immunosuppressive therapy affects the course of *pre-existing* tumours. Penn studied the recurrence rates of pre-existing malignancies that occurred in renal transplant recipients [3]. In a group of 78 patients a tumour was diagnosed and/or treated at an average period of 3 months after transplantation. Interestingly, 63% did not develop recurrences during an average follow-up period of 53 months. This figure underlines the negligible influence of the immune system with regard to the progression of existing tumours, even in a situation of marked immunosuppression.

CLINICAL TRIALS

Blood transfusions administered during cancer surgery are given for various reasons which by themselves may influence cancer prognosis. These transfusion-associated variables may function as confounding factors when the relationship between transfusions is studied. In a nutshell, this is the difficulty in establishing the existence of a deleterious effect of blood transfusions. In evaluating the impact of various clinical studies, it is important to realise that the susceptibility for confounding factors is clearly associated with the type of study which is performed. This susceptibility is high in retrospective studies, moderate in prospective observational studies and low in prospectively randomised studies.

Up to now 31 observational and three prospectively randomised, controlled, clinical trials on the effect of blood transfusions on recurrence rate and survival in patients with colorectal cancer have been published. Of the 31 studies, 16 reported a detrimental effect of transfusions and 15 failed to detect any transfusion effect. Recently, Vamvakas performed a meta-analysis on 28 of these observational studies (21 retrospective, seven prospective) [4]. He found that the association of peri-operative transfusion with a negative outcome was significant when all retrospective studies were combined. However, in the case of the prospective studies, the transfusion effect did not attain significance. Of the seven teams of investigators who had conducted the prospective investigations, only one team concluded that transfusions had a deleterious effect. Three prospective, randomised controlled trials have been performed thusfar. In two studies, performed by ourselves [5] and Heiss and colleagues [6], transfusion of predonated autologous blood was compared with allogeneic blood. In the study by Houbiers and associates leucocyte-poor allogeneic blood was compared with leucocyte-depleted allogeneic blood [7].

The results of our own study comprising 475 patients were clear: there was no significant difference in disease-free survival or patient survival rates at 4 years between the two groups. However, we found that the risk of recurrence was increased in transfused patients, either allogeneic or autologous, as compared with patients who had not required a transfusion. Thus, regardless of their type, transfusions appeared to be associated with a poor prognosis, probably because of the (confounding) circumstances that necessitated them.

In the second randomised trial from The Netherlands, Houbiers and associates compared the impact of leucocyte-poor versus leucocyte-free transfusions in 697 patients. No differences were found with regard to survival, disease-free survival or cancer recurrence rates after an average follow-up period of 36 months. Similar to the autologous transfusion trial, non-transfused patients had a longer 3 year survival than patients who had been transfused with blood of any sort.

The third randomised trial was performed by Heiss and colleagues in 120 patients and had a comparable format to the autologous trial mentioned above. After a median follow-up duration of 22 months no significant difference in disease-free survival was noticed. Multivariate analysis showed that the need for allogeneic blood was an independent predictor of tumour recurrence.

The results of these randomised trials indicate that two alternatives for allogeneic blood, namely autologous blood or leucocyte-depleted blood, do not lead to a better prognosis for patients with colorectal cancer. In our opinion this is the only clinically relevant conclusion that can be drawn because it reflects the intention of the trials.

Therefore, we hold the view that allogeneic blood is acceptable for patients with colorectal cancer, simply because the alternatives have been demonstrated to not be beneficial.

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EVIDENCE FOR AN ALLOGENEIC BLOOD TRANSFUSION-ASSOCIATED IMMUNOSUPPRESSION

CONCERNS OVER allogeneic transfusions in cancer surgery stem from the belief that the resulting immunosuppression, in some cases, affects prognosis. Do these transfusions cause immunosuppression? There are observational studies, which analysed the immunosuppression following allogeneic blood transfusion by correlating postoperative infections to transfusion. As shown in Table 1, these studies entail very different clinical situations from elective abdominal surgery to trauma patients and heart surgery. It has to be mentioned that most of these studies were performed retrospectively and neither the transfusion trigger point nor the specificity of the blood product were given. Also, the transfusion frequency between these studies was very variable from 23 to 65%. However, transfusion of allogeneic blood was found to be the strongest prognostic variable in comparison with all other tested confounders. For postoperative infections, no other known factor shows such a strong and reproducible statistical coherence.

