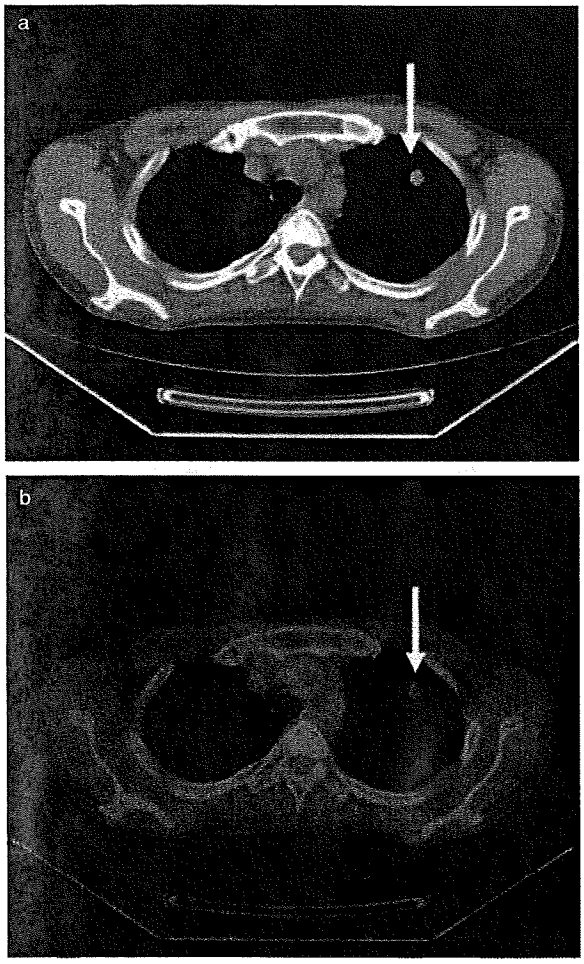

Figure 2 A 50-year-old male patient with hepatocellular carcinoma (HCC). (a) Multi-detector helical computed tomography (MDCT) showed lung metastasis measuring 5 mm in diameter in the left lung (white arrow). (b) The corresponding positron emission tomography – computed tomography (PET–CT) showed no accumulation of 18F-FDG in the left lung lesion.

DISCUSSION

PET IS A new, important imaging technique in the diagnosis of malignancy and has the potential to greatly enhance pre-operative staging of patients with cancer. In fact, PET–CT has been increasingly used for tumor staging.[6–8]

The pathology of extrahepatic metastases from primary HCC is usually moderately differentiated, poorly differentiated, or undifferentiated HCC.[16] PET can detect extrahepatic metastases with high sensitivity, probably due to the relationship between histological grading and *in vitro* enzymatic activity of glucose metabolism. Aerobic glycolysis and glucose metabolism are increased in moderately differentiated, poorly differentiated and undifferentiated hepatoma cells.[17]

Few studies have investigated the relationship between PET–CT and extrahepatic metastases of HCC.

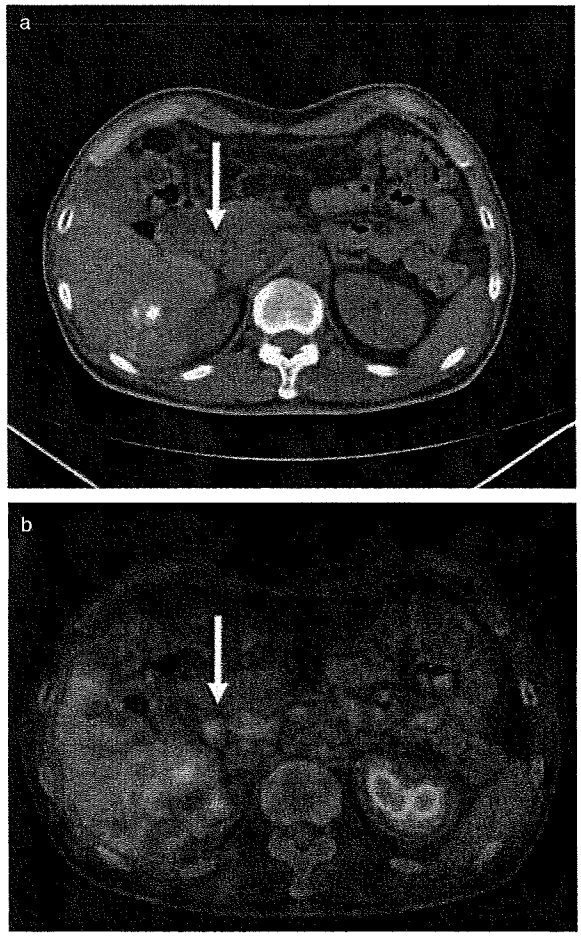

Figure 3 A 62-year-old male patient with hepatocellular carcinoma (HCC). This patient had lymph node swelling measuring 12 mm in diameter in the abdomen (a). The lesion was detected by multi-detector helical computed tomography (MDCT) (white arrow). However, the size of this lesion did not change over a 6-month period and the tumor marker was negative (b). The maximum standardized uptake value (SUV) was 2.7 in positron emission tomography – computed tomography (PET–CT) (white arrow) and this lesion was diagnosed as benign.

Table 4 Az value, sensitivity, specificity and positive predictive value in detection of bone metastasis

Observer	Az value			Sensitivity (%)			Specificity (%)			Positive predictive value (%)		
	MDCT	PET–CT	BS	MDCT	PET–CT	BS	MDCT	PET–CT	BS	MDCT	PET–CT	BS
1	0.640	0.801	0.609	50.0	91.7	50.0	100.0	75.0	83.3	100.0	78.5	71.4
2	0.506	0.884	0.627	41.7	83.3	50.0	91.7	83.3	83.3	83.3	83.3	85.7
3	0.638	0.968	0.625	33.3	75.0	58.3	91.7	100.0	83.3	80.0	100.0	66.7
Mean	0.594	0.883	0.620	41.6	83.3	52.7	94.5	86.1	83.3	87.7	87.3	74.6
P value	0.027*		0.027†	0.002*		0.053†	0.18*		1.0†	0.70*		0.27†

BS, bone scintigraphy; MDCT, multi-detector helical computed tomography; PET–CT, positron emission tomography – computed tomography.
*Compared MDCT with PET-CT.
†Compared BS with PET-CT.

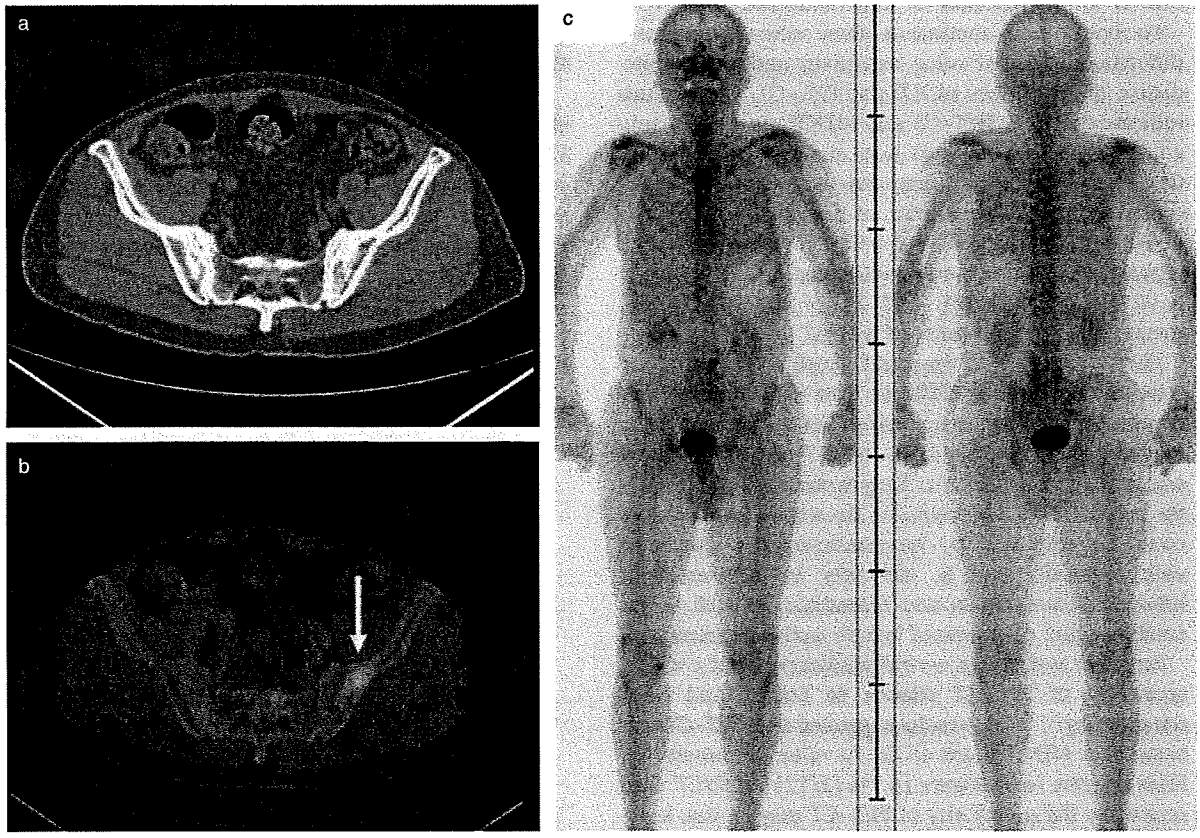

Figure 4 A 76-year-old male patient with hepatocellular carcinoma (HCC). This patient had a bone metastatic lesion measuring 18 mm in diameter in the left iliac bone. (a) The lesion was not detected by multi-detector helical computed tomography (MDCT). (b) The same tumor was clearly detected by positron emission tomography – computed tomography (PET–CT) and showed accumulation of ^{18}F-FDG (SUV = 3.3) (white arrow). (c) The same tumor was not detected by bone scintigraphy.

Sugiyama *et al.*[9] reported a detection rate of 83% for extrahepatic metastases in patients with HCC, including lesions more than 1 cm in diameter. Nagaoka *et al.*[10] also reported that PET alone detected 52 of 58 (89.6%) extrahepatic metastases. However, there are no reports that compared the efficacy of PET–CT as a detection tool for metastatic HCCs with that of MDCT using ROC analysis.

In the present study, the sensitivity of MDCT in the detection of lung metastasis was significantly higher than that of PET–CT, and the Az value of MDCT was significantly higher than that of PET–CT. This is probably mainly due to the higher sensitivity for detection lesions with maximum diameter of ≤10 mm by MDCT than PET–CT. These results are compatible with the findings of Sugiyama *et al.*[9] who suggested that PET–CT is a potentially useful diagnostic tool for the identification of extrahepatic HCC larger than 10 mm. These results indicate that MDCT is a better modality than PET–CT in the detection of lung metastases from HCC.

For lymph node metastases, there were no significant differences in the Az value, sensitivity and positive predictive value between MDCT and PET–CT. These results indicate that both PET–CT and MDCT are equally suitable for detection of lymph node metastases from HCC. One reason for the similarity may be the lack of significant difference in sensitivity of detecting large lymph nodes between MDCT and PET–CT. Nagaoka *et al.*[10] reported that lymph node metastases ranged from 1.3 to 4.7 cm in diameter, and 21 of the 22 (95.4%) metastases were also detected by PET.

The kappa values for lung and lymph node metastases were not significantly different. This is probably due to differences in the detection of lesions with a maximum diameter of ≤10 mm between MDCT and PET–CT and due to the small number of lung metastases examined in the present study. Furthermore, the similar kappa values could be explained by lymphadenopathy associated with hepatitis, that is, difficulty in differentiating between inflammation and metastasis, as well as the small number of examined lymph node metastases.

