

[ CASE REPORT ]

## Robust Effect of Hepatic Arterial Infusion Chemotherapy and Radiation Therapy on Hepatocellular Carcinoma Arising from Fontan-associated Liver Disease

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### Abstract:

Fontan-associated liver disease (FALD) caused by long-term systemic venous congestion following the Fontan procedure may eventually lead to hepatocellular carcinoma (HCC). Treatment strategies for HCC due to FALD (FALD-HCC) remain unclear. We herein report a 35-year-old man with FALD-HCC that was well controlled by 3 cycles of continuous infusion of 5-fluorouracil and low-dose cisplatin (low-dose FP therapy) combined with 60 Gy of radiation therapy. However, the patient ultimately died of extrahepatic metastases. A pathological autopsy revealed more than 90% necrosis in the primary HCC lesion. This case suggests that low-dose FP therapy might be effective in FALD-HCC.

**Key words:** Fontan-associated liver disease, hepatocellular carcinoma, low-dose FP therapy, radiation therapy

(Intern Med 61: 1145-1150, 2022)

(DOI: 10.2169/internalmedicine.8154-21)

### Introduction

The Fontan procedure is a palliative surgery that separates the systemic and pulmonary circulations in patients with univentricular hearts (1). Owing to significant advances in paediatric cardiology, the number of long-term survivors without cyanosis has increased. In these patients, haemodynamic changes that occur during a prolonged lifespan often develop into pathological conditions, such as chronic heart failure and Fontan-associated liver disease (FALD), including liver cirrhosis (LC) and hepatocellular carcinoma (HCC) (2, 3). In patients with FALD, hepatic congestion and systemic hypoxia caused by chronic heart failure and systemic-to-pulmonary shunt enhance hepatic fibrogenesis, which is one of the main risk factors for HCC (4).

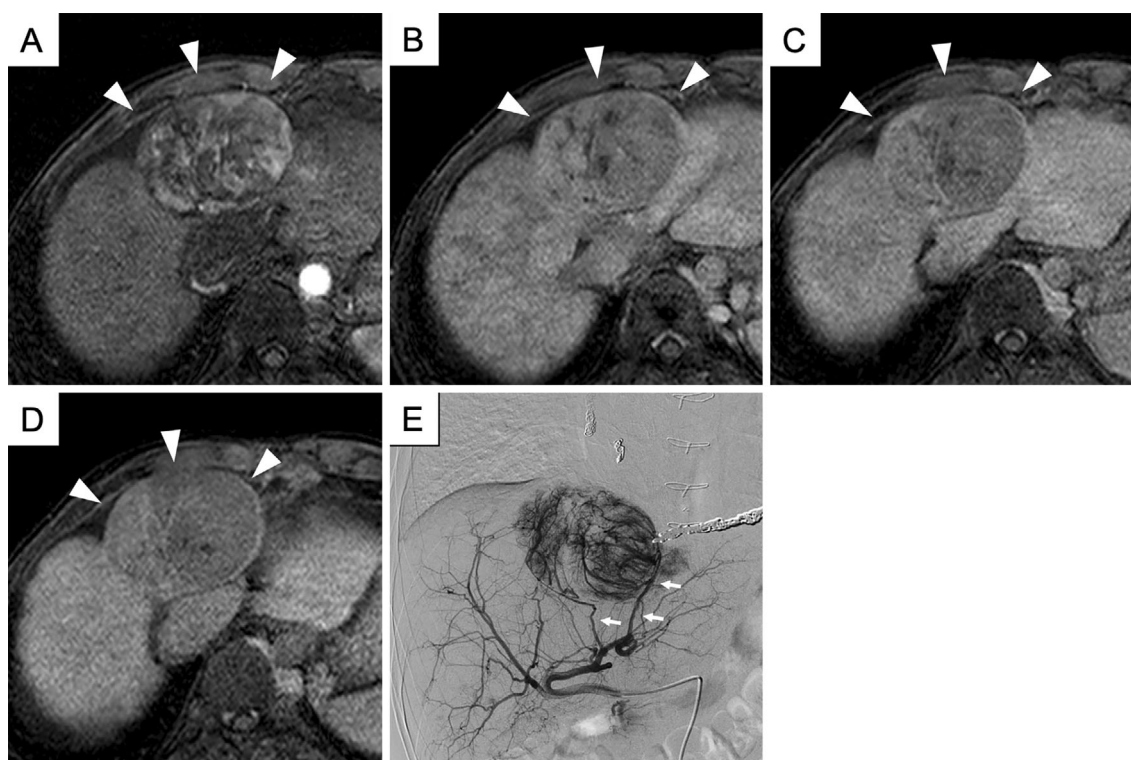
The incidence of HCC due to FALD (FALD-HCC) is 2.9% at 20 years after the Fontan procedure, with a median age at the diagnosis of 32.5 years old (4). It has also been reported that the survival rate 25 years after this procedure in patients without FALD-HCC was significantly higher than in those with FALD-HCC (4).