Table 2 summarises the results of nine studies. In these studies, blood transfusion was a significant risk factor for postoperative infections. In seven of these studies allogeneic blood was associated with an increased infection rate. In the study of Busch and colleagues the infection risk was also increased when autologous blood was transfused [22]. A comparison of all these different studies is problematic because the blood products (whole blood, erythrocyte concentrates, leucocyte-depleted erythrocytes) and also the transfusion triggers were very heterogeneous. Whereas the trials of Murphy and colleagues [16, 17], Vignali and associates [21] and Fernandez and co-workers [19] have to be analysed separately, better prerequisites for comparison are given in the colorectal cancer studies. However, these studies show heterogeneity in respect of the study design (open prospective or randomised) and used blood products (whole blood, buffy-coat-poor-erythrocytes, and leucocyte-depleted erythrocytes).

In seven of nine performed studies allogeneic blood transfusion was significantly associated with higher postoperative infection rates. In our randomised study [25] of resected colorectal cancer patients we saw a significant difference of infections with 12% in the autologous blood group versus 27% in the allogeneic blood group ($P = 0.036$). In multivariate Cox analysis this was found to be an independent prognostic risk factor for postoperative infections, as were performance status (ASA index) and tumour localisation. These results could only be explained by the significant larger amount of allogeneic transfusions in the randomised allogeneic blood group, as all other confounders for postoperative infections were equally distributed between both study groups [25].

The study designed by Busch and Jeekel was very similar to ours, but they did not find an independent transfusion effect [22]. The authors' conclusion was 'that not the blood transfusion itself but confounding surgical variables were causal for this statistical association'. This contradictory finding might be caused by methodological differences [26]. Most important, the Dutch trial was multicentric in 16 hospitals of two countries. Important confounders for postoperative infections, e.g. general condition of patients, technical difficulties of operation, operation time and qualification of the surgeon, were not controlled. Furthermore, a clear a priori definition of what counted as 'postoperative infection' was not formulated [26].

Three randomised studies tried to control the allogeneic blood effect by generating immunological neutral blood products by leucocyte depletion [27–29]. In two large monocentric randomised studies Jensen and colleagues found a significant association of allogeneic blood transfusion with postoperative infections, which could be decreased by leucocyte depletion [28, 29]. However, in a multicentric study with similar study design performed by Houbiers and associates in 16 hospitals in The Netherlands, no diminished infection rate by leucocyte depletion could be detected [27]. Again the results are comparable to the findings in the study design

Table 1. *Clinical observational studies of the relationship between blood transfusion and postoperative infection risk*

First authors [ref.]	Study design	No. of patients	Operation	% transfusion frequency	Transfusion product	Postoperative infections	*P* value*
Miholic [1]	Prospective	246	CABG ($n = 162$); valve ($n = 84$)	–	–	Defined infection	0.0006 (valve)
Ottino [2]	Retrospective	2579	CABG; valve; CHD	–	–	Sternal infection	0.0310*
Nicholas [3]	Prospective	145	Bowel perforation	–	–	Defined infection	0.0519
Dawes [4]	Retrospective	137	Colon perforation	–	–	Abdominal infection	0.0004
Wobbes [5]	Retrospective	548	Abdominal surgery	40.5	ery conc.	Septicaemia	0.0030 (>3 units)
Maetani [6]	Retrospective	565	Abdominal surgery	–	–	Organ failure	< 0.0010
Dellinger [7]	Prospective	126	Penetrating abdominal injuries	–	–	Defined infection	< 0.0001
Dellinger [7]	Retrospective	212	Penetrating abdominal injuries	–	–	Defined infection	< 0.0001
NORGAS [8]	Prospective	1537	Elective abdominal surgery	23.2	–	Defined infection	< 0.0001
Graves [9]	Retrospective	594	Thermal injuries	–	–	Pneumonia, wound infection	< 0.0500
Tartter [10]	Retrospective	169	Morbus Crohn's disease	55.0	–	Defined infection	0.0007
Pinto [11]	Retrospective	196	Gastric cancer	–	–	Defined infection	0.0100
Jensen [12]	Prospective	311	Colorectal cancer	65.0	–	Defined infection	< 0.0010
Dellinger [13]	Prospective	240	Open fractures	38.3	–	Defined infection	< 0.0030*
Agarwal [14]	Prospective	5366	Trauma patients	25.0	ery conc.	Defined infection	< 0.0010
Tartter [15]	Prospective	343	Colorectal cancer	41.7	–	Defined infection	< 0.0010
Murphy [16]	Retrospective	238	CABG	70.5	–	Defined infection	0.0170

CABG, coronary artery bypass grafting; CHD, congenital heart disease; ery conc., erythrocyte concentrate. *Multivariate analysis.

