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Impact of fresh frozen plasma transfusion on postoperative inflammation and prognosis of colorectal liver metastases

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ARTICLE INFO

Article history:
Received 26 March 2017
Received in revised form
4 August 2017
Accepted 28 September 2017
Available online 22 February 2018

Keywords:
Colorectal liver metastasis
Blood transfusion
Fresh frozen plasma
Inflammatory response

ABSTRACT

Background: Blood transfusion has been reported to be associated with immunomodulation and poor oncologic outcomes in several malignancies. The aim of the study is to investigate the influence of the use of fresh frozen plasma (FFP) on long-term outcomes in patients with colorectal liver metastases (CRLM) after hepatic resection.

Materials and methods: The study comprised 127 patients who had undergone first hepatic resection for CRLM between April 2000 and December 2013. We retrospectively investigated the influence of the use of FFP on disease-free survival as well as overall survival and assessed the impact of such a practice on postoperative inflammation markers.

Results: In multivariate analysis, more than four lymph node metastases of the primary cancer ($P = 0.001$), bilobar distribution ($P = 0.002$), and perioperative FFP transfusion ($P = 0.005$) were independent risk factors for cancer recurrence, while more than four lymph node metastases of the primary cancer ($P < 0.001$), presence of neoadjuvant chemotherapy ($P = 0.002$), and perioperative FFP transfusion ($P = 0.004$) were independent risk factors for poor overall survival. In patients who underwent FFP transfusion, tumor size ($P = 0.004$), anatomic resection ($P < 0.001$), duration of operation ($P = 0.039$), and intraoperative blood loss ($P < 0.001$) were significantly greater. Moreover, FFP transfusion was associated with a higher white blood cell level on postoperative day 3 ($P < 0.001$) and day 5 ($P = 0.010$) and lower serum C-reactive protein level on postoperative day 1 ($P < 0.001$) and day 3 ($P = 0.017$).

Conclusions: Perioperative FFP transfusion is independently associated with poor long-term outcomes in patients with CRLM after hepatic resection. FFP may have an influence on postoperative inflammation because of its immunosuppressive effects.

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https://doi.org/10.1016/j.jss.2017.09.030

Introduction

The liver is the organ to which colorectal cancer most frequently metastasizes, with 15%-25% of patients having synchronous colorectal liver metastases (CRLM) at presentation and further 25%-50% ultimately developing CRLM after resection of the primary tumor.[1] Hepatic resection is the most effective and potentially curative therapy for CRLM.[2-4] In both surgical and oncologic perioperative managements, significant advances have been made for the treatment of CRLM. However, intraoperative blood loss remains a significant concern in hepatic resection, which is associated with a rather high incidence of blood transfusions including red blood cell concentrate (RBC), fresh frozen plasma (FFP), platelet concentrate (PC), and albumin products.

Recent studies have reported that allogenic blood transfusion exerts immunomodulatory effects,[5-7] and blood transfusion may be associated with postoperative complications, earlier disease recurrence, and prognoses of malignancies.[8] Our previous study reported that FFP transfusion had a negative impact on the overall survival in patients with CRLM.[9] However, the relationship between FFP transfusion and cancer recurrence or the influence of FFP transfusion on postoperative inflammation is unclear.

Therefore, in this study, we retrospectively investigated the relationship between perioperative FFP transfusion and disease-free as well as overall survival in patients with CRLM after hepatic resection, and we assessed the immunological effect on postoperative inflammatory response.

Patients and methods

Patient selection

Between January 2000 and December 2013, 133 patients with CRLM underwent first hepatic resection at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Of them, six patients were excluded, two patients for the lack of data and four patients who were lost to follow-up, leaving the remaining 127 patients for this study. We performed a retrospective review of a prospectively maintained database of patients. This retrospective study was approved by the Ethics Committee of Jikei University School of Medicine (#21-121).

Treatment and patient follow-up

All patients underwent macroscopic curative resection for liver, lung, and lymph node metastases. Preoperative chemotherapy was given when liver metastases were unresectable or borderline resectable and discontinued for more than 6 wk before hepatic resection to reduce liver injury and bone marrow suppression by chemotherapy. The extent of hepatic resection was generally determined based on retention rate of indocyanine green at 15 min before surgery and hepatic reserve, as described by Miyagawa *et al.*,[10] and percutaneous transhepatic portal embolization was performed for patients with estimated residual hepatic volume of less than 30%. The type of resection was classified into two groups: anatomic resection (extended lobectomy, lobectomy, segmentectomy, or subsegmentectomy) and nonanatomic limited partial resection.

