REVIEW

Blood Transfusion and Cancer Recurrence: A Brief Review

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ABSTRACT

There is a growing evidence to support the hypothesis that blood transfusion is associated with an increased risk of cancer recurrence and survival. Evidence is also accumulating to suggest that whole blood transfusion or at least certain type of blood components have immunomodulatory effects in man. The mechanisms by which these effects are produced are unclear. There are many negative and conflicting studies concerning this hypothesis and the overall data should not deter the careful investigation of transfusion practice in cancer patients. The benefits must be weighed against risks. Despite concern about transfusion transmitted diseases, there is evidence that unnecessary transfusion still practiced with a tendency to use multiple units during surgery. Pre-operative anaemia should be corrected by haematinics. It may be necessary to put more effort to prevent surgical bleeding and consider the use of autologous donation if the anaemia is not a concern. Use of washed red cells or plasma and leucocyte depleted red cells may help in preventing recurrence in patients undergoing surgery for aforesaid malignancies. Also a sagacious consultation with transfusion service may be helpful.

Although the blood transfusions are beneficial in many clinical situations they only temporarily improve the physical state of the patient but exert wide spread effects on non-immune and immune systems.[1, 2, 3] In recent years data has accumulated to suggest that blood transfusions are associated with changes in the immune functions, which are at times advantageous or detrimental to the patients depending on the medical condition. Example of its adverse effects comes from various studies which have shown that blood transfusions predispose to the recurrence of malignant neoplasia such as those of colorectal,[4, 5, 6] breast, [7] lung, [8] kidney, [9-11] gastric, [12] head and neck,[13] cervical,[14] vulvar[15] and prostate[16] cancers. Conversely, transfusion has been shown to be advantageous in improving the survival of renal allografts[17, 18, 19]. Although many studies strongly support the view that transfusions are associated with immunosuppression and subsequent recurrence and poor prognosis of solid tumors, these findings are not universal. The aim of the present paper is to review the benefits and risks of blood transfusion in patients with malignancies.

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Blood Transfusion and Immune Functions

There is an overwhelming data which shows that blood transfusion may alter host immune defences, but the mechanism by which these immune defences are altered remains unclear. These altered immune defences, whether beneficial or deletarious to the patients, are also unclear. A common assumption is that the exposure of recipients to similar antigenic material prior to transplantation making rejection more likely, proved exactly the opposite to prior transfusion of buffy coat, whole blood and red cell concentrates which leads to the improvement in the acceptance of renal allograft in patients with renal failure and in experimental models[17, 20, 21]. The induction of immunological unresponsiveness, the activation of suppressor cells, antigen presenting cells, idiotypic networks and clonal deletion all have been proposed as possible mechanisms for the beneficial effect of transfusion[22, 23, 24, 25, 26]. The evidence of possible harmful effect of transfusion in patients with cancer came from the laboratory study of transfused rats which suggested a decreased lymphocyte reactivity and increased plasma suppressive activity with marked increase in tumour growth.[27] Although, a recent study in rats has shown no such effect on tumour growth,[28] Gantt's[29] speculation is that patients with malignant tumours, who receive transfusion of whole blood, are suppressed to the point where the malignant growth has a better chance to survive.

There is a growing literature describing changes in T4/T8 Lymphocyte ratio, natural killer (NK) cell activity, Lymphocyte counts, skin test reactivity, HLA-DR expression on T cells and immunoglobulins in transfused patients with various diseases. The interest in this field was generated by the evidence of the development of acquired immune defeciency syndrome (AIDS) in haemophilic and transfusion recipients.[3, 30, 31] Moffat et al while studying 26 patients with factor VIII deficiency showed low helper T lymphocyte count, low T helper and suppressor ratio and diminished response to lymphocyte mitogen phytohaemagglutinins and decreased NK cell activity in these patients. Similar results were observed by Jason et al[3] in their study of 47 haemophilic patients. It was also found that patients with haematological diseases (sickle cell anaemia, thalassaemia, and haemophilia) who had received multiple transfusion had severely depressed NK cell function as compared to untransfused patients or normal subjects.[2] Tartter et al[31] while studying 59 patients of inflammatory bowel disease showed that the total lymphocyte count and T cells of patients receiving pre-operative blood transfusion remained low or unchanged from pre-operative levels but reached normal levels 6 to 18 months after operation when compared with patients who did not receive pre-operative blood transfusion. The potential of long term immunosuppressive effect of blood transfusion was shown in the immunological work of Beek et al[32] on 23 women (mean age 26 yrs) who had received neonatal exchange transfusions, 9 women (mean age 29 yrs) who had been transfused on average 4.5 years earlier, and 10 women (mean age 28) who had never been transfused. The mixed lymphocyte reaction of both transfused groups were reduced significantly as compared to those of the non-transfused group.

