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A Case of Hepatocellular Carcinoma with a Complete Response to Second-Line Chemotherapy with Ramucirumab

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Abstract

Introduction: Ramucirumab has become the standard of care in second-line systemic therapy for advanced Hepatocellular Carcinoma (HCC) (AFP ≥400 ng/ml). A Complete Response (CR) to systemic therapy is generally very rare. We encountered a patient who achieved CR to second-line therapy with ramucirumab.

Case presentation: We herein report a case of a 62-year-old male diagnosed with HCC and lung metastases 6 months after liver surgery. AFP and PIVKA-II were elevated and his liver function was Child-Pugh A. Sorafenib at 800 mg as the first-line therapy was administered for 6 weeks, and after the progression of the first-line therapy ramucirumab was administered as second-line systemic therapy. The tumor decreased in size and this was judged to be a partial response. Due to the absence of recurrence for approximately 5 years after the cessation of treatment, the present case was considered to have achieved CR.

Conclusion: We encountered a case of HCC with CR to second-line systemic therapy with ramucirumab after sorafenib. The high affinity of ramucirumab to vascular endothelial growth factor receptor 2 (VEGFR2) may have exerted additional anti-tumor effects in cases refractory to systemic therapy having anti-VEGF effects.

Keywords: Hepatocellular carcinoma • Ramucirumab • Sorafenib • Complete response

Abbreviations: BSC: Best Supportive Care; CR: Complete Response; CT: Computed Tomography; HCC: Hepatocellular Carcinoma; PR: Partial Response; RECIST: Response Evaluation Criteria in Solid Tumors; VEGF: Vascular Endothelial Growth Factor; VEGFR: VEGF Receptor

Introduction

Hepatocellular Carcinoma (HCC) is the 6th most common cancer with an estimated number of new cases each year of approximately 841,000. HCC has a high mortality rate and a 5-year survival rate of 8.9%. It causes 781,000 deaths worldwide each year [1]. Systemic therapy is recommended for advanced HCC with extrahepatic spread or major vascular invasion with Child-Pugh a liver function by the NCCN guidelines for Hepatobiliary Cancers Version 2.2019 [2], ESMO Clinical Practice Guidelines [3], and the Clinical Practice Guidelines for Hepatocellular Carcinoma 2013 in Japan [4]. Sorafenib, a molecular-targeted agent that suppresses tumor cell proliferation and angiogenesis by inhibiting RAF serine-threonine kinase, Vascular Endothelial Growth Factor (VEGF), PDGF, Flt-3, and the c-kit receptor, is the standard of care for HCC [5], while regorafenib is the standard of care as second-line chemotherapy [6], but it is a limited option for patients who can tolerate sorafenib. Many newly developed agents have failed to prolong survival, while some, such as cabozantinib and ramucirumab, were beneficial in second-line chemotherapy for HCC [7,8]. A previous study reported that ramucirumab failed to prolong survival in second-line therapy for HCC (REACH) [9]; however, in the AFP high (≥400 ng/ml) subgroup, significant improvements were observed in the ramucirumab group. A randomized phase III trial on ramucirumab limited to AFP high (≥400 ng/ml) patients was recently performed (REACH2) and reported superior survival [8]. We herein report a case of HCC with a Complete Response (CR) to ramucirumab, which is very rare in systemic therapy for advanced HCC. The patient provided informed consent for publication of the case. This case report was approved by the ethical committee of Kanagawa Cancer Center.

Case Presentation

The patient was a 62-year-old male who was diagnosed with HCC based on Computed Tomography (CT) images and underwent partial hepatectomy of the right lobe. Pathological findings were moderately-poorly differentiated HCC of 8.5 × 5.5 × 5 cm with tumor-free margins. His complications were hypertension, angina, positivity for the HCV antibody, and unknown for HCV RNA. Lung metastases were detected 6 months after liver surgery. CT with intravenous contrast revealed both multiple lung metastases and lymph node metastases of mediastinum and hilum of lung. AFP was elevated to 78000 ng/ml and PIVKA-II to 81400 mAU/ml. His liver function was Child-Pugh A. He was treated with sorafenib at 800 mg b.i.d. in the first-line setting in 2012. He developed fatigue grade 2 as defined by the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0) and his response was progressive disease based on CT after 6 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, with the progression of lung and lymph node metastases (Figure 1) and elevated AFP to 308000 ng/ml and PIVKAII to 93100 being detected.