Recurrence of colorectal cancer was defined as newly detected local, hepatic, lung, or extrahepatic tumors by ultrasonography, computed tomography, or magnetic resonance imaging with or without an increase in serum carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9. For recurrent liver metastasis, repeated hepatic resection, local ablation therapy, or systemic chemotherapy was performed based mainly on number, size, and location of the recurrent liver tumors as well as hepatic functional reserve including the retention rate of indocyanine green at 15 min and remnant liver volume. For lung metastasis, limited partial lung resection or systemic chemotherapy was performed. For local recurrence, tumor resection, radiotherapy, or systemic chemotherapy was selected. As to chemotherapy, 5-fluorouracil (5-Fu)–based regimen was chosen as adjuvant and/or neoadjuvant chemotherapy before 2003. Since 2004, the patients received infusional 5-Fu/l-leucovorin with oxaliplatin and/or infusional 5-Fu/l-leucovorin with irinotecan. Since 2007, patients have received 5-Fu/l-leucovorin with oxaliplatin and/or 5-Fu/l-leucovorin with irinotecan with molecular targeting drugs.

Blood products use

Hemogram, chemistry profile, and blood coagulation were routinely measured for each patient preoperatively and on

Table 1 – Patient characteristics.

Factor	Mean ± SD or ratio	Range
Age (y)	64.9 ± 10.2	39-90
Gender (male:female)	91:36	
Primary site (colon:rectum)	79:48	
No. of lymph node metastases (<4:≥4)	102:25	
Timing of tumor (synchronous:metachronous)	67:60	
Neoadjuvant chemotherapy (yes:no)	27:100	
Tumor number (solitary:multiple)	64:63	
Tumor distribution (unilobar:bilobar)	93:34	
Tumor size (mm)	40.8 ± 30.0	4-200
Serum CEA (ng/mL)	180.2 ± 435.3	1.9-2428
Type of resection (anatomic: nonanatomic)	66:61	
Duration of operation (min)	353.9 ± 144.7	85-867
Intraoperative blood loss (g)	1147.7 ± 1890.5	0-19,155
RBC transfusion (yes:no)	43:84	
FFP transfusion (yes:no)	30:97	
PC transfusion (yes:no)	5:122	
Postoperative complications (yes:no)	39:88	

SD = standard deviation; No. = number.

Table 2 – Univariate and multivariate analyses of clinical variables in relation to disease-free survival after elective hepatic resection for colorectal cancer liver metastases.

Factors	*n*	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)					
≥65	65	1.326 (0.867-2.027)	0.193		
<65	62				
Gender					
Female	36	0.987 (0.613-1.588)	0.956		
Male	91				
Primary site					
Rectum	48	1.043 (0.676-1.608)	0.850		
Colon	79				
No. of lymph node metastases					
≥4	25	2.975 (1.587-5.575)	0.001	2.333 (1.425-3.820)	0.001
<4	102				
Timing of tumor					
Synchronous	67	1.321 (0.867-2.014)	0.196		
Metachronous	60				
Neoadjuvant chemotherapy					
Yes	27	1.475 (0.833-2.610)	0.183		
No	100				
Tumor number					
Multiple	63	1.510 (0.988-2.307)	0.057		
Solitary	64				
Tumor distribution					
Bilobar	34	2.061 (1.219-3.483)	0.007	2.098 (1.304-3.375)	0.002
Unilobar	93				
Tumor size (mm)					
≥50	33	1.101 (0.676-1.793)	0.700		
<50	94				
Serum CEA (ng/mL)					
≥20	52	1.293 (0.835-2.001)	0.250		
<20	75				
Type of resection					
Anatomic	66	1.165 (0.763-1.778)	0.480		
Nonanatomic	61				
Duration of operation (min)					
≥300	82	1.079 (0.695-1.677)	0.735		
<300	45				
Intraoperative blood loss (g)					
≥1000	52	1.031 (0.671-1.585)	0.888		
<1000	75				
RBC transfusion					
Yes	43	1.484 (0.942-2.338)	0.088		
No	84				
FFP transfusion					
Yes	30	1.737 (1.023-2.947)	0.041	1.977 (1.227-3.250)	0.005
No	97				
PC transfusion					
Yes	5	0.574 (0.215-1.534)	0.269		

(*continued*)

Table 2 – (continued)

Factors	n	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
No	122				
Postoperative complications					
Yes	39	0.923 (0.592-1.440)	0.725		
No	88				

CI = confidence interval; No. = number.

postoperative day 1, 3, and 5. Since 2003, the use of blood products and dose have been determined by the preference of the attending surgeons based on guidelines for administration of blood products by the Japanese Ministry of Health and Welfare issued in 1999,[11] as well as intraoperative blood loss, postoperative hemoglobin levels, platelet counts, serum albumin, and prothrombin time. FFP was transfused when prothrombin time was below 40% and hemorrhage was concerned.

