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CASE REPORT

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간 이식 후 재발한 간세포암의 Sorafenib 치료: 4예 보고

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Sorafenib in the Treatment of Recurrent Hepatocellular Carcinoma after Liver Transplantation: A Report of Four Cases

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With an increasing number of patients with hepatocellular carcinoma (HCC) undergoing liver transplantation (LT), tumor recurrence remains the main limiting factor for long-term survival. Although sorafenib is available for advanced HCC, there is still a lack of data on the use of sorafenib for treatment of recurrent HCC after LT. Here, we report on four cases of the use of sorafenib for treatment of recurrent HCC after LT. The median time of recurrence from LT was 4 months (range, 1-16 months). Two of the four evaluated patients showed stable disease, which was the best response and the duration of stabilization was 11 months and 5 months, respectively. One patient also experienced stable disease and remained in stable disease without sorafenib therapy for 29 months and the total duration of stabilization was 38 months. The remaining patient showed partial response but stopped treatment due to radiological tumor progression during treatment. Although all cases were high risk group for recurrence such as above Milan criteria, vascular invasion and tumor biology, clinical outcomes showed some good results. Therefore, sorafenib may be an acceptable treatment option for recurrent HCC after LT. **(Korean J Gastroenterol 2015;65:246-251)**

Key Words: Hepatocellular carcinoma; Liver transplantation; Recurrence; Sorafenib

INTRODUCTION

The worldwide incidence of hepatocellular carcinoma (HCC) is rising and is actually estimated as 750,000 new patients per year.[1] Liver transplantation (LT) offers a potential cure by complete elimination of the tumor and underlying liver cirrhosis which will develop HCC. Although recurrence of HCC after LT has decreased significantly since using the Milan criteria, 8-12% of patients will develop HCC recurrence and will have a significantly diminished overall survival. The majority of patients with HCC recurrence after LT have multifocal or extrahepatic metastases; therefore, they are less likely to be candidates for loco-regional therapy such as resection, radiofrequency ablation, or transarterial chemoembolization (TACE). Therefore, palliative or systemic therapy is often the only treatment option in these patients. Sorafenib is a multi-tyrosine kinase and angiogenesis inhibitor and randomized phase 3 trials have shown an overall

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survival benefit in patients with advanced HCC[2,3]; however, little has been reported on the safety and efficacy of sorafenib in the recurrent HCC after LT. We have herein reported our experience with sorafenib treatment for HCC recurrence after LT.

CASE REPORTS

A summary of patient demographics, clinical characteristics and outcomes of the four patients is shown in Tables 1 and 2.

1. Case 1

A 54-year old man was followed up for HBV-associated liver cirrhosis and diagnosed as HCC without extrahepatic metastases in October 2010. He received living donor liver transplantation (LDLT) in November 2010 and the pathology revealed Edmondson-Steiner grading II/III. In our institute, after LT, patients were monitored with abdomen CT on the day of one month after discharge and then abdominal CT scan every 3 months and chest CT every 6 months for the first 2 years, and then biannually. Monitoring of AFP was performed together with radiological controls. After LDLT, he was routinely followed up. Five months later, routine tumor marker levels including AFP and protein-induced by vitamin K absence or antagonist II (PIVKA-II) were increased and abdominal and chest CT were performed. A chest CT showed variable sized multiple nodules on both lungs (largest, lingular segment, 8 mm) (Fig. 1A, B). Based on the diagnosis of HCC metastasis to the lung, we started therapy with sorafenib at a dose of 400 mg twice daily in April 2011 and one month later, dose adjustment (400 mg once daily) was required due to diarrhea. He improved after dose adjustment and could maintain sorafenib administration with a full dose of 400 mg twice daily. Two months after sorafenib administration, chest CT showed that the majority of variable sized multiple nodules on both lungs had disappeared and some indeterminate nodules remained (Fig. 1C, D). Further routine chest CT showed no interval change and we considered that he had achieved stable disease to sorafenib according to the response evaluation criteria in solid tumors (RECIST). We recommended continuation of sorafenib administration, but he wanted to stop sorafenib therapy because of economic burden. Total duration of treatment was 9 months and he remains in stable disease without sorafenib therapy and is still alive for 38 months after recurrence.

