Successful Treatment of Hepatocellular Carcinoma with Regorafenib after Sorafenib-induced Hypersensitivity

Naoki Yoshioka, Teiji Kuzuya, Takanori Ito, Yoji Ishizu, Takashi Honda, Tetsuya Ishikawa, Masatoshi Ishigami and Mitsuhiro Fujishiro

Abstract:
Sorafenib and regorafenib are tyrosine kinase inhibitors that are used in the treatment of hepatocellular carcinoma and which have similar chemical structures and toxicity profiles. We herein report a case in which regorafenib treatment could be continued for 10 months and stable disease could be maintained for a long period despite the discontinuation of sorafenib due to grade 4 liver injury and grade 3 fever. The severe adverse events could be attributed to drug hypersensitivity, since a drug-induced lymphocyte stimulation test (DLST) indicated sensitivity to sorafenib. A DLST for regorafenib was negative. This is the first report showing that regorafenib could be safely administered after the discontinuation of sorafenib due to hypersensitivity.

Key words: hepatocellular carcinoma, hypersensitivity, regorafenib, sorafenib

Introduction
Regorafenib as a second-line therapy has been shown to improve overall survival in hepatocellular carcinoma (HCC) patients who show progression under sorafenib treatment (1). However, the use of regorafenib is only recommended for patients who have tolerated sorafenib. We herein present the case of a patient in whom regorafenib could be continued for 10 months without severe adverse events after the discontinuation of sorafenib due to hypersensitivity.

Case Report
The patient was a 58-year-old man who was taken to a local hospital with acute abdominal pain in July 2011. Contrast-enhanced computed tomography (CT) revealed a ruptured tumor of 33 mm in diameter in hepatic segment 2. Hepatectomy was performed and a pathological examination of the resected specimen revealed moderately differentiated HCC without vascular invasion. The surrounding tissue was cirrhotic, which was considered to be the result of chronic alcohol abuse. Tests for hepatitis B surface antigens, hepatitis C antibodies and anti-nuclear antibodies were negative. He had no comorbidities and was not receiving medication for any conditions other than liver disease. In 2015, radiofrequency ablation and transarterial chemoembolization (TACE) were performed to treat regional recurrence.

He was referred to our hospital for further management in January 2016. On presentation to our hospital, his Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0 and his Barcelona Clinic Liver Cancer classification (BCLC) stage was C with multiple intrahepatic recurrences and peritoneal dissemination. Liver function tests revealed a Child-Pugh score of 5 (Table 1). Sorafenib was started at a dose of 800 mg/day and was continued without symptoms. After 32 days, liver injury developed and sorafenib was discontinued. However, nausea and loss of appetite appeared, and the patient’s liver injury showed progression. Intravenous methylprednisolone (1,000 mg) was administered for 3 days, followed by oral prednisolone until the patient made a full recovery from the liver injury. Prednisolone was slowly tapered over one month and was discontinued (Fig. 1). At one month after the discontinuation of prednisolone, a drug-induced lymphocyte stimulation test (DLST) for sorafenib was negative. The stimulation index (SI) was...
developed a fever of >40°C. On the 5th day after restarting sorafenib, the patient was restarted at a low dose of 200 mg/day with safety in mind. In August 2016, sorafenib would have an effect. In August 2016, sorafenib was approved for the treatment of Sorafenib. In June 2017, regorafenib was approved for the treatment of Sorafenib.

**Table 1. Laboratory Data at the Start of Sorafenib Treatment.**

| Parameter     | Value            |
|---------------|------------------|
| White blood cell | 7,200 /µL      |
| Red blood cell    | 4.38 x10^6/µL   |
| Hemoglobin       | 13.7 g/dL       |
| Platelet         | 144 x10^9/µL    |
| Total protein    | 7.1 g/dL        |
| Albumin          | 3.8 g/dL        |
| AST              | 21 U/L          |
| ALT              | 17 U/L          |
| LDH              | 160 U/L         |
| γGTP             | 52 U/L          |
| Cholinesterase   | 275 U/L         |
| Total bilirubin  | 1.0 mg/dL       |
| BUN              | 11.1 mg/dL      |
| Creatinine       | 0.77 mg/dL      |
| AFP              | 7 ng/mL         |
| DCP              | 136 mAU/mL      |

γGTP: γ-glutamyl transferase, AFP: α-fetoprotein, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, DCP: des-γ-carboxy protein, PT-INR: prothrombin time-international normalized ratio, LDH: lactate dehydrogenase.