Analyses of risk factors for recurrence and overall survival

At first, we investigated the relationship between clinicopathological variables and recurrence-free survival as well as overall survival after hepatic resection by univariate and multivariate analyses. The following 17 variables were evaluated: age, gender, primary site, number of regional lymph node metastases of primary colorectal cancer, synchronous or metachronous CRLM, status of neoadjuvant chemotherapy, number of tumors, tumor distribution, diameter of the largest tumor, serum CEA, type of resection, duration of operation, intraoperative blood loss, postoperative complications, and perioperative RBC or FFP or PC transfusion. Clinicopathological continuous variables were classified into two groups as follows for the log-rank test and the Cox proportional hazard regression model: age <65 or ≥65 y, number of lymph node metastases of the primary cancer <4 or ≥4, tumor size <50 or ≥50 mm, CEA levels before hepatic resection <20 or ≥20 ng/mL, duration of operation <300 or ≥300 min, and intraoperative blood loss <1000 or ≥1000 g, according to previous studies.[12,13]

Next, in order to assess the risk factors for perioperative FFP transfusion, we investigated the relationship between clinicopathological variables and perioperative FFP transfusion by univariate analyses. The following 16 factors were considered: age, gender, primary site, number of regional lymph node metastases of primary colorectal cancer, synchronous or metachronous CRLM, status of neoadjuvant chemotherapy, number of tumors, tumor distribution, diameter of the largest tumor, serum CEA, type of resection, duration of operation, intraoperative blood loss, postoperative complications, postoperative hospital stay, and perioperative RBC or FFP or PC transfusion. These analyses were performed according to method of previous study.[9]

Statistical analysis

Data are expressed as a mean ± standard deviation. Univariate analysis was performed using the Mann-Whitney's U test and Chi-square test. Univariate analysis of disease-free and overall survival was performed using the log-rank test. Multivariate analysis was performed using the Cox proportional regression model incorporating all variables with $P < 0.05$ on univariate analysis. All P values were considered statistically significant when the associated probability was less than 0.05. These analyses were conducted using IBM® SPSS statistics, version 20.0, (IBM Japan, Tokyo, Japan).

Results

Patients' characteristics

Patient characteristics are listed in Table 1 as a mean ± standard deviation and range. Among the study

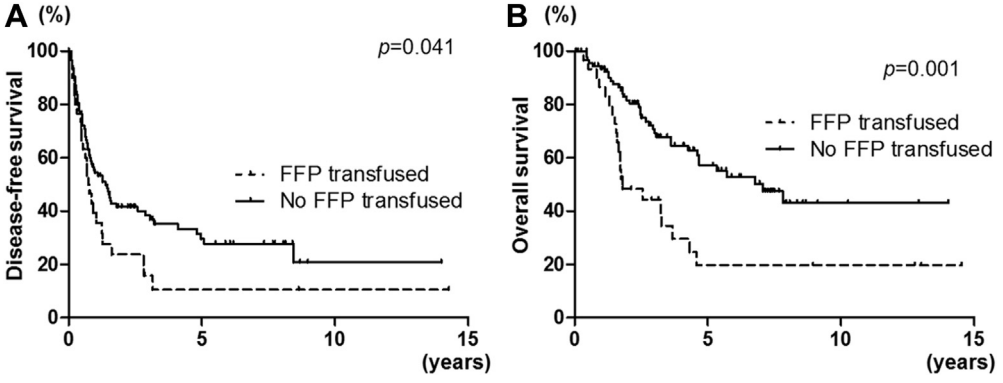

Fig. 1 – Kaplan-Meier curves of disease-free (A) and overall survival (B) after hepatic resection for CRLM. Perioperative FFP transfusion was significantly associated with worse disease-free survival ($P = 0.041$) and overall survival ($P = 0.001$).

Table 3 — Univariate and multivariate analyses of clinical variables in relation to overall survival after elective hepatic resection for colorectal cancer liver metastases.