Table 1. Demographics and Clinical Characteristics of the Patients

Patient No.	Gender/ age (yr)	Milan criteria	preLT AFP (ng/mL)	preLT PIVKA-II (mAU/mL)	MELD score	preLT PET uptake	Microvascular invasion	Macrovascular invasion	Patholigic differentiation	Recurrence	Time to recurrence
1	M/54	Beyond	150.4	>2,000	26	Uptake	Yes	Yes	II/III	Lung	5
2	F/57	Within	80.98	59	11	Uptake	Yes	No	IV/III	Lung	16
3	M/58	Beyond	481.9	692	11	Uptake	No	No	IIL/II	Lung	4
4	M/51	Within	2,957	995	22	NA	No	No	II/III	Bone	1

preLT, before liver transplantation; PIVKA-II, vitamin K absence or antagonist II; MELD, model for end-stage liver disease; NA, not applicable.

Table 2. Characteristics of Patients Treated with Sorafenib for Recurrent Hepatocellular Carcinoma after Liver Transplantation

Patient No.	Gender/ age (yr)	Immunosuppressants	Dose of sorafenib (mg)	Significant toxicities	AFP at recurrence (ng/mL)	Nadir AFP after sorafenib (ng/mL)	Best response	Follow up peroid from recurrence (mo)	Total time of sorafenib use (mo)	Current status
1	M/54	Cyclosporin A+MMF	400 (bid) →200 (bid)	Diarrhea G3	46.9	2.42	SD	38	9	Alive
2	F/57	Tacrolimus+MMF →Cyclosporin+MMF	400 (bid)	Alopecia	2.91	1.47	SD	21	19	Alive
3	M/58	Tacrolimus+MMF →Tacrolimus	400 (bid)	HFSR G2	30.1	15.47	SD	23	5	Alive
4	M/51	Tacrolimus→ Tacrolimus+silorimus	400 (bid) →400 (qd)	HFSR G3	180	22.92	PR	14	12	-

MMF, mycophenolate mofetil; bid, twice daily; qd, daily; HFSR, hand-foot skin reaction; SD, stable disease; PR, partial response.

