Original Article

Effect of Substituting Allogenic Blood Transfusion with Autologous Blood Transfusion on Outcomes after Radical Oesophagectomy for Cancer

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Background: The oncologic benefit of avoiding allogenic blood transfusion in oesophageal cancer resection has not been studied.

Methods: The medical records of 68 patients (Auto group) who underwent a potentially curative oesophageal cancer resection without allogenic blood transfusion from 1996 to 1999 receiving 800 g of autologous blood donated preoperatively, and 97 patients (Allo group) who underwent the same operation with allogenic blood transfusion from 1990 to 1995 were compared.

Results: There were no differences in age, gender, stage of disease, number of retrieved nodes, or perioperative hemoglobin concentration between the two groups. The survival of the 45 patients with nodal involvement in the Auto group was better than that of the 59 patients in the Allo group (p=0.0435), and the survival of the 35 patients with T3 or T4 lesions in the Auto group was better than that of the 61 patients in the Allo group (p=0.0408). According to logistic regression analysis, allogenic blood transfusion correlated with tumour recurrence in patients with either nodal involvement or a T3-4 lesion. The natural killer cell activity remained higher in the Auto group than in the Allo group (p<0.05).

Conclusion: Avoidance of allogenic blood transfusion favorably effected the survival of patients with oesophageal cancer at risk for recurrence. (Ann Thorac Cardiovasc Surg 2005; 11: 293–300)

Key words: oesophageal cancer, allogenic blood transfusion, autologous blood transfusion, prognosis

Introduction

Although the safety of allogenic blood transfusion has increased as a result of improved screening of donors and of donated blood, the risks associated with allogenic blood transufusion, such as infection by blood-borne pathogens and graft-versus-host disease, cannot be avoided completely.[1-3] Consequently autologous blood transfusion has attracted attention as a safer alternative to allogenic blood transfusion.

In the mid-1980's, autologous blood transfusion was instituted for elective surgery in the fields of cardiac, gynecologic, and orthopaedic surgery.[4,5] It has been reported perioperative allogenic blood transfusion is associated with tumour recurrence and decreased survival in surgery for gastrointestinal malignancies, as well as an increased incidence of postoperative infection.[1,2] However, autologous blood transfusion was instituted in surgery for gastrointestinal malignancies later than in surgery for benign disorders because malnutrition prohibited preoperative blood donation in the patients with gastrointestinal malignancy. Oesophagectomy and reconstruction, as well as extensive lymphadenectomy, necessitates blood transfusion more commonly than radical operations for other gastrointestinal malignancies.[6] Therefore, a substantial amount of autologous blood must be prepared to avoid allogenic blood transfusion in cases of oesophageal resection.

Use of autologous blood transfusion for oesopha-

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gectomy became feasible with the advent of recombinant human erythropoietin (rHu-EPO), which strongly stimulates erythropoiesis.[7-9] However, the value of avoiding allogenic blood transfusion in oesophageal cancer surgery has received little attention.[10-12] Our department has routinely performed autologous blood transfusion for radical oesophagectomy since 1996, when rHu-EPO became generally available in Japan.[13] In this paper, we retrospectively examined whether avoiding allogenic blood transfusion by the use of autologous blood transfusion favourably effected the clinical course after macroscopically curative oesophagectomy by comparing patients who did and did not receive an allogenic blood transfusion.

Subjects and Methods

Patients

The medical records of 245 consecutive patients with squamous cell carcinoma of the thoracic oesophagus, who had undergone oesophagectomy and lymphadenectomy of the neck, chest, and abdomen without adjuvant therapy in our department from 1990 to 1999, were reviewed. Patients with enlarged intraabdominal paraaortic nodes on computed tomography, fixed cervical nodes, or multiorgan involvement did not undergo a 3-field lymph node dissection because these findings were felt to represent advanced disease that was not curable surgically. Sixty-nine consecutive patients operated on in 1996 or later and who fit the following conditions were included in the study, 1) no history of allogenic blood transfusion, 2) no synchronous or other antecedent malignancy, 3) haemoglobin concentration of 11.0 g/dL or higher, 4) 75 years of age or younger, and 5) absence of serious concomitant medical condition, such as liver cirrhosis. These patients each donated 800 g of blood preoperatively. One patient required allogenic blood transfusion. The other 68 patients (99%) who did not undergo allogenic blood transfusion were classified as the Auto group. One hundred five consecutive patients operated on in 1998 or earlier and who fit the same conditions underwent the same operation without blood donation. Eight patients were managed without blood transfusion. The other 97 patients (93%) received an allogenic blood transfusion were classified as the Allo group.