For bone metastases, several studies reported a higher sensitivity of PET–CT relative to MDCT and bone scintigraphy.[5,9,10] Our results suggested that PET–CT was better than MDCT based on the Az value and sensitivity. False negative lesions were 16.7% (2/12) in MDCT. One reason for the superiority of PET–CT may be that bone metastatic lesions from HCC are more likely to be osteolytic than osteoblastic lesions.[18] It has been documented that PET–CT is more sensitive than bone scintigraphy in detecting osteolytic metastatic lesions from primary cancers of the breast and non-small-cell lung cancer.[19] This difference was attributed to differences in the osteoblastic bone response and glucose uptake by tumor cells.[20] Bone metastasis is painful and reduces the quality of life of patients. Thus, early detection of bone metastasis by PET–CT should allow early treatment of pain by radiotherapy, chemotherapy, radiofrequency ablation therapy, or cementoplasty.[21]

In general, extrahepatic metastases are not limited to a single lesion in a single organ and many patients present with multiple metastases in different organs.[22] Katyal *et al.*[5] reported the presence of multiple metastatic lung lesions in 28% of their patients by MDCT and Yuki *et al.*[23] reported bone metastases in 39 patients (16.3%) of their 240 patients who had HCC at autopsy. When a patient is suspected of having one metastasis by MDCT, we recommend performing PET–CT, since bone metastases are more accurately detected by PET–CT, thus allowing early therapy and perhaps a better prognosis. In fact, 16.7% (2/12) of bone metastases that were not detected by MDCT were clearly detected by PET–CT in our study.

In conclusion, our study compared the detection of extrahepatic metastatic lesions from primary HCC by PET–CT using ROC analysis. PET–CT has high sensitivity and is more suitable for the detection of bone metastases from primary HCC, relative to MDCT. PET–CT may be effective for the diagnosis of bone metastases.

REFERENCES

1 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; 340: 745–50.
2 Poon RT, Fan ST, Lo CM *et al.* Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg* 2001; 234: 63–70.
3 Kim SR, Ando K, Mita K *et al.* Superiority of CT arterioportal angiography to contrast-enhanced CT and MRI in the diagnosis of hepatocellular carcinoma in nodules smaller than 2 cm. *Oncology* 2007; 72 (Suppl 1): 58–66.
4 Matsui O, Kadoya M, Suzuki M *et al.* Work in progress: dynamic sequential computed tomography during arterial portography in the detection of hepatic neoplasms. *Radiology* 1983; 146: 721–7.
5 Katyal S, Oliver JH 3rd, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000; 216: 698–703.
6 Rigo P, Paulus P, Kaschten B J *et al.* Oncological application of positron emission tomography with

fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med* 1996; 23: 1641–74.
7 Giannopoulou C. The role of SPECT and PET in monitoring tumor response to therapy. *Eur J Nucl Med Mol Imaging* 2003; 30: 1173–200.
8 Böhm B, Voth M, Geoghegan J. *et al.* Impact of positron emission tomography on strategy in liver resection for primary and secondary liver tumors. *J Cancer Res Clin Oncol* 2004; 130: 266–72.
9 Sugiyama M, Sakahara H, Torizuka T *et al.* 18F-FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. *J Gastroenterol* 2004; 39: 961–8.
10 Nagaoka S, Itano S, Ishibashi M *et al.* Value of fusing PET plus CT images in hepatocellular carcinoma and combined hepatocellular and cholangiocarcinoma patients with extrahepatic metastases: preliminary findings. *Liver Int* 2006; 26: 781–8.
11 Yoon KT, Kim JK, Kim DY *et al.* Role of 18F-Fluorodeoxyglucose positron emission tomography in detecting extrahepatic metastases in pretreatment staging of hepatocellular carcinoma. *Oncology* 2007; 72 (Suppl 1): 104–10.
12 Obuchowski NA. New methodological tools for multiple-reader ROC studies. *Radiology* 2007; 243: 10–12.
13 Liver Cancer Study Group of Japan. The General Rules for the Clinical and Pathological Study of Primary Liver Cancer (in Japanese), 4th edn, Tokyo: Kanehara, 2000.
14 Metz CE. ROC methodology in radiological imaging. *Invest Radiol* 1986; 21: 720–33.
15 Koch GG, Landia JR, Freeman JL, Freeman DH Jr, Lehnen RC. A general methodology for the analysis of experiments with repeated measurement of categorical data. *Biometrics* 1977; 33: 133–58.
16 Kaczynski J, Hansson G, Wallerstedt S. Metastases in cases with hepatocellular carcinoma in relation to clinicopathologic features of the tumor. An autopsy study from a low endemic area. *Acta Oncol* 1995; 34: 43–8.
17 Torizuka T, Tamaki N, Inokuma T *et al.* In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG–PET. *J Nucl Med* 1995; 36: 1811–17.
18 Schirrmeister H, Guhlmann A, Elsner K *et al.* Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET. *J Nucl Med* 1999; 40: 1623–9.
19 Bradley JD, Dehdashti F, Muntun MA, Ramaswamy G, Trinkaus K Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004; 22: 3248–54.
20 Cook GJ, Houston S, Rubens R, Maisey MN, Fogelman I. Detection of bone metastases in breast cancer with FDG-PET. Differing metabolic activity in osteoblastic and osteolytic lesion. *J Clin Oncol* 1998; 16: 3375–9.
21 Kodama H, Aikata H, Uka K *et al.* Efficacy of percutaneous cementoplasty for bone metastasis from hepatocellular carcinoma. *Oncology* 2007; 72: 285–92.
22 Uka K, Aikata H, Takaki S *et al.* Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol* 2007; 13: 414–20.
23 Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimosato Y. Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. *Cancer* 1990; 66: 2174–9.

Hepatology Research 2009; 39: 415–420 doi: 10.1111/j.1872-034X.2008.00448.x

Case Report

Successful treatment of pulmonary metastases associated with advanced hepatocellular carcinoma by systemic 5-fluorouracil combined with interferon-α in a hemodialysis patient

Yoshio Katamura, Hiroshi Aikata, Yuki Kimura, Takahiro Azakami, Tomokazu Kawaoka, Shintaro Takaki, Koji Waki, Akira Hiramatsu, Yoshiiku Kawakami, Shoichi Takahashi and Kazuaki Chayama

Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

A 54-year-old man maintained on hemodialysis had a relapse of multiple pulmonary metastases after multimodal therapy for primary hepatocellular carcinoma (HCC). He was treated with tegafur-uracil (UFT; 400 mg/day) and interferon alfa (IFN-α; 5×10^6 units three times per week) for 4 weeks. Following this he was treated with systemic 5-fluorouracil (5-FU; 1000 mg/day, 5 days per week) and cisplatin (CDDP; 10 mg/day, 5 days per week for 2 weeks). The response to the above treatments was inadequate; pulmonary metastasis deteriorated. Finally, we selected systemic chemotherapy of 5-FU (750 mg/day, 5 days per week) and recombinant IFN-α-2b (3×10^6 units three times per week) for 2 weeks. This therapy resulted in excellent shrinkage of pulmonary metastases, without severe adverse reactions. Hemodialysis was performed three times a week. We report a case of successful treatment of pulmonary metastases by systemic combination chemotherapy of 5-FU–IFN, previously unsuccessfully treated with UFT–IFN and 5-FU–CDDP in a patient on hemodialysis. Further studies are needed to select appropriate drugs with fluoropyrimidine-based systemic chemotherapy, and to analyze the pharmacokinetics of those agents in hemodialysis patients with HCC and extrahepatic metastases.

Key words: extrahepatic metastases, 5-fluorouracil, hemodialysis, hepatocellular carcinoma, interferon, pulmonary metastasis, systemic combination chemotherapy

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most common cancers and causes of cancer death worldwide.[1] Development of new diagnostic techniques, such as ultrasonography, computed tomography (CT), magnetic resonance imaging, and angiography, and advancements in therapeutic modalities such as surgical resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transcatheter arterial chemoembolization (TACE), and intra-arterial infusion via implantable drug delivery systems have gradually improved the prognosis of HCC patients. Nevertheless, the prognosis of patients with advanced HCC and extrahepatic metastases is still poor[2–4] and the standard therapeutic modality for HCC with extrahepatic metastases is still not established. Several investigators suggested recently the use of combination systemic chemotherapies of 5-fluorouracil (5-FU) and cisplatin (CDDP) (5-FU/CDDP), 5-FU with mitoxantrone and CDDP, tegafur/uracil (UFT) and interferon (IFN) (UFT/IFN), 5-FU and IFN (5-FU/IFN), for advanced HCC with extrahepatic metastases.[5–8] It is of note that every regimen is based on fluoropyrimidine, and IFN or CDDP is used concomitantly. However, in an individual case, many questions remain unanswered. For example (i) which concomitant drug should been selected? (ii) What is the mechanism of the antitumor effects of the combination chemotherapeutic agents? (iii) When one concomitant drug is not effective, will the other(s) achieve a good response?, and (iv) Should fluoropyrimidine-based combination chemotherapy be

Correspondence: MD Hiroshi Aikata, Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. Email: aikata@hiroshima-u.ac.jp
Received 10 July 2008; revised 20 August 2008; accepted 21 August 2008.

used in hemodialysis patients? We and other investigators reported the use of the combination chemotherapy of S-1 and IFN (S-1/IFN) for HCC with extrahepatic metastases.[9,10] However, because 50% of 5-chloro-2,4-dihydroxypyridine (CDHP), an inhibitor of dihydropyrimidine dehydrogenase (DPD), is excreted into the urine, S-1 is considered contraindicated for hemodialysis patients.[11]

We report a patient with HCC and pulmonary metastases who was on maintenance hemodialysis. Although the patient did not show a satisfactory response to two fluorouracil-based regimens of systemic combination chemotherapy, an excellent outcome was finally achieved with systemic combination of 5-FU/IFN.

CASE REPORT

A 54-YEAR-OLD man with hepatitis C virus-related chronic hepatitis was admitted to our hospital for HCC in April 2005. He was on hemodialysis three times a week for chronic renal failure. Computed tomography (CT) showed a solitary tumor measuring 5 cm in diameter in the posterior liver segment and a tumor thrombus in the inferior vena cava (IVC). The intrahepatic tumor and tumor thrombus were treated by TACE and radiotherapy (RT) (30 Gy), respectively. Additional TACE was performed twice in July and October 2005. In November 2005, he underwent a posterior segmentectomy and resection of the right hepatic vein.

In April 2006, chest CT scans showed multiple pulmonary metastases (Fig. 1), but abdominal CT scans performed at the same time did not show any tumors in the liver. Laboratory tests showed α-fetoprotein (AFP) 114 ng/mL, AFP-L3 18% and protein induced by vitamin K antigen II (PIVKA-II) 20 mAU/mL. We selected the combination chemotherapy of UFT/IFN. One course of the chemotherapy consisted of oral UFT (400 mg/day for 4 weeks) and subcutaneous injections of IFN-α (5×10^6 units, three times per week for 4 weeks). After three courses, CT showed deterioration of pulmonary metastases in October 2006 (Fig. 2a–d), and tumor markers were elevated (AFP 749 ng/mL, AFP-L3 30% and PIVKA-II 31 mAU/mL). Therefore, we preferred systemic combination chemotherapy of 5-FU/CDDP. We used intravenous 5-FU (1000 mg/day, three times per week for 2 weeks) and intravenous CDDP (10 mg/day, three times per week for 2 weeks) for two courses. Clinical assessment after these two courses showed no severe adverse reactions. Accordingly, 5-FU and CDDP were administered at the same doses (1000 and 10 mg/day, respectively) but increased to 5 days per week for 2 weeks, per course, for another three courses. 5-FU and CDDP were administered at 1000 mg/24 h and 10 mg/h, respectively. Hemodialysis was performed after one hour of administration of CDDP. In June 2007, after completion of the above five courses of 5-FU/CDDP, a repeat CT showed deterioration of pulmonary metastases (Fig. 2e–h), and laboratory tests showed further elevation of tumor markers (AFP 2300 ng/mL, AFP-L3 33% and PIVKA-II 71 mAU/mL). In August 2007, we switched chemotherapy to systemic 5-FU/IFN; one course consisted of daily intravenous 5-FU (750 mg/day, 5 days per week for 2 weeks) and subcutaneous injection of IFN-α-2b (3×10^6 units three times per week for 2 weeks). 5-FU was administrated at 750 mg/24 h. The dose of 750mg/body instead of 1000 mg/day, was selected for 5-FU because at the latter dose, the patient developed NCI-CTC grade 2 anorexia and diarrhea[12]. Concomitantly, the patient received RT (39 Gy) for the pulmonary metastases infiltrating the right pulmonary artery. After three courses, a repeat CT taken in April 2008 showed excellent shrinkage of pulmonary metastases (Fig. 3), and laboratory tests indicated precipitous falls in AFP and PIVKA-II to < 5.0 ng/mL and 14 mAU/mL, respectively (Fig. 4). Chest CT also showed the appearance of pleuritis at right posterior site and right pleural effusion (Fig. 3). These changes probably represented radioactive pleuritis and pleural effusion. However, they were not associated with any symptoms such as chest pain, dyspnea, or