Table 2. Comparison of the relationship of allogeneic blood transfusion versus autologous blood transfusion (or leucocyte-depleted allogeneic blood) for postoperative infection risk

First authors [ref.]	Study design	No. of patients	Type of surgery	% Transfusion frequency	Transfusion product	Transfusion trigger	Postoperative infection rate	*P* value
Murphy [17]	Retrospective ('case-control')	84	TEP	100	ery conc./ whole blood	–	3% autologous blood ($n=34$) 32% allogeneic blood ($n=50$)	0.0029
Triulzi [18]	Open prospective	109	Spinal surgery	–	allog. ery conc./ autol. ery conc./ whole blood	–	20.8% allogeneic blood ($n=24$) 3.5% no allogeneic blood ($n=85$)	0.0160
Fernandez [19]	Retrospective	376	Orthopaedic surgery	32.4	whole blood/ ery conc.	–	5% no blood ($n=122$) 5% autologous blood ($n=140$) 6.9% allogeneic blood ($n=72$) 11.9% autol./allogeneic blood ($n=42$)	0.0010
Jensen [12]	Randomised	197	Colorectal cancer	52.8	whole blood/ leucocyte-depl. whole blood	Hkt < 0.35 Hb < 7.2 nmol/l	2% without blood ($n=93$) 2% filtrated/allogeneic blood ($n=48$) 23% allogeneic blood ($n=56$)	< 0.0100
Houbiers [20]	Randomised	697	Colorectal cancer	64.0	leucocyte-depl. ery conc./ery conc.	–	35% filtration/allogeneic blood ($n=337$) 32% allogeneic blood ($n=360$)	0.0010
Vignali [21]	Open prospective	161	Colorectal cancer	53.0	autol. whole blood allog. ery conc/ whole blood	–	9% no blood ($n=75$) 14% autologous blood ($n=36$) 33% allogeneic blood ($n=48$)	< 0.0050
Busch [22]	Randomised	475	Colorectal cancer	67.0	autol.ery conc./ allog.ery conc.	Hb < 10.5; blood loss > 500 ml	27% autologous blood ($n=236$) 25% allogeneic blood ($n=239$)	< 0.0010*
Heiss [23]	Randomised	120	Colorectal cancer	75.0	autol.ery conc./ allog. ery conc.	Hb < 10.0	12% autologous blood ($n=58$) 27% allogeneic blood ($n=62$)	0.0470
Jensen [24]	Randomised	589	Colorectal cancer	44.1	leucocyte-depl. ery/ery conc.	Hkt < 0.70 Hb < 7.0 nmol/l	11.4% filtered/allogeneic blood ($n=290$) 30.1% allogeneic ($n=299$)	< 0.05

TEP, hip prosthesis; ery conc., erythrocyte concentrate; leucocyte-depl., leucocyte-depletion; allog., allogeneic, autol., autologous; Hkt, haematocrit; Hb, haemoglobin. **P* significant for blood transfusion, independent of blood modality (autologous or allogeneic).

using autologous blood transfusion. A significant allogeneic transfusion effect which was shown in very well controlled monocentric trials was not reproducible in a multicentric design. The most important methodological problem in the multicentric studies was the lack of control of variations in important confounders.

ASSOCIATION BETWEEN ALLOGENEIC TRANSFUSIONS AND WORSE PROGNOSIS

Since 1982 when Burrows and Tartter [30] reported for the first time the prognostic effect of allogeneic transfusion in colorectal cancer surgery, more than 60 studies from different settings in surgical oncology have been published. Studies concerning colorectal cancer surgery represented the majority. Despite this large amount of published data, the hypothesis of a direct prognostic impact of allogeneic blood transfusion is still discussed controversially. Whereas most of the published studies demonstrated a negative prognostic effect of allogeneic blood transfusion, other contradictory results have been published indicating no independent prognostic value. Most of the studies were performed without an adequate control group, so the interpretation of the results with respect to confounding variables is very difficult. The number of patients might be of particular importance, as in studies with a significant transfusion effect as the number of patients was on average 40% larger than in studies without effects [31].

Two large meta-analyses published in 1993 covered most of the published data for colorectal cancer surgery [32, 33]. The corresponding conclusion was that allogeneic blood transfusion was significantly associated with prognosis. The study of Chung and colleagues [32] summarised 20 studies with more than 5000 patients. Twelve studies performed a multivariate Cox regression analysis in which 11 found allogeneic blood transfusion to be an independent prognostic variable. Seventeen studies yielded enough information for the calculation of the cumulative relative risk. Fifteen of these 17 studies found a positive correlation between allogeneic transfusion and poor tumour prognosis (relative risk > 1.0). This was seen in an increased relative risk of tumour recurrence to 1.8 (95% confidence interval (CI) 1.30–2.51), a tumour specific death rate of 1.76 (95% CI 1.15–2.66) and a general death rate of 1.63 (95% CI 1.12–2.38). Vamvakas and Moore [33] collected data from 11 published colorectal cancer studies which they evaluated by defined statistical quality criteria. The cumulative relative risk was significantly increased to 1.37 (95% CI 1.20–1.56) (chi-square 22.71; $P = 0.000$).