Surgical procedure and perioperative management

Autologous blood transfusion consisted of 800 g of blood donated 14 and 7 days, 400 g each, before surgery. Ferric oxide (40 mg), vitamin B12 (250 μg), and rHu-EPO (6,000 IU) (Epoetin beta, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) were administered intravenously 6 times over these 2 weeks. The donated blood was stored as whole blood with citrate-phosphate-dextrose at 2°C. Informed consent for autologous blood transfusion was obtained from all patients who donated blood. Standard leukocyte-poor red blood cell concentrates collected in citrate-phosphate-dextrose preservative were matched and used for allogenic blood transfusion.

All patients underwent standardized oesophagectomy together with extended lymphadenectomy. Thoracic oesophagectomy and mediastinal lymph node dissection was performed through a right thoracotomy. Creation of a gastric tube perfused by the right gastroepiploic artery and abdominal lymph node dissection were performed through a laparotomy. Finally, cervical lymph node dissection and cervical oesophagogastric anastomosis were performed through a collar incision. Thoracic and abdominal epidural anesthesia was utilized for postoperative analgesia for 5 days.

Blood transfusion was considered when the operative blood loss exceeded 15.0 g/body weight (Kg) or the hematocrit decreased to less than 25% and tachycardia persisted after correction of hypovolemia and other conditions besides anemia. The indication for blood transfusion and the amount of blood transfusion were decided by the surgeon.

Factors compared

Patient characteristics, stage of the disease according to UICC classification system,[14] number of retrieved lymph nodes, survival, and postoperative complications were compared between the two groups. The risk factors for tumour recurrence also were studied. The activity of natural killer (NK) cells in the peripheral blood was determined by monitoring the release of radioactivity from ^{51}Cr-labeled K562 target cells[15] preoperatively and 1, 2, 3, 7, 14, and 30 days after surgery and was compared between 45 consecutive patients in the Allo group, and 58 consecutive patients in the Auto group.

Statistics

Values are expressed as the mean ± standard deviation. The Chi-square test was used to analyze intergroup differences in patient characteristics and clinicopathologic factors, and the incidence of complications. Student's unpaired *t* test was used to analyze intergroup differences in haemoglobin concentration, time of operation, operative blood loss, and number of retrieved nodes. The dif-

Table 1. Clinical and pathologic characteristics of patients

Factors		Allo group (n=97)		Auto group (n=68)		*p* value	
Gender	Male	74	(35)	56	(48)	0.439	(0.618)
	Female	23	(10)	12	(10)		
Age		62.4±7.9 years	(61.1±6.2 years)	61.4±8.4 years	(60.1±6.9 years)	0.398	(0.433)
Haemogrobin concentration (g/dl) (immediately before operation)		13.1±1.4	(13.0±1.6)	13.1±1.3	(13.2±1.6)	0.999	(0.794)
Operative blood loss		1,035±685 g	(816±553 g)	597±543 g	(639±577 g)	<0.001	(0.003)
Time of operation		535±130 min	(519±98 min)	473±77 min	(489±80 min)	<0.001	(0.114)
Retrieved nodes (number)		62±24	(66±25)	67±26	(63±26)	0.241	(0.678)
Location of tumour	Upper thoracic esophagus	14	(8)	11	(9)	0.909	(0.987)
	Middle thoracic esophagus	55	(26)	39	(35)		
	Lower thoracic esophagus	28	(11)	18	(14)		
Classification of tumour	Well differentiated SCC	17	(7)	11	(10)	0.298	(0.062)
	Moderately differentiated SCC	45	(21)	39	(35)		
	Poorly differentiated SCC	33	(17)	15	(19)		
	Other type	2	(0)	3	(3)		
Depth of tumour invasion	pTis-pT1	23	(14)	23	(21)	0.187	(0.535)
	pT2	13	(9)	10	(7)		
	pT3-pT4	61	(22)	35	(20)		
Lymph node metastasis	pN+	59	(29)	45	(38)	0.623	(0.999)
	pN–	36	(16)	23	(20)		
Stage of disease	p0	4	(0)	1	(1)	0.112	(0.550)
	pI	11	(8)	16	(14)		
	pIIA, B	37	(17)	21	(16)		
	pIII	44	(19)	29	(26)		
	pIV	1	(1)	1	(1)		