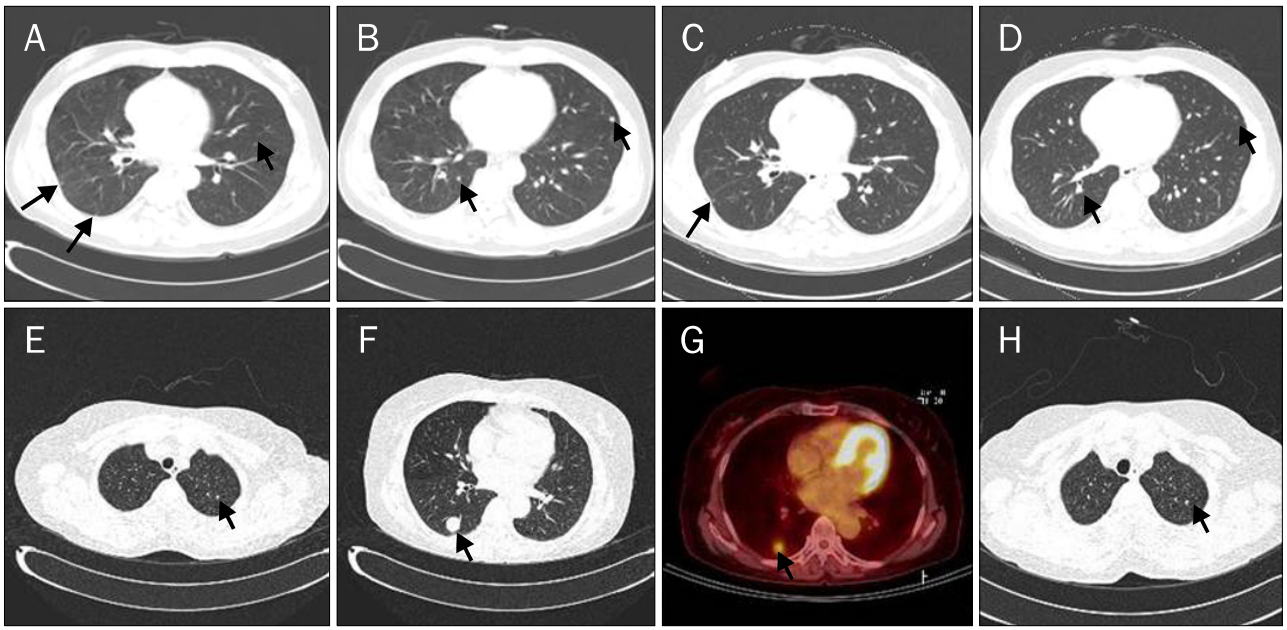

Fig. 1. (A-D) The radiologic features of Case 1. (A, B) Chest CT showed multiple lung nodules on both lobes (arrows) before sorafenib treatment. (C, D) Two months after sorafenib administration, chest CT showed that the majority of variable sized multiple nodules on both lungs (arrows) had disappeared and some indeterminate nodules remained. (E-H) The radiologic features of Case 2. Chest CT (E, F) showed a 19 mm sized dense round nodule (arrows) in the right lower lobe (RLL) and a 3 mm sized indeterminate nodule in the left upper lobe (LUL). (G) PET-CT also showed a hypermetabolic nodule (SUVmax 3.4) on RLL (arrow). (H) Two months after sorafenib administration, chest CT showed no interval change of lung nodule in LUL (arrow).

2. Case 2

A 57-year old woman was followed up for HBV-associated liver cirrhosis and diagnosed as HCC without extrahepatic metastases in February 2011. After diagnosis, she was initially treated with TACE in March 2011 and received LDLT in May 2011. The pathology revealed Edmondson-Steiner grading IV/III. After LDLT, she was routinely followed up. In September 2012, routine chest CT showed a 19 mm sized round nodule in the right lower lobe (RLL) superior segment and a 3 mm sized indeterminate nodule in the left upper lobe (Fig. 1E, F). PET-CT also showed a hypermetabolic nodule (SUVmax 3.4) on RLL (Fig. 1G). Based on the diagnosis of HCC metastasis to the lung, we performed wedge resection for metastatic RLL lesion in October 2012 and pathology also revealed metastatic HCC. After surgery, we started therapy with sorafenib at a dose of 400 mg twice daily in December 2012 for palliative therapy and one month later, dose adjustment (400 mg once daily) was required due to diarrhea. Her symptoms improved after dose adjustment and she was able to maintain sorafenib administration with a full dose of 400 mg twice daily. Further routine chest CT showed no interval change of a 3 mm sized lung nodule in the left upper lobe (Fig. 1H). Total duration of treatment was 19 months and she is still alive for 21 months after recurrence.

3. Case 3

A 58-year old man was followed up for HBV-associated liver cirrhosis and diagnosed as HCC without extrahepatic metastases in October 2011. After diagnosis, he was initially treated with TACE in December 2011 and received LDLT in February 2012. The pathology revealed Edmondson-Steiner grading III/II. After LDLT, he was routinely followed up. Four months later, routine tumor marker levels, such as AFP, were increased and abdominal and chest CT were performed. A chest CT showed variable sized multiple nodules on both lungs (largest, 12 mm) (Fig. 2A, B). Based on the diagnosis of HCC metastasis to the lung, we started therapy with sorafenib at a dose of 400 mg twice daily in July 2012. Five months after sorafenib administration, a chest CT showed that several variable sized multiple nodules on both lungs had decreased and some nodules remained (Fig. 2C, D). Further routine chest CT showed an interval increase in size of multiple lung nodules, which we considered as progressive