Table 3. *Meta-analysis of* 60 *observational studies by cancer site* [31]

Cancer site	No. of studies	*Q* statistic*	*P* value	RR	95% CI–RR
Colorectal	28	62.2	< 0.001	1.49	1.23–1.79
Breast	8	2.8	0.90	1.06	0.90–1.24
Head and neck	7	3.8	> 0.75	3.62	2.15–6.08
Lung	6	3.9	> 0.50	1.30	1.02–1.66
Prostate	6	6.0	0.25	1.51	1.13–2.01
Stomach	5	11.2	0.025	2.44	1.60–3.71

RR, relative risk; CI, confidence interval. *Hypothesis of homogeneity of effects reported from individual studies for each cancer site. If $P < 0.05$ the hypothesis of homogeneity is rejected.

In a following meta-analysis Vamvakas [31] analysed the data from 60 studies performed between 1982 and 1994, which covered different tumour localisations, if at least five publications were available. With the exception of breast cancer, the accumulated allogeneic blood effect was significant. For colorectal cancer, 22 studies were analysed and again the relative risk was significantly increased to 1.49 (95% CI 1.23–1.79). Also this meta-analysis indicated the problem mentioned above that the confounding parameters varied largely between different studies (Table 3). However, these results clearly argue for the existence of a significant blood transfusion effect in colorectal cancer surgery. Studies where such an effect could not be found might be the result of the natural variability of biological phenomena in epidemiological studies.

In the monocentric randomised study of our group we saw a significant transfusion effect. The tumour recurrence rate was 42% less in the autologous blood group. The difference in long-term survival (median follow-up 68 months) between both randomised study groups showed a clear trend but did not reach significance ($P = 0.067$). A reason for this might be the limited number of patients and especially the fact that, similar to the observation in the Dutch trial, one-third of all patients in the autologous blood group needed additional allogeneic blood transfusions. A subgroup analysis of patients with limited transfusion up to two units of blood was able to eliminate this interfering effect of additional allogeneic transfusion in the autologous blood group. The result of this analysis showed a significant prognostic difference [23]. In a study of gastric cancer, we found evidence that the allogeneic transfusion effect might be transmitted by its influence on minimal residual disease after curative tumour resection, an unknown and uncontrolled phenomenon in all former studies, which significantly influenced long-term prognosis [34]. If the 104 curatively resected patients of this study were stratified according to the immunocytochemical detection of disseminated tumour cells in bone marrow as the indicator of minimal residual disease, a significant allogeneic transfusion effect was found only in patients with detection of tumour cells in bone marrow ($P = 0.048$; relative risk 2.91; 95% CI 1.51–5.61). This was not seen in patients without disseminated tumour cells. This finding may be able to explain in part the contradictory results observed by the various clinical trials. As early as 1989 it was discussed that the reported differences in clinical studies might be due to incompletely controlled prognostic factors including the extent of undetected dissemination of micrometastatic disease [35].

CONCLUSION

Allogeneic blood transfusions are still absolutely essential for many types of medical and surgical therapies of tumour patients. Therefore, the clinical consequences of the immunosuppressive allogeneic blood effect on peri-operative infections and tumour recurrence after curative resection should be considered very seriously. New developments, such as leucocyte depletion of blood products, haematopoietic stimulation by erythropoietin or intra-operative cell-saving, might be future alternatives and substitutes for allogeneic transfusions. However, the clinical benefit and efficiency of these methods still has to be proven. This is also true for autologous transfusions, as a short-term pre-operative autologous blood donation programme is not feasible for many patients with primary colorectal carcinoma.

Estimates of the mortality associated with allogeneic transfusion immunomodulation suggest that, even if only 10% of the association is causal, immunomodulation could be quantitatively more significant than the total of all other currently identified risks of allogeneic transfusions [36]. Nevertheless, opponents of this suggested allogeneic blood transfusion effect can still argue that the discussed consequences are not due to the transfusion itself but to the undefined clinical variables that lead to transfusion. Thus, blood transfusion may act as a surrogate marker for higher risk. However, the opinion that the association of allogeneic transfusions is coincidental with worse clinical outcome is contradicted for several reasons. Firstly the association between allogeneic transfusion and postoperative infections and worse prognosis is seen in most studies and is not significant in only a minority. Potential confounding variables were almost always less statistically significant than allogeneic transfusion itself and none of them seem to act in a surrogate manner. Furthermore, all studies showed that blood transfusions are given non-systematically. So it is very unlikely that blood transfusion acts as a surrogate variable for a yet unknown and undetermined relevant clinical variable. There are extensive experimental data supporting the hypothesis that the underlying immunological mechanism induces a down-regulation of macrophage and T-cell function.