Factors	*n*	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)					
≥65	65	1.079 (0.643-1.812)	0.773		
<65	62				
Gender					
Female	36	1.213 (0.672-2.189)	0.522		
Male	91				
Primary site					
Rectum	48	1.147 (0.678-1.941)	0.609		
Colon	79				
No. of lymph node metastases					
≥4	25	3.855 (1.883-7.893)	<0.001	3.998 (2.197-7.277)	<0.001
<4	102				
Timing of tumor					
Synchronous	67	0.995 (0.592-1.674)	0.986		
Metachronous	60				
Neoadjuvant chemotherapy					
Yes	27	2.185 (1.010-4.726)	0.047	3.038 (1.484-6.219)	0.002
No	100				
Tumor number					
Multiple	63	1.392 (0.829-2.338)	0.211		
Solitary	64				
Tumor distribution					
Bilobar	34	1.460 (0.774-2.754)	0.243		
Unilobar	93				
Tumor size (mm)					
≥50	33	1.865 (1.002-3.472)	0.049	1.737 (0.940-3.210)	0.078
<50	94				
Serum CEA (ng/mL)					
≥20	52	1.833 (1.081-3.109)	0.024	1.695 (0.955-3.011)	0.072
<20	75				
Type of resection					
Anatomic	66	1.278 (0.763-2.140)	0.351		
Nonanatomic	61				
Duration of operation (min)					
≥300	82	1.146 (0.665-1.975)	0.623		
<300	45				
Intraoperative blood loss (g)					
≥1000	52	1.516 (0.893-2.575)	0.124		
<1000	75				
RBC transfusion					
Yes	43	1.832 (1.053-3.188)	0.032	0.891 (0.453-1.751)	0.737
No	84				
FFP transfusion					
Yes	30	3.107 (1.606-6.012)	0.001	2.593 (1.358-4.943)	0.004
No	97				
PC transfusion					
Yes	5	1.555 (0.392-6.166)	0.530		
No	122				

(*continued*)

Table 3 – (continued)

Factors	*n*	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Postoperative complications					
Yes	39	1.061 (0.614-1.834)	0.832		
No	88				

CI = confidence interval; No. = number.

population, the mean age was 64.9 y with a range from 39 to 90 y, and 91 of them (71.7%) were male. Forty-three patients (33.8%) received RBC transfusion, 30 patients (23.6%) received FFP transfusion, and five patients (3.9%) received PC transfusion. In this study, the 5-y disease-free survival and overall survival rates after hepatic resection for CRLM were 24.7% and 47.7%, respectively.

Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after hepatic resection for CRLM

Table 2 lists the relationship between the clinical variables and disease-free survival after hepatic resection for CRLM. In univariate analysis, the disease-free survival was significantly worse in patients having more than four lymph node metastases ($P = 0.001$), bilobar distribution ($P = 0.007$), and perioperative FFP transfusion ($P = 0.041$, Fig. 1A). In multivariate analysis, more than four lymph node metastases ($P = 0.001$), bilobar tumor distribution ($P = 0.002$), and perioperative FFP transfusion ($P = 0.005$) were independent and significant risk factors for poorer disease-free survival.

Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after hepatic resection for CRLM

Table 3 lists the relationship between the clinical variables and overall survival after hepatic resection for CRLM. In univariate analysis, the overall survival was significantly worse in following conditions: in patients having more than four lymph node metastases ($P < 0.001$), presence of neoadjuvant chemotherapy ($P = 0.047$), tumor size $\geq$ 50 mm ($P = 0.049$), serum CEA $\geq$ 20 ng/mL ($P = 0.024$), and perioperative RBC ($P = 0.032$) as well as FFP transfusion ($P = 0.001$, Fig. 2A). In multivariate analysis, more than four lymph node metastases ($P < 0.001$), presence of neoadjuvant chemotherapy ($P = 0.002$), and perioperative FFP transfusion ($P = 0.004$) were independent and significant risk factors for poorer overall survival.