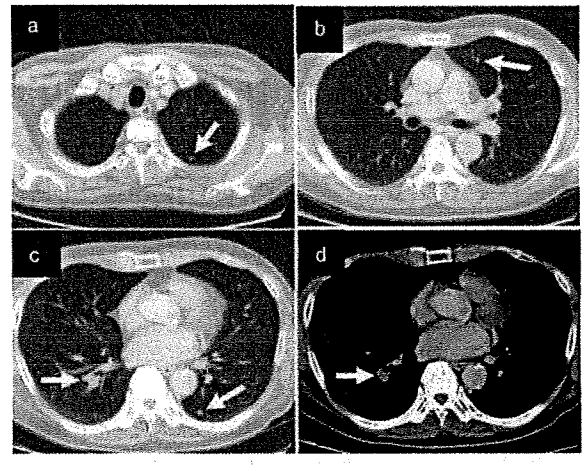

Figure 1 (a–d) Chest computed tomography showed multiple pulmonary metastases in both lung fields (arrows), five months after posterior segmentectomy.

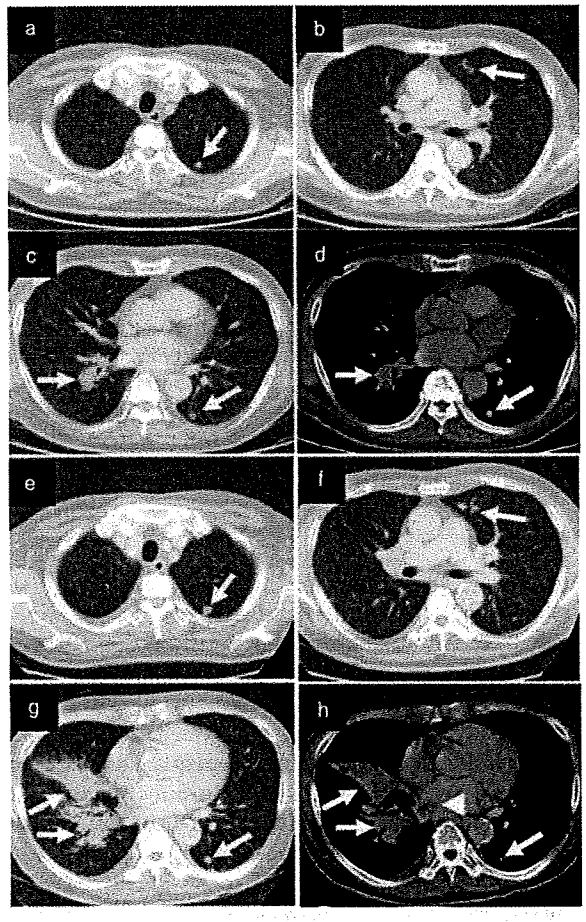

Figure 2 (a–d) Chest computed tomography showed deterioration of pulmonary metastases after three courses of systemic combination chemotherapy of tegafur–uracil and interferon-α (arrows). (e–h) Chest computed tomography showed further deterioration of pulmonary metastases after five courses of systemic combination chemotherapy of 5-fluorouracil and cisplatin (arrows). (h) Pulmonary metastases in the right lung infiltrated the right pulmonary artery (arrowhead).

cough. The adverse reactions to 5-FU/IFN combination chemotherapy included Grade 2–3 anorexia and diarrhea. Laboratory tests showed Grade 4 leukopenia and neutropenia (baseline [before 5-FU/IFN therapy]/lowest; leukocyte count, 2870/980 (/mm^3); neutrophil count 2181/470 (/mm^3); hemoglobin, 8.2/7.7 (g/dL); platelet count, $6.2 \times 10^4/3.5 \times 10^4$ (mm^3), prothrombin activity, 79/70 (%); total bilirubin, 0.3/0.5 (mg/dL); and albumin, 3.5/3.1 (g/dL)). These adverse effects necessitated the administration of granulocyte colony-stimulating factor, but no discontinuation of the chemotherapy since hepatic reserve was preserved. After 5-FU/IFN, the Eastern Cooperative Oncology Group (ECOG) performance status (PS)[13] worsened from 0 to 1 due to Grade 2–3 anorexia and diarrhea, although anorexia and diarrhea disappeared and PS returned to 0 at 2 months after 5-FU–IFN.

DISCUSSION

THERE IS NO standard therapeutic regimen for HCC with extrahepatic metastases. The prognosis of patients with advanced HCC and extrahepatic metastases is still poor.[2–4] Various systemic combination chemotherapies such as UFT–IFN, 5-FU–CDDP, 5-FU–mitoxantrone–CDDP, 5-FU–IFN and S-1–IFN are used.[5–10] With regard to the use of UFT–IFN and 5-FU–CDDP,[5,6] only case reports have been published. One report describes the use of 5-FU–IFN[7] in 7 patients with HCC and distant metastases but does not elaborate on the response rate. Reported response rates are 27% to 5-FU–mitoxantrone–CDDP,[8] and 17 and 25% to S-1–IFN.[9,10] Each of these combination chemotherapies consists of fluoropyrimidine as the key drug, and CDDP or IFN as a concomitant modulator of fluoropyrimidine. To our knowledge, the present case is the first describing the ineffectiveness of 5-FU–CDDP combination

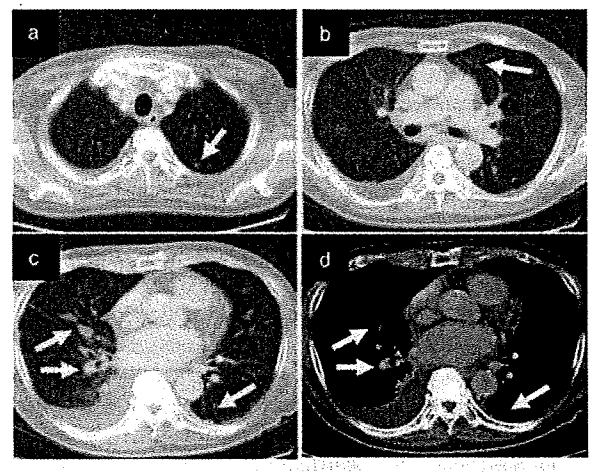

Figure 3 (a–d) Chest computed tomography showed excellent shrinkage of pulmonary metastases after three courses of systemic combination chemotherapy of 5-fluorouracil and interferon-α-2b (arrows). (d) Disappearance of pulmonary metastases infiltrating the right pulmonary artery and appearance of pleuritis at right posterior site with right pleural effusion.

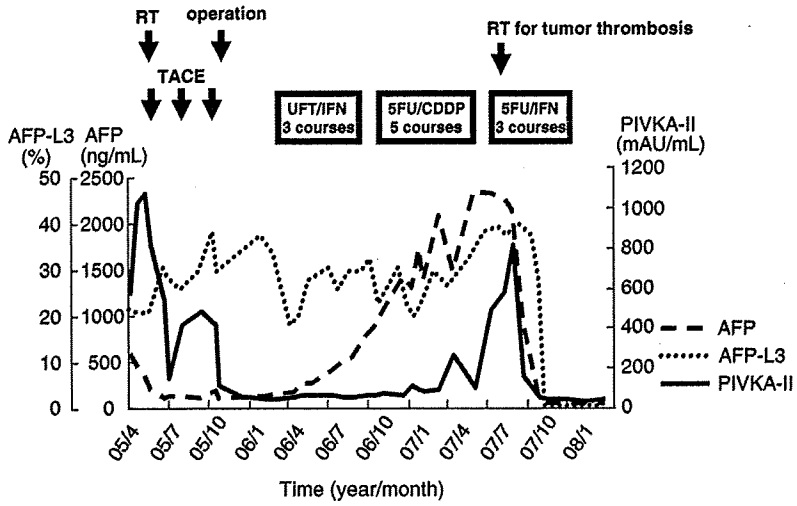

Figure 4 Clinical course. Serum levels of α-fetoprotein (AFP), AFP-L3 and vitamin K antigen II fell precipitously to the normal ranges after systemic combination chemotherapy of 5-fluorouracil and interferon-α-2b and radiotherapy.

therapy, and the effectiveness of 5-FU–IFN for pulmonary metastases associated with primary HCC.

In our hospital, we select systemic combination chemotherapy of S-1–IFN for HCC with extrahepatic metastases if intrahepatic HCC is well controlled.[2,9] As we reported previously, the overall response rate (complete response + partial response) to S-1–IFN is 17%, and the response rate among patients with lung metastases is 21%.[9] With regard to drug metabolism, 53.7% of CDHP, an inhibitor of dihydropyrimidine dehydrogenase, is excreted into the urine,[11] and thus S-1 promotes high plasma concentrations of 5-FU in hemodialysis patients.[14,15] In this regard, the safety of S-1 is yet to be ascertained in hemodialysis patients.

A previous report indicates that although plasma concentrations of 5-FU in hemodialysis patients treated with UFT were about double than in patients with normal renal function on the same combination therapy, no severe adverse reactions were observed in these patients.[16] In addition, because more than 80% of 5-FU is inactivated by DPD, dose modification of intravenously administrated 5-FU for hemodialysis patient is considered unnecessary.[17,18] Based on this background, we selected oral UFT and intravenous 5-FU as one arm of the systemic combination chemotherapy.

Accordingly, we selected UFT–IFN as a first-line therapy. However, when UFT–IFN did not attain clinical efficacy, we speculated that plasma concentrations of 5-FU with oral UFT were inadequate, or IFN was inadequate as a modulator of fluoropyrimidine. Therefore, we tried a systemic combination chemotherapy of 5-FU–CDDP as a second-line therapy. Again, the results of 5-FU–CDDP were unsatisfactory, and thus we selected 5-FU–IFN as the third choice.

In the case reported here, combination chemotherapy of UFT–IFN did not, while that of 5-FU–IFN could attain clinical efficacy. While the exact reason for the different response is not clear at present, we speculate that it is due to therapeutically inadequate plasma concentrations of 5-FU by oral UFT. In our case, we used 10 mg/kg/24 h of 5-FU and 200 mg of UFT twice a day with IFN. We speculate that the former regimen allowed plasma concentration of 5-FU to be higher than the other regimen in the hemodialysis patient. Unfortunately, there is limited information on the pharmacokinetics of 5-FU in hemodialysis patients treated with oral UFT and intravenous 5-FU. Further pharmacokinetic studies are needed to provide safe and effective chemotherapies for hemodialysis patients.