Contrast-enhanced CT during sorafenib treatment showed that most of the tumors changed from high-density to isodensity in the early arterial phase, and it was predicted that sorafenib would have an effect. In August 2016, sorafenib was restarted at a low dose of 200 mg/day with safety in mind. On the 5th day after restarting sorafenib, the patient developed a fever of >40°C. The fever resolved quickly after the discontinuation of sorafenib. There was no skin disorder, eosinophilia, or liver injury. The DLST for sorafenib was repeated, and the result was positive (SI: 380%; actual values: 650 cpm/171 cpm).

Treatment with uracil-tegafur, TACE for intrahepatic recurrence, and transcatheter arterial infusion for peritoneal metastasis were carried out. However, the response, according to the Response Evaluation Criteria in Solid Tumors, was progressive disease.

In June 2017, regorafenib was approved for the treatment of Sorafenib.
Table 2. Laboratory Data at the Start of Regorafenib Treatment.

| Test                  | Value     |
|-----------------------|-----------|
| White blood cell      | 6,500 /μL |
| Red blood cell        | 3.74 ×10^9/μL |
| Hemoglobin            | 12.5 g/dL  |
| Platelet              | 177 ×10^3/μL |
| Total protein         | 7.2 g/dL   |
| Albumin               | 3.8 g/dL   |
| AST                   | 23 U/L     |
| ALT                   | 17 U/L     |
| LDH                   | 203 U/L    |
| ALP                   | 356 U/L    |
| γGTP                  | 90 U/L     |
| Cholinesterase        | 217 U/L    |
| Total bilirubin       | 0.6 mg/dL  |
| PT-INR                | 0.97       |
| BUN                   | 14.7 mg/dL |
| Creatinine            | 0.87 mg/dL |
| AFP                   | 6,212 ng/mL|
| Total bilirubin       | 0.6 mg/dL  |
| Albumin               | 3.8 g/dL   |
| PT-INR                | 0.97       |
| BUN                   | 14.7 mg/dL |
| Creatinine            | 0.87 mg/dL |
| AFP                   | 6,212 ng/mL|
| Cholinesterase        | 217 U/L    |
| Total bilirubin       | 0.6 mg/dL  |
| PT-INR                | 0.97       |
| BUN                   | 14.7 mg/dL |
| Creatinine            | 0.87 mg/dL |
| AFP                   | 6,212 ng/mL|

γGTP: γ-glutamyl transferase, AFP: α-fetoprotein, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, DCP: des-γ-carboxy protein, PT-INR: prothrombin time-international normalized ratio, LDH: lactate dehydrogenase

Figure 2. The clinical course of the patient’s alanine aminotransferase (ALT) level and body temperature (BT) in the two weeks after regorafenib was initiated at a dose of 120 mg/day. The patient did not develop liver injury or fever.

of HCC in Japan. The approval was based on the results of the RESORCE trial, which used distinct criteria to include patients who tolerated sorafenib. Although the patient did not fulfill the criteria, he requested regorafenib treatment since no other systemic therapies were available. A multidisciplinary team was consulted, and it was thought that the absence of hypersensitivity to regorafenib should be confirmed before its administration. A DLST for regorafenib was performed, and the result was negative (SI:155%; actual values: 328 cpm/211 cpm). In September 2017, regorafenib was started at a reduced dose of 120 mg/day. The dosage was increased to 160 mg/day after 32 weeks. At the start of regorafenib therapy, he had an ECOG-PS score of 0 and BCLC stage C with portal vein invasion (Vp2). Liver function tests revealed a Child-Pugh score of 5 (Table 2). Regorafenib was continued for 10 months during a long period of stable disease (SD). In July 2018, regorafenib was withdrawn after new vascular invasion and pulmonary metastasis were observed. The patient did not develop liver injury or fever and only showed mild side effects, such as hoarseness and grade 1 hand-foot skin reaction (Fig. 2).

Since a good performance status and liver function were maintained, with a Child-Pugh score of 6 and an ECOG-PS score of 0, regorafenib could be switched to lenvatinib. The patient continued to receive lenvatinib treatment at the time of writing this report (November 2018) (Fig. 3).

