Original article

Influence of perioperative blood transfusion on the prognosis of patients with gastric cancer receiving anticancer chemotherapy

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Abstract

Background. The deleterious effect of blood transfusions on survival has been reported in patients with cancers of various organs. However, it remains unclear whether there is any adverse effect of blood transfusion when the patients are administered anticancer drugs after surgery for gastric cancers.

Methods. Data from patients with gastric resection for advanced gastric cancer were retrospectively analyzed to determine the influence of perioperative blood transfusion on the survival rate. All patients were administered anticancer drugs (mitomycin C [MMC] and tegafur-uracil [UFT]). Sixty-nine (33%) of 208 patients received blood transfusion perioperatively, while 139 patients (67%) did not receive transfusion. Multivariate analysis of clinicopathologic prognostic factors, including blood transfusion, was performed. Lymphocyte subsets were measured to investigate the immunosuppressive effect of blood transfusion.

Results. The 5-year survival rate was 48.8% in the 69 transfused patients and 66.9% in the 139 non-transfused patients ($P < 0.01$). Cox's multiple regression analysis showed that, when patients received anticancer drugs, perioperative blood transfusion was not a significant factor affecting survival after the gastric cancer surgery. However, the CD4/CD8 ratio at 3 months after the surgery was significantly lower in the transfused group than in the non-transfused group.

Conclusion. Blood transfusion did not affect the survival of operated patients who received postoperative adjuvant chemotherapy. However, the finding that the ratio of CD4/CD8 after surgery was significantly higher in the non-transfused group than in the transfused group supports the notion that transfusion causes broad-spectrum immunosuppression.

Key words Gastric carcinoma · Blood transfusion · Adjuvant chemotherapy · Survival · Immunosuppression

Introduction

There have been many reports regarding the effect of perioperative blood transfusions on the prognosis of patients with a variety of digestive organ cancers [1–5]. Although some studies report a deleterious effect of blood transfusions on survival; others report no harmful effects [6–8]. The effect of perioperative blood transfusion remains controversial. However, in all except one [1] of the studies related to gastric cancer that we found, there was no description of whether the patients were administered anticancer drugs after surgery. Anticancer chemotherapy has been widely employed for patients with gastric cancer, because of its improving effect on prognosis [9–10]. We therefore conducted a retrospective multicenter study in patients with gastric cancer to define whether perioperative blood transfusion affected the prognosis after they had curative surgery and postoperative chemotherapy, compared with a group who had no perioperative transfusion and curative surgery with the same protocol about postoperative chemotherapy.

Patients and methods

We carried out a prospective randomized multicenter study of supportive treatment after curative resection of gastric cancer in 259 patients with stage II and stage III disease between February 1988 and July 1990. The main focus of that study was a comparison between chemotherapy (tegafur-uracil [UFT]) only and chemotherapy plus immunotherapy (OK-432). The results of the study were reported in another journal by Konishi et al. [11]. When we initiated that study, we also planned to concomitantly investigate the effect of perioperative blood transfusion on prognosis. All medical records that we collected included data pertaining to blood transfusion services, that is, types of blood products transfused, number of units, and date of transfusions.

Patients

Two hundred and fifty-nine patients were diagnosed with advanced gastric cancer, stage II or stage III between February 1988 and July 1990. They were divided into two groups, a chemotherapy group and chemotherapy with immunotherapy group, before subtotal or total gastrectomy was performed as a curative procedure. The patients in the chemotherapy group were injected with 0.4 mg/kg of mitomycin C (MMC) intravenously soon after surgery and received UFT (300 mg/day) orally from 2 weeks to 2 years postoperatively. UFT (300 mg) contained tegafur and uridine. Patients receiving chemotherapy with immunotherapy received the same chemotherapy as the former group but also received OK-432 (5KE) injections intracutaneously once every 2 weeks for 2 years postoperatively. We obtained informed consent for participation in the study from each patient. Fifty-one of the 259 patients were excluded from our study because of protocol violations in treatment rules, early stage of gastric cancer, or lack of sufficient data. Sixty-nine (33%) of the remaining 208 patients received blood transfusions perioperatively, and 139 patients (67%) did not. Citrate-phosphate-dextrose (CPD) blood was given to 6 patients, mannitol-adenine-phosphate (MAP) blood to 54 patients, and both to 3 patients. The blood product in the remaining 3 patients was not identified. The timing of the transfusions is shown in Table 1.

Immunological assay

Blood samples were obtained from all patients preoperatively and again 1 month, 3 months, and 12 months postoperatively and were delivered to the same laboratory (BML, Tokyo, Japan). Lymphocyte subsets in each blood sample were measured by an enzymatic method, using a commercially available kit.

Statistics

The Log-rank and Wilcoxon test were used to compare the survival rates of the two groups, the blood transfusion group and the no-transfusion group. Multivariate analysis was done using Cox's proportional hazards model. The unpaired *t*-test was used to compare parameters of immune status between the two groups. Data values are expressed as means $\pm$ SD. *P* values less than 0.05 were regarded as significant.

