g/dl, mixed venous pO_2 less than 25 torr, or oxygen extraction ratios greater than 50% [15].

Blood transfusions prudently administered remain an important part of our treatment of the surgical cancer patient. As we await the outcome of prospective studies that may possibly identify safer preparations, what should our policy be relative to the administration of blood transfusions to the surgical cancer patient? First, we must maintain our vigilance to assure that donors are properly selected, that blood is properly screened for contaminated biologic agents, that blood is properly preserved, screened and crossmatched and that errors are not made in identifying the patient that is to receive a particular unit. Second, when we administer red cells, we must take care that we transfuse only those patients that are in need of the increased oxygen carrying capacity that the red blood cells will provide. Frequently volume expansion can be accomplished with crystalloid solutions. Many of the historical criteria for the use of blood transfusions are in need of revision.

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