Univariate analysis of clinicopathological variables in relation to perioperative FFP transfusion after hepatic resection for CRLM

Table 4 lists the relationship between clinicopathological variables in patients with and without FFP transfusion. In univariate analysis, tumor size ($P = 0.004$), duration of operation ($P = 0.039$), intraoperative blood loss ($P < 0.001$), and postoperative hospital stay ($P = 0.003$) were significantly greater in patients who underwent FFP transfusion. The ratio of anatomic resection ($P < 0.001$) and presence of perioperative RBC ($P < 0.001$) and PC transfusion ($P = 0.001$) were significantly greater in patients who underwent FFP transfusion. Moreover, FFP transfusion was associated with higher white blood cell level on postoperative day 3 ($P < 0.001$) and day 5 ($P = 0.01$) (Fig. 2A) and lower serum C-reactive protein level on postoperative day 3 ($P < 0.001$) and day 5 ($P = 0.017$) (Fig. 2B). Preoperative aspartate aminotransferase ($P = 0.514$), alanine aminotransferase ($P = 0.264$), total bilirubin ($P = 0.693$), alkaline phosphatase ($P = 0.704$), and gamma-glutamyltransferase ($P = 0.59$) were comparable between the patients with or without FFP transfusion. In patients who underwent FFP transfusion, aspartate aminotransferase level on postoperative day 1 ($P < 0.001$), day 3 ($P < 0.001$), and day 5

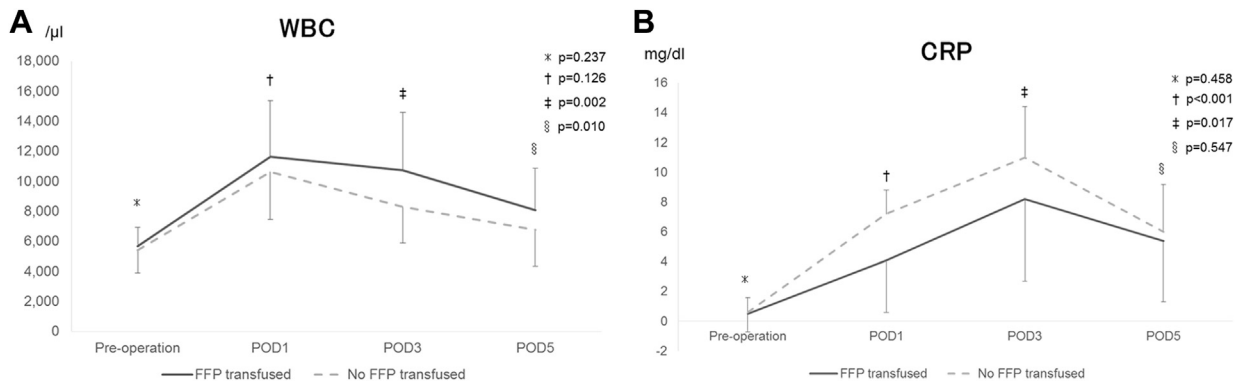

Fig. 2 – Postoperative inflammatory response of WBC count (A) and serum CRP level (B) in relation to perioperative FFP transfusion. Perioperative FFP transfusion was associated with significantly higher white blood cell level on POD 3 ($P < 0.001$) and 5 ($P = 0.010$) (A) and significantly lower serum C-reactive protein level on postoperative day 1 ($P < 0.001$) and 3 ($P = 0.017$) (B). CRP = C-reactive protein; POD = postoperative day; WBC = white blood cell.

Table 4 – Univariate analysis of clinical variables in relation to perioperative FFP transfusion after hepatic resection for colorectal cancer liver metastases.

Factors	FFP transfusion		P value
	Yes ($n = 30$)	No ($n = 97$)	
Age (y)	*62.0 ± 11.9	65.8 ± 9.5	0.088
Gender (male:female)	21:9	70:27	0.820
Primary site (colon:rectum)	22:8	57:40	0.197
No. of lymph node metastases (<4:≥4)	26:4	76:21	0.433
Timing of tumor (synchronous:metachronous)	15:15	52:45	0.835
Neoadjuvant chemotherapy (yes:no)	8:22	19:78	0.447
Tumor number (solitary:multiple)	13:17	51:46	0.410
Tumor distribution (unilobar:bilobar)	25:5	68:29	0.237
Tumor size (mm)	49.8 ± 28.7	38.0 ± 30.0	0.004
Serum CEA (ng/mL)	191.3 ± 388.3	84.4 ± 303.0	0.194
Type of resection (anatomic:nonanatomic)	25:5	41:56	<0.001
Duration of operation (min)	415.6 ± 179.6	334.9 ± 127.2	0.039
Intraoperative blood loss (g)	2778.3 ± 3336.2	642.1 ± 489.2	<0.001
RBC transfusion (present:absent)	25:5	18:79	<0.001
PC transfusion (present:absent)	5:25	0:97	0.001
Postoperative complications (present:absent)	9:21	13:84	0.052
Postoperative hospital stay (d)	27.7 ± 14.5	21.2 ± 13.1	0.003

* mean ± standard deviation.