Liver transplantation, hepatectomy, transarterial chemoembolization (TACE), and molecular-targeted agents (MTAs), including sorafenib and atezolizumab plus bevacizumab combination therapy (5), have been established as standard treatments in patients with HCC, which is commonly caused by hepatitis B/C virus infection, excessive alcohol consumption, and nonalcoholic steatohepatitis. However, these treatments are frequently ineffective in patients with FALD-HCC due to cardiac complications and congenital abnormalities. Since the treatment strategies for these patients are not well

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Received: June 15, 2021; Accepted: August 1, 2021; Advance Publication by J-STAGE: September 25, 2021

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**Figure 1.** Representative images of hepatocellular carcinoma. (A-D) Dynamic Gd-DTPA-EOB-enhanced magnetic resonance imaging showing the tumour in the (A) arterial phase, (B) portal phase, (C) delayed phase, and (D) hepatobiliary phase. Arrowheads represent the tumour. (E) Digital subtraction angiography showing the tumour being fed from the left hepatic arteries (A2-4). Arrows represent the left hepatic arteries.

established and their prognosis is very limited (2, 6), an effective treatment method is required.

To our knowledge, this is the first report of continuous infusion of 5-fluorouracil and low-dose cisplatin (low-dose FP therapy) and radiation therapy in a patient with FALD-HCC, with an autopsy-proven robust effect on HCC described herein.

### Case Report

A 35-year-old man with a single ventricle and tricuspid atresia before birth presented to our clinic for a regular checkup. He had undergone a Glenn procedure at 5 years old and a Fontan procedure at 10 years old.

Since regular HCC checkups had not been performed following the Fontan procedure, a large asymptomatic hepatic tumour (75×72 mm) was incidentally detected by abdominal ultrasonography. Subsequent Gd-DTPA-EOB dynamic magnetic resonance imaging showed enhancement of the tumour in the arterial phase, washout in the delayed phase, and mixed hypointensity and hyperintensity in the hepatobiliary phase, in the left lobe of the liver (S4; Fig. 1A-D). Contrast-enhanced computed tomography showed a pulmonary arteriovenous fistula in the right lower lobe of the lung. There was a small amount of ascites at the surface of the liver and no metastasis.

Laboratory test results revealed that his liver function was

well preserved (albumin-bilirubin score: -2.899, grade 1). (7). His serum alpha-fetoprotein level was 480,874 ng/mL. Liver fibrosis parameters were as follows: serum type IV collagen, 198.0 ng/mL; hyaluronic acid, 50 ng/mL; M2 BPGi, 1.24 [1+]; and fibrosis-4 index, 2.87 (Table). Furthermore, the liver stiffness obtained by transient elastography (FibroScan®) was 24.0 kPa. The patient had no common risk factors for cirrhosis, including excessive alcohol intake, hepatitis B/C virus infection, autoimmune disease, or metabolic disease.

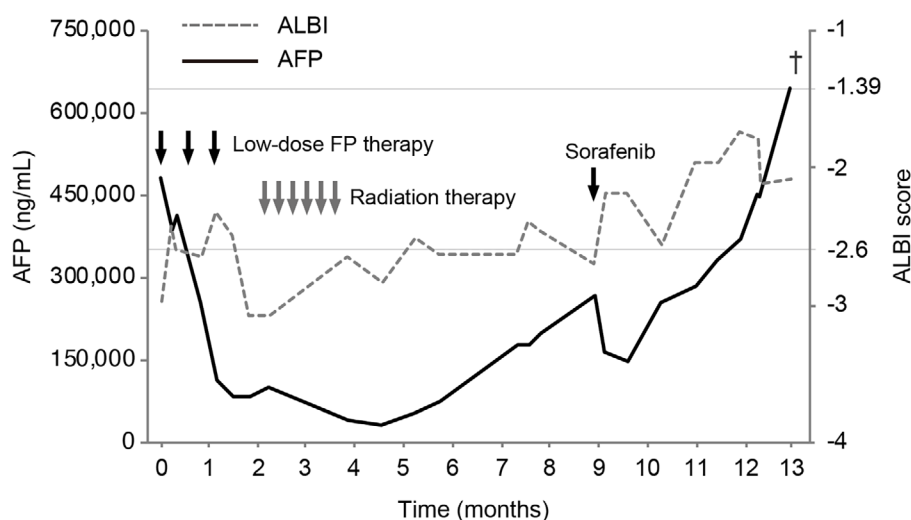
Abdominal ultrasonography showed a dilated inferior vena cava without respiratory variation. On cardiac catheterization, the inferior vena cava mean pressure was 13 mmHg. Esophagogastroduodenoscopy did not reveal any esophagogastric varices. The patient was diagnosed with FALD-HCC and referred to our hospital for advanced HCC treatment.

