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Feature Articles

Do Perioperative Blood Transfusions Increase the Risk of Cancer Recurrence?

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PREVIOUS EXPOSURE to histocompatibility antigens by allogeneic blood transfusion can sensitise a potential organ recipient and result in "hyperacute" rejection of a subsequent organ graft. It therefore came as a surprise in 1973 when Opelz *et al.* [1] reported that previous blood transfusions were associated with improved graft survival in recipients of cadaver kidney transplants. This observation was confirmed by others, some of whom demonstrated that graft survival was even better if the recipient had been transfused with blood from the renal donor [2]. Although it was initially argued that improved graft survival after blood transfusion resulted from the selection of donors against whom the recipient is immunologically unresponsive, subsequent data suggest that the mechanisms involved are more complex and involve active suppression of both specific and non-specific responses to the transplanted organ. Interestingly, these important observations of the 1970s and early 1980s are no longer as relevant for renal transplantation, since better donor–recipient matching and the use of cyclosporin post-transplantation have substantially reduced the likelihood of graft rejection.

TRANSFUSIONS AND THE CANCER PATIENT

A transfusion-induced state of decreased immune responsiveness, while potentially beneficial to the renal allograft recipient, might be detrimental to the cancer patient. This possibility was first suggested in 1981 by Gantt who asked whether "... patients who receive transfusions of ... blood are suppressed to the point where the malignant tumour has a better chance to survive?" [3]. Frances and Shenton [4] reported that rats transfused with allogeneic blood had significantly larger tumours following injection of a transplantable sarcoma than did controls. Furthermore, the rats that received allogeneic blood not only had larger tumours, but also had depressed *in vitro* lymphocyte reactivity and raised plasma lymphocyte inhibitory activity. However, allogeneic blood transfusion was shown to inhibit growth of other rat tumours in two different studies [5, 6], neither of which attracted the attention of the "positive" study of Frances and Shenton [4].

Around the same time there were clinical reports of a possible adverse association between perioperative blood transfusions and cancer recurrence in patients with colorectal cancer [7, 8]. Although these reports were retrospective, other known prognostic factors such as disease stage, tumour location, other therapies, duration of surgery, preoperative anaemia and age were accounted for. Subsequent studies yielded a variety of results. Fourteen of these studies are summarised in three well-written reviews [9–11] and two more have recently been published [12, 13]. All these studies, except that of Bentzen *et* al. [13], were retrospective and most included patients with different stages and sites of colorectal cancer. In most studies, 5 year recurrence-free survival was the primary endpoint. Non-transfused patients fared better than transfused patients in twelve studies. Fourteen studies included multivariate analyses to consider other variables that might affect patient outcome; transfusion remained an independent predictor of either earlier tumour recurrence or survival in only eight of the fourteen studies. Heterogeneity of patient population and clinical management was reflected in the variable frequency of transfusion (45–78% of patients) and in the wide range of recurrence-free survival reported—from 44% to 97% for non-transfused patients and from 34% to 81% for transfused patients.

In a meta-analysis of fourteen studies relating transfusion to recurrence of colorectal cancer [10], the 5 year recurrence rate in transfused patients was 1.7-fold higher than that in patients not transfused, and the 5 year cancer-related death rate was 1.3-fold higher in transfused patients. Nevertheless, the question remains whether transfusion is a surrogate marker for one or more clinical factors predisposing to tumour recurrence rather than being causally related to it [13].

While the possible detrimental effects of perioperative blood transfusions have been most extensively studied in patients with colorectal cancer, similar observations have been made for patients with other malignancies, including cancers of the lung, breast, kidney, soft tissue sarcoma, gastric carcinoma, squamous cell carcinoma of the cervix and head and neck, vulvar and prostatic cancer [9–11]. In only one of five studies in patients with breast cancer has perioperative blood transfusion been associated with an increased likelihood of cancer recurrence. On the other hand, in the other malignancies reports of an adverse association between transfusion and tumour recurrence or survival range from suggestive to reasonably compelling.