Figures as numbers of patients. Figures in parenthesis indicate number of patients in whom natural killer cell activity was measured.
Stage of disease was classified according to the Union Internationale Contre le Cancer classification system.
SCC, squamous cell carcinoma

ference in changes in NK cell activity was evaluated by two-way repeated ANOVA. The risk factors for recurrence were calculated by logistic regression analysis. Survival was calculated using the Kaplan-Meier method, and the significance was evaluated with the log-rank method. A *p* value less than 0.05 was considered to be significant.

Results

No adverse affect was recorded secondary to preoperative blood collection or administration of rHu-EPO, vitamin B12, and ferric oxide. There was no difference in the patient characteristics, preoperative haemoglobin concentration, stage of disease, or number of retrieved nodes (Table 1). Postoperative infection occurred in 34 and 21% of patients in the Allo and Auto group, respectively, but this difference was not significant (p=0.0794, Table 2). The follow-up periods for survivors were 1,535±778 days and 1,980±1,060 days in the Auto and Allo group, respectively. Twenty patients in Auto group had recurrent disease (hematogenous in 9, lymph node in 8, locoregional in 3). On the other hand, 41 patients in the Allo group had recurrent disease (hematogenous in 25, lymph node in 11, locoregional in 1 and dissemination in 4). The number of the patients with hematogenous recurrence in the Allo group was significantly larger than that in the Auto group (p=0.0165). Survival rate tended to be better in the Auto group than Allo group, but the difference was not significant (p=0.0629) when compared in all patients (Fig. 1). Survival in the Auto group was similar to that in the Allo group for patients without nodal involvement, whereas the survival of the 45 patients with nodal involvement in the Auto group was better than that of the 59 patients in the Allo group (p=0.0435, Fig. 2). Survival in the Auto group was similar to that in the Allo group for patients with the tumour that did not invade beyond the muscular layer, whereas the survival of the 35 patients with tumour invading the adventitia or deeper in the Auto group was better than that of the 61 patients in the Allo group (p=0.0408, Fig. 3). Characteristics were similar between the 35 patients in the Allo group and the 56 in the Auto group whose NK cell activity was monitored,

Table 2. Postoperative complications

Complications	Allo group (n=97) No. of patients	Auto group (n=68) No. of patients	*p* value
Recurrent laryngeal nerve palsy	8	9	
Arrythmia	1	1	
Pericardial effusion	1	0	
Chylothorax	1	1	
Infectious complications	33	14	0.0794
Pneumonia	19	10	
Wound infection	2	2	
Leakage	12	1	
Mediastinitis	0	1	
No complication	56*	46*	0.2545

*Three patients had 2 complications.

with the exception of operative blood loss (Table 1). The NK cell activity remained higher in the Auto group than in the Allo group ($p<0.05$, Fig. 4).