In our patient, the clinical course indicated that while 5-FU/CDDP was ineffective, 5-FU/IFN achieved an excellent outcome. Though both CDDP and IFN play synergistic roles as modulators of fluoropyrimidine, the underlying mechanisms are different. CDDP acts as a modulator by inhibiting intracellular L-methionine metabolism and consequently increases the reduced folate pool such as 5,10-methylenetetrahydrofolate (CH2FH4) and tetrahydrofolate (FH4), which are essential cofactors for the formation of a tight ternary complex of thymidylate synthase (TS) and 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP) derived from 5-FU, resulting in enhancement of its antitumor effects.[19,20] On the other hand, IFN-α acts as a modulator by increasing the level of thymidine phosphorylase,

which is an enzyme responsible for biochemical activation of 5-FU.[21,22] In addition, IFN suppresses cancer cells directly or indirectly via several pathways such as inhibition of cell cycle, boosting p53 activation, and activation of immunocytes.[23–28] With regard to intra-arterial combination chemotherapy for advanced HCC with portal vein tumor thrombosis (PVTT), the response rates to 5-FU–IFN and 5-FU–CDDP seem similar.[29–36] In an individual case, it remains unclear whether 5-FU–CDDP or 5-FUIFN is more effective. Several studies attempted to predict the response to 5-FU–IFN and 5-FU–CDDP chemotherapy. For example, Ota *et al.*[35] reported that the response to 5-FU–IFN combination therapy correlated significantly with the expression level of type I interferon receptor 2 (IFNAR2). Furthermore, Kogure *et al.*[37] reported that the DPD mRNA level could predict the response of human hepatoma cell lines to 5-FU–CDDP. Nishiyama *et al.*[38] indicated that the expression levels of DPD, multidrug resistance-associated protein (MRP), glutathione S-transferase π (GSTπ), and TS gene after exposure to 5-FUCDDP correlated with drug resistance in human gastrointestinal cancer cell lines. Further studies are needed to identify factors that could predict in an individual case the response to 5-FU–CDDP or IFN–5FU and hence help select the most suitable combination chemotherapy.

In our case, the patient received RT for the pulmonary metastases infiltrating the right pulmonary artery concomitantly with 5-FU–IFN. It is possible that this RT also contributed to the fall in tumor markers and shrinkage of tumor at irradiated area. However, the irradiated area was limited to the right pulmonary artery. Thus, we consider that RT did not affect pulmonary metastases other than pulmonary arterial thrombosis.

In conclusion, 5-FU–IFN may be a useful, alternative systemic combination chemotherapy for patients on hemodialysis with HCC and extrahepatic metastases, who do not respond to 5-FU–CDDP.

REFERENCES

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74–108.
2 Uka K, Aikata H, Takaki S *et al.* Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol* 2007; 13: 414–20.
3 Natsuizaka M, Omura T, Akaike T *et al.* Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol* 2005; 20: 1781–7.
4 Okusaka T, Okada S, Ishii H *et al.* Prognosis of hepatocellular carcinoma patients with extrahepatic metastases. *Hepatogastroenterology* 1997; 44: 251–7.
5 Miyamoto A, Umeshita K, Sakon M *et al.* Advanced hepatocellular carcinoma with distant metastases, successfully treated by a combination therapy of alpha-interferon and oral tegafur/uracil. *J Gastroenterol Hepatol* 2000; 15: 1447–51.
6 Anami Y, Oguma S, Matsuda Y *et al.* [Complete disappearance of metastatic lung tumors and mediastinal lymph-node in a case of hepatocellular carcinoma treated by low-dose 5-fluorouracil/CDDP therapy.] *Gan To Kagaku Ryoho* 2005; 32: 1977–80 (in Japanese).
7 Patt YZ, Hassan MM, Lozano RD *et al.* Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon Alfa-2b for treatment of hepatocellular carcinoma. *J Clin Oncol* 2003; 21: 421–7.
8 Ikeda M, Okusaka T, Ueno H, Takezako Y, Morizane C. A phase II trial of continuous infusion of 5-fluorouracil, mitoxantrone, and cisplatin for metastatic hepatocellular carcinoma. *Cancer* 2005; 103: 756–62.
9 Uka K, Aikata H, Mori N *et al.* Combination therapy of oral fluoropyrimidine anticancer drug S-1 and interferon alpha for HCC patients with extrahepatic metastases. *Oncology* 2008; 75: 8–16.
10 Nakamura M, Nagano H, Marubashi S *et al.* Pilot study of combination chemotherapy of S-1, a novel oral DPD inhibitor, and interferon-alpha for advanced hepatocellular carcinoma with extrahepatic metastasis. *Cancer* 2008; 112: 1765–71.
11 Hirata K, Horikoshi N, Aiba K *et al.* Pharmacokinetic study of S-1: a novel oral fluorouracil antitumor drug. *Clin Cancer Res* 1999; 5: 2000–5.
12 NCI Common Toxicity Criteria. http://ctep.cancer.gov/reporting/ctc.html.
13 Oken MM, Creech RH, Tormey DC *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5: 649–55.
14 Tominaga K, Higuchi K, Okazaki H *et al.* Safety and efficacy of S-1, a novel oral fluorouracil anticancer drug, for a chronic renal failure patient maintained on hemodialysis. *Oncology* 2004; 66: 358–64.
15 Tanaka T, Fujita S, Tanaka N, Ooka M, Okajima S, Tanaka N. [TS-1 treatment for progressive gastric cancer in a patient on chronic dialysis – assessment of dosage regimen by monitoring blood concentrations of therapeutic drugs (TDM).] *Gan To Kagaku Ryoho* 2005; 32: 841–5 (in Japanese).
16 Sakamoto K, Arita S, Hisikawa E *et al.* [Pharmacokinetic study of UFT in cancer patients receiving maintenance dialysis.] *Gan To Kagaku Ryoho* 1995; 22: 239–44 (in Japanese).
17 Pinedo HM, Peters GF. Fluorouracil: biochemistry and pharmacology. *J Clin Oncol* 1988; 6: 1653–64.
18 Schilsky RL. Renal and metabolic toxicities of cancer chemotherapy. *Semin Oncol* 1982; 9: 75–83.

19 Scanlon KJ, Newman EM, Lu Y, Priest DG. Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. *Proc Natl Acad Sci USA* 1986; 83: 8923–5.
20 Shirasaka T, Shimamoto Y, Ohshimo H, Saito H, Fukushima M. Metabolic basis of the synergistic antitumor activities of 5-fluorouracil and cisplatin in rodent tumor models in vivo. *Cancer Chemother Pharmacol* 1993; 32: 167–72.
21 Braybrooke JP, Propper DJ, O'Byrne KJ *et al.* Induction of thymidine phosphorylase as a pharmacodynamic endpoint in patients with advanced carcinoma treated with 5-fluorouracil, folinic acid and interferon alpha. *Br J Cancer* 2000; 83: 219–24.
22 Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. *Cancer Res* 1990; 50: 3473–86.
23 Yano H, Iemura A, Haramaki M *et al.* Interferon alfa receptor expression and growth inhibition by interferon alfa in human liver cancer cell lines. *Hepatology* 1999; 29: 1708–17.
24 Murphy D, Detjen KM, Welzel M, Wiedenmann B, Rosewicz S. Interferon-alpha delays S-phase progression in human hepatocellular carcinoma cells via inhibition of specific cyclin-dependent kinases. *Hepatology* 2001; 33: 346–56.
25 Takaoka A, Hayakawa S, Yanai H *et al.* Integration of interferon-α/β signalling to p53 responses in tumor suppression and antiviral defence. *Nature* 2003; 424: 516–23.
26 Ortaldo JR, Mantovani A, Hobbs D, Rubinstein M, Pestka S, Herberman RB. Effects of several species of human leukocyte interferon on cytotoxic activity of NK cells and monocytes. *Int J Cancer* 1983; 31: 285–9.
27 Brinkmann V, Geiger T, Alkan S, Heusser CH. Interferon alpha increases the frequency of interferon gamma-producing human CD4$^+$ T cells. *J Exp Med* 1993; 178: 1655–63.
28 Uno K, Shimizu S, Ido M *et al.* Direct and indirect effects of interferon on in vivo murine tumor cell growth. *Cancer Res* 1985; 45: 1320–7.
29 Uka K, Aikata H, Takaki S *et al.* Pre-treatment predictor of response, time to progression and survival to intraarterial 5-fluorouracil/interferon combination therapy in patients with advanced hepatocellular carcinoma. *J Gastroenterol* 2007; 42: 845–53.
30 Ando E, Yamashita F, Tanaka M, Tanikawa K. A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. *Cancer* 1997; 79: 1890–6.
31 Ando E, Tanaka M, Yamashita F *et al.* Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. *Cancer* 2002; 95: 588–95.
32 Lai YC, Shih CY, Jeng CM *et al.* Hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombosis. *World J Gastroenterol* 2003; 9: 2666–70.
33 Urabe T, Kaneko S, Matsushita E, Unoura M, Kobayashi K. Clinical pilot study of intrahepatic arterial chemotherapy with methotrexate, 5-fluorouracil, cisplatin, and subcutaneous interferon-alpha-2b for patients with locally advanced hepatocellular carcinoma. *Oncology* 1998; 55: 39–47.
34 Sakon M, Nagano H, Dono K *et al.* Combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. *Cancer* 2002; 94: 435–42.
35 Ota H, Nagano H, Sakon M *et al.* Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-a and intra-arterial 5-fluorouracil: role of type I interferon receptor expression. *Br J Cancer* 2005; 93: 557–64.
36 Obi S, Yoshida H, Toune R *et al.* Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. *Cancer* 2006; 106: 1990–7.
37 Kogure T, Ueno Y, Iwasaki T, Shimosegawa T. The efficacy of the combination therapy of 5-fluorouracil, cisplatin and leucovorin for hepatocellular carcinoma and its predictable factors. *Cancer Chemother Pharmacol* 2004; 53: 296–304.
38 Nishiyama M, Yamamoto W, Park JS *et al.* Low-dose cisplatin and 5-fluorouracil in combination can repress increased gene expression of cellular resistance determinants to themselves. *Clin Cancer Res* 1999; 5: 2620–8.

LIVER TRANSPLANTATION 15:208-215, 2009

ORIGINAL ARTICLE

Significant Correlation Between Spleen Volume and Thrombocytopenia in Liver Transplant Patients: A Concept for Predicting Persistent Thrombocytopenia

Masahiro Ohira,[1] Minoru Ishifuro,[2] Kentaro Ide,[1] Toshimitsu Irei,[1] Hirotaka Tashiro,[1] Toshiyuki Itamoto,[1] Katsuhide Ito,[2] Kazuaki Chayama,[3] Toshimasa Asahara,[1] and Hideki Ohdan[1]

[1]Department of Surgery, Division of Frontier Medical Science, Programs for Biomedical Research, [2]Department of Radiology, Division of Medical Intelligence and Informatics, Programs for Applied Biomedicine, and [3]Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Interferon (IFN) therapy with or without ribavirin treatment is well established as a standard antiviral treatment for hepatitis C virus (HCV)–infected patients. However, susceptibility to thrombocytopenia is a major obstacle for initiating or continuing this therapy, particularly in liver transplant (LTx) recipients with HCV. Studies have reported that splenectomy performed concurrently with LTx is a feasible strategy for conditioning patients for anti-HCV IFN therapy. However, the relationship between the severity of splenomegaly and alterations in the blood cytopenia in LTx recipients remains to be clarified. Here, we analyzed the relationship between spleen volume (SV) and thrombocytopenia in 45 patients who underwent LTx at Hiroshima University Hospital. The extent of pre-LTx splenomegaly [the SV to body surface area (BSA) ratio in an individual] was inversely correlated with both the post-LTx white blood cell count and platelet (PLT) count ($P < 0.001$). Furthermore, the PLT count of patients with thrombocytopenia (PLT count $\leq 5 \times 10^4/mm^3$) increased significantly in the group without splenomegaly (SV/BSA value < 400) versus that in the group with splenomegaly ($P = 0.005$). Thus, if both splenomegaly and thrombocytopenia coexist (PLT count $\leq 5 \times 10^4/mm^3$ and SV/BSA value ≥ 400), persistent thrombocytopenia is predictable after LTx. *Liver Transpl 15:208-215, 2009.* © 2009 AASLD.

Received May 8, 2008; accepted September 2, 2008.