Blumberg and Heal [10] pooled their data relating transfusion and cancer recurrence in a group of patients treated for cancer

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of the colon, rectum, cervix or prostate to see if differences in the amount or kind of transfusions were associated with varying recurrence and death rates. For each type of cancer patients receiving only a small number of red blood cells (as opposed to whole blood or larger numbers of units of red blood cells) had less tumour recurrence and better overall survival. In general, patients receiving 3 or fewer units of blood that included only packed red blood cells had recurrence and survival rates identical to those in patients receiving no transfusion. In contrast, patients receiving even one unit of whole blood had significantly worse outcomes. Transfusion of red blood cells rather than whole blood was recommended in patients with cancer.

POSSIBLE BIASES

However, there may be investigator bias towards reporting retrospective reviews relating blood transfusion to cancer recurrence when the result is "positive" (i.e. when transfusion does influence the rate of tumour recurrence) compared to when the result is "negative". For example, in 1983, we embarked upon a prospective randomised trial of adjuvant postoperative portal vein chemotherapy in patients with resected colorectal cancer [14]. Patients were followed prospectively after randomisation; transfusion data, although not initially a variable, were available for review. Of 249 patients, 78 received 1–3 units of red blood cells or whole blood, 34 received more than 3 units and 137 did not receive transfusions. After 5 years of follow-up, we could detect no difference in either tumour recurrence or overall survival by transfusion status for all patients, or for patients subdivided by tumour site (colon vs. rectum), Dukes' stage (B vs. C), type of transfusion product (red cells vs. other) or number of units transfused (0, 1–3, greater than 3).

Closer examination of the report of Liewald *et al.* [12] again highlights the two major problems that plague resolution of this controversy—i.e. investigator bias and the possibility that transfusion is a surrogate marker for other clinical factors predisposing to tumour recurrence. The summary states that "tranfused patients showed significantly ... higher recurrence rates" and yet the multivariate logistic regression analysis showed that tumour recurrence rate was *not* significantly related to blood transfusion. Also "homologous blood transfusions are negatively correlated to survival rates"; while this conclusion was supported ($P = 0.022$) by the logistic regression, the transfused patients had several features for which blood transfusion could have been a surrogate marker. These "negative" features that correlated with transfusion included more patients older than 70 years (37% vs. 24%), more patients with weight loss (29% vs. 17%), more patients with tumour size greater than 5 cm (34% vs. 21%), more patients with rectal cancer (52% vs. 35%) and more patients with postoperative complications (34% vs. 16%). 21% of the patients who received transfusions received 6 or more units of blood, suggesting either extensive preoperative blood loss, complicated surgery or a difficult postoperative course. Given the small number of patients when subdivided by many clinical characteristics, the power of a multivariate analysis may be insufficient to identify a combination of features predisposing both to increased likelihood of transfusion and tumour recurrence.

These points are highlighted by the analysis of Bentzen *et al.* [13] who investigated the influence of blood transfusion on the endpoint "death with cancer" in a prospective randomised trial of adjuvant postoperative radiotherapy in 468 patients with carcinoma of the rectum or rectosigmoid colon. Univariate analysis initially revealed a highly significant worsened prognosis with increasing volume of transfused blood. By multivariate methods, however, patients receiving whole blood or packed red blood cells fared no worse than non-transfused patients. Transfusion thus appeared to be a proxy or surrogate variable for other indices associated with poor prognosis.

PROSPECTIVE STUDIES

Our ability to proceed rationally through these conflicting data or to design prospective studies is complicated further by a lack of knowledge of the components of blood transfusions that may be responsible for the deterimental effects of perioperative blood transfusions. Plasma components, lymphocytes, red cells or red cell components or immunosuppressive viruses are potentially involved [9–11]. Transmission of immunosuppressive viruses also provides a potential explanation for the variable effects of transfusion on cancer recurrence and survival. It is, for example, conceivable that biologically important differences in the blood donor population are responsible for some of the variability observed, since such a transmissible agent might be present in some geographical locations during some periods, but not in other locations or periods.