($P = 0.013$), alanine aminotransferase level on postoperative day 1 ($P < 0.001$), day 3 ($P = 0.001$), and day 5 ($P < 0.001$), and total bilirubin level on postoperative day 1 ($P < 0.001$), day 3 ($P < 0.001$) and day 5 ($P < 0.001$) were higher than those in patients without FFP transfusion (Supplementary Table 1).

Discussion

Management of CRLM is an important and common problem because of the importance of liver metastases on the prognosis of patients with colorectal cancer. Recent advances in chemotherapy may facilitate the resectability of liver lesions. However, hepatic resection for CRLM is still related to risks of excessive bleeding and postoperative liver failure because several chemotherapeutic agents worsen liver function and make liver tissue fragile.[14] Therefore, assessment of blood transfusion is important to improve prognosis of CRLM. In the present study, we found that perioperative FFP transfusion was significantly related to reduced disease-free as well as overall survival after hepatic resection for CRLM. Moreover, we also found correlation between postoperative inflammatory response and FFP transfusion. To the best of our knowledge, this is the first study to report the negative impact of FFP transfusion on cancer recurrence and postoperative inflammation in patients with CRLM.

The mechanism for the relation between the perioperative FFP transfusion and long-term survival in patients with cancer remains unclear. In the present study, FFP transfusion was associated with sustained elevation of white blood cell and suppression of reacted serum C-reactive protein after operation. It had been reported that FFP transfusion decreased the ability of immune cells to produce proinflammatory cytokines and increased the production of antiinflammatory cytokines because stored human whole blood showed a significant decrease in endotoxin-stimulated tumor necrosis factor-α as well as a stimulation of interleukin-10 release, similar to the results with leukocyte-depleted blood products.[15] Moreover, the significant contamination of FFP may also contribute to the observed changes in stimulated cytokine response in Schneider's *in vitro* model of transfusion.[16] These immunomodulatory effects might have suppressed postoperative reaction of serum C-reactive protein and sustained elevation of white blood cells. On the other hand, FFP transfusion was reported to be permissive for systemic inflammatory response syndrome, infection, and sepsis.[17] Recently, several studies have indicated that systemic inflammatory response predicts cancer-specific survival in patients with CRLM.[18,19] The host's inflammatory response to cancer and/or the systemic effects exerted by the cancer cells lead to up-regulation of the inflammatory process, predisposing the cancer to proliferation and metastasis through the inhibition of apoptosis, promotion of angiogenesis, and repair of DNA damage.[20,21] Neutrophil contributes to continuous angiogenic stimulation such as release of endothelial growth factor.[22] This condition may accelerate the growth of cancer cells or micrometastases.[23] Moreover, systemic inflammation also causes the suppression of antitumor immunity by recruitment of regulatory T cells and activation of cytokines.[24] These results suggested that sustained postoperative inflammatory response might contribute to both growth of cancer cells and decreased cell-mediated immunity and might lead to poor long-term outcomes in patients with CRLM.

Concerning the other mechanisms of immunosuppressive effects of blood transfusion, especially in FFP transfusion, soluble human leukocyte antigen class I molecules and soluble fibroblast-associated surface ligand released by leukocytes

present in the serum of blood products inhibit the activity of natural killer cells and cytotoxic T cells, which are known to reduce immune capacity and therefore may predispose transfused patients to postoperative infections.[7,25-29] These reports suggest that plasma-rich blood products, such as FFP and PC, may lead to greater immunosuppressive effects by perioperative blood transfusion in patients during elective hepatic resection for CRLM.

In summary, the perioperative FFP transfusion has a negative impact on cancer recurrence and patients' prognosis after hepatic resection for CRLM presumably due to postoperative immunosuppression. Further investigation to clarify the relationship between immunosuppressive mechanisms caused by FFP transfusion and systemic inflammatory response is important to improve the therapeutic outcome of oncologic surgery.

Conclusion

Perioperative FFP transfusion is independently associated with poor long-term outcomes in patients with CRLM after hepatic resection. FFP may influence postoperative inflammation by its immunosuppressive effect.

Acknowledgment

Authors' contribution: The study was conceptualized and designed by Y.N., K.H. and H.S. The acquisition of data was carried out by Y.N., K.H., T.H., and N.S. The analysis and interpretation of data were done by Y.N., K.H., T.S., and T.G. The drafting of the manuscript was done by Y.N. The critical revision of the manuscript was done by K.H., H.S, and K.Y.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jss.2017.09.030.

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