In the second-line setting, he participated in a randomized, double-blind, placebo-controlled phase III trial with ramucirumab *vs*. best supportive care (REACH) in December 2012. He was randomized to receive ramucirumab and the size of the tumor decreased to a partial response by 45% in first 6 weeks. His tumor decreased by 77%, with only a small fibrotic mass remaining in 36 months (Figure 2). AFP and PIVKAII also decreased to 1 ng/ml and 33 mAU/ml. His adverse effects were proteinuria Grade 2, arthralgia Grade 1, and hypoalbuminemia Grade 1 from first 6weeks. These were observed without

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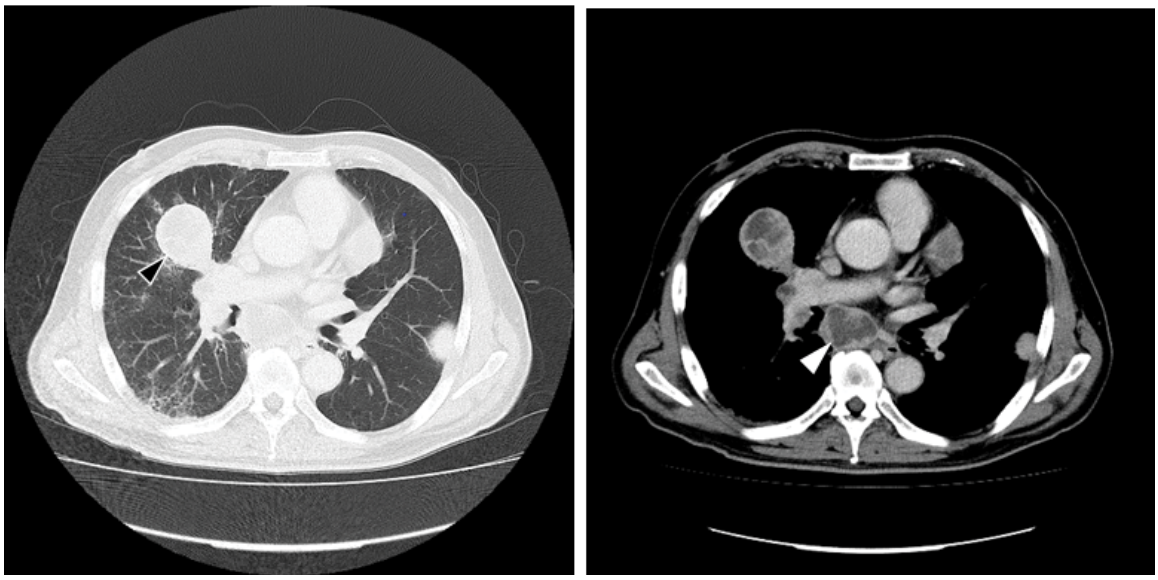

Figure 1. The lung metastases and lymph node metastases of mediastinum and hirum of lung before ramucirumab in CT.

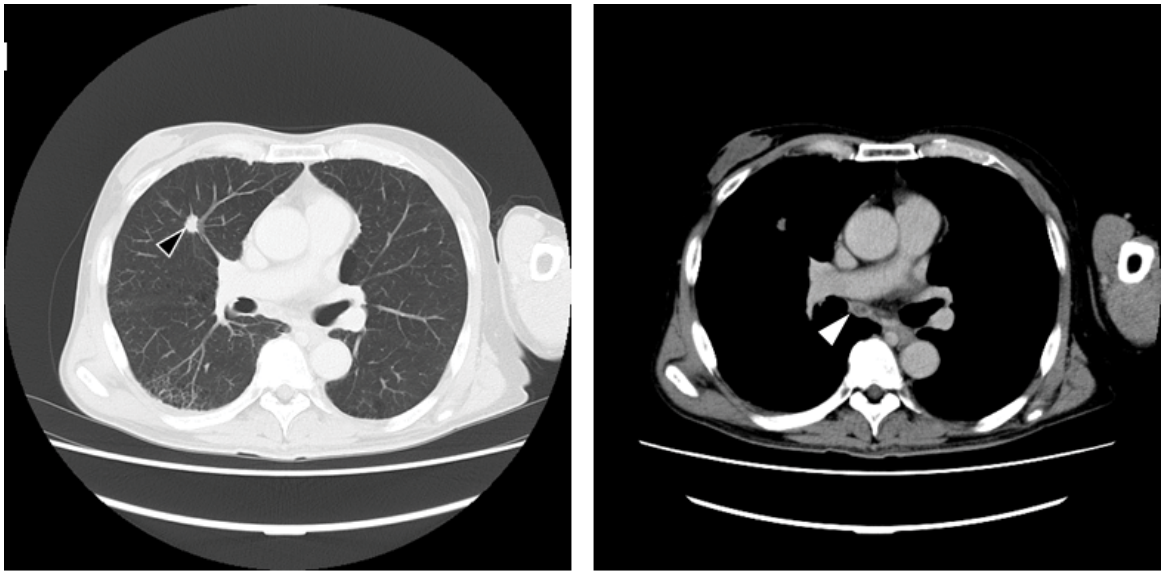

Figure 2. The lung metastasis and lymph node metastasis of mediastinum and hirum of lung after ramucirumab after 3 years by 77% decrease in CT.

