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Case Report

The Efficacy of Sorafenib after Progression on Atezolizumab and Bevacizumab Combination Therapy in a Patient with Advanced Hepatocellular Carcinoma

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Abstract

Sorafenib was approved for the treatment of hepatocellular carcinoma more than 10 years ago; however, the efficacy is limited. The IMbrave150 trial demonstrated better overall survival and progression-free survival with atezolizumab plus bevacizumab combination therapy compared to sorafenib, and so it has become the choice of first-line treatment. However, the optimal choice of subsequent therapy after atezolizumab plus bevacizumab is unknown. We present a case with advanced hepatocellular carcinoma who achieved a complete response for more than 2 years under sorafenib treatment after progression with atezolizumab and bevacizumab combination therapy.

Keywords: Atezolizumab, bevacizumab, hepatocellular carcinoma, sorafenib

Introduction

Hepatocellular carcinoma is the most common form of primary liver cancer, and liver cancer including intrahepatic cholangiocarcinoma was the second most common cause of cancer death in 2020 in Taiwan according to the Taiwan Ministry of Health and Welfare. The most common risk factors are hepatitis B virus, hepatitis C virus, and alcohol.[1] With the rapid development of antiviral treatments, vaccination, and safe blood transfusion, the incidence of hepatocellular carcinoma is declining gradually; however, many patients still have advanced or metastatic disease which is ineligible for curative therapies at diagnosis. Systemic therapies for hepatocellular carcinoma include tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors. In 2008, sorafenib was shown to be effective for the treatment of advanced hepatocellular carcinoma, with a median overall survival (OS) of 10.7 months and time to progression of 4.1 months.[2] In 2020, the combination of atezolizumab and bevacizumab was shown to result in better OS and progression-free survival (PFS) than sorafenib.[3] Recently,

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some studies have reported the potential benefits of TKIs in patients who failed prior immune checkpoint inhibitor treatment.[4,5] Herein, we report the efficacy of sorafenib in a patient who failed prior treatment with a combination of atezolizumab and bevacizumab.

Case Report

A 70-year-old man had a past medical history of chronic hepatitis B virus infection and hepatocellular carcinoma since 2011. The initial TNM stage was cT1N0M0, and the Barcelona Clinic Liver Cancer stage was A. Hepatectomy was performed, and local recurrence was noted 2 years later. Transcatheter arterial chemoembolization and radiofrequency ablation were performed from 2013 to 2018. An alpha-fetoprotein level of 22.4 ng/mL was found in January 2018 [Figure 1], and recurrence with lung metastasis was confirmed by biopsy [Figure 2a]. He was enrolled in a clinical trial and received 1200 mg of atezolizumab plus 15 mg/kg body weight of bevacizumab intravenously every 3 weeks from May 2018. During the treatment, his alpha-fetoprotein level fluctuated but did not decline [Figure 1]. The first follow-up computed tomography (CT) scan revealed stable disease according to the RECIST 1.1 criteria and Immune-modified RECIST criteria. However, there was a progressive disease that CT scan showed enlarged pulmonary metastasis in the right upper lung in April 2019 [Figure 2b], and so atezolizumab and bevacizumab were discontinued.

Video-assisted thoracoscopic surgery wedge resection of the right upper lung was performed for the metastatic lung lesion, and sorafenib was prescribed 2 weeks after the operation. The initial dose was 400 mg twice daily and tapered gradually to 200 mg daily due to grade 3 hand–foot skin reactions. His alpha-fetoprotein level returned to the normal range [Figure 1], and serial follow-up CT scans showed no evidence of lesions [Figure 2c]. He achieved complete response for more than 2 years under sorafenib alone.

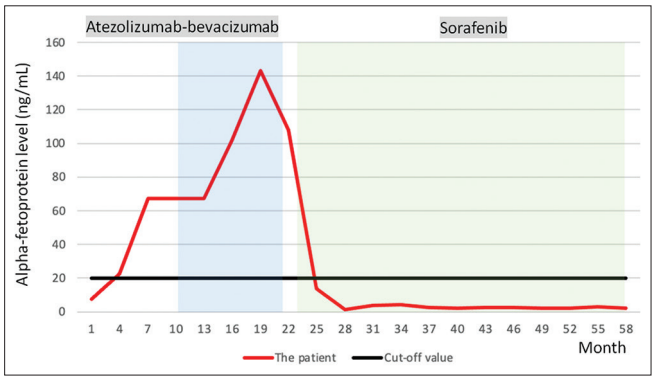

Figure 1: The alpha-fetoprotein level of the patient progressively increased during combination therapy with atezolizumab-bevacizumab (blue area), and then dropped to the normal range after resection of the lung metastasis and starting sorafenib (green area)

Discussion

In the IMbrave150 trial, first-line atezolizumab combined with bevacizumab showed better OS and PFS than sorafenib in patients with unresectable hepatocellular carcinoma.[3] However, the optimal subsequent choice of therapy after failure of atezolizumab-bevacizumab combined therapy is unknown, and several ongoing studies are investigating this clinical problem. Some case reports have revealed better than expected efficacy with TKIs after progression with immune checkpoint inhibitors in hepatocellular carcinoma[4,5] and renal cell carcinoma.[6]

A *post hoc* analysis of 14 patients in the CELESTIAL study who received cabozantinib as third-line treatment following immune checkpoint inhibitor treatment showed a median OS of 7.9 months.[7] According to a meeting, abstract presented at Gastrointestinal Cancers Symposium, 30 patients with unresectable or advanced hepatocellular carcinoma who received TKIs (11 lenvatinib, 10 sorafenib, 6 regorafenib, and 3 axitinib) after immune checkpoint inhibitors had a median OS from the index TKI (TKI postimmunotherapy) of 602 days.[4] In addition, Aoki *et al*. presented the first real-world data analysis of lenvatinib efficacy for unresectable hepatocellular carcinoma after failure of PD-1/PD-L1 blockade, and it showed high antitumor activity and good survival benefit. The median PFS was 10 months, the median OS was 15.8 months, the objective response rate was 55.6%, and the disease control rate was 86.1%.[5] The median OS with the first-line treatment was 29.8 months, which was longer than with first-line lenvatinib (13.6 months).

According to the phase III STORM trial, treatment with sorafenib after curative resection or ablation of hepatocellular carcinoma did not improve recurrence-free survival compared with placebo.[8] Several studies have shown the benefit of adjuvant sorafenib in patients with hepatocellular carcinoma and microvascular invasion.[9-11] However, these studies did not include extrahepatic metastatic hepatocellular carcinoma, and the outcome of pulmonary metastasectomy with adjuvant sorafenib therapy has not been studied. The adjuvant setting of sorafenib is therefore still controversial.

In our patient, combined therapy with atezolizumab and bevacizumab showed only stable disease which persisted for <1 year. After resection of the lung metastasis, we started

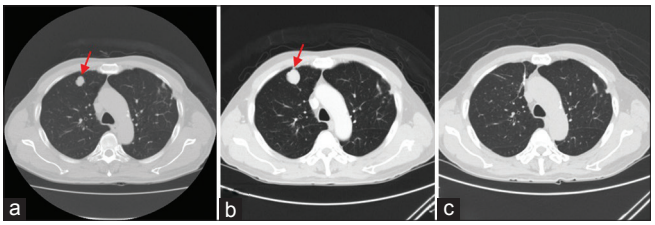

Figure 2: (a) A pulmonary nodule about 1.7 cm in size in the RUL. (b) The pulmonary nodule enlarged despite 11 months of combination therapy with atezolizumab plus bevacizumab. (c) No definite lung metastasis was identified after surgery under sorafenib for more than 2 years. RUL: right upper lobe

sorafenib as subsequent therapy. The patient is still alive with a complete response for more than 2 years, which is much longer than that reported in clinical trials of first-line sorafenib (10.7 months).[12]

Angiogenic factors such as vascular endothelial growth factor (VEGF) are considered to have an immunosuppressive effect, and various mechanisms have been proposed, such as inhibition of dendritic cell maturation,[13] and inhibition of the differentiation of hematopoietic progenitor cells.[14] Sorafenib has been shown to reverse the effects of VEGF and restore immunity.[15] The immunomodulatory effects of sorafenib have also been reported, such as the reduction and function suppression of regulatory T-cells,[16,17] macrophage modulation,[18,19] and myeloid-derived suppressor cell suppression.[20] Osa *et al*. reported sustained binding of nivolumab to PD-1 for more than 20 weeks after the last infusion.[21] These findings may explain why molecule-targeted agents may be effective when used after disease progression on immune checkpoint inhibitors. Some serum biomarkers have been studied for their ability to predict the outcome of hepatocellular carcinoma patients treated with sorafenib, such as insulin-like growth factor-1,[22] transforming growth factor-β1,[23] granulocyte colony-stimulating factor, VEGF-A, and angiopoietin-2.[24] However, there are currently no established biomarkers to predict the efficacy of TKIs after immune checkpoint inhibitors in patients with advanced hepatocellular carcinoma. Several studies have suggested that failure to respond to atezolizumab and bevacizumab combination therapy may be due to β-catenin-activating mutations,[25,26] and that fibroblast growth factor receptor 4 (FGFR4) expression is higher in these patients. This may also explain why TKIs have a good response after the failure of immune checkpoint inhibitors. Further prospective studies are required to validate the efficacy of TKIs after progression on immune checkpoint inhibitors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, *et al.* The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: Results from the global burden of disease study 2015. JAMA Oncol 2017;3:1683-91.
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al.* Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
3. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, *et al.* Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-905.
4. Yau TC, Tang V, Chan J, Kwok GW, Chiu J, Leung RC, *et al*. Outcomes of tyrosine kinase inhibitors (TKI) after immunotherapy in unresectable or advanced hepatocellular carcinoma (HCC) patients. Am Soc Clin Oncol 2019;37:361.
5. Aoki T, Kudo M, Ueshima K, Morita M, Chishina H, Takita M, *et al.* Exploratory analysis of lenvatinib therapy in patients with unresectable hepatocellular carcinoma who have failed prior PD-1/PD-L1 checkpoint blockade. Cancers (Basel) 2020;12:3048.
6. Barata PC, De Liano AG, Mendiratta P, Crolley V, Szabados B, Morrison L, *et al.* The efficacy of VEGFR TKI therapy after progression on immune combination therapy in metastatic renal cell carcinoma. Br J Cancer 2018;119:160-3.
7. Abou-Alfa G, Cheng A, Saletan S, Kelley K, El-Khoueiry A. PB02-04 clinical activity of cabozantinib in patients with advanced hepatocellular carcinoma previously treated with anti-VEGF and immuno-oncology therapy: Subgroup analysis from the phase 3 CELESTIAL trial. In: Liver Cancer Summit-Abstract Book. Prague: EASL; 2020. p. 234.
8. Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, *et al.* Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): A phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344-54.
9. Zhuang L, Wen T, Xu M, Yang J, Wang W, Wu H, *et al.* Sorafenib combined with hepatectomy in patients with intermediate-stage and advanced hepatocellular carcinoma. Arch Med Sci 2017;13:1383-93.
10. Huang Y, Zhang Z, Zhou Y, Yang J, Hu K, Wang Z. Should we apply sorafenib in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy? Onco Targets Ther 2019;12:541-8.
11. Zhang XP, Chai ZT, Gao YZ, Chen ZH, Wang K, Shi J, *et al.* Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: A propensity score matching analysis. HPB (Oxford) 2019;21:1687-96.
12. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, *et al.* Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
13. Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, *et al.* Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med 1996;2:1096-103.
14. Ohm JE, Gabrilovich DI, Sempowski GD, Kisseleva E, Parman KS, Nadaf S, *et al.* VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression. Blood 2003;101:4878-86.
15. Alfaro C, Suarez N, Gonzalez A, Solano S, Erro L, Dubrot J, *et al.* Influence of bevacizumab, sunitinib and sorafenib as single agents or in combination on the inhibitory effects of VEGF on human dendritic cell differentiation from monocytes. Br J Cancer 2009;100:1111-9.
16. Cabrera R, Ararat M, Xu Y, Brusko T, Wasserfall C, Atkinson MA, *et al.* Immune modulation of effector CD4+ and regulatory T cell function by sorafenib in patients with hepatocellular carcinoma. Cancer Immunol Immunother 2013;62:737-46.
17. Chen ML, Yan BS, Lu WC, Chen MH, Yu SL, Yang PC, *et al.* Sorafenib relieves cell-intrinsic and cell-extrinsic inhibitions of effector T cells in tumor microenvironment to augment antitumor immunity. Int J Cancer 2014;134:319-31.
18. Sprinzl MF, Reisinger F, Puschnik A, Ringelhan M, Ackermann K, Hartmann D, *et al.* Sorafenib perpetuates cellular anticancer effector functions by modulating the crosstalk between macrophages and natural killer cells. Hepatology 2013;57:2358-68.
19. Wei X, Tang C, Lu X, Liu R, Zhou M, He D, *et al.* MiR-101 targets DUSP1 to regulate the TGF-β secretion in sorafenib inhibits macrophage-induced growth of hepatocarcinoma. Oncotarget 2015;6:18389-405.
20. Cao M, Xu Y, Youn JI, Cabrera R, Zhang X, Gabrilovich D, *et al.* Kinase inhibitor Sorafenib modulates immunosuppressive cell populations in a murine liver cancer model. Lab Invest 2011;91:598-608.
21. Osa A, Uenami T, Koyama S, Fujimoto K, Okuzaki D, Takimoto T,

et al. Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients. JCI Insight 2018;3:59125.
22. Shao YY, Huang CC, Lin SD, Hsu CH, Cheng AL. Serum insulin-like growth factor-1 levels predict outcomes of patients with advanced hepatocellular carcinoma receiving antiangiogenic therapy. Clin Cancer Res 2012;18:3992-7.
23. Lin TH, Shao YY, Chan SY, Huang CY, Hsu CH, Cheng AL. High serum transforming growth factor-β1 levels predict outcome in hepatocellular carcinoma patients treated with sorafenib. Clin Cancer Res 2015;21:3678-84.
24. Miyahara K, Nouso K, Tomoda T, Kobayashi S, Hagihara H, Kuwaki K, *et al.* Predicting the treatment effect of sorafenib using serum angiogenesis markers in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2011;26:1604-11.
25. Pinyol R, Sia D, Llovet JM. Immune exclusion-Wnt/CTNNB1 class predicts resistance to immunotherapies in HCC. Clin Cancer Res 2019;25:2021-3.
26. Luke JJ, Bao R, Sweis RF, Spranger S, Gajewski TF. WNT/β-catenin pathway activation correlates with immune exclusion across human cancers. Clin Cancer Res 2019;25:3074-83.