Discussion

The preoperative collection of 800 g of blood using rHu-EPO stimulation with ferric oxide and vitamin B12 supplementation caused no complications, including anemia, in any patients. Ninety-nine percent of the patients who donated blood underwent radical oesophagectomy without allogenic blood transfusion, whereas only 8% patients who did not donate did. Not only preparation of 800 g of autologous blood, but also reduction in operative blood loss may have reduced the need for allogenic blood transfusion. In a randomized study comparing blood loss in two methods of hepatic resection, the amount of blood lost during the study was less when compared to the historical control.[16] Therefore, the surgeon's awareness of managing patients with a limited amount of blood available for transfusion might itself have reduced the operative blood loss. In patients with cancer, many factors in addition to allogenic blood transfusion, such as time of surgery, amount of blood loss, stage of disease, and magnitude of the surgical procedure, relate to outcomes. The superiority of autologous over allogenic blood transfusion would be more clearly assessed by a randomized study. However, the randomization of patients for autologous or allogenic blood transfusion would be difficult, ethically and practically. Although oesophageal cancer is among the ten most common cancers in the world,[17] the incidence of potentially curative resection is less than that of gastric or colorectal cancer.[18,19] Additionally, the outcome of oesophagectomy is affected greatly by the surgeon's experience,[6] so a multi-institutional study would be difficult. Moreover, malnutrition and excessive surgical stress,[18] as well as the advanced age of a patient,[20] can prevent radical oesophagectomy from being, completed with only autologous blood transfusions, and to date only two retrospective studies have studied the question of autologous blood transfusion for oesophageal cancer resection.[7,13,21,22] Our study is also retrospective.

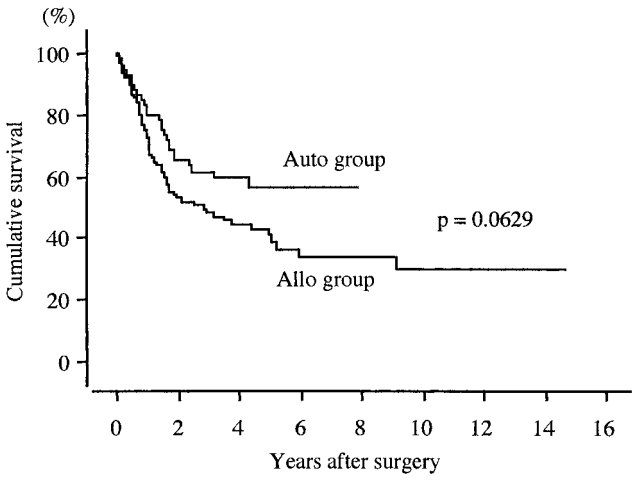

Fig. 1. Kaplan-Meier survival curves comparing survival after oesophagectomy with extended lymphadenectomy in patients who did and did not receive allogenic blood transfusion perioperatively.

However, all patients were treated by a single surgical team and operated on by a surgeon (Osugi H.) who had more than 10 years of experience.[6] Additionally, demographics and clinical characteristics in the two groups were similar, except for time of operation and operative blood loss.