Some of the difficulties with the design of prospective studies to resolve whether perioperative blood transfusions increase the risk of cancer recurrence have been discussed [11]. These issues include the uncertainty in identifying a controlled red blood cell product devoid of the immunomodulatory effects of blood transfusions, the difficulty in controlling for subtle differences in operative procedure or underlying tumour prognosis and the problem of attaining sufficient patient numbers to avoid both alpha and beta statistical error. Data on all patients can be collected in a retrospective study but accrual to a prospective study is more limited. For example, during the 5 year period in which we did our prospectively randomised adjuvant therapy trial [14], we screened 579 patients, but only 249 [43%] ultimately entered the study. Of the patients screened, 10% were found to have metastatic disease, 5% were excluded for surgical reasons, 20% were not eligible because of benign disease, other malignancy or other disease and 19% were excluded because of patient or physician refusal. Thus, to accrue 600 patients to a prospective trial, as has been suggested [11], might involve screening of 1400 patients. Finally, the existence of a prospective study attempting to confirm the detrimental effect of transfusion might significantly affect transfusion practice (i.e. the proportion of cancer patients receiving allogeneic blood would decrease).

CONCLUSIONS

I reiterate our 1987 statement that it is difficult to reconcile conflicting data in this area [15]. Do I, however, continue to feel that "it appears premature to radically alter current blood transfusion practices" [15]? Tartter [11] concluded that the available evidence does not support any changes in the use of blood for patients with malignancies. Others [9] have concluded that it seems appropriate to infer that perioperative transfusion in any patient undergoing cancer surgery adversely affects prognosis or that it seems probable that transfusion affects the outcome after surgical treatment of some cancers [10]. Certainly the results to date do not prove that perioperative blood transfusions *per se* increase the likelihood of tumour recurrence, thereby decreasing patient survival. However, the combined data suggest this possibility and certainly provide no support for a contention that blood transfusions might be beneficial. There are other risks associated with transfusion, including tranfusion reactions and transmission of hepatitis, cytomegalo-

virus and retroviruses. Transfusions also pose issues associated with cost and scarcity. Thus, I conclude today, as we did in 1987 [15], that "avoidance of unneeded tranfusions or use of erythrocytes in preference to whole blood is sound medical practice for a number of reasons ... even if a decrease in tumour recurrence has not been established".

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Novel Approaches to the Endocrine Therapy of Breast Cancer

M. Dowsett

INTRODUCTION

THE DEPENDENCE of some breast cancers on ovarian function for their continued growth has been recognised for nearly a century [1]. This led to the successful development and application of several different treatments based on depriving the breast carcinoma of its oestrogenic stimulation. Some of these, such as tamoxifen, have a well-established place in therapy while others are still in preclinical or early clinical stages. More recently the recognition that breast carcinomas are subject to many other stimuli that influence their growth has led to the development of new groups of compounds which have mechanisms of action other than oestrogen deprivation.

Endocrine treatment of breast cancer was established as a major therapeutic option in the early 1970s with the availability of tamoxifen which remains the dominant drug in the field [2]. The successful use of tamoxifen over the past 20 years might argue against the value of developing other agents directed at oestrogen deprivation. However, there are several observations to support such research: (a) tamoxifen is not effective in all patients with oestrogen and progesterone receptor positive tumours, which would be expected to be responsive to oestrogen deprivation; (b) some patients who do not respond to tamoxifen do respond to some other modes of endocrine therapy; (c) at relapse, responders to tamoxifen frequently respond to other types of endocrine therapy; and (d) many (probably the majority) of the pharmacological effects of tamoxifen are oestrogenic, which argues against tamoxifen's mechanism of action solely as an oestrogen antagonist.

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ENDOCRINE THERAPIES

New anti-oestrogens

The side-effect profile of tamoxifen is excellent to the degree that the drug has been accepted by the UK Coordinating Committee for Cancer Research for study as a chemopreventive for breast cancer in healthy women following encouraging feasibility studies [3]. New anti-oestrogens are therefore likely to be of value only if they have improved efficacy or are effective in patients in which tamoxifen is ineffective, possibly because tamoxifen is a mixed agonist/antagonist. For antitumour effects, agonist activity is undesirable and pure antagonists may be more effective in suppressing breast cancer growth. The mainstream approach to this problem has been the synthesis of triphenylethylene analogues, such as toremifene and droloxifen, with close structural similarity to tamoxifen [4, 5]. In laboratory and animal experiments, however, none of these compounds is purely anti-oestrogenic. It would therefore be surprising if such compounds target different cells and have a different clinical profile from tamoxifen.

Zindoxifene is an anti-oestrogen with a different structure, being an acetylated indole. However, it also has mixed agonist and antagonist activities and although studies with carcinogen-induced rat mammary tumours were encouraging, none of 25 patients showed an objective response in a phase I/II study [6].