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Intraoperative blood transfusion on long-term outcomes of liver transplantation for hepatocellular carcinoma

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ABSTRACT

Objective: To investigate the impact of intraoperative blood transfusion on the long-term outcomes of liver transplantation for hepatocellular carcinoma.

Method: Adult patients who had non-salvage liver transplantation at our center between January 2005 and December 2012 for hepatocellular carcinomas that were within the UCSF criteria and could not be resected or ablated were divided into groups with and without intraoperative blood transfusion. Comparisons were made between groups.

Results: Ninety-nine patients were included in the study. Sixty-two (62.6%) patients received intraoperative blood transfusion. Patients without transfusion were younger (54 vs. 56 years; $p=0.04$) and had a lower Model for End-stage Liver Disease score (11 vs. 14; $p<0.001$). More of them had stage-1 tumors (64.9% vs. 37.1%; $p=0.007$) and fewer of them had postoperative complications of grade IIIA or above in the Clavien-Dino classification (21.6% vs. 48.4%; $p=0.008$). The groups were comparable in hospital mortality (3.2% vs. 2.7%; $p=1.00$), 5-year overall survival (90.8% vs. 89.2%; $p=0.611$), and 5-year disease-free survival (90.5% vs. 89.2%; $p=0.835$). On multivariate analysis, postoperative complications of grade IIIA or above were associated with worse survival (hazard ratio 7.108; 95% confidence interval 1.455-34.712; $p=0.015$).

Conclusion: Intraoperative blood transfusion was shown to have no significant impact on the long-term outcomes of liver transplantation for hepatocellular carcinoma, whereas postoperative complications of grade IIIA or above were associated with worse recipient survival.

Introduction

It has been reported that blood loss and blood transfusion during hepatectomy for hepatocellular carcinoma (HCC) promote disease recurrence and worsen postoperative overall and disease-free survival [1-11]. Harmful effects of perioperative blood transfusions on recurrence of other malignancies have also been reported [12-25]. It is speculated that perioperative blood transfusions cause immunomodulation reactions and thus have a deleterious effect on the recurrence of malignancies and the survival of patients.

The proportion of patients who undergo liver transplantation for HCC is increasing and HCC comprises one third of the indications for liver transplantations in Asia [26]. Liver transplantation remains a surgical procedure associated with major bleeding despite recently improved understanding and management of coagulation defects [27, 28]. The association between blood transfusion and recurrence-free survival after transplantation for HCC remains controversial.

This retrospective study was conducted to investigate the relation between perioperative blood transfusion and overall and disease-free survival after liver transplantation for HCC.

Patients and Methods

Our objective was to investigate intraoperative blood transfusion requirement as a risk factor for overall survival after liver transplantation, and to identify independent risk factors associated with overall survival using logistic regression.

Included in the study were adult patients who had non-salvage liver transplantation at the Department of Surgery, The University of Hong Kong, for HCCs that were within the UCSF (University of California, San Francisco) criteria and could not be resected or ablated. The study period was from January 2005 to December 2012.

The strategies adopted for selection of patients with known HCC for transplantation have been described elsewhere [29, 30]. In brief, tumor evaluation was done with computed

tomography of the abdomen and thorax, in addition to radionuclide bone scan at initial diagnosis. In recent years dual-tracer [¹¹C-acetate and ¹⁸F-fluorodeoxyglucose (FDG)] positron emission tomography were performed to exclude extrahepatic metastasis. There was no mandatory waiting period prior to liver transplantation and bridging therapy with transarterial chemoembolization was offered to those listed for liver transplantation with reasonable liver function.

Trigger for the administration of packed red blood cells was not standardized and relied entirely on the assessment of the overall clinical situation by the individual highly experienced surgeons in charge. We used only allogenic blood for transfusion and cell-saved blood was not used for patients with known hepatocellular carcinoma.

Definitions

Blood transfusion: Only transfusion of red cell concentrate was regarded as blood transfusion. Transfusion of other blood products (fresh-frozen plasma, platelets, or albumin) was not considered blood transfusion.