Allogenic blood transfusion modifies postoperative

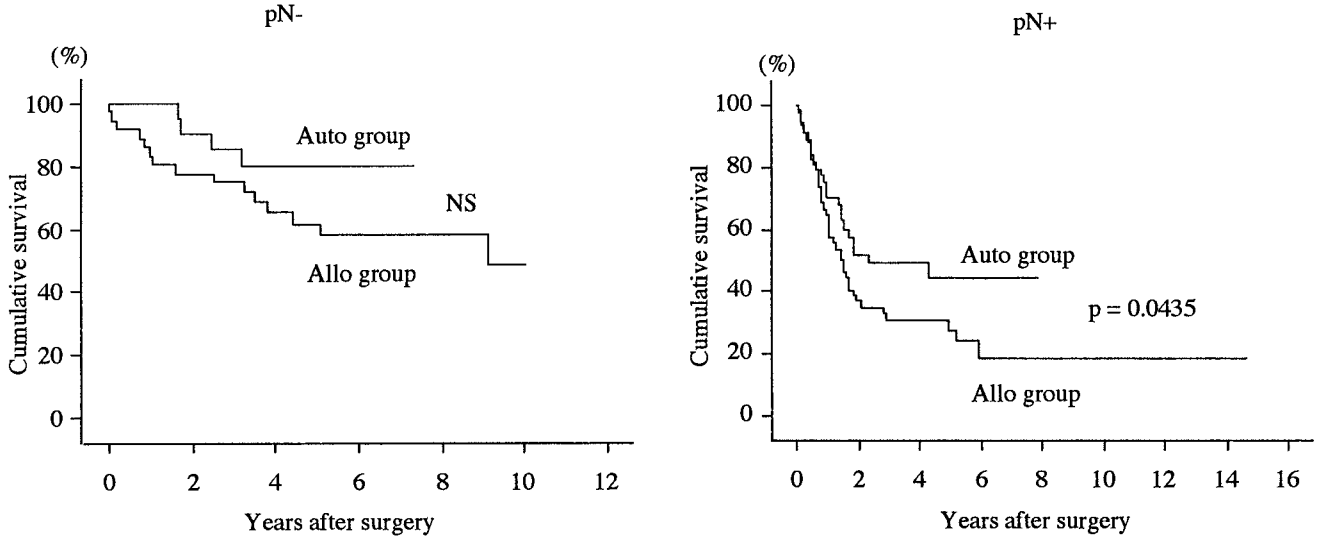

Fig. 2. Survival after oesophagectomy with extended lymphadenectomy stratified by presence of nodal metastasis.
NS, not significant

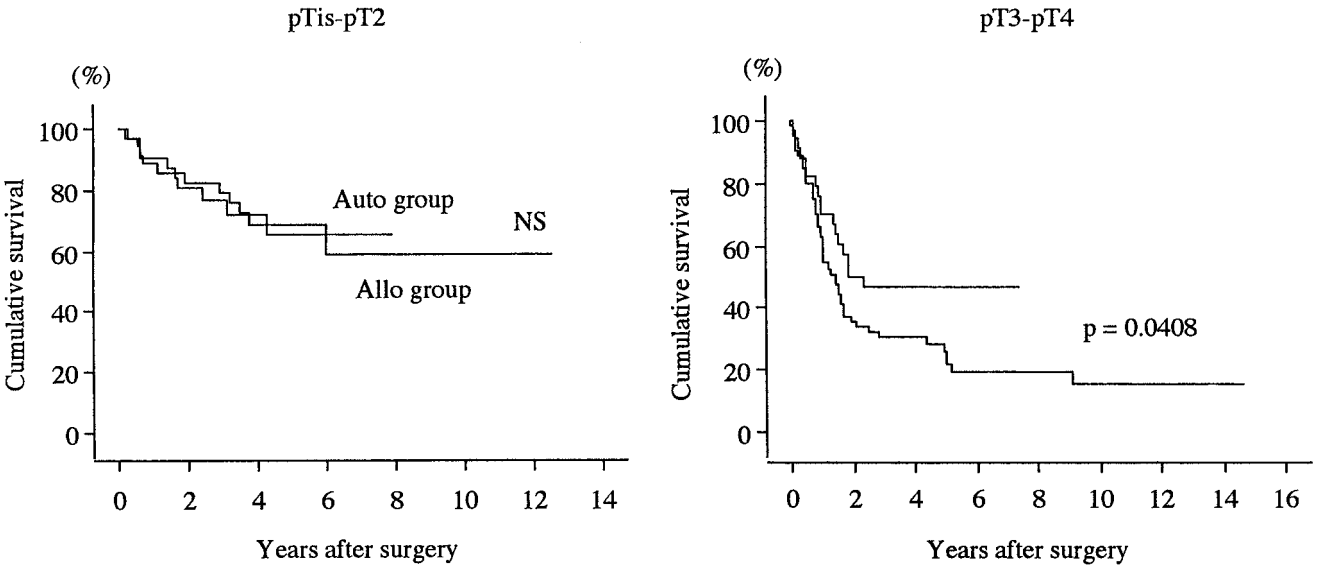

Fig. 3. Survival after oesophagectomy with extended lymphadenectomy stratified by tumour penetration.
NS, not significant

immunosuppression,[1-3] and the leukocytes and serum in transfused blood play an important role in modulating the immune response.[23-25] We used leukocyte-poor red blood cell concentrates for allogenic blood transfusion, which is probably immunosuppresive.[13] There are substantive studies concerning the effects of autologous blood transfusion in gastric and colorectal cancer resection. Some reports found that autologous blood transfusion is beneficial in terms of reducing infectious complications but others have not.[20,26-28] Duffy and Neal[27] performed a meta-analysis of the infection rate after resection of various type of gastrointestinal malignancy. They concluded that the risk of postoperative infection is greater in patients who underwent allogenic blood transfusion than in those who did not, with the odds ratio of 2.37. The high incidence of pulmonary complication associated with radical oesophagectomy is well documented,[18] especially when extended lymphadenectomy is performed concomitantly.[29] Kinoshita et al.[21] clearly demonstrated by logistic regression analysis that preoperative autolo-