His underlying disease appeared to be a risk factor for embolism due to material flowing into the systemic artery via a systemic-to-pulmonary venous shunt. To assess this risk, we performed carbon dioxide contrast echocardiography, in which the contrast material injected into the systemic vein was detected in the ventricle. Therefore, TACE was not performed in this case. Instead, hepatic arterial infusion chemotherapy (HAIC), also known as low-dose FP therapy (8), was performed using an implanted reservoir system (Fig. 1E). After three cycles of low-dose FP therapy, the

**Table. Laboratory Data on Admission.**

Blood chemistry		tumour markers	
TP	7.6 g/dL	AFP	480,874 ng/mL
Alb	4.4 g/dL	AFP-L3%	2.5 %
AST	47 IU/L	DCP (warfarin)	143,845 nAU/mL
ALT	43 IU/L	CEA	2.0 ng/mL
ALP	387 IU/L	CA19-9	23.9 U/mL
$\gamma$ -GTP	202 IU/L	Coagulation (warfarin)	
T-Bil	1.1 mg/dL	PT-INR	2.86
BUN	19 mg/dL	PT%	21 %
Cr	0.86 mg/dL	APTT	42.8 s
CRP	0.18 mg/dL	Haematology	
NH <sub>3</sub>	37 $\mu$ g/L	WBC	4,500 / $\mu$ L
HbA1c	6.3 %	RBC	5.28 $\times$ 10 <sup>6</sup> / $\mu$ L
Type IV collagen	198.0 ng/mL	Hb	15.1 g/dL
Hyaluronic acid	50 ng/mL	Ht	44.3 %
M2BPGi	1.24 C.O.I.	Plt	14.6 $\times$ 10 <sup>4</sup> / $\mu$ L
Fibrosis-4 index	2.87		
ALBI score	-2.899		

TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase,  $\gamma$ -GTP:  $\gamma$ -glutamyl transpeptidase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cr: creatinine, CRP: C reactive protein, M2BPGi: Mac-2 binding protein glycosylation isomer, ALBI: albumin-bilirubin, AFP: alpha-fetoprotein, DCP: des- $\gamma$ -carboxy-prothrombin, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, WBC: white blood cell, RBC: red blood cell, Hb: haemoglobin, Ht: haematocrit, Plt: platelet count



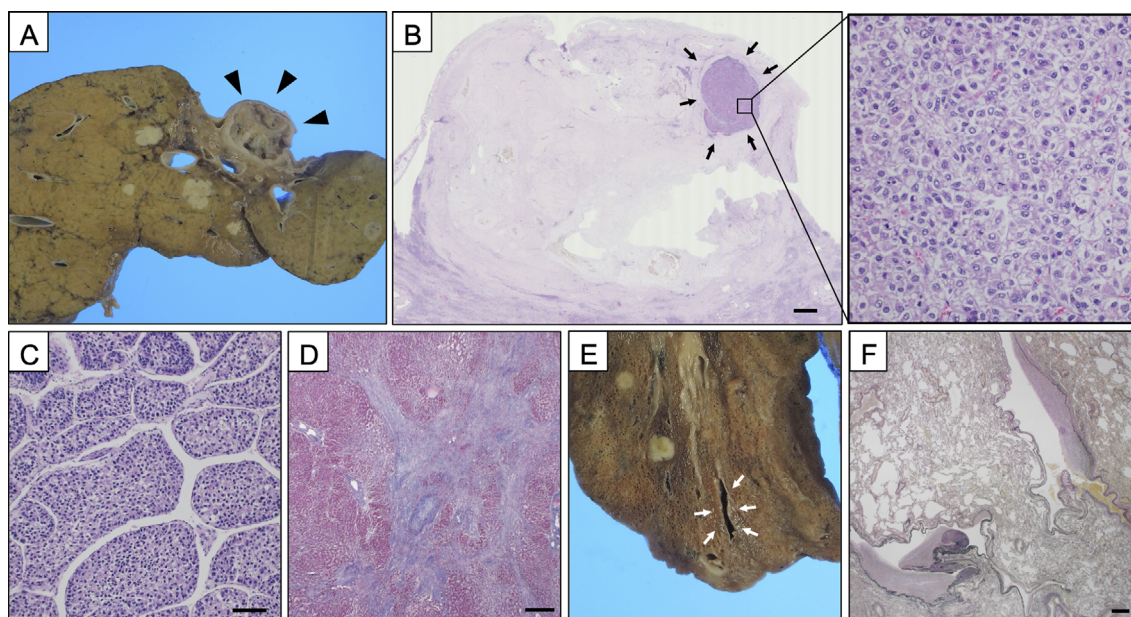
**Figure 2.** Transient hepatic reserve and serum AFP levels during the clinical course. The liver function is well preserved at each point of treatment initiation. AFP: alpha-fetoprotein, ALBI: albumin-bilirubin, low-dose FP therapy: continuous infusion of 5-fluorouracil and low-dose cisplatin