Postoperative thrombocytopenia is a common feature in liver transplant (LTx) patients.[1,2] The mechanism underlying this thrombocytopenia is considered to involve the peripheral destruction and/or consumption of platelets (PLTs)[2,3] because megakaryotic hyperplasia has been observed in the bone marrow aspirates of LTx recipients.[2] Severe thrombocytopenia resulting from bleeding complications during the postoperative period may lead to increased morbidity and mortality.[4,5] Furthermore, the PLT count is one of the crucial determinants for the discontinuation of interferon (IFN) administration, which is used as a preemptive measure or as a treatment strategy for recurrent hepatitis C virus (HCV) infections.[6] Thrombocytopenia in patients with cirrhosis has been reported to be caused by an increased PLT pool in the enlarged spleen.[7-9] Splenectomy may alleviate the postoperative thrombocytopenia in LTx patients; however, the septic complications following this procedure have generally been reported to have an adverse effect on LTx outcome.[10-13] Therefore,

Abbreviations: ALT, alanine aminotransferase; BSA, body surface area; HCV, hepatitis virus C; Hgb, hemoglobin; IFN, interferon; LTx, liver transplant; MELD, Model for End-Stage Liver Disease; PLT, platelet; PSE, partial splenic embolization; SD, standard deviation; SV, spleen volume; T-Bil, total bilirubin; WBC, white blood cell.

Address reprint requests to Hideki Ohdan, M.D., Ph.D., Department of Surgery, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. Telephone: +81-82-257-5222; FAX: +81-82-257-5224; E-mail: hohdan@hiroshima-u.ac.jp

DOI 10.1002/lt.21663
Published online in Wiley InterScience (www.interscience.wiley.com).

the conditions under which splenectomy can be performed to prevent the development of thrombocytopenia following LTx should be carefully defined. Analyzing the association between the extent of splenomegaly and thrombocytopenia in LTx recipients would provide important information in this respect.

In this study, we report an analysis of the relationship between preoperative spleen volume (SV) and blood cytopenia in 45 patients who underwent LTx at the Hiroshima University Hospital.

PATIENTS AND METHODS

Patients

Between January 2002 and May 2007, 83 LTx on 81 patients were underwent at the University of Hiroshima. Of these, 36 patients were excluded from the study because of death within 1 year (n = 13), fulminant hepatitis as the primary disease (n = 7), retransplantation (n = 2), splenectomy that had already been performed at LTx (n = 2), or insufficient clinical examinations (n = 12). The remaining 45 patients who had undergone LTx because of liver cirrhosis were analyzed. The profiles of these patients are shown in Table 1. Computed tomography was performed preoperatively and at 1 and 6 months after LTx. The hemoglobin (Hgb) levels and the serial white blood cell and PLT counts were obtained from the medical charts of the LTx recipients. The SV was measured from computed tomography images obtained with a workstation (Virtual Place Advance 300, AZE, Ltd.). The body surface area (BSA) was calculated as follows with the equation of Whitington et al.[14]:

$$BSA\ (m^2) = Body\ weight\ (kg)^{0.425} \times Body\ height\ (cm)^{0.725} \times 0.007184$$

In this study, the SV/BSA value was used as a parameter for assessing splenomegaly.

Statistical Analysis

The postoperative data were compared with an unpaired Student t test. The correlations between variables were assessed with the Spearman rank order correlation coefficient, and a P value < 0.05 was considered statistically significant. The data are expressed as mean ± standard deviation.

RESULTS

The extent of thrombocytopenia and splenomegaly prior to LTx varied in the 45 patients. This might reflect various degrees of liver cirrhosis. The PLT count ranged from $2.6 \times 10^4/mm^3$ to $18.0 \times 10^4/mm^3$, and the SV ranged from 98 to 1299 mL. The average PLT count and SV of the 45 patients before and after LTx are shown in Table 2. The PLT count was observed to increase significantly 1 month after LTx. However, no further increase was observed thereafter. In contrast, the SV values demonstrated a downward trend until 1 month after LTx and plateaued thereafter.

Because both the PLT count and SV stabilized at 1 month after LTx, we investigated the correlation be-

TABLE 1. Perioperative Clinical Characteristics of Liver Transplant Recipients

Number of patients	45
Gender (male/female)	26/19
Recipient age (years, mean ± SD)	54.5 ± 6.3
Donor age (years, mean ± SD)	34.4 ± 12.9
MELD score (mean ± SD)	13.8 ± 7.5
Blood loss (mL, mean ± SD)	4245 ± 3806
Graft weight/standard liver volume (%, mean ± SD)	51.0 ± 10.9
Spleen volume (cm^3, mean ± SD)	516 ± 304
SV/BSA (mean ± SD)	306.5 ± 177.6
Portal venous pressure (mm Hg, mean ± SD)	
Initial	22.9 ± 6.3
Closure	17.1 ± 6.3
WBC count (mean ± SD)	3901 ± 2097
Hgb (mean ± SD)	10.0 ± 1.4
T-Bil (mg/dL, mean ± SD)	6.0 ± 9.4
ALT (IU/L, mean ± SD)	40.8 ± 28.2
Platelet count ($\times 10^4/mm^3$, mean ± SD)	6.6 ± 3.0
Etiology of liver disease	
Alcoholic	4
Primary biliary cirrhosis	1
Autoimmune liver disease	3
Chronic hepatitis B	15
Chronic hepatitis C	18
Hepatocellular carcinoma	27
Other	3

Abbreviations: ALT, alanine aminotransferase; Hgb, hemoglobin; MELD, Model for End-Stage Liver Disease; SD, standard deviation; SV/BSA, spleen volume to body surface area ratio; T-Bil, total bilirubin; WBC, white blood cell.

TABLE 2. Changes in the Spleen Volume and Platelet Count After Liver Transplantation

Spleen volume (cm^3, mean ± SD)	
Before LTx	516 ± 304
1 month after LTx	421 ± 220
6 months after LTx	417 ± 212
Platelet count ($\times 10^4/mm^3$, mean ± SD)	
Before LTx	6.6 ± 3.0
1 month after LTx	12.4 ± 6.0
6 months after LTx	12.3 ± 5.7

Abbreviations: LTx, liver transplant; SD, standard deviation.

TABLE 3. Correlation Between Postoperative Thrombocytopenia and Clinical Variables

	Correlation Coefficient	*P* Value
Recipient age	0.20	0.180
Donor age	−0.09	0.574
MELD score	−0.05	0.745
Blood loss	−0.15	0.333
Graft weight/standard liver volume	0.38	0.010
Portal venous pressure		
Initial	−0.18	0.260
Closure	−0.26	0.101
Pre-LTx WBC count	0.37	0.012
Pre-LTx hemoglobin	−0.10	0.500
Pre-LTx PLT count	0.61	0.00001
Pre-LTx T-Bil	−0.24	0.111
Pre-LTx ALT	−0.13	0.400
SV/BSA	−0.67	0.000006

Abbreviations: ALT, alanine aminotransferase; LTx, liver transplant; MELD, Model for End-Stage Liver Disease; PLT, platelet; SV/BSA, spleen volume to body surface area ratio; T-Bil, total bilirubin; WBC, white blood cell.

tween the thrombocytopenia at 1 month after LTx and the perioperative clinical variables by a simple linear regression analysis. The PLT count at 1 month after LTx was clearly inversely related to the pre-LTx SV/BSA value and positively related to the PLT count prior to LTx (Table 3).

The relationship between the pre-LTx SV/BSA value and the PLT count at 1 month after LTx is shown in Fig. 1A. On the basis of the regression line, thrombocytopenia of less than 10×10^4 PLTs/mm^3 at 1 month after LTx could be expected in patients who demonstrated pre-LTx SV/BSA levels of >400. The patients were divided into 2 groups: those with a pre-LTx SV/BSA value < 400 (SV < 400 group; n = 33) and those with a pre-LTx SV/BSA value ≥ 400 (SV ≥ 400 group; n = 12). No significant differences were observed in the Hgb concentrations between the groups. The PLT count in the SV < 400 group significantly increased immediately after LTx and was maintained until 6 months. In contrast, during the observation period, the PLT count was maintained at a lower level and the SV was maintained at a high level in the SV ≥ 400 group ($P < 0.01$; Fig. 1). Thus, preoperative splenomegaly may influence the SV and PLT count at 1 and 6 months after LTx.

A plot of the PLT count before LTx versus the PLT count 1 month after LTx is shown in Fig. 2A. As indicated by the regression line, thrombocytopenia of $<10 \times 10^4$ PLTs/mm^3 at 1 month after LTx could be expected in patients who demonstrated pre-LTx PLT counts of less than 5×10^4/mm^3. The patients were divided into 2 groups: those in whom the PLT count prior to LTx was greater than 5×10^4/mm^3 (PLT > 50K group; n = 28) and those in whom the PLT count prior to LTx was less than or equal to 5×10^4/mm^3 (PLT ≤ 50K group; n = 17). During the observation period, the white blood cell and PLT counts in the PLT > 50K group were significantly higher than those in the PLT ≤ 50K group ($P < 0.05$ and $P < 0.01$, respectively). Furthermore, the SV in the PLT > 50K group was lower than that in the PLT ≤ 50K group ($P < 0.05$). Among the various immunosuppressants, inhibitors of nucleic acid synthesis such as mycophenolate mofetil and azathioprine possibly worsen thrombocytopenia.[15] In this study, 23, 7, 22, and 8 patients were orally administered mycophenolate mofetil within 6 months after LTx in the SV < 400 group, SV ≥ 400 group, PLT > 50K group, and PLT ≤ 50K group, respectively. The dosage of this immunosuppressant was not significantly different among the groups.

Thus, the pre-LTx values of both the SV/BSA level and the PLT count had a significant impact on the PLT count at 1 month after LTx. We further examined whether these factors mutually influence the PLT count at 1 month after LTx. The patients were categorized as follows: the PLT > 50K, SV < 400 group, which consisted of 26 patients without severe thrombocytopenia (pre-LTx PLT count > 5×10^4/mm^3) and with an SV/BSA value < 400; the PLT > 50K, SV ≥ 400 group, which consisted of 2 patients without severe thrombocytopenia and with an SV/BSA value ≥ 400; the PLT ≤ 50K, SV < 400 group, which consisted of 7 patients with severe thrombocytopenia (pre-LTx PLT count ≤ 5×10^4/mm^3) and an SV/BSA value < 400; and the PLT ≤ 50K, SV ≥ 400 group, which consisted of 10 patients with severe thrombocytopenia and an SV/BSA value ≥ 400 (Fig. 3A). The PLT > 50K, SV < 400 group did not suffer from severe splenomegaly, and their PLT count was 15.2 ± 6.2/mm^3 at 1 month after LTx (data not shown). The number of patients in the PLT > 50K, SV ≥ 400 group was too small for a meaningful analysis. The PLT ≤ 50K, SV ≥ 400 group suffered from splenomegaly, and their PLT count at 1 month after LTx was only 7.0 ± 2.1/mm^3. The PLT ≤ 50K, SV < 400 group did not suffer from splenomegaly, and their PLT count increased to 11.3 ± 3.0/mm^3 at 1 month after LTx. The PLT count in the PLT ≤ 50K, SV < 400 group was observed to be significantly elevated versus the PLT ≤ 50K, SV ≥ 400 group ($P = 0.005$; Fig. 3B). Thus, in LTx recipients without splenomegaly, the PLT count can be expected to increase shortly after the operation.