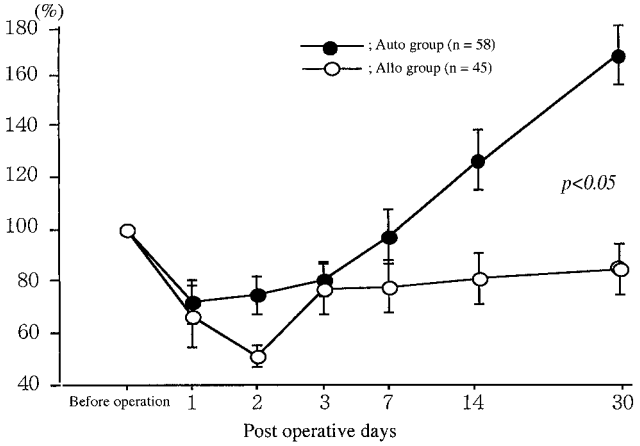

Fig. 4. Differences in natural killer cell activity in patients who received autologous and allogenic blood transfusions.

gous blood collection reduces the need for allogenic blood transfusion and avoidance of allogenic blood transfusion reduces the risk of infectious complications (11% vs. 27%). In our study, the incidence of infection was lower in the Auto group than the Allo group, but not significantly (p=0.062).

Immunosuppression caused by allogenic blood transfusion may be related to tumour recurrence. Some investigators have reported that allogenic blood transfusion is a risk factor for tumour recurrence after resection of gastric and colorectal cancer.[30-32] On the other hand, other investigators have found no effect of transfusion on survival.[33-35] In our study, overall survival in the Auto and the Allo groups were significantly different (p=0.0356). NK cell activity, which is inversely related to tumour progression experimentally,[36,37] is suppressed for a long-term period after allogenic transfusion.[20] In our study, the Allo group was followed longer than the Auto group. However, the follow-up period of 1,535±778 days in the Auto group seems to be sufficient for data analysis because most recurrences of oesophageal cancer occur within 24 months after oesophagectomy.[38] NK activity was suppressed for 3 days after oesophagectomy in both groups.

However, in the Auto group, the activity had recovered to the preoperative level by 7 days after surgery, whereas recovery in the Allo group was not documented until 30 days after surgery. This suppression may affect patients at risk for tumour recurrence more than those who are not. Bentzen et al.[39] found that colon cancer recurred more frequently after allogenic blood transfusion than after autologous transfusion in patients at risk for recurrence, stratified according to Duke's classification system. In our study, survival of patients who underwent allogenic blood transfusion was similar to those who did not in patients at low risk for recurrence, such as those without nodal involvement or with a preinvasive tumour. However, in patients at risk for recurrence, such as patients with nodal involvement or adventitial invasion, allogenic blood transfusion adversely affected survival (p=0.0435 and 0.0408, respectively).

Because neoadjuvant treatment has not been proven to prolong survival in a randomized study that included a large number of patients,[40] our treatment strategy is resection for any patients in whom resection may be curative.

In addition to the reduction in operative blood loss, the other reason why blood transfusions might have been avoided in our patients may have been that our patients had not received preoperative chemo- or radiotherapy. Although the difference was not significant, preoperative treatment tends to increase operative blood loss.[41] Theoretically, bone marrow suppression caused by neoadjuvant treatment interferes with recovery from anemia. Autologous blood transfusion initially was instituted with the idea of avoiding iatrogenic infection of unknown bloodborne pathogens, especially in patients expected to have a good prognosis.[42] However, avoiding immunosuppression caused by allogenic blood transfusion is another important consideration when treating patients with malignant disease. The adverse affects of allogenic blood transfusion should be taken into consideration when determining the treatment strategy for oesophageal cancer patients.

Oesophageal cancer resection often requires blood transfusion. However, preoperative blood donation makes it possible to complete radical oesophagectomy without allogenic blood transfusion. Avoidance of blood transfusion may reduce the incidence of postoperative infections and have a favourable effect on the survival of patients at high risk for recurrence.

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