Operative mortality: Death occurring within 30 days of transplantation.

Complication: Postoperative complications were defined and classified according to the modified Clavien-Dindo classification [31]. Briefly, grade I is any deviation from the normal postoperative course not requiring any special treatment. Grade II complications are those requiring pharmacological treatment. Grade III complications are complications that require surgical or radiological intervention with (IIIB) or without (IIIA) general anesthesia. Grade IV refers to life-threatening complications involving single (IVA) or multiple (IVB) organ dysfunction. Grade V is death of the patient.

As postoperative complication was concerned, the patients were divided into two groups: those with no complications or only grade-I or grade-II complications, and those with complications of grade III or above. In the case of multiple complications in a patient, the

complication grade was based on the most serious complication.

Statistical analysis

Continuous variables were expressed as medians and ranges and compared by the Mann-Whitney U test. Pearson's chi-squared test was used to compare categorical variables. Survival analysis was performed using the Kaplan-Meier method and compared between groups by the log-rank test. A multivariable analysis by Cox regression (step-wise forward model) was performed for variables reaching significance on univariate analysis that impacted upon overall survival. All analyses were performed by PASW Statistics for Windows, version 18.0 (SPSS, Chicago, IL, USA). Statistical significance was indicated by p values <0.05.

Results

A total of 99 patients underwent liver transplantation for HCC. The median follow-up period was 42.9 (0.9-108.1) months. Amongst them, 61 underwent living donor liver transplantation (LDLT) and 38 underwent deceased donor liver transplantation (DDLT). The median waiting time to transplantation was 0.89 (0.03-56) months for our LDLT patients and 7.98 (0.03 – 90) months for the DDLT patients. 9 (14.8%) and 18 (47.4%) underwent bridging therapy prior to the LDLT and DDLT respectively.

Intraoperative blood transfusion was given to 62 (62.6%) patients. A comparison of demographic and perioperative clinical data between patients with and without intraoperative blood transfusion is shown in Table 1.

Figure 1 and Figure 2 are Kaplan-Meier plots of the overall survival and disease-free survival of the patients respectively. Compared with their counterparts, patients who received intraoperative blood transfusion showed no differences in terms of hospital mortality (3.2% vs. 2.7%; p=1.00), 5-year overall survival (90.8% vs. 89.2%; p=0.611), and 5-year disease-free

survival (90.5% vs. 89.2%; $p=0.835$). The 1-year, 3-year and 5-year graft survival was 95.2%, 95.2% and 90.8% for the patients who received intraoperative blood transfusion and 94.6%, 89.2% and 89.2% for those without intraoperative blood transfusion ($p=0.611$).

Table 2 shows the results of univariate and multivariate analyses of risk factors associated with overall survival. On multivariate analysis, the presence of a postoperative complication of grade IIIA or above was the only factor associated with worse survival (hazard ratio 7.108; 95% confidence interval 1.455-34.712; $p=0.015$).

Discussion

It has been reported that blood loss and blood transfusion during hepatectomy for HCC promote disease recurrence and worsen postoperative overall and disease-free survival [1-11]. Similar findings have also been made with malignancies of the breast, the stomach, and the colon and rectum [12-25]. It is speculated that perioperative blood transfusions cause immunomodulation reactions and thus have a deleterious effect on the recurrence of malignancies and the survival of patients, which was demonstrated in recent studies [30-34].

Experimental animal models have suggested that immunomodulation associated with allogeneic blood transfusion is primarily related to the infusion of allogeneic leukocytes [35]. It may be mediated by allogeneic mononuclear cells, soluble mediators derived from white blood cells, and soluble HLA peptides circulating in allogeneic plasma [36]. Transfusion of allogeneic whole blood products has been shown to induce variations in certain immune functions [37, 38], such as reduced NK cell activity, T lymphocyte blastogenesis, and increased suppressor T lymphocyte activity, which may impair host resistance to infection and the spread of neoplastic cells.