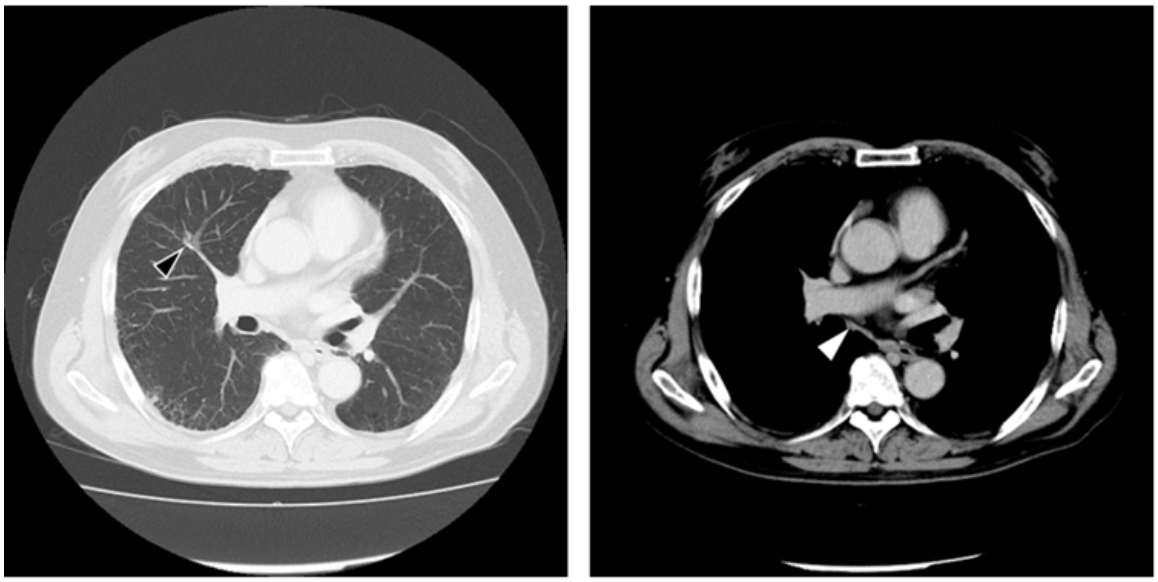

Figure 3. The lung metastasis and lymph node metastasis of mediastinum and hirum of lung after ramucirumab in the current status in CT.

any treatment. Unblinding was performed on 28th August 2014. He continued to receive ramucirumab, however developed hypoalbuminemia Grade 2 in December 2015; therefore, drug administration was stopped. No recurrence or progression was observed over 4 years up to December 2019. Therefore, the complete tumor response was suggested although the best overall response was Partial Response (PR) according to RECIST v1.1. The patient remains alive without recurrence. We show the current status of metastases in CT (Figure 3). AFP and PIVKAII also decreased to 1 ng/ml and 11 mAU/ml that are within normal ranges and maximum reductions.

Discussion

The response rate of HCC to targeted agents is generally 4-18% [9,10], while that of sorafenib in the SHARP trial was 4%. The SHARP trial did not achieve CR. However, CR cases have been reported. Regarding other agents in the first-line setting, CR cases were reported at 1% with lenvatinib [10]. In the second-line setting, regorafenib showed superiority to Best Supportive Care (BSC) after sorafenib [6]; however, no CR cases were reported. These findings were similar to those of a randomized phase III trial on cabozantinib and ramucirumab (REACH2). Only one CR was reported in REACH study. In the present case, progressive disease occurred in the administration of sorafenib. However, the complete response was suggested during ramucirumab treatment, indicating the additional effects of this agent. Ramucirumab has been reported to inhibit the VEGF pathway. Although sorafenib also exerts this effect, the difference between sorafenib and ramucirumab appears to be the higher affinity of ramucirumab to VEGF receptor (VEGFR) 2, which may have played an important role in achieving complete response in this case. AFP is recognized as a biomarker, especially a marker for patient selection, based on the results from REACH and REACH2 study. In this case, baseline AFP was very high and decreased with tumor shrinkage. AFP also appeared to be a good indicator for the efficacy of ramucirumab. Other agents have recently exhibited efficacy in the second-line setting. Nivolumab, which blocks the PD-L1 receptor, achieved good survival of 20 months [11], and cabozantinib, an inhibitor of VEGFR1, 2, and 3, MET, and AXL, showed superiority to BSC [7]. Since ramucirumab has a different mechanism of action to nivolumab and cabozantinib from the viewpoint of high affinity to VEGFR2, it represents an important choice in second-line systemic therapy for HCC.

Conclusion

We encountered a case of HCC potentially with CR to second-line systemic therapy with ramucirumab after sorafenib. The high affinity of ramucirumab to VEGFR2 may have exerted additional anti-tumor effects in cases refractory to systemic therapy having anti-VEGF effects.

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