treatment was discontinued due to the occurrence of contrast media allergy, but the tumour shrank to 28 mm in diameter. Thereafter, a total of 60 Gy divided into 20 fractions of radiation therapy was additionally performed for viable HCC lesions that were fed from the right inferior phrenic artery.

The primary HCC lesion was well controlled by low-dose FP therapy and radiation therapy, and the serum alpha-fetoprotein level decreased to 30,469 ng/mL (Fig. 2). Six months later, intra- and extrahepatic (bone and lung) metastases emerged, but no brain metastasis was detected by head

magnetic resonance imaging. His liver function was preserved (albumin-bilirubin score: -2.621, grade 1) (7), and systemic sorafenib therapy (400 mg/day) was initiated; however, it was discontinued 1 week after its initiation due to an alanine aminotransferase increase of Common Terminology Criteria for Adverse Events, version 4.0 grade 3.

Unfortunately, the disease progressed with extensive extrahepatic metastases, and the patient eventually died of rupture of a metastatic brain tumour 16 months after the detection of primary HCC. We performed a pathological autopsy



**Figure 3.** Macroscopic and microscopic examinations of the liver and lung at the autopsy. (A) Arrowheads represent the primary HCC lesion. (B) Left: more than 90% of the tumour cells in the primary HCC lesion show necrosis. A viable HCC area is only observed in part [arrows and right; Hematoxylin and Eosin (H&E) staining]. Scale bar represents 1 mm. (C) Intrahepatic metastatic lesion showing a thick trabecular pattern (H&E staining). Scale bar represents 100  $\mu$ m. (D) Non-cancerous lesion; varying degrees of fibrosis are apparent around the central vein, portal vein, and intra-sinusoid. In highly fibrotic lesions, irregular-shaped fibrosis without bridging fibrosis is apparent, which is different from that observed in ordinary liver cirrhosis. Invasion of inflammatory cells is not observed (H&E staining). Scale bar represents 500  $\mu$ m. (E) Arrows represent an arteriovenous fistula in the right lower lobe of the lung. (F) An increasing number of arteriovenous fistulas connected to abnormal vessels with irregular intimal thickening is apparent (Elastica van Gieson staining). Scale bar represents 500  $\mu$ m. HCC: hepatocellular carcinoma

after obtaining consent to do so from his family, which revealed that more than 90% of the tumour cells in the primary HCC lesion were necrotic, indicating that a good therapeutic response of the primary site had been obtained by low-dose FP therapy and radiation therapy (Fig. 3A, B). Histologically, the intrahepatic metastatic lesions showed a thick trabecular pattern (Fig. 3C), and non-cancerous liver tissues demonstrated irregular-shaped fibrosis without bridging fibrosis (Fig. 3D). In the right lower lobe of the lung, an increased number of arteriovenous fistulas with irregular intimal thickening were observed (Fig. 3E, F).

### Ethical statement

Written informed consent for the publication of this case report and any accompanying images was obtained from the patient before his death.

## Discussion

The Fontan procedure was first described by Dr. Fontan in 1971 and has since become the standard treatment in patients with univentricular hearts (1). Significant progress in paediatric cardiology has prolonged the lifespan of these patients. However, the number of patients with late complica-

tions after the Fontan procedure has concurrently increased. The severity of liver damage and hepatic fibrosis is strongly associated with the interval from the first Fontan procedure, which indicates a prolonged duration of hepatic congestion and systemic hypoxia caused by inadequate cardiac output from the single ventricle (9).