Results

Survival

The survival rate 5 years postoperatively was 66.9% in the no-transfusion group, and 48.8% in the blood transfusion group; this difference was significant. Survival curves are shown in Fig. 1. Univariate analysis suggested that blood transfusion was a strong predictor of overall survival. Multivariate analysis was performed, using data from all patients. The factors analyzed were blood transfusion, age, the largest diameter of the tumor, and the stage of the cancer. Other factors such as sex, tumor location, histological type, administration of OK-432, and extent of resection were not analyzed, because these were found not to be significant on stepwise analysis using the Statistical Analysis System ([SAS], SAS Institute, Cary, NC, USA).

The multivariate analysis results are shown in Table 2. As can be seen, stage proved to be an independent predictor of overall survival. Blood transfusion was not a predictor of survival.

Immunologic assay

The values for CD3, CD4, CD8, and Leu-7 did not differ between the blood transfusion group and the no-transfusion group. At 3 months, the CD4/CD8 ratio was

Fig. 1. Kaplan Meier survival curves for transfused and non-transfused patients. Survival was significantly lower in the transfused patients ($P < 0.002$). Log-rank, $P = 0.0013$; Wilcoxon, $P = 0.0016$. BT, Blood transfusion

Table 1. Timing of blood transfusions performed in 69 patients

	Preoperation	During operation	Postoperation	Perioperative
Number of patients	22	55	21	69

Table 2. Multivariate analysis of factors affecting the overall survival of patients with gastric cancer, by Cox's proportional hazards model

	Risk ratio	Lower CL	Upper CL
Blood transfusion	1.282	0.792	2.066
Stage	2.491	1.783	3.571
Largest diameter of tumor	1.051	0.980	1.120
Age	1.013	0.990	1.037

CL, Confidence limits

Fig. 2. Postoperative changes in CD4/CD8 ratio. At 3 months (M), the ratio was significantly higher in the no-transfusion group than in the blood transfusion group. Error bars show SD. * $P < 0.05$. Preop, Preoperative

significantly higher in the no-transfusion group (1.83 ± 0.98 ; $n = 40$) than in the blood transfusion group (1.48 ± 0.64 ; $n = 16$) ($P < 0.05$). Changes in the CD4/CD8 ratio after surgery are shown in Fig. 2.

Discussion

Opelz et al. [12] reported the effect of blood transfusions on cadaver kidney graft survival, and suggested that blood transfusion could create a state of immune tolerance. Since the time that Gantt [13] speculated that blood transfusion affected the prognosis of cancer patients, many clinical studies have found evidence suggesting a possible detrimental effect of blood transfusion on survival in patients with various cancers [1–5].

Kaneda et al. [1] reported that patients with gastric cancer, given blood transfusions during the perioperative period after curative resection had a significantly higher rate of recurrence compared with patients not given blood transfusions. Sugezawa et al. [14] also

reported that perioperative blood transfusion was one of the factors associated with poorer survival of patients with gastric cancer. Kampschöer et al. [15], using multivariate analysis with the Cox model, did not find any difference between 5-year survival rates in transfused and non-transfused patients, although in the subgroups of patients with stage Ib, II, and IIIb disease, there was an adverse tendency toward decreased survival in the transfused patients. Moriguchi et al. [6], using the same multivariate analysis, revealed the lack of any relationship between perioperative blood transfusion and survival time of patients who underwent curative resection for advanced gastric cancer. Fong et al. [2] showed, by multivariate analysis using the proportional hazards model, that blood transfusion was an independent predictor of poor outcome in patients with gastric cancer. The adverse effect of allogeneic blood remains unclear.

However, none of these reports, except that by Kaneda et al. [1], considered the adjuvant chemotherapy that is frequently administered after curative resection of gastric cancer. It has been demonstrated that postoperative adjuvant chemotherapy with tegafur improves survival in gastric cancer patients [9–10]. The effect of adjuvant chemotherapy has to be considered an important predictor of survival if patients are administered these drugs. Kaneda et al. [1] reported that prognosis was significantly poorer in the transfused group than in the non-transfused group when no adjuvant therapy was given, whereas the difference was not significant after adjuvant therapy. As theirs was a comparative study on a rather small number of patients receiving adjuvant therapy, the findings were not conclusive.

The Swiss Group for Clinical Research [16] recently reported the association between blood transfusion and survival in a randomized multicenter trial of perioperative adjuvant portal chemotherapy in patients with colorectal cancer. They found that the survival outcome was worse for patients receiving transfusions after curative resection for colonic cancer, and that patients not given transfusions who received perioperative adjuvant portal chemotherapy had the best prognosis.

We showed that perioperative blood transfusion did not influence survival rates in gastric cancer patients who received radical surgery combined with postoperative adjuvant chemotherapy. This indicates that there was no immunosuppressive effect of blood transfusion on survival in patients who received adjuvant chemotherapy with the same protocol. However, our observation that, at 3 months there was a significantly higher ratio of CD4/CD8 in the no-transfusion group of patients with the adjuvant chemotherapy than in the blood transfusion group supports the notion that transfusion causes broad-spectrum immunosuppression. The finding that blood transfusion did not affect the survival of

surgical patients receiving postoperative adjuvant chemotherapy is probably explained in terms of the adjuvant chemotherapy having a much greater effect on the prognosis than the immunosuppression of the blood transfusion.

Our results indicate the need for a prospective study of blood transfusion and its effect on the prognosis of patients with gastric cancer who do not receive any postoperative adjuvant chemotherapy.

Acknowledgments The authors thank Mr. Yasuhiko Tsujino for his technical help in statistical analysis.

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