Furthermore this impaired cellular function was reproducibly demonstrated in different animal models *in vivo* and might be able to influence the establishment of minimal residual disease after curative tumour resection towards disseminated metastatic disease.

Despite the fact that the question concerning the allogeneic blood effect cannot be answered finally on the basis of available scientific facts, we think that the clinical potential of this effect calls for our awareness to use all our surgical, anaesthesiological and transfusional probabilities to reduce allogeneic blood transfusion to a minimum in elective colorectal cancer surgery.

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INTRODUCTION

THERE IS no doubt that the introduction of blood transfusions has allowed surgeons to perform successfully even the most delicate operations. However, the risks associated with the use of allogeneic blood are not negligible, and can represent a substantial hazard for exposed patients [1].

In 1981, Gantt hypothesised that the immunosuppressive effect of blood transfusions, largely used in renal transplantation, could also be applicable to cancer patients [2]. The mechanism of this recognised effect in dialysis patients is still obscure and mostly involves a generalised suppression of cell-mediated immunity [3–5]. However, both in normal and in cancer surgery, a specific immunosuppression attributable to transfusions is not always documented and, in a sizeable percentage of cases, even an immune reaction is recorded. However, transfusions are being increasingly associated with postoperative infections, a sign of immune suppression [6–8]. Moreover, it is debatable whether the immunological status of cancer patients can be compared with that of allograft recipients, who differ largely with respect to the type and duration of antigen expression [9].

Many animal studies have been performed with the aim of improving the understanding of the role of blood transfusions on cancer growth, but their results are conflicting due to large differences in timing and route of transfusions, as well as in tumours and species tested [10, 11]. Specifically, these studies have failed to identify the blood component(s) responsible for the immunosuppressive effect: red blood cells, white blood cells, platelets and plasma proteins have all been involved [12, 13].

CLINICAL STUDIES

In the last 17 years many authors have investigated the relationship between the outcome of patients with various cancers and blood transfusions, the greatest amount of research having been conducted on colorectal cancer: our recent meta-analysis has identified 131 papers published up to December 1996, leading to 32 clinical studies analysing colorectal cancer recurrence in over 11 000 patients [14]. These studies were widely differing in their populations (especially in the proportion of patients with rectal cancer), designs (only seven were randomised trials) and type of analysis. However, nearly two-thirds of them reported a significant detrimental effect of transfusions on recurrent tumours and 11 of 19 found transfusions to have an independent effect on recurrence after controlling for possible confounders with multivariate analyses [14]. The pooled estimates from these studies showed a harmful transfusion effect, with overall odds of recurring 68% higher in the transfused patients (odds ratio (OR) 1.68, 95% confidence interval (CI) 1.54–1.83). Stratified analyses confirmed the overall results (Figure 1) and agreed with our initial findings, reported in 1991 [15], and the more recent findings of Chung and colleagues [16] and Vamvakas and Moore [17]. In particular, Vamvakas and Moore computed an effect which was similar to ours when only prospective studies were taken into account and their subsequent meta-analysis 'for explanation' led them to conclude that a possible effect of confounding could not completely explain the unadjusted transfusion effect [18].

Four randomised controlled trials have been performed with the specific aim of verifying the detrimental association between transfused blood and colorectal cancer recurrence. Tartter designed his study to test the effect of allogeneic packed red cells and showed a 2.5 times larger detrimental effect of blood transfusions [19]. Two of the other three studies compared the allegedly less immunogenic autologous blood to allogeneic blood: Heiss and colleagues showed a two times higher risk of recurrence with transfusions, although their 95% CI was not significant [20], and Busch and associates highlighted a detrimental effect of transfusions (OR = 1.85, 95% CI 1.22–2.82), although they attributed the increased transfusion risk to the conditions necessitating the transfusions [21]. Finally, Houbiers and co-workers showed a non-significant effect of allogeneic leucocyte-free blood on recurrence (OR = 1.23, 95% CI 0.87–1.73) but, surprisingly, they did find a difference in survival [22]. The latter studies have raised some methodological questions, especially about the feasibility of effective autologous blood donation programmes, given the high proportion of patients receiving