LC is a major risk factor for HCC. However, the prevalence and severity of cirrhotic changes in patients with FALD have not yet been clarified. A liver biopsy, the gold standard for diagnosing LC, is difficult to perform in patients with FALD due to hepatic congestion and prophylactic anticoagulation. Several non-invasive diagnostic tools, such as ultrasound elastography and magnetic resonance elastography, are useful for diagnosing LC (10, 11). Consistent with previous reports, the imaging findings in this patient showed an LC pattern. However, the general serum markers for hepatic fibrosis, such as type IV collagen and M2BPGi, were only slightly elevated (4). Therefore, an accurate multimodality assessment of hepatic fibrosis is important.

A previous study reported a FALD-HCC incidence of 2.9% at 20 years after the Fontan procedure, and the survival rate after 25 years was significantly lower in patients with FALD-HCC than in those without FALD-HCC (4).

Consistent with this report, HCC occurred 25 years after the Fontan procedure in our patient. Furthermore, a nationwide survey from Japan revealed that the mortality rate of patients with FALD with LC and/or FALD-HCC (29.4%) was markedly higher than that of patients without LC and/or FALD-HCC (0.19%) (12).

Since information on the management of FALD-HCC is limited, the optimal treatment strategy needs to be discussed. Liver transplantation, hepatectomy, HAIC, TACE, proton beam therapy, and best supportive care have been suggested as treatments of FALD-HCC. However, their therapeutic effects are very limited, resulting in a poor prognosis in patients with FALD-HCC (9). In patients with FALD-HCC, liver transplantation and hepatectomy are generally very difficult due to a poor cardiac function and three to four times higher systemic venous pressure than in normal patients (9). Several reports have demonstrated that TACE was useful for the treatment of FALD-HCC, so we did consider performing TACE (2, 4, 9). In general, the presence of systemic-to-pulmonary venous shunt may cause unexpected embolism due to the embolic material used in TACE, as described in a previous case report of post-TACE cerebral infarction and retinal artery occlusion in a patient with FALD-HCC (13). Therefore, it is important to carefully assess the risk of embolism when performing TACE, especially in patients with cyanosis due to systemic-to-pulmonary venous shunts. To assess the risk of developing unexpected embolisms, contrast echocardiography is used. HAIC, which does not use embolic substances, carries a lower risk of inducing embolism than TACE. Therefore, HAIC may be an appropriate treatment in patients with FALD-HCC (8).

Despite the particularity of the HAIC procedure, it has been performed in a large number of patients with advanced HCC without extrahepatic metastases in Japan. The most commonly used regimen is low-dose FP therapy (14). Factors associated with the survival and therapeutic efficacy of low-dose FP therapy include the liver function and tumour spread status (15). Based on these findings, the present case was considered a good candidate for low-dose FP therapy.

In the present patient, although the primary HCC lesion was well treated with low-dose FP therapy (8) and radiation therapy, it was difficult to control extrahepatic lesions. MTAs, including sorafenib, are widely used for the treatment of unresectable HCCs showing multiple nodules or extrahepatic metastases. However, treatment with these drugs in patients with FALD-HCC seems difficult, as it is associated with a high risk of unexpected systemic adverse events due to cardiac complications and congenital abnormalities. In a previous report, shortly after sorafenib administration in patients with FALD-HCC, gastrointestinal bleeding occurred (16). In our report, the alanine aminotransferase levels increased one week after sorafenib initiation, and the treatment was discontinued. Recently, atezolizumab plus bevacizumab, a combination therapy of immunotherapy plus MTA, was approved as first-line therapy for patients with unresectable HCC. However, immunotherapy has been re-

ported to be less effective in patients with HCC of a non-viral aetiology than in those with a viral aetiology (hepatitis B/C virus infection) (17). In addition, one of the most frequent severe adverse events of bevacizumab was gastrointestinal bleeding (5). Given that FALD-HCC has a non-viral aetiology and patients with FALD are often being treated with anticoagulant therapy, such as warfarin, this combination therapy might be unsuitable for patients with FALD-HCC.

To our knowledge, this is the first report to show the robust effects of low-dose FP therapy and radiation therapy for FALD-HCC in an autopsy case.

## Conclusion

Low-dose FP therapy and radiation therapy exert a robust effect on primary HCC due to Fontan-associated cirrhosis. Further research is needed to establish a method of making an early diagnosis of FALD-HCC and determining the most suitable treatment of this disease. As the number of adult patients with a post-Fontan status increases, the establishment of treatment strategies for FALD-HCC will become more and more important.

**The authors state that they have no Conflict of Interest (COI).**

## Acknowledgments

The authors thank the patient and his family for being involved in this case.

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*Intern Med* 61: 1145-1150, 2022