A Possible Association Between Survival Time and Transfusion in Cervical Cancer

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Received April 27, 1988

Some studies suggest that transfusion may be associated with an increased risk of recurrence of and death due to malignant human neoplasms. We examined retrospective data from patients with cervical cancer to see if any association between transfusion of blood at the time of initial treatment and the time interval to recurrence and death could be detected in this cancer. In 130 patients with cervical cancer, seen over a ten-year period at our institution, there was a trend toward earlier recurrence in transfused patients, but this trend did not achieve statistical significance. Death due to cervical cancer recurrence occurred after a median of 12 months in the transfused patients and a median of 68 months in the non-transfused individuals, which was statistically significant. Transfused patients had, on average, more favorable prognostic factors than those not transfused, such as less advanced clinical stage of disease. Analysis using a proportional hazards risk model failed to demonstrate a significant association between transfusion and time to recurrence when other prognostic factors were considered, but a significant association between transfusion and time to cancer-related death (p < 0.05) was found. While these results cannot be viewed as conclusive due to the small number and heterogeneity of the patients analyzed, our data support the possibility of an association between transfusion and cervical cancer survival. Further studies are warranted to confirm or refute this relationship.

INTRODUCTION

An extensive body of data demonstrates that blood transfusions have immunological effects on patients and experimental animals, and that these effects may have clinical consequences [1–3]. The most thoroughly characterized clinical consequence is that of improved renal allograft survival in transfused patients, as compared with those not receiving blood transfusions. These findings have led to investigations of whether transfusion at the time of cancer surgery is correlated with immunologic alterations in patients and with increased rates of tumor recurrence. The first study in humans demonstrating this relationship is that of Burrows and Tartter on patients with colon cancer [4]. Numerous studies documenting associations between perioperative transfusion and poorer outcome in patients with colon and rectal [5–6], lung [7–8], breast [9], and renal [10] cancers as well as soft-tissue sarcomas [11] have appeared. Other investigators have not found such associations, or have found small differences that do

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not achieve statistical significance [12–18]. One recent study demonstrated an adverse association between transfusion and colorectal cancer outcome, but no such relationship for breast cancer [19]. The possibility of such a relationship in cervical cancer has not yet been investigated.

We performed a retrospective case review to determine whether there are associations between cervical cancer recurrence and survival, and transfusion at the time of initial diagnosis and treatment.

PATIENTS AND METHODS

The methods employed to collect data on patients with cervical cancer were identical to those reported in our retrospective study of colon and rectal tumors [5]. In brief, the names and identifying numbers of hospital patients seen between 1970–80 with this diagnosis were retrieved from a computerized data base and the medical record reviewed, collecting data on age, date and duration of surgery, transfusion status, clinical stage, hematocrit at diagnosis, whether radiation therapy or chemotherapy was received for cervical cancer, recurrence and death data, and last date of follow-up. Transfusion data were also verified from blood bank records, including whether red cell transfusions were given as “packed” red cells or as whole blood (whole blood units contain approximately 300 ml of plasma and anticoagulant; red blood cells, approximately 50 ml). The attending physician’s staging assessment was accepted unless data to the contrary existed. Clinical stage was defined in our institution according to the American Joint Committee system, as follows: 0 is carcinoma in situ; IA is microinvasive carcinoma; IB is carcinoma restricted to the cervix; IIA is carcinoma extending to the lateral wall; IIB is carcinoma extending into the vagina; IIIA is carcinoma penetrating the lateral wall; and IIIB is carcinoma extending to the introitus. Patients were included in the study if they had undergone surgery at our institution, had documented follow-up of at least six months, had no evidence of metastatic disease at diagnosis, and had an unambiguous transfusion history and diagnosis of cancer. We designated patients as transfused if the transfusions occurred within one month before or after surgery. Patients receiving transfusions at other times are not included in this analysis. All transfusions in fact occurred within a several-day span perioperatively. We excluded 78 patients from the study for the following reasons: 25 had less than six months’ follow-up; 11 had stage IV disease (distant metastases) at presentation; 34 had their initial surgery at another institution; four had missing medical records; three had more than one malignancy, and one refused any therapy. The remaining 130 patients were included in the analysis.

STATISTICAL ANALYSIS

The methods detailed in our previous study on colon and rectal cancer were employed [5]. We used chi-square statistics to compare the transfused and non-transfused groups with respect to the various prognostic factors [20]. We also used such statistics to compare the incidence of recurrence or death in the various groups defined by the variables under study. These latter analyses were followed by statistical techniques which allow adjustment for differences in prognostic factors. A multivariate stepwise logistic regression analysis [21] showed that pre-operative anemia, younger age, less advanced clinical stage, and more prolonged surgery were associated with transfusion. When fitting proportional hazards models to time to recurrence and to survival time, we first included the prognostic factors, but not the transfusion status,
as predictors [22]. The non-significant factors were excluded; transfusion status was then added to the proportional hazards model obtained to see if the change in the log likelihood after adding transfusion status was significant. By entering information on transfusion last, we could measure the effect of blood transfusion on time to recurrence and survival time after adjustment for other factors. We thus obtained an estimate of the effect on recurrence and on death attributable to blood transfusion status. Kaplan-Meier's product-limit method was used to estimate the distributions of time to recurrence and survival time of transfused and non-transfused patients [23].

RESULTS

There were no significant differences in the raw frequency of recurrence or death in the transfused (26 percent had recurrences; 16 percent died of cancer) and non-transfused (30 percent had recurrences; 9 percent died of cancer) groups. When Kaplan-Meier's product-limit method was employed, however, the survival rate of the transfused patients was worse compared with that of the non-transfused patients (Fig. 1). A similar trend was seen in the analysis of time to recurrence, but this difference was not statistically significant (data not shown).

The patients in the transfused and non-transfused groups were markedly different from each other in a number of variables that are potentially relevant to the likelihood of cancer recurrence. The transfused group had been followed for a median of 30 months after diagnosis and initial treatment, whereas the non-transfused patients had been followed for 46 months ($p < 0.01$ by Mann-Whitney test). Thus the comparable raw recurrence rates in the transfused and non-transfused groups may be misleading. Non-transfused patients were followed for 50 percent longer on the median than were transfused patients and thus are more likely to have had recurrences detected. Tables 1 and 2 demonstrate that the transfused and non-transfused patients were significantly different with regard to age, anemia at the time of diagnosis, duration of surgery, clinical stage, whether radiation therapy was received, and year of diagnosis. Of these, age and duration of surgery were not significantly associated with recurrence or death; however, anemia at the time of diagnosis, advanced clinical stage, receipt of radiation therapy, and surgery prior to 1975 were all associated with higher rates of recurrence.

Transfused patients were more likely to be anemic at diagnosis, an unfavorable
Chi-square for $2 \times 2$ tables was employed to determine $p$ values. The choice of intervals for variables such as age, surgical duration, and year of diagnosis was determined by contingency table analysis of the association between these factors and cancer recurrence. Information was not available on all patients for all prognostic factors. Age and surgical duration were not prognostically significant factors for recurrence or death due to cancer. Anemia, receipt of radiotherapy, and diagnosis prior to 1975 were significantly associated with earlier recurrence and death due to cancer.

prognostic feature. Contrarily, transfused patients were less likely to have stage IIIB disease, less likely to have received radiation therapy, and less likely to have been diagnosed prior to 1975, all of which are favorable prognostic associations for the transfused patients. In general, transfused patients had more favorable clinical prognostic settings than those who were not transfused.

A proportional hazard model was fitted to time to recurrence, the results indicating that pre-operative anemia and presence of stage IIIB disease were the most significant factors in predicting time to recurrence. Adding transfusion status to this model did not yield a statistically significant improvement in the log-likelihood ratio. When a similar approach was applied to survival time, however, transfusion was significantly associated with shortened survival ($p < 0.05$).

The transfused patients tended in general to have more favorable prognostic features and had been followed for a much shorter time. Nonetheless, the raw data on time to recurrence and survival time show a trend toward earlier recurrence (Fig. 2) and shorter survival time (Fig. 3) in the transfused patients. Among those with recurrence, the median time to recurrence for transfused patients was nine months, as compared

### Table 1
Other Prognostic Variables versus Transfusion Status

| Age <50 years | Non-Transfused (%) | Transfused (%) | $p$ |
|---------------|---------------------|----------------|-----|
| 15/61 (25)    | 47/69 (68)          | <0.0001        |
| Hematocrit <38| 14/59 (24)          | 34/67 (51)     | <0.005 |
| Surgical duration <120 minutes | 44/59 (75) | 13/66 (20) | <0.0001 |
| Radiation therapy given | 50/61 (82) | 38/68 (56) | <0.005 |
| Year of diagnosis prior to 1975 | 26/61 (43) | 15/69 (22) | <0.05 |

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### Table 2
Clinical Stage and Transfusion Status versus Outcome

| Stage* (%) | Died | Recurred |
|------------|------|----------|
|            | Transfused | Non-Transfused | Transfused | Non-Transfused |
| 0 (20)     | 0/1   | 1/4       | 0/1        | 2/4          |
| IA (44)    | 0/7   | 0/9       | 0/7        | 1/9          |
| IB (69)    | 4/35  | 1/16      | 6/35       | 5/16         |
| IIA (40)   | 2/4   | 0/6       | 2/4        | 1/6          |
| IIB (50)   | 3/13  | 3/13      | 5/13       | 3/13         |
| IIIA (50)  | 0/1   | 0/1       | 0/1        | 0/1          |
| IIIIB (40) | 2/8   | 0/12      | 5/8        | 6/12         |

*Percentage refers to the percentage of patients with that clinical stage who were transfused.

Chi-square for the distribution of stages between transfused and non-transfused groups = 9.87, $p = 0.13$. 
FIG. 2. For the patients with recurrence, months from diagnosis to detection of recurrence are shown according to transfusion status. Several patients with recurrence are omitted because the exact date recurrence was detected is not known. The open circle indicates a patient whose recurrence was detected at 192 weeks.

with 24 months for non-transfused patients. Of those dying of cervical cancer, the median survival time for transfused patients was 12 months, versus 68 months for the non-transfused patients. These results are statistically significant at the \( p < 0.05 \) level only for survival time.

A recent study which included some of the patients in this report demonstrated that recurrence of cancers of the colon, rectum, prostate, and cervix was more likely in patients receiving transfusions of whole blood than in those receiving red cells [24]. An analysis of the cervical cancer patients alone was performed to determine if recurrence

FIG. 3. For the patients dying of cervical cancer, months from diagnosis to death are shown according to transfusion status. The open circle indicates a patient dying of cervical cancer at 144 weeks.
was more likely to be associated with transfusions of whole blood, as opposed to red blood cell concentrates. The association of recurrence with amount of blood transfused was also investigated. For seven of the transfused patients, the kinds and/or exact amounts of blood received were unavailable or uncertain. Using chi-square analysis, a significant association between amount and kind of blood components administered and recurrence was found. The recurrence rate for those receiving $\leq 3$ red blood cell transfusions was 2 of 20, significantly different from 3 of 3 for those receiving $\geq 4$ red blood cell transfusions ($p = 0.006$ by Fisher's exact test). The recurrence rate for those receiving $\leq 3$ units of whole blood was 3 of 13, not significantly different from 8 of 26 for those receiving $\geq 4$ units of whole blood. Thus, although the numbers evaluated are very small, those receiving any whole blood or $\geq 4$ units of red cells had a greater frequency of cancer recurrence.

**DISCUSSION**

Despite the striking heterogeneity of the patients, our data suggest the possibility of a relationship between death from cervical cancer and transfusion at the time of initial surgical treatment. The patients in the transfused and non-transfused groups are clearly dissimilar in a number of potentially important respects, but the biases are toward worse prognostic factors in the non-transfused group. Thus the population studied is potentially biased against the detection of an adverse effect of transfusion. Nonetheless, an independent unfavorable association was found between transfusion at the time of diagnosis and death due to cervical cancer.

Counter to what one might expect, the transfused patients had somewhat less advanced clinical stage disease than did those who were not transfused. The raw frequencies of recurrence were similar in the transfused and non-transfused patients despite the fact that the transfused patients had been followed for much shorter periods of time. Although multifactorial statistical analysis only demonstrated a significant association between transfusion and survival time, examination of the raw data for time to recurrence showed a possible advantage to the non-transfused patients. This finding is of interest as the non-transfused patients had less favorable clinical features: they were more likely to have been diagnosed prior to 1975, to have received radiation therapy, and to have more advanced clinical stage of disease. Our data also confirmed that patients receiving plasma-rich products, i.e., whole blood in any amount, or $\geq 4$ units of red blood cells, had higher recurrence and death rates as compared to those patients receiving only small numbers of red blood cell transfusions ($\leq 3$ units). Because of the small number of patients who died and the heterogeneity of those studied, our overall analysis of the significance of transfusion in cervical cancer outcomes is not definitive and will require further study.

In general, our data on cervical cancer tend to support the possibility of an association between cancer recurrence and transfusion seen in some patients with other solid tumors [4–7,9–11]. It remains to be determined whether this association is causal or coincidental. If the relationship is causal, the mechanisms at work are as yet unknown. Many previous workers have attributed the immunomodulatory effects of transfusion to the lymphocyte or white cell content of the blood infused. We have reason to believe that the red cell and whole blood transfusions to our patients did not differ in lymphocyte or white cell content. Thus, our previous finding [24] that whole blood transfusions are associated with higher cancer recurrence rates than red blood cell transfusions suggests a role for plasma substances [25–27] as one potential cause of
reduced immunologic function in transfused cancer patients. Further studies in patients might include investigation of the effects of plasma transfusions, unmodified red cell transfusions, and white cell and plasma-depleted red cell transfusions on immunologic functions such as natural killer cell activity, antigen presentation function of macrophages, and the like, as well as on clinical outcomes.

Whether transfusion causes increased rates of cancer recurrence is still an open question. Our previous data do argue for the use of red blood cells, rather than whole blood, when transfusing patients with solid tumors. Nonetheless, the results reported here are preliminary and tentative when taken alone and cannot justify changes in the approach to transfusing cervical cancer patients at this time. Our results do argue in favor of further study of the relationship between transfusion and cervical cancer recurrence, and suggest a possible prognostic role for transfusion in this cancer. We believe that our data in general [5,24–26] strongly support the need for investigations of the potential benefits of white cell- and plasma-depleted transfusions for cancer patients requiring red blood cell replacement.

ACKNOWLEDGEMENTS

We thank Doctors Dean Arvan, Jackson Beecham, John Bennett, and Joanna Heal for helpful discussions and the staff of the Blood Bank of Strong Memorial Hospital for their efforts in verifying transfusion records. We are deeply appreciative to Carol Cole for secretarial and clerical assistance.

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