At our institute, preemptive IFN therapy for HCV-infected recipients has been practiced since 2005. We decided to administer preemptive IFN therapy to 9 HCV-infected recipients within 6 months after LTx. In 8 of the 9 HCV patients, neither pre-LTx splenomegaly (SV/BSA value ≥ 400) nor thrombocytopenia (PLT count ≤ 5×10^4/mm^3) existed. They were able to continuously receive IFN therapy without severe thrombocytopenia. In the remaining HCV patient, pre-LTx splenomegaly and thrombocytopenia coexisted. This particular patient suffered from persistent thrombocy-

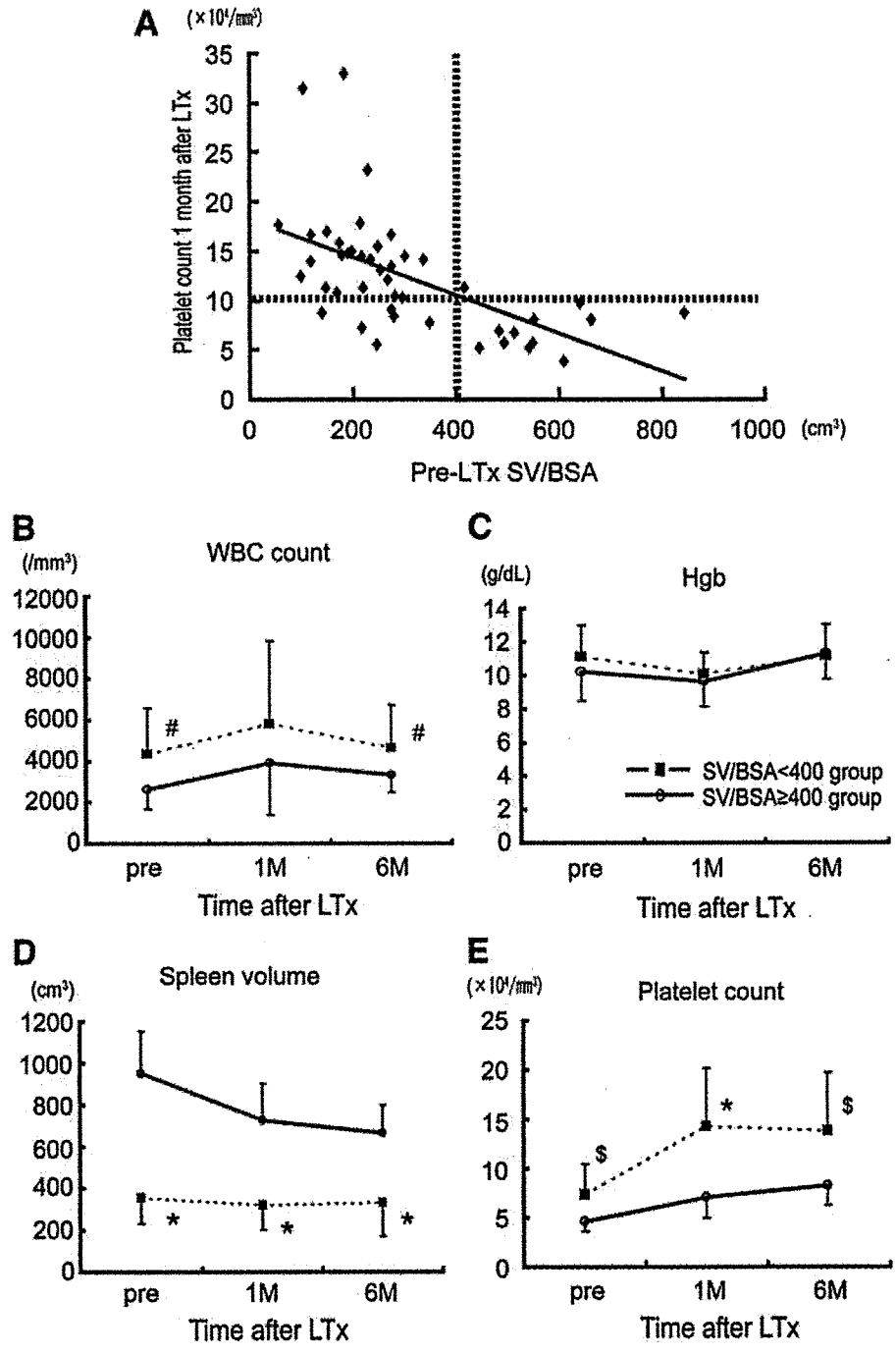

Figure 1. (A) Correlation between the pre-LTx SV/BSA value and PLT count at 1 month after LTx ($r = 0.67$, $P < 0.0001$). A regression line is superimposed on the plot: $y = -0.02x + 18.23$ (x axis: SV/BSA value; y axis: post-LTx PLT count at 1 month). Changes in (B) the WBC count, (C) hemoglobin concentration, (D) spleen volume, and (E) PLT count. The post-LTx values of these variables in the SV < 400 group (broken line with closed squares) and SV ≥ 400 group (thick line with open circles) are shown. There was a significant difference between the groups with respect to the WBC count, PLT count, and spleen volume (#P < 0.05, $P < 0.01, and *P < 0.001 for the SV < 400 group versus the SV ≥ 400 group). Abbreviations: BSA, body surface area; Hgb, hemoglobin; LTx, liver transplant; PLT, platelet; SV, spleen volume; WBC, white blood cell.

topenia and eventually underwent splenectomy so that IFN therapy could be commenced only 9 months after LTx.

DISCUSSION

Thrombocytopenia is an extremely common complication in LTx patients. Several causes have been postulated for this reduced concentration of PLTs, including hypersplenism,[16,17] decreased thrombopoietin levels,[18,19] and destruction by anti-PLT antibodies.[20,21] It has also been reported that serum thrombopoietin levels or anti-PLT antibodies levels correlate with the spleen size.[22-24] This fact is consistent with the finding that the spleen size correlates with portal hypertension and the PLT count in patients with cirrhosis.[16] Our data also demonstrate that pre-LTx splenomegaly is associated with the pre-LTx PLT count. Uneventful LTx is expected to improve splenomegaly.[25,26] However, our data show that splenomegaly remained unchanged in

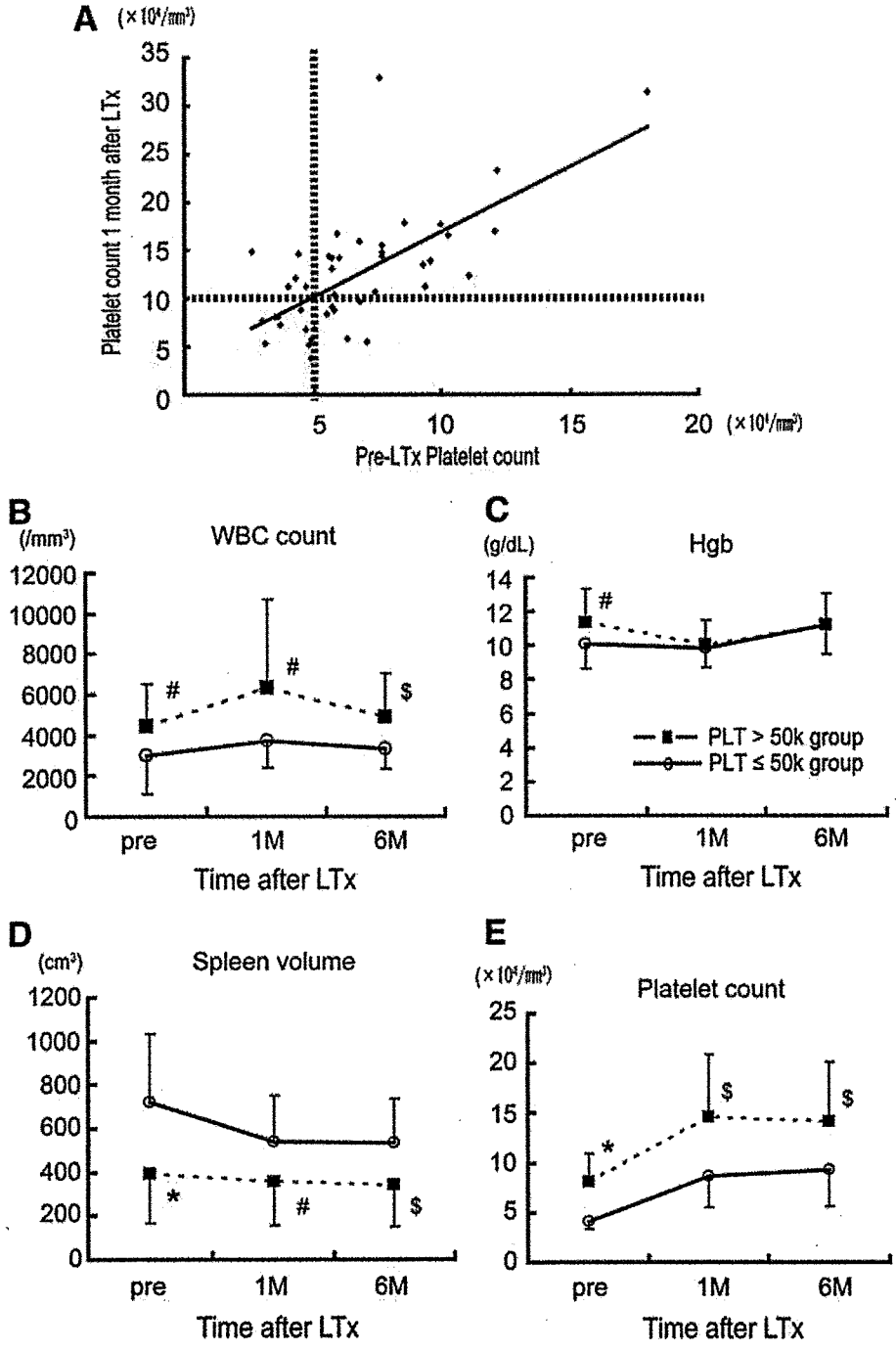

Figure 2. (A) Correlation between the pre-LTx PLT count and PLT count at 1 month after LTx ($r = 0.61$, $P < 0.0001$). A regression line is superimposed on the plot: $y = 1.35x + 3.48$ (x axis: pre-LTx PLT count; y axis: post-LTx PLT count at 1 month). Changes in (B) the WBC count, (C) hemoglobin concentrations, (D) spleen volume, and (E) PLT count. The values of these variables after LTx in the PLT > 50K group (broken line with closed squares) and PLT ≤ 50K group (thick line with open circles) are shown. There was a significant difference between the groups with respect to the WBC count, hemoglobin concentration, PLT count, and spleen volume (#$P < 0.05$, $P < 0.01$, and *$P < 0.001$ for the PLT > 50K group versus the PLT ≤ 50K group). Abbreviations: Hgb, hemoglobin; LTx, liver transplant; PLT, platelet; WBC, white blood cell.

LTx recipients whose pre-LTx SV/BSA level exceeded 400. Among the various perioperative clinical factors, the SV/BSA level was the most significant determinant of the PLT count after LTx. In the present analysis, the PLT count of patients with pre-LTx thrombocytopenia (PLT count $\leq 5 \times 10^4/mm^3$) increased significantly after LTx in the group with no pre-LTx splenomegaly (SV/BSA value < 400) versus the group with pre-LTx splenomegaly ($P < 0.01$).