The patient provided his written informed consent for the publication of the clinical details of the present case.
For intrahepatic recurrence

For peritoneal metastasis

Systemic therapy

| Drug            | Dose          |
|-----------------|---------------|
| Sorafenib       | 800 mg/day    |
| Sorafenib       | 200 mg/day    |
| UFT             | 600 mg/day    |
| Regorafenib     | 120 mg/day    |
| Regorafenib     | 160 mg/day    |
| Lenvatinib      | 12 mg/day     |

**Figure 3.** The clinical course of the alanine aminotransferase (ALT) and serum alpha-fetoprotein (AFP) levels and the timing of therapies in this male patient with multiple intrahepatic recurrences and peritoneal dissemination after hepatectomy for hepatocellular carcinoma. At the beginning of regorafenib treatment (in September 2017), the patient’s AFP level was 6212 ng/mL. At one month after the initiation of regorafenib, the AFP level decreased (3742 ng/mL). At the discontinuation of regorafenib, the AFP level was 19283 ng/mL. Regorafenib treatment had been continued for 10 months in a long period of stable disease. TACE: transcatheter arterial chemoembolization, TAI: transcatheter arterial infusion, UFT: uracil-tegafur

**Discussion**

This is the first report to show that regorafenib could be administered safely for advanced HCC after the discontinuation of sorafenib due to hypersensitivity.

The expected 1-year survival of patients with advanced HCC with vascular invasion or extrahepatic spread is reported to be 30-50% in cases that follow a natural course (2, 3). In the present case, the patient has survived for approximately three years since the peritoneal recurrence of HCC, as a result of multimodal treatment, including molecular targeted drugs and intra-arterial chemotherapy. This patient’s long-term survival was attributed to regorafenib treatment, which was continued for 10 months in a long period of SD, despite the discontinuation of sorafenib due to severe adverse events, including liver injury and fever.

In treatment with tyrosine kinase inhibitors (TKIs), including sorafenib, serum aminotransferase elevation occurs in 20-50% of patients (4, 5). The liver injury caused by sorafenib is mild in most cases and improves with the discontinuation of the drug (6, 7). However, some fatal cases have been reported (8, 9). Drug-induced liver injury (DILI) has been considered idiosyncratic (10). The mechanisms underlying the development of idiosyncratic DILI can be broadly divided into hypersensitivity (i.e., immunologic) and metabolic mechanisms (11). In the present case, a DLST for sorafenib was negative at one month after recovery from the liver injury. Thus, the patient’s liver injury might have been associated with a metabolic mechanism and not hypersensitivity.

It has been reported that it is possible to restart sorafenib at a low dose after discontinuation due to severe adverse events, and that the dose can then be gradually increased to the usual therapeutic dose (12). Some studies have reported that patients with either disappearance or a decrease in tumor enhancement on contrast-enhanced CT during sorafenib treatment showed a better prognosis than patients without these CT findings (13, 14). In the present case, most tumors changed from high-density to iso-density during the first sorafenib treatment. Five days after restarting sorafenib at a dose of 200 mg/day, the patient developed a fever of >40°C without liver injury. Considering the small dose and the short duration of treatment, the fever could be attributed to drug hypersensitivity. In fact, the DLST for sorafenib was positive at the time of the fever. The re-administration of sorafenib was abandoned due to the patient’s drug hypersensitivity. The patient was probably sensitized to sorafenib during the first treatment and developed a fever due to hypersensitivity as a result of retreatment. Liver injury might
have been avoided as a result of the early cessation and the small dose of sorafenib.

Regorafenib provided improved overall survival in HCC patients who showed progression during sorafenib treatment in the RESORCE trial (1). Since the only subjects eligible for inclusion in this trial were patients who could tolerate sorafenib (≥400 mg daily for at least 20 of the 28 days before discontinuation), not all patients with PD after sorafenib treatment can be treated with regorafenib (15). The present case did not meet this criterion. Nevertheless, regorafenib was administered for the following reasons. First, some reports have shown that the patients who developed severe liver injury with erlotinib or gefitinib, which are TKIs for lung cancer, successfully switched to the other agent without signs of recurrent liver injury. It is presumed that this is caused by the difference in the metabolic pharmacokinetics between the two TKIs, which share a 4-anilinoquinazoline base structure (16, 17). In the present case there were some differences between the pharmacological activities of sorafenib and regorafenib, which have a very similar chemical structure (18, 19). Second, in contrast to sorafenib, the DLST for regorafenib was negative. The DLST, also referred to as the lymphocyte transformation test, is used to identify the culprit drug in cases of adverse drug reactions. The test is a procedure that measures the proliferation of drug-specific T cells in vitro. The T cell receptor can interact directly with the drug itself. Additionally, the positive rate was approximately 78%, which is considered low (20). Thus, attention must be paid to the interpretation of this result. In the present case, the patient had been hospitalized two weeks after the start of regorafenib at a reduced dose and was followed constantly. Third, there was no other therapeutic agent available at that time, and the patient therefore strongly desired regorafenib treatment.