Blood loss during liver transplantation is usually high due to portal hypertension and intra-abdominal varices as a consequence of end-stage liver failure, in addition to clotting

disorders related to liver failure. Even though emphasis has been placed on reducing blood loss during the procedure, it still carries a risk of excessive blood loss, which is associated with higher risks of mortality, infectious complications, postoperative multi-organ dysfunction, early surgical re-intervention, and reduced graft survival [32-41]. Rana et al. [42] recently reported that intraoperative blood loss was an important risk factor for mortality after liver transplantation. However, studies on the influence of intraoperative allogeneic blood transfusion on cancer recurrence and patient survival after transplantation for HCC are scarce, and the topic remains controversial [43].

In our current study, the long-term (5-year) overall survival and disease-free survival were similar between patients with and without intraoperative blood transfusion, which is different from results reported by studies on hepatectomy. There may be various reasons. Firstly, although all the patients had HCC, those who received hepatectomy and those who received transplantation were two distinct groups of patients. In HCC patients undergoing hepatectomy, those who need transfusion generally have larger lesions that either are close to the vena cava or require major resection, while those who do not need blood transfusion usually have smaller, more peripheral lesions that can be resected under close hemostatic control. Various factors (e.g. preoperative level of serum alpha-fetoprotein, tumor size, tumor number, tumor cell differentiation, and the incidence of vascular invasion or liver cirrhosis) could have biased the results of those studies. When clinicopathological biases were adjusted, the overall survival rates of transfused patients were not significantly lower than those of non-transfused patients [44, 45]. In our study, all the patients were within the UCSF criteria. Although the non-transfused group had significantly more stage-I tumors compared with the transfused group, preoperative level of serum alpha-fetoprotein, tumor size, tumor differentiation, and the incidence of vascular permeation were comparable between the two groups. The major determinant for blood transfusion might be more related to the Model for End-stage Liver Disease scores of the patients (a median of 14 in the transfused group

vs. 11 in the non-transfused group; $p < 0.001$) rather than the tumors.

Secondly, since all the transplant recipients were put on immunosuppressants in the postoperative period, the immunomodulatory effect of allogeneic blood transfusion might not be as significant as that in patients who received hepatectomy. However, despite the blood transfusions and the immunosuppressants, we were able to achieve a 5-year disease-free survival rate of 90.5% in the transfusion group and 89.2% in the non-transfused group ($p=0.835$).

Thirdly, in spite of the improvement in transplant techniques, blood loss during liver transplantation remains an issue. On the contrary, the problem of blood loss during hepatectomy has improved greatly. At our center, the overall transfusion rate for hepatectomy was 55.4% before 1999 but has reduced to 13.6% after 1999 [46]. A high-volume center in Japan also made a similar finding [47]. However, 63% of the transplant recipients in our current study required blood transfusion. The relatively small number of non-transfused patients has limited the power of the study.

There is another important finding in this study. The presence of a postoperative complication of grade IIIA or above was the only clinicopathological factor with an independent influence on overall survival. Postoperative complications may have adverse effects on the long-term outcomes of various kinds of surgery, including that for HCC and colorectal cancer [48]. In another study, specifically postoperative sepsis was shown to be an independent predictor of disease-free and overall survival after hepatic resection for colorectal liver metastasis [49]. The mechanism underlying the effects of postoperative complications on overall survival remains to be elucidated. It has been postulated that blood transfusion and septic complications might lead to a period of immunosuppression, which might in turn lead to disease recurrence and patient death [50]. In fact, previous studies have shown a correlation between blood transfusion and complication development [51-54]. Further clinicoimmunological studies would be helpful in elucidating exactly how postoperative complications increase the risk of poor long-term survival.

This study has a number of drawbacks. It has a retrospective nature, a small sample size, and a heterogeneous patient population. In addition, it is a single-center study with inevitable selection bias. Nonetheless, it has shed some light on the survival outcome of HCC patients with and without blood transfusion during liver transplantation.

