

Case Report

Nivolumab combined with sorafenib successfully treats a difficult-to-treat patient with hepatocellular carcinoma: a case report

Wen-Ju Sun¹, Chao Zhu², Yan Xu¹, Lan-Qiu Wang¹

Departments of ¹Radiotherapy, ²General Oncology, Qingdao Cancer Hospital, Qingdao 266042, China

Received November 1, 2018; Accepted March 7, 2019; Epub June 15, 2019; Published June 30, 2019

Abstract: Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide, and the prognosis is poor even when aggressive therapies are initiated. For patients in the advanced stages of the disease, systemic therapy is the only option, but the results are often poor. Sorafenib is a first-line treatment for HCC approved drug by the Food and Drug Administration (FDA); it prolongs patients' survival by 2.8 months in the advanced stages compared to the best supportive care. Nivolumab, a checkpoint inhibitor, has clinical indications for several kinds of cancers. In this case report, we present a patient with metastatic HCC who had slow disease progress after 6 months of treatment with sorafenib; after combined treatment with nivolumab for 4 cycles, the tumor shrank and reached partial a response. The patient's disease maintained a partial response at the last follow-up at 6 months of nivolumab therapy. Sorafenib combined with nivolumab may have a synergetic effect in advanced hepatocellular carcinoma; it may prolong patients' survival, and more patients are needed to be enrolled in combination studies.

Keywords: