Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1226–1228, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00174-3

The Effect of Blood Transfusions on Survival After Surgery for Colorectal Cancer

O.R.C. Busch, W.C.J. Hop, R.L. Marquet and J. Jeekel

The immunosuppressive effect of allogeneic blood transfusions can be associated with a poor prognosis for cancer patients. Predeposit autologous blood transfusions could be a solution to overcome this putative deleterious effect. We performed a randomised clinical study to compare the effects of autologous with allogeneic blood transfusions in colorectal cancer patients. There was no significant difference in disease-free survival between both randomisation arms. However, the transfused patients had a significantly shorter disease-free interval as compared with the non-transfused patients. This association of transfusions with recurrent disease was only the case for local recurrences, whereas the incidence of distant metastases was unaffected. We conclude that the use of a predeposit autologous blood transfusion programme does not improve the prognosis in colorectal cancer patients. The negative association between blood transfusions and cancer recurrence is only true for local recurrences, which suggests that not the blood transfusions themselves but rather the circumstances necessitating them are the real predictors of prognosis.

Key words: colorectal cancer, prognosis, blood transfusions, autologous, clinical trial
Eur J Cancer, Vol. 31A, Nos 7/8, pp. 1226–1228, 1995

INTRODUCTION

ALLOGENEIC blood transfusions have an immunosuppressive effect which is shown to be beneficial for patients who receive a kidney transplant [1]. The question of whether this immunosuppression has a deleterious effect on the prognosis of patients operated on for solid tumours has interested many investigators [2, 3]. After more than 20 retrospective reports investigating the association between blood transfusions and prognosis in colorectal cancer patients, the results are still inconclusive [4]. Even two meta-analyses, which have been published recently, presented different conclusions.

In the first study, 20 papers were reviewed, including over 5000 patients [5]. The authors concluded that the cumulative odds ratio of negative outcomes after peri-operative blood transfusions was 1.80 for disease recurrence and 1.76 for death from cancer. In a second meta-analysis [6], pooling the data of 11 clinical studies, a significant increase of 37% in the risk of cancer recurrence or cancer-related death in the transfused patients was found. However, the authors concluded that this transfusion effect might be ascribed to the effects of uncontrolled confounding.

If a negative association between peri-operative blood transfusions and colorectal cancer prognosis exists, two questions ought to be answered. First, whether this association is causal or simply indirect and second, if causal, whether such a detrimental effect can be prevented [7]. The only way to control adequately for confounding by indication is to perform a randomised trial [8]. Obviously, randomisation between transfusion and no transfusion in patients would be the most interesting design scientifically, but is, of course, ethically unacceptable. We designed a randomised clinical trial in which we used predeposit autologous blood transfusions to reduce the exposure to allogeneic blood transfusions and thereby reduce the immunological changes which follow those transfusions. The main objective was to investigate whether a predeposit autologous blood donation programme is able to reduce the risk of recurrence and to improve survival in surgically treated colorectal cancer patients as compared with the standard transfusion policy.

PATIENTS AND METHODS

Patients were enrolled in 15 medical centres from August 1986 to November 1991, after written informed consent had been obtained. Patients with a potentially curative resection of a colorectal carcinoma were eligible if they fulfilled the criteria for autologous blood donation [9] and were randomly assigned to either the allogeneic group or the autologous group. Patients randomised into the autologous group had to donate two units of blood prior to surgery. The collected blood was separated into packed red cells and fresh frozen plasma, which were available during operation. Patients in the allogeneic group received standard packed cells. The transfusion procedure was the same in both randomised groups: transfusions were allowed to be given if blood loss exceeded 500 ml or if the haemoglobin concentration fell below 10.5 g/dl (6.5 mmol/l). Tumours were staged according to the Turnbull [10] modification of the Dukes' classification. En-bloc resected tumours with adjacent organ fixation were not staged as Dukes' D. Patients were followed up

Correspondence to O.R.C. Busch.
O.R.C. Busch, R.L. Marquet and J. Jeekel are at the Department of Surgery, University Hospital Rotterdam-Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam; and W.C.J Hop is at the Department of Epidemiology and Biostatistics, Erasmus University, Rotterdam, The Netherlands.

using a standard programme. More detailed information on the study design has been published elsewhere [11].

Cumulative percentages of patients with recurrent disease, and for local recurrence and distant metastases separately, were calculated according to the Kaplan–Meier method [12]. Comparisons were made by using the log-rank test. Cox-regression was used to perform multivariate analyses [13]. Two-sided P value ≤ 0.05 was considered the limit of statistical significance.

RESULTS

Of the 475 patients with colorectal carcinoma, 423 patients underwent curative surgery. The characteristics of these patients are shown in Table 1 and there were no significant differences between the groups. The median blood loss was 775 ml in the allogeneic group and 750 ml in the autologous group, and did not differ significantly. Of the 216 allogeneic patients, 94 (44%) did not receive transfusions and 122 (56%) did. In the autologous group, 49 (24%) of the 207 patients did not need transfusions, 102 (49%) received only autologous transfusions, and 56 (27%) received both autologous and allogeneic transfusions. A significant reduction in the exposure to allogeneic blood in the autologous group was achieved by the predeposit donation programme [14].

As previously reported, there was no significant difference between the groups [11]; the disease-free survival at 4 years was 66% in the allogeneic group and 63% in the autologous group ($P = 0.93$). Comparable differences were found in overall survival and colorectal cancer specific survival. Using Cox-regression, adjusting for various factors, randomisation was not a factor influencing prognosis. Whether a patient received blood transfusions or not appeared to be a significant determinant of prognosis in this model. The rate of recurrence, adjusted for Dukes' stage, was increased by a factor of 2.1 ($P = 0.004$) in transfused patients. The disease-free survival of the transfused ($n = 280$) versus the non-transfused patients ($n = 143$) is shown in Figure 1. Percentages without recurrence were 59% and 73% at 4 years, respectively ($P = 0.001$).

Table 1. Characteristics of the patients who underwent curative surgery

Characteristic	Allogeneic group ($n = 216$)	Autologous group ($n = 207$)
Median age, years (range)	68 (33–88)	65 (31–88)
Sex		
Male	119 (55%)	124 (60%)
Female	97 (45%)	83 (40%)
Tumour location		
Ascending colon	23 (11%)	13 (6%)
Flexures and transverse colon	11 (5%)	15 (7%)
Descending colon and sigmoid	63 (29%)	58 (28%)
Rectosigmoid and rectum	119 (55%)	121 (58%)
Dukes' classification		
A	53 (25%)	55 (27%)
B	85 (39%)	80 (39%)
C	78 (36%)	72 (35%)
Histological differentiation		
Well	35 (16%)	27 (13%)
Moderate	155 (72%)	159 (77%)
Poor	25 (12%)	20 (10%)
Adjacent organ fixation	15 (7%)	17 (8%)

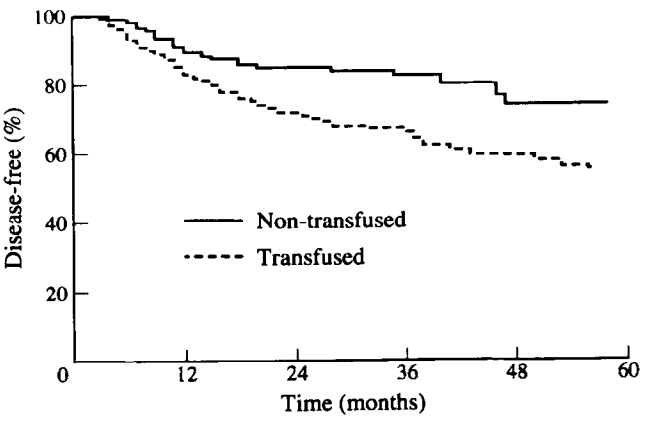

Figure 1. Actuarial percentages of patients without recurrent disease comparing non-transfused and transfused patients ($P = 0.001$).

Subdividing the group of transfused patients into the different types of transfusion in Cox regression showed that the influence of transfusions on recurrence was of the same magnitude for all types of transfusions; Dukes' stage adjusted relative recurrence rates were 2.3 ($P = 0.001$) for only allogeneic transfusions, 1.8 ($P = 0.044$) for only autologous transfusions and 2.5 ($P = 0.009$) if both types of transfusions were given. These rates were not significantly different from each other. For transfused patients, no relationship with the number of transfusions received could be demonstrated.

In further exploring the observed blood transfusion effect, the incidence of recurrence was investigated separately for local recurrence and distant metastases. The cumulative percentage of patients having distant metastases in the non-transfused and transfused group did not differ significantly and at 4 years were 25% and 27%, respectively (Figure 2).

However, the cumulative percentage of patients having local recurrence was significantly less in the non-transfused group as compared with the transfused group ($P = 0.0006$); the percentages at 4 years were 3% and 20%, respectively (Figure 3). Comparing the different types of transfusions, it was found that

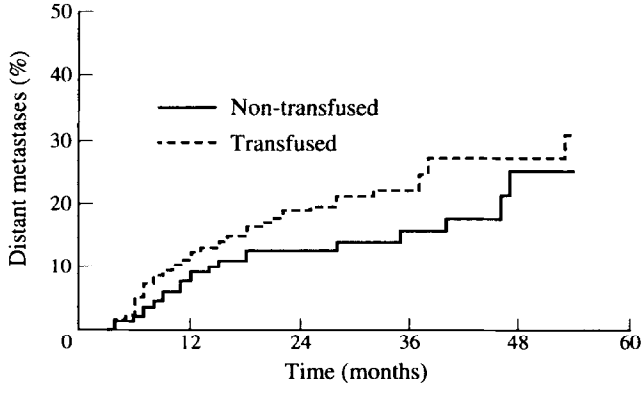

Figure 2. Cumulative percentages of patients having distant metastases comparing the non-transfused and the transfused group (not significant).

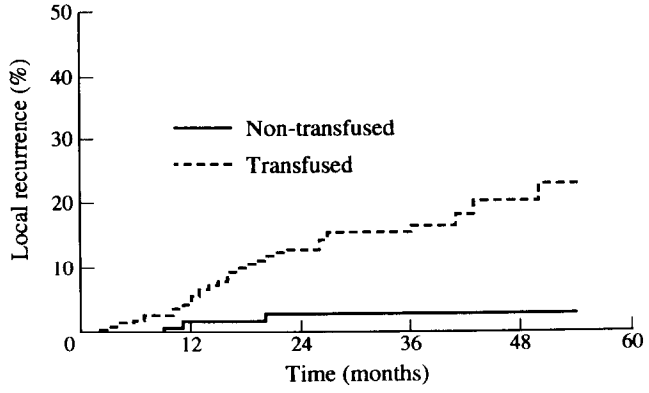

Figure 3. Cumulative percentages of patients having local recurrence comparing the non-transfused and the transfused group ($P = 0.0006$).

the incidence of local recurrence did not differ significantly between the various transfusion groups.

In multivariate analysis, allowing for various factors including tumour location in the rectum, the rate of local recurrence was significantly elevated in the transfused group as compared with the non-transfused group (relative rate 5.2; $P = 0.008$). No increased risk of distant metastases was found in transfused patients.

DISCUSSION

The results of our study show that the use of predeposit autologous blood either to avoid or to reduce the exposure to allogeneic blood did not lower the recurrence rate in patients who had received curative surgery for colorectal cancer, as compared with the use of allogeneic blood alone. The same applied to the survival of the patients. In agreement with several retrospective studies, the recurrence rate was higher in patients who had been transfused, as compared with those who did not need transfusions. We found that the increase in the risk of recurrence was of the same magnitude for patients transfused with allogeneic blood as for those patients who received only autologous blood [11, 15].

According to the intention-to-treat principle, we conclude from this randomised study, that the use of a predeposit autologous blood donation programme does not improve the prognosis in colorectal cancer patients. Apparently, it does not diminish putative detrimental effects of standard allogeneic blood transfusions in these patients.

This study also shows that the relationship between blood transfusions and the increased risk of recurrent disease is due to an increased risk of local recurrences [16]. No association was found between blood transfusions and the incidence of distant metastases. Apart from Dukes' stage and blood transfusions, another prognostic factor, when considered alone, only affecting local recurrence and not metastatic disease, was an operation for a rectal tumour, as compared with an intra-abdominal tumour. However, although it is known that resections of rectal tumours are associated with larger amounts of blood loss and, therefore, require more transfusions, multivariate analysis showed blood transfusions to be an independent factor on the incidence of local recurrence.

The finding that the negative association between blood transfusions and colorectal cancer prognosis is the same for allogeneic as for autologous blood, and the finding that this transfusion effect is only present for the incidence of local recurrence, suggests that this relationship is not causal but indirect. Therefore, we conclude that it is not the blood transfusions as such, but rather the circumstances that necessitate transfusions that are the real determinants of prognosis.

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Acknowledgements——We thank M.A.W. Hoynck van Papendrecht for coordinating this trial for many years and we thank the principle investigators of the participating centres for enrolment of the patients: R.U. Boelhouwer, I. Ziekenhuis, Rotterdam; E.D.M. Bruggink, C.-W. Ziekenhuis, Nijmegen; C.J. van Duin, De Wever Ziekenhuis, Heerlen; J.J. Jakimowicz, C. Ziekenhuis, Eindhoven; C.K. Jongsma, Havenziekenhuis, Rotterdam; B.L.A.M. Langenhorst, Academisch Ziekenhuis Dijkzigt, Rotterdam; F.T.T. Liem, C. Ziekenhuis, Den Bosch; W.S. Meijer, St. C. Ziekenhuis, Rotterdam; J.J. Petit, Zeeweg Ziekenhuis, IJmuiden; K.M. Rigg, Medical School, University of Newcastle Upon Tyne, U.K; M.K.M. Salu, Zuiderziekenhuis, Rotterdam: Th.J. van Straaten, St. Joseph Ziekenhuis, Veldhoven; B.C. de Vries, Westeinde Ziekenhuis, Den Haag; W.F. Weidema, Reinier de Graaf Gasthuis, Delft; J.C.J. Wereldsma, St. Franciscus Ziekenhuis, Rotterdam. This work was supported by grants from the Dutch Cancer Society (KWF; No. 86-13) and the Dutch Foundation for Preventive Medicine (Preventive Funds: No. 28–1953).