We recently reported that splenectomy should be performed simultaneously with LTx in HCV patients with a PLT count $< 6 \times 10^4/mm^3$ in order to complete preemptive IFN therapy at an earlier time point in the postoperative period.[27] Several authors have reported that the only indication for simultaneous splenectomy in LTx is the preoperative PLT count[12,28,29] because thrombocytopenia in the immediate posttransplant period is correlated with a low preoperative PLT count.[30]

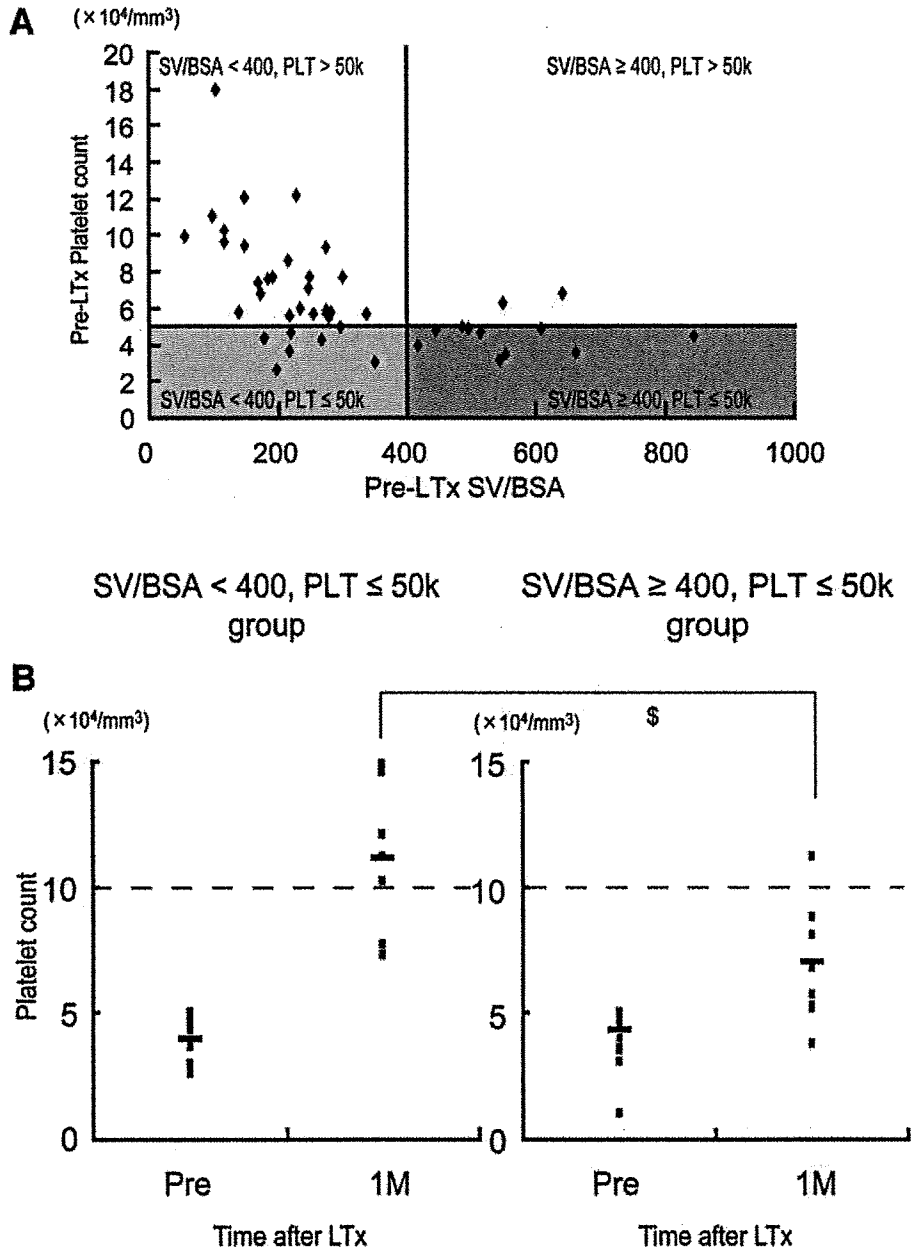

Figure 3. (A) Correlation between the pre-LTx SV/BSA value and pre-LTx PLT count. The patients were categorized as follows: the PLT > 50K, SV < 400 group, which consisted of patients without severe thrombocytopenia (pre-LTx PLT count > 5 × 10^4/mm^3) and without severe splenomegaly (pre-LTx SV/BSA level < 400); the PLT > 50K, SV ≥ 400 group, which consisted of patients without severe thrombocytopenia and with severe splenomegaly (pre-LTx SV/BSA value ≥ 400); the PLT ≤ 50K, SV < 400 group, which consisted of patients with severe thrombocytopenia (pre-LTx PLT count ≤ 5 × 10^4/mm^3) and without severe splenomegaly; and the PLT ≤ 50K, SV ≥ 400 group, which consisted of patients with severe thrombocytopenia and with severe splenomegaly. (B) Changes in the PLT count in the PLT ≤ 50K, SV < 400 group and PLT ≤ 50K, SV ≥ 400 group. The PLT count in the PLT ≤ 50K, SV < 400 group was significantly elevated versus that in the PLT ≤ 50K, SV ≥ 400 group (*P < 0.01). Abbreviations: BSA, body surface area; LTx, liver transplant; PLT, platelet; SV, spleen volume.

Studies have also reported that the routine administration of simultaneous splenectomy and LTx in all HCV patients conditions them for anti-HCV IFN therapy.[31] Although splenectomy strongly affects thrombocytopenia, it might predispose patients to develop portal vein thrombosis or increase the risk of sepsis, which is particularly lethal for immunosuppressed subjects.[32] Thus, caution is advised when recommending splenectomy for patients undergoing LTx. Compared with splenectomy, splenic artery ligation is a technically simpler procedure that can easily be included in a complicated transplant operation.[33] However, the benefit of splenic artery ligation in reducing posttransplant thrombocytopenia is controversial.[34,35] Recently, partial splenic embolization (PSE) has been described as a useful procedure for severe post-LTx thrombocytopenia,[36,37] and PSE could also be an option for pre-LTx.[38] However, several groups have reported complications generally observed after PSE, including splenic infarction, abscess formation, reduced immunity-related septic complications, and portal thrombosis.[39,40] Thus, the most appropriate methods among the strategies or alternative methods for avoiding persistent thrombocytopenia remain to be elucidated.

In conclusion, the pre-LTx SV/BSA value and PLT count have been correlated with post-LTx thrombocytopenia. If both splenomegaly and thrombocytopenia coexist (PLT count ≤ 5 × 10^4/mm^3 and SV/BSA

value ≥ 400), persistent thrombocytopenia is predictable after LTx.

ACKNOWLEDGMENT

The authors thank Dr. Kohei Ishiyama, Dr. Masayuki Shishida, Dr. Hiroyuki Tahara, and Dr. Masataka Banshodani for their advice.

REFERENCES

1. Plevak DJ, Halma GA, Forstrom LA, Dewanjee MK, O'Connor MK, Moore SB, et al. Thrombocytopenia after liver transplantation. Transplant Proc 1988;20(suppl 1):630-633.
2. McCaughan GW, Herkes R, Powers B, Rickard K, Gallagher ND, Thompson JF, et al. Thrombocytopenia post liver transplantation. Correlations with pre-operative platelet count, blood transfusion requirements, allograft function and outcome. J Hepatol 1992;16:16-22.
3. Richards EM, Alexander GJ, Calne RY, Baglin TP. Thrombocytopenia following liver transplantation is associated with platelet consumption and thrombin generation. Br J Haematol 1997;98:315-321.
4. Mor E, Jennings L, Gonwa TA, Holman MJ, Gibbs J, Solomon H, et al. The impact of operative bleeding on outcome in transplantation of the liver. Surg Gynecol Obstet 1993;176:219-227.
5. Tabasco-Minguillan J, Jain A, Naik M, Weber KM, Irish W, Fung JJ, et al. Gastrointestinal bleeding after liver transplantation. Transplantation 1997;63:60-67.
6. Shergill AK, Khalili M, Straley S, Bollinger K, Roberts JP, Ascher NA, et al. Applicability, tolerability and efficacy of preemptive antiviral therapy in hepatitis C-infected patients undergoing liver transplantation. Am J Transplant 2005;5:118-124.
7. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. J Clin Invest 1966;45:645-657.
8. Kutti J, Weinfeld A, Westin J. The relationship between splenic platelet pool and spleen size. Scand J Haematol 1972;9:351-354.
9. Wadenvik H, Denfors I, Kutti J. Splenic blood flow and intrasplenic platelet kinetics in relation to spleen volume. Br J Haematol 1987;67:181-185.
10. Neumann UP, Langrehr JM, Kaisers U, Lang M, Schmitz V, Neuhaus P. Simultaneous splenectomy increases risk for opportunistic pneumonia in patients after liver transplantation. Transpl Int 2002;15:226-232.
11. Lusebrink R, Blumhardt G, Lohmann R, Bachmann S, Knoop M, Lemmens HP, et al. Does concomitant splenectomy raise the mortality of liver transplant recipients? Transpl Int 1994;7(suppl 1):S634–S636.
12. Troisi R, Colle I, Van Vlierberghe H, Hesse UJ, Cuomo O, de Hemptinne B. Splenectomy and liver transplantation. Transplant Proc 2001;33:1500-1501.
13. Samimi F, Irish WD, Eghtesad B, Demetris AJ, Starzl TE, Fung JJ. Role of splenectomy in human liver transplantation under modern-day immunosuppression. Dig Dis Sci 1998;43:1931-1937.
14. Whitington PF, Emond JC, Whitington SH, Broelsch CE, Baker AL. Small-bowel length and the dose of cyclosporine in children after liver transplantation. N Engl J Med 1990; 322:733-738.
15. Danesi R, Del Tacca M. Hematologic toxicity of immunosuppressive treatment. Transplant Proc 2004;36:703-704.
16. Adinolfi LE, Giordano MG, Andreana A, Tripodi MF, Utili R, Cesaro G, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. Br J Haematol 2001;113:590-595.
17. Bashour FN, Teran JC, Mullen KD. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. Am J Gastroenterol 2000;95:2936-2939.
18. Martin TG III, Somberg KA, Meng YG, Cohen RL, Heid CA, de Sauvage FJ, et al. Thrombopoietin levels in patients with cirrhosis before and after orthotopic liver transplantation. Ann Intern Med 1997;127:285-288.
19. Tsukahara A, Sato Y, Yamamoto S, Suzuki S, Nakatsuka H, Watanabe T, et al. Thrombopoietin levels and peripheral platelet counts following living related donor liver transplantation. Hepatogastroenterology 2003;50:227-230.
20. Pockros PJ, Duchini A, McMillan R, Nyberg LM, McHutchison J, Viernes E. Immune thrombocytopenic purpura in patients with chronic hepatitis C virus infection. Am J Gastroenterol 2002;97:2040-2045.
21. Nagamine T, Ohtuka T, Takehara K, Arai T, Takagi H, Mori M. Thrombocytopenia associated with hepatitis C viral infection. J Hepatol 1996;24:135-140.
22. Giannini E, Borro P, Botta F, Fumagalli A, Malfatti F, Podesta E, et al. Serum thrombopoietin levels are linked to liver function in untreated patients with hepatitis C virus-related chronic hepatitis. J Hepatol 2002;37:572-577.
23. Kuwana M, Okazaki Y, Kaburaki J, Kawakami Y, Ikeda Y. Spleen is a primary site for activation of platelet-reactive T and B cells in patients with immune thrombocytopenic purpura. J Immunol 2002;168:3675-3682.
24. Sanjo A, Satoi J, Ohnishi A, Maruno J, Fukata M, Suzuki N. Role of elevated platelet-associated immunoglobulin G and hypersplenism in thrombocytopenia of chronic liver diseases. J Gastroenterol Hepatol 2003;18:638-644.
25. Egami S, Sugawara Y, Mizuta K, Kaneko J, Kawarasaki H, Makuuchi M. Effect of pediatric living-donor liver transplantation on splenomegaly. Transplantation 2002;74: 1639-1642.
26. Kaneko J, Sugawara Y, Akamatsu N, Kokudo N, Makuuchi M. Spleen volume and platelet number changes after living donor liver transplantation in adults. Hepatogastroenterology 2004;51:262-263.
27. Tashiro H, Itamoto T, Ohdan H, Fudaba Y, Kohashi T, Amano H, et al. Should splenectomy be performed for hepatitis C patients undergoing living-donor liver transplantation? J Gastroenterol Hepatol 2007;22:959-960.
28. Cescon M, Sugawara Y, Takayama T, Seyama Y, Sano K, Imamura H, et al. Role of splenectomy in living-donor liver transplantation for adults. Hepatogastroenterology 2002; 49:721-723.
29. Hashikura Y, Kawasaki S, Okumura N, Ishikawa S, Matsunami H, Ikegami T, et al. Prevention of hepatic artery thrombosis in pediatric liver transplantation. Transplantation 1995;60:1109-1112.
30. Chatzipetrou MA, Tsaroucha AK, Weppler D, Pappas PA, Kenyon NS, Nery JR, et al. Thrombocytopenia after liver transplantation. Transplantation 1999;67:702-706.
31. Kishi Y, Sugawara Y, Akamatsu N, Kaneko J, Tamura S, Kokudo N, et al. Splenectomy and preemptive interferon therapy for hepatitis C patients after living-donor liver transplantation. Clin Transplant 2005;19:769-772.
32. Settmacher U, Nussler NC, Glanemann M, Haase R, Heise M, Bechstein WO, et al. Venous complications after orthotopic liver transplantation. Clin Transplant 2000;14:235-241.
33. Lo CM, Liu CL, Fan ST. Portal hyperperfusion injury as the cause of primary nonfunction in a small-for-size liver graft—successful treatment with splenic artery ligation. Liver Transpl 2003;9:626-628.
34. Matsukura A, Kita Y, Harihara Y, Kubota K, Takayama T, Kawarasaki H, et al. Is splenic artery ligation effective for thrombocytopenia early after liver transplantation? Transplant Proc 1999;31:2906-2907.