In the present case, regorafenib treatment was continued safely for 10 months, despite sorafenib having been discontinued due to severe adverse events, such as DILI and drug hypersensitivity. Although sorafenib and regorafenib have similar structures, the survival benefit provided by the sequential use of regorafenib after progression on sorafenib suggests that there are some differences in their mechanisms of action. Those differences are poorly understood and might account for the differences in side effects.

In conclusion, under multimodal treatment, including three molecular targeted drugs and intra-arterial chemotherapy, the present patient has survived for approximately 3 years since the peritoneal recurrence of HCC. The patient’s long-term survival was attributed to the administration of regorafenib for 10 months during a long period of SD, despite the discontinuation of sorafenib due to severe adverse events (e.g., liver injury and fever). Physicians should exercise caution when switching therapy from sorafenib to regorafenib because the two drugs have a very similar chemical structure. This is the first report showing that regorafenib could be safely administered for advanced HCC after the discontinuation of sorafenib due to hypersensitivity.

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

Acknowledgement
No additional acknowledgments.

References
1. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RE-SORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2017; 389: 56-66.
2. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Seminars in liver disease 1999; 19: 329-338.
3. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology (Baltimore, Md) 1999; 29: 62-67.
4. Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug safety 2013; 36: 491-503.
5. Bunchromvatkul C, Reddy KR. Drug Hepatotoxicity: Newer Agents. Clin Liver Dis 2017; 21: 115-134.
6. Di Lorenzo G, Carteni G, Autorino R, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. J Clin Oncol 2009; 27: 4469-4474.
7. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Oncology 2015; 16: 1344-1354.
8. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol 2008; 26: 4714-4719.
9. Fairfax BP, Pratap S, Roberts IS, et al. Fatal case of sorafenib-associated idiosyncratic hepatotoxicity in the adjuvant treatment of a patient with renal cell carcinoma. BMC cancer 2012; 12: 590.
10. Kullak-Ublick GA, Andrade RJ, Merz M, et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut 2017; 66: 1154-1164.
11. Fisher K, Vuppulanchi R, Saxena R. Drug-Induced Liver Injury. Archives of pathology & laboratory medicine 2015; 139: 876-887.
12. Bauer C, Przybilla B, Rueff F. Severe cutaneous reaction to sorafenib: induction of tolerance. Acta Derm Venereol 2008; 88: 627-628.
13. Arizumi T, Ueshima K, Chishina H, et al. Decreased blood flow after sorafenib administration is an imaging biomarker to predict overall survival in patients with advanced hepatocellular carcinoma. Digestive diseases (Basel, Switzerland) 2014; 32: 733-739.
14. Kuzuya T, Ishigami M, Ishizu Y, et al. Early Clinical Response after 2 Weeks of Sorafenib Therapy Predicts Outcomes and Anti-Tumor Response in Patients with Advanced Hepatocellular Carcinoma. PloS one 2015; 10: e0138776.
15. Kuzuya T, Ishigami M, Ishizu Y, et al. Prognostic Factors Associated with Postprogression Survival in Advanced Hepatocellular Carcinoma Patients Treated with Sorafenib Not Eligible for Second-Line Regorafenib Treatment. Oncology 2018; 95: 91-99.
16. Nakatomi K, Nakamura Y, Tetsuya I, Kohno S. Treatment with gefitinib after erlotinib-induced liver injury: a case report. Journal of medical case reports 2011; 5: 593.
17. Kunimasa K, Yoshioka H, Iwasaku M, et al. Successful treatment of non-small cell lung cancer with gefitinib after severe erlotinib-related hepatotoxicity. Internal medicine (Tokyo, Japan) 2012; 51: 431-434.
18. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progres-
sion and angiogenesis. Cancer research 64: 7099-7109, 2004.

19. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. International journal of cancer 129: 245-255, 2011.

20. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy 59: 809-820, 2004.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).