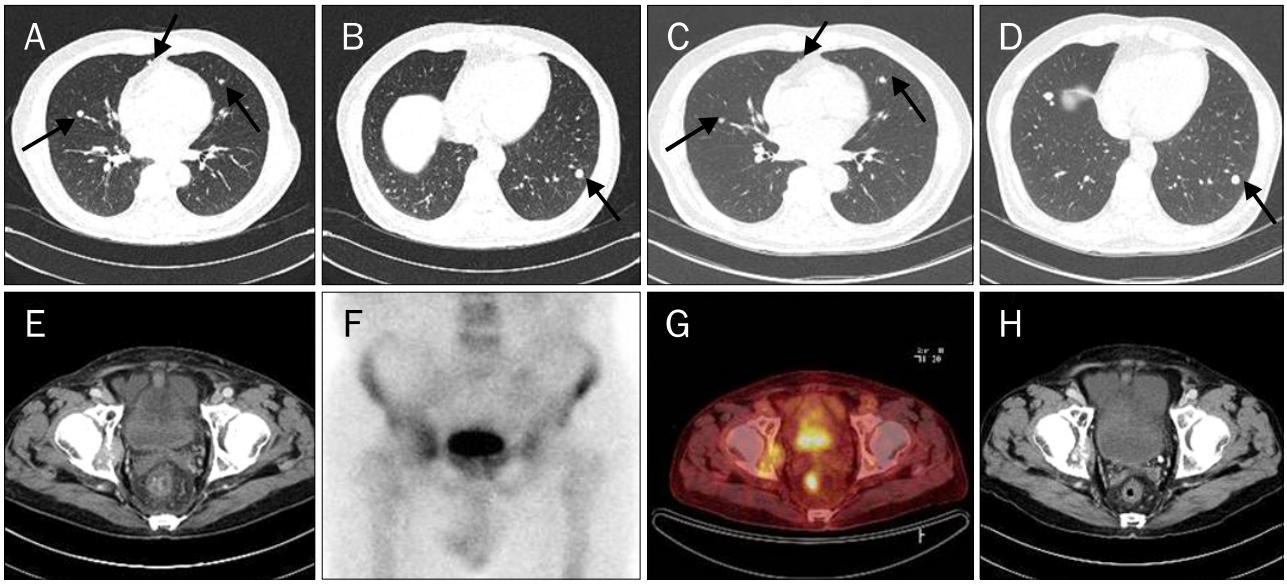

Fig. 2. (A-D) The radiologic features of Case 3. (A, B) Chest CT showed variable sized multiple nodules on both lungs (largest, 12 mm) (arrows) before sorafenib treatment. (C, D) Five months after sorafenib administration, chest CT revealed that several variable sized multiple nodules on both lungs had decreased and some nodules remained (arrows). (E-H) The radiologic features of Case 4. (E) Abdomen CT showed an enhancing mass (4.0×2.9 cm) at the right acetabulum. (F, G) Bone scan and PET-CT also showed bone metastasis in the right pelvic bone. (H) Three month after sorafenib administration, abdomen CT showed interval decrease in the size of metastasis at the right acetabulum.

disease. Total duration of treatment was 5 months and he is still alive for 23 months after recurrence.