Tartter et al[33] studied T cell subsets and NK cytotoxicity in patients with colorectal cancer and correlated the results with patients transfusion history. Twelve percent of the 115 patients were transfused an average of 19 years previously.[14] Recipients of blood transfusion had low levels of peripheral lymphocytes, T cells, helper cells and suppressor cells compared to previously untransfused patients. NK cytotoxicity was also significantly reduced in transfused patients although NK cell numbers were comparable in both groups. The T4/T8 lymphocyte ratio and NK cells activity appear to have an important protective function against tumour metastasis. These cells may also be involved in immunosurveillance against the development of certain tumours. Henna et al[35] demonstrated a close correlation between the levels of NK cell activity and the capacity to eliminate blood-born tumour cells.

Blood Transfusion effects in patients treated for cancers: Colorectal Cancer

Burrows and Tartter[36] were the first to show the detrimental effect of blood transfusion in the treatment of patients with colorectal cancer. One of the first public presentation of this work was at the 1983 annual meeting of the American Association of Blood Banks[37, 38]. In their study of 58 transfused and 65 non-transfused patients who underwent colectomy for cancer of colon showed that in patients with comparable stage of tumour growth transfused patients had a significantly higher recurrence rate of

cancer[36]. Blumberg et al[5] reported a series of 129 transfused and 68 non-transfused patients treated surgically for cancer of the colon and followed thereafter for 6 months to 11 years and showed that within each pathologic stage, transfused patients had a much higher rate of recurrence than non-transfused patients. Foster et al[4] in their study of 65 transfused and 81 non-transfused reported a decreased disease-free survival in patients with cancer of colon transfused pre-operatively. Similar results were also shown in various other studies[39, 40]. These retrospective studies included variety of factors such as duration of surgery (surrogate measure of technical difficulty of tumour removal), histologic tumour stage, tumour location within the bowel, pre-operative anaemia and age which could influence the prognosis and survival of patients. However, these studies emphasized the fact that the association between transfusion and recurrence of cancer cannot be explained merely by the association of transfusion with these known prognosis factors. In some studies multivariate analysis (Cox regression) showed a significant independent effect of transfusion or cancer recurrence and death[4, 5, 39, 40, 43]. The five-year-recurrence rates of transfused and non-transfused patients were found to be 50% and 10% respectively.

The relationship of transfusion with cancer recurrence or decreased survival is not entirely uniform[41, 42, 43]. A study by Tartter et al [45] on 345 patients of colorectal cancer did not support the association of blood transfusion to recurrence of malignancy. A prospective study from New Zealand on 103 transfused and 71 non-transfused patients followed for 3 to 4 years reported that the recurrence rate was not different within similar pathologic stages.[46] On the other hand several different approaches at multivariate analysis yielded different results.[47] In most studies, the five-year-recurrence free survival or five-year survival corrected for non-cancer deaths was estimated. Transfusion was an independent unfavourable predictor of earlier recurrence or cancer related death in 7 of the 12 studies. Non-transfused patients fared better in 11 of the 14 studies. Twelve studies analyzed other variables such as surgical difficulty at operation, clinical aggressiveness of the tumour (histologic stage) and overall clinical condition of the patients, eg. pre-operative anaemia. In view of the multiple conflicting studies, Blumberg and Heal[47] carried out a meta-analysis (pooling of the data of all published studies) on the results of all the studies with only few exceptions. They reviewed the data in toto as well as the data from (a) studies in which multivariate analysis supported an independent prognostic role of transfusion and (b) the data from the studies in which no such difference was found or the difference was insignificant. In six studies taken together in their review, the five-year-recurrence rates were 31% (147 out of 472 patients) in non-transfused patients and 52% (447 out of 886 patients) in transfused patients. Thus a recurrence rate in transfused patients was 70% higher than in the non-transfused patients. They also suggested that if transfusion is a non-specific marker for other factors, then it is almost as good a predictor of recurrence as any clinical or histologic staging system known. A similar meta-analysis was done for the five year survival (counting only deaths due to colorectal cancer). The number of patients dying of cancer in all the nine studies (four studies in which transfusion was an independent significant predictor of death due to cancer, and five studies where transfusion was not associated with excess deaths due to cancer) was 464 out of 1139 (41%) of those who were transfused, as compared with 193 out of 599 (32%) of those not transfused. Therefore, those receiving transfusion had a cancer related death rate of 30% higher than those not receiving blood transfusion. When all the published studies were evaluated, including those without a significant transfusion effect, the differences in the pooled data suggested a marked advantage for non-transfused patients. Moreover, the study by Blumberg et al[48] suggested that transfusion and tumour stage are independent and are cumulative predictors of the outcome in cancer patients, ie for patients at any given stage of the disease the addition of transfusion as a risk factor moves the patient into the next more severe stage in terms of outcome.