35. Troisi R, Cammu G, Militerno G, De Baerdemaeker L, Decruyenaere J, Hoste E, et al. Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? Ann Surg 2003;237:429-436.
36. Herrero JI, Sangro B, Quiroga J, Bilbao JI, Yuste JR, Longo J, et al. Partial splenic embolization in the treatment of thrombocytopenia after liver transplantation. Transplantation 1997;63:482-484.
37. Sangro B, Bilbao I, Herrero I, Corella C, Longo J, Beloqui O, et al. Partial splenic embolization for the treatment of hypersplenism in cirrhosis. Hepatology 1993;18:309-314.
38. Umeda Y, Yagi T, Sadamori H, Matsukawa H, Matsuda H, Shinoura S, et al. Preoperative proximal splenic artery embolization: a safe and efficacious portal decompression technique that improves the outcome of live donor liver transplantation. Transpl Int 2007;20:947-955.
39. Sekikawa T, Shatney CH. Septic sequelae after splenectomy for trauma in adults. Am J Surg 1983;145:667-673.
40. Bader-Meunier B, Gauthier F, Archambaud F, Cynober T, Mielot F, Dommergues JP, et al. Long-term evaluation of the beneficial effect of subtotal splenectomy for management of hereditary spherocytosis. Blood 2001;97:399-403.

Evaluation of Patients with Esophageal Varices After Endoscopic Injection Sclerotherapy Using Multiplanar Reconstruction MDCT Images

Hideaki Kodama[1]
Hiroshi Aikata[1]
Shintaro Takaki[1]
Shoichi Takahashi[1]
Naoyuki Toyota[2]
Katsuhide Ito[2]
Kazuaki Chayama[1]

OBJECTIVE. The purpose of our study was to assess the relationship between hemodynamic changes in portosystemic collaterals and the prognosis of patients with esophageal varices after endoscopic injection sclerotherapy using multiplanar reconstruction (MPR) MDCT images.

SUBJECTS AND METHODS. The subjects of this prospective study were 53 patients who underwent endoscopic injection sclerotherapy for esophageal varices. We evaluated the reconstructed MPR images of portosystemic collaterals before and after endoscopic injection sclerotherapy. Patients were divided into three groups based on the rate of change in the diameter of the feeding vessel into complete eradication (group A), narrowing (group B), and no change (group C). We analyzed the relationship between hemodynamic change in portosystemic collaterals and prognosis.

RESULTS. The left gastric vein, posterior gastric vein, and left gastric vein plus posterior gastric vein were the main feeding vessels (n = 44 [83%] of patients, n = 5 [9%], and n = 4 [8%], respectively). The proportions of patients of groups A, B, and C were 19% (n = 10), 24% (n = 13), and 57% (n = 30), respectively. The relapse-free rates at 2 years after endoscopic injection sclerotherapy were 100%, 65%, and 52% in groups A, B, and C, respectively ($p < 0.05$). For group C, the relapse-free rate at 2 years after endoscopic injection sclerotherapy of patients with a large-diameter paraesophageal vein (≥ 3 mm, 63%) was significantly higher than in those with a small-diameter paraesophageal vein (< 3 mm, 36%; $p < 0.05$). However, there were no significant differences in the survival rate among the three groups.

CONCLUSION. MPR MDCT images on portosystemic collaterals can accurately predict relapse of esophageal varices after endoscopic injection sclerotherapy.

Keywords: endoscopic injection sclerotherapy, esophageal varices, multiplanar reconstruction image, portosystemic collaterals, recurrence

DOI:10.2214/AJR.08.1268

Received May 2, 2008; accepted after revision July 11, 2008.

[1]Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan. Address correspondence to H. Aikata (aikata@hiroshima-u.ac.jp).

[2]Department of Radiology, Division of Medical Intelligence and Informatics, Programs for Applied Biomedicine, Graduate School of Biomedical Science, Hiroshima University, Hiroshima, Japan.

AJR 2009; 192:122–130

0361–803X/09/1921–122

Hemorrhage from esophageal or gastric varices is one of the main causes of death in patients with liver cirrhosis. The reported prevalence of esophageal varices in patients with cirrhosis ranges from 80% to 90% [1, 2], and 10–30% of patients with esophageal varices per year develop variceal hemorrhage [3]. Despite substantial improvements in early diagnosis and treatment of variceal hemorrhage, the associated mortality remains high (20–35%) [4–6]. Therefore, proper management of esophageal varices could improve the prognosis of patients with liver cirrhosis. Although several treatment techniques for esophageal varices have been developed, including pharmacologic therapy [7, 8], transjugular intrahepatic portosystemic shunts [9], endoscopic sclerotherapy [10, 11], endoscopic ligation [12, 13], percutaneous transhepatic obliteration [14], and surgery [15], complete eradication of esophageal varices by endoscopic injection sclerotherapy is effective in preventing variceal hemorrhage and recurrence after therapy [16–19]. Because of the close relationship between the effects of endoscopic injection sclerotherapy and changes in hemodynamics in portosystemic collaterals, it is important to carefully assess the hemodynamics before beginning treatment.

The portal venous system is evaluated by invasive methods such as angiography and percutaneous transhepatic portography (PTP) [19]. However, these techniques do not visualize about 20–25% of varices-related portosystemic collaterals seen at endoscopy [20].

MDCT represents a major advancement in the field of diagnostic imaging because it provides a fast table speed and, when slices are combined, permits data collection that is well suited for workstation analysis. Multiplanar

reconstruction (MPR) MDCT images provide rapid assessment of portosystemic collaterals along different planes without losing information about the surrounding structures. MDCT can achieve rapid acquisition and higher longitudinal resolution than single-detector CT [21]. The use of MPR significantly improves the images of portosystemic collaterals and the sites of confluence compared with those obtained by axial CT [22, 23].

Noninvasive MDCT with MPR before endoscopic injection sclerotherapy for patients with esophageal varices provides detailed information on the hemodynamics of portosystemic collaterals [23]. Thus, MPR imaging potentially could be an important tool for evaluation of esophageal varices before other invasive imaging techniques, such as angiography and PTP, and thus the management and outcome of endoscopic injection sclerotherapy.

The aim of the present study was to evaluate the utility of MDCT with MPR for visualizing the portal venous system and to measure the long-term effect of endoscopic injection sclerotherapy on portosystemic collaterals, including the rate of relapse and overall prognosis.

Subjects and Methods

Patients

This study was approved by the institutional review board and was based on the Declaration of Helsinki as declared by the World Health Organization; all subjects gave informed consent. All patients were prospectively enrolled in this study and underwent endoscopy and MDCT. The endoscopy was performed by a single endoscopist in the presence of another endoscopist. The final assessment of the endoscopic findings was determined by agreement between the two endoscopists. MDCT findings were interpreted by two radiologists blinded to the clinical and endoscopic findings. The interobserver agreement between the radiologists and endoscopists was determined. The endoscopic findings of esophageal varices were evaluated according to the classification system of the Japanese Society for Portal Hypertension and Esophageal Varices [24]. The form (F) of esophageal varices was classified as complete eradication after treatment (F0), small straight (F1), enlarged tortuous (F2), and large coiled-shaped (F3). The red color sign (RC) was also used in the present study based the criteria of the Japanese Society for Portal Hypertension and Esophageal Varices [24]. RC was defined as endoscopically detected dark-red-colored spots on the mucosa of the lower end of the esophagus. To evaluate the risk of hemorrhage and provide a rough estimate of intravascular pressure within the esophageal varices, RC was classified into four grades: RC0, no mucosal coloring; RC1, a few localized red-colored spots; RC2, between RC1 and RC3; and RC3, several mucosal red-colored spots throughout the circumference of the lower end of the esophagus.

Seventy-two consecutive patients with esophageal varices underwent endoscopic therapy at Hiroshima University Hospital between January 2002 and December 2006. The inclusion criteria were as follows: esophageal varices evaluated as F2 or F3 or RC on endoscopy according to the classification system of the Japanese Society for Portal Hypertension and Esophageal Varices [24], Child-Pugh classification of grade A or B, performance status of grade 0 or 1, absence of tumor thrombus in portal vein trunk, and absence of refractory ascites. Of those patients, five were excluded because they preferred to undergo endoscopic ligation for esophageal varices rather than endoscopic injection sclerotherapy. We also excluded two patients who had a tumor thrombus in the portal vein trunk. Two other patients who had refractory ascites also were excluded. Three patients were excluded because they refused to enroll in the study and sign a consent form. Therefore, 60 patients were included in this study. We defined relapse of esophageal varices as the primary end point. Seven patients who showed lack of complete eradication of esophageal varices on endoscopy were also excluded because relapse could not be recognized in these patients without endoscopically confirmed eradication of esophageal varices. After exclusion of those patients, data of the remaining 53 patients were analyzed for this study.

Endoscopic injection sclerotherapy resulted in evaluation of F0 on endoscopy in all 53 patients. The endoscopic findings of esophageal varices were evaluated according to the classification system of the Japanese Society for Portal Hypertension and Esophageal Varices [24]. Table 1 lists the clinical characteristics of patients. They consisted of 42 men and 11 women with an age range of 30–84 years (mean age [± SD], 60 ± 11 years). The cause of liver cirrhosis was hepatitis B virus infection (n = 9), hepatitis C virus infection (n = 34), alcohol abuse (n = 4), and other causes (n = 6). The severity of liver dysfunction before treatment was evaluated according to Child's classification as A in 18 patients and B in 35 patients. Endoscopic findings of esophageal varices before treatment were evaluated as F1 in nine patients, F2 in 30 patients, and F3 in 14 patients as well as RC0 in 10 patients, RC1 in 11 patients, and RC2 in 32 patients.

TABLE 1: Clinical Characteristics of Patients

Characteristic	Value
Sex	
M	42
F	11
Age range (y) (mean ± SD)	30–84 (60 ±11)
Cause	
Hepatitis B virus	9
Hepatitis C virus	34
Alcohol	4
Other	6
Child-Pugh classification	
A	18
B	35
Variceal size	
F1	9
F2	30
F3	14
Red color sign	
RC0	10
RC1	11
RC2	32
RC3	0

Note—The red color sign (RC) was defined as endoscopically detected dark-red-colored spots on the mucosa of the lower end of the esophagus. To evaluate the risk of hemorrhage and provide a rough estimate of intravascular pressure within the esophageal varices, RC was classified into four grades: RC0, no mucosal coloring; RC1, a few localized red-colored spots; RC2, between RC1 and RC3; RC3, several mucosal red-colored spots throughout the circumference of the lower end of the esophagus. The form (F) of esophageal varices was classified as small straight (F1), enlarged tortuous (F2), and large coiled-shaped (F3) according to the classification system of the Japanese Society for Portal Hypertension and Esophageal Varices [24].

Endoscopic Injection Sclerotherapy Procedure

The concept of our endoscopic injection sclerotherapy technique is embolization of feeding vessels of esophageal varices within portosystemic collaterals by injecting a sclerosing agent. Before endoscopic injection sclerotherapy, each patient was premedicated with an intramuscular injection of 0.5% atropine sulfate, 15–30 mg of pentazocine, and 7.5 mg of timepidium bromide. Lidocaine jelly or spray was applied to the pharyngeal area as a topical anesthetic. A balloon, referred to as the oral side balloon in this study, was attached to the tip of an endoscope (GIF-XQ 240, Olympus) and inflated as the contrast medium (iopamidol)