4. Case 4

A 51-year old man was followed up for alcohol-associated liver cirrhosis and diagnosed as HCC without extrahepatic metastases in August 2008. Although he received repeated TACE, he underwent deceased donor liver transplantation (DDLT) in May 2012 due to aggravation of liver function and the pathology revealed Edmondson-Steiner grading II/III. After DDLT, he was routinely followed up and one month later, routine tumor marker levels such as AFP and PIVKA-II were increased and abdominal CT showed an enhancing mass (4.0×2.9 cm) at the right acetabulum (Fig. 2E). Bone scan and PET-CT also showed bone metastasis in the right pelvic bone and the right third rib (Fig. 2G, H). Based on the diagnosis of HCC metastasis to the bone, we started combination therapy with sorafenib at a dose of 400 mg twice daily and radiotherapy. Three weeks later, dose adjustment (400 mg once daily) was required due to grade 3 hand-foot skin reaction. Three months after sorafenib administration, an abdomen CT showed an interval decrease in the size of metastasis at the right acetabulum (Fig. 2H). However, because further abdominal CT revealed new HCC at the liver, sorafenib administration was stopped. Unfortunately, despite receiving TACE for new HCC at the liver, he died due to poor general condition after TACE. Total duration of treatment was 12 months and overall survival was 14 months.

DISCUSSION

LT provides the optimal treatment for selected cirrhotic patients and HCC achieving a 5-year patient survival of $>70\%$ and a HCC recurrence rate at 5 years of $<15\%$.[4] Due to the scarcity of donor livers, expansion of the Milan criteria is continuously discussed. Although selected patients with larger tumors may achieve similar survival rates after LT as patients who are fulfilling expansion criteria of the Milan,[5-9] recurrence rate is significantly higher.[10] Currently, there is no established adjuvant treatment and treatment options after HCC recurrence are limited.

Although studies have shown that patients with localized tumor recurrence which are amenable to surgical resection appear to have better survival, the majority of recurrences are multicenter and not amenable to surgical or percutaneous approaches. In our cases, all recurrences occurred in extrahepatic sites (lung, bone). Therefore systemic therapy is required for effective management of extrahepatic meta-

stases. To date, sorafenib is the only drug approved for advanced HCC. Sorafenib is a multi-tyrosine kinase and angiogenesis inhibitor with activity against vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), c-Kit receptors, b-RAF, and p38, signal transduction pathways, which are involved in HCC pathogenesis.[11] In patients with advanced HCC and compensated liver cirrhosis (Child-Pugh A), sorafenib has been shown to improve survival by approximately 3 months.[12]

Since its approval in 2007, only a few small series and case reports have reported safety data for sorafenib in patients with recurrent HCC after LT. A literature review of 78 cases receiving sorafenib treatment for recurrent HCC after LT demonstrated a median post-LT survival of 12 months (range, 1.45-20.1 months) from the beginning of sorafenib therapy and immunosuppression with an mammalian target of rapamycin (mTOR) inhibitor was applied in the majority of cases (79%).[13-17] Also, several recent studies reported that overall survival was significantly greater in patients on sorafenib compared with patients not on sorafenib.[18-20] The overall efficacy of sorafenib in our cases seems similar those of the above mentioned studies and does not seem inferior to that reported in the Asia-pacific trial, of which median time to progression and overall survival were 2.8 months and 6.5 months.[3] We found that all patients experienced adverse effects and grade 3 toxicity occurred in two patients. One patient experienced grade 3 diarrhea and the other patient grade 3 hand-foot skin reaction, but all symptoms were manageable with dose interruption and adjustment. Thus, there seems to be no clinically significant toxicity to administration of sorafenib.

According to RECIST guidelines, complete response means disappearance of all lesions and is very rare. Although there was no complete response in our cases, three of four cases showed some good results in spite of high risk group for recurrence such as above Milan criteria, vascular invasion and tumor biology; in particular, case 1 remains in stable disease without sorafenib therapy and is still alive for 38 months after recurrence. Recently, several centers have reported their retrospective experience with sorafenib, in most cases in combination with an mTOR-based immunosuppression.[13-17] Because of the heterogeneity of immunosuppression regimens, especially combination of mTOR inhibitor, these studies often limit interpretation of sorafenib efficacy. Thus, in our case, we experienced efficacy of sorafenib on recurrent HCC after LT.

Therefore, with careful monitoring, sorafenib may be used safely for recurrent HCC after LT. However, large prospective trials are required to determine the efficacy and safety of sorafenib for treatment of recurrent HCC after LT.

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