Breast Cancer

The evidence of a transfusion effect on the outcome of patients with breast cancer is not overwhelming as seen in those with colorectal cancer. Foster et al[49] in their retrospective study of patients with breast cancer followed from one to seven years after surgical treatment with similar stage of tumour and nodal involvement for transfused and non-transfused patients reported no effect of transfusion on the outcome of the patients. However, Tartter et al[7] reported 39 transfused and

130 non-transfused patients of breast cancer followed for 5 to 13 years and found the five-year-recurrence free survival was found to be 51% in transfused patients and 65% in non-transfused patients. Adjuvant therapy study was given significantly to more of the transfused patients. The results were also analysed for 89 patients operated on by the same surgeon and the effects of transfusion were still found to be significant, but no details were given. A recent study by Kieckbusch et al[50] on 229 patients with stage II disease concluded on the multivariate and recursive partitioning analysis that transfusion before or at mastectomy are not associated with increased recurrence or reduced survival in patients with breast cancer. However, in the same study 34 of 299 patients receiving first transfusion after mastectomy were associated with decreased survival. The recurrence rate of the disease was 85% in this group. These patients received transfusion because of recurrent disease.

Effect of Blood Transfusion in other Cancers

There are a number of reports of single studies, suggesting at least the same adverse association of transfusion with early or more frequent recurrence and shortened survival. Rosenberg et al[51] studied patients with high grade soft tissue sarcoma of the extremities and observed a highly significant association between pre-operative transfusion and decreased survival. 130 patiens with stage 0 to III B of cervical cancer were studied by Blumberg et al.[14] The study suggested an early recurrence in transfused patients. While evaluating the effect on cervical[14] and prostate[16] cancers by multivariate analysis, it was suggested that the association between transfusion and poor clinical outcome could not be readily explained by other prognostic factors. Records of 179 patients of head and neck cancer suggested that the disease free survival rate declined progressively in patients given increasing numbers of transfusions.[13]

The results are conflicting on patients with lung and renal cancer. A sixty two percent five-year-recurrence free survival was shown in transfused patients as against 76% in non-transfused patients with lung cancer by Tartter et al[8] whereas in the study by Hyman et al[52] the rates were 33% and 47% respectively. However the work of Pastorino et al[53] on 283 patients of lung cancer found no significant association.

The five-year-survival rate in transfused patients with renal cell carcinoma was 49% as compared to 69% "in non-transfused patients". Mikulin et al[10] calculated the rates of 39% and 77% for transfused and non-transfused patients respectively.

Role of Blood Banking Practices in Immune Modulation and Cancer Recurrence.

The data presented indicates that there is a possible relationship between blood transfusion, immunosuppression and clinical sequelae of poor outcome in cancer patients. Blumberg et al[47] suggested that the possible predictors of severity such as duration of surgery, histologic tumour stage, tumour location, pre-operative anaemia, and age of patients with colorectal cancers cannot explain the adverse outcome in transfused patients. Moreover, in their meta-analysis they suggested that transfusion and tumour stage are independent and are cumulative predictors of the outcome. Since then many variables were considered from the surgical point of view as well from blood banks. Is it the type of blood, the type of plastic storage bags, anticoagulant, preservative solution, the number of platelets and white cells removed from RBC preparation and the period of storage of component, responsible for the immunomodulation of the recipient? There are also data indicating that the transfusion of plasma or plasma derivatives and not the cellular blood products[3] can be immunomodulatory in haemophilic patients receiving factor VIII. Transfusion of whole blood has been associated with early recurrence and death in various cancer patients.[54] When recipients of one or more units of RBCs were compared with recipients of one or more units of whole blood at five years after diagnosis of malignancy, those receiving less than three units of whole blood had a recurrence rate of 45% and those receiving no transfusion or less than three units of RBCs alone had a recurrence rate of approximately 25%[55]. Since immunosuppressive substance in the blood are more likely to be in the white cells and plasma, it has been suggested that RBCs depleted of plasma and white cells may lower the recurrence rate of some cancers.

The plasticizer used in blood storage bags, phthalic acid ester known as di (2-ethylhexyl) phthalate (DEHP), has been reported as carcinogenic substance in humans and animal models,[56] but the difference in survival between patients transfused with whole blood and those receiving RBC concentrates does not explain its sole effect on recurrence. Preliminary evidence also suggests that immune function could be induced by use of stored plasma and the use of adenine alone.[57]

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