Conclusion

Transfusion of allogeneic blood has been reported to be associated with potentially devastating complications such as infections, transfusion reactions, and pulmonary edema. However, this study has shown that perioperative blood transfusion may not be a poor prognostic factor for tumor recurrence and overall survival for recipients of liver transplantation for HCC. However, the adverse effect of serious postoperative complications on long-term survival outcome has highlighted the importance of good perioperative care and meticulous surgical techniques in the avoidance of morbidity.

Table 1. Comparison of demographic and perioperative clinical data of the two groups of patients

	With transfusion (n=62)	No transfusion (n=37)	P
Age (years)	56 (30-65)	54 (40-67)	0.040
Male : Female	48 : 14	34 : 3	0.065
Etiology			
Hepatitis B virus	45 (72.6%)	32 (86.5%)	0.055
Hepatitis C virus	10 (16.1%)	3 (8.1%)	
Hepatitis B and C viruses	1 (1.6%)	1 (2.7%)	
Cryptogenic	2 (3.2%)	0	
Alcoholic	2 (3.2%)	1 (2.7%)	
Autoimmune hepatitis	1 (1.6%)	0	
Primary biliary cirrhosis	1 (1.6%)	0	
Model for End-stage Liver Disease score	14 (6-37)	11 (6-17)	<0.001
Alpha-fetoprotein (ng/ml)	15 (1-11210)	25 (2-3114)	0.483
Number of tumor	1 (1-3)	1 (1-3)	0.034
Largest size of tumors (cm)	2.5 (0.9-5.5)	2.3 (1-6.5)	0.772
Vascular permeation	16 (25.8%)	9 (24.3%)	0.870
Differentiation			0.347
Well differentiated	19 (30.6%)	16 (43.2%)	
Moderately differentiated	34 (54.8%)	16 (43.2%)	
Poorly differentiated	5 (8.1%)	1 (2.7%)	
No data	4 (6.5%)	4 (10.8%)	
Tumor-node-metastasis staging			0.007
Stage I	23 (37.1%)	24 (64.9%)	
Stage II	39 (62.9%)	13 (35.1%)	
Live donor graft : Deceased donor graft	34 : 28	27 : 10	0.073
Graft weight (g)	727.5 (395-1800)	650 (350-1975)	0.316
Cold ischemic time (min)	144 (71-633)	120.5 (82-447)	0.114
Warm ischemic time (min)	50.5 (26-108)	53 (35-70)	0.356
Operation duration (min)	663 (300-1086)	671 (344-1027)	0.443
Blood loss (ml)	4500 (1000-30800)	1300 (500-2000)	< 0.001
Unit of blood transfusion	5 (1-56)	0	
Hospital mortality	2 (3.2%)	1 (2.7%)	1
Complication (Clavien-Dindo grade IIIA or above)	30 (48.4%)	8 (21.6%)	0.008
Hospital stay (d)	17 (8-84)	11 (1-65)	<0.001

Data are presented in median (range) or number (percentage).

Table 2. Results of univariate and multivariate analyses of risk factors associated with overall survival

Variable	Univariate analysis		Multivariate analysis		
	Hazard ratio (95% confidence interval)	P	Hazard ratio	95% confidence interval	P
Age	0.9986 (0.896-1.086)	0.780			
Sex	0.754 (0.157-3.631)	0.725			
Hepatitis B virus infection	0.867 (0.178-4.216)	0.860			
Hepatitis C virus infection	0.411 (0.083-2.034)	0.276			
Model for End-stage Liver Disease score	1.060 (0.984-1.142)	0.125			
Alpha-fetoprotein	1.000 (0.999-1.001)	0.747			
Graft type (live donor v. deceased donor graft)	1.063 (0.263-4.302)	0.932			
Blood transfusion	1.059 (0.995-1.128)	0.073			
Complication (Clavien-Dindo grade IIIA or above)	7.108 (1.455-34.712)	0.015	7.108	1.45-34.71	0.015
Cold ischemic time	1.000 (0.995-1.005)	0.963			
Warm ischemic time	1.011 (0.967-1.058)	0.620			
Operation duration	1.002 (0.999-1.006)	0.233			
Number of tumor	1.445 (0.549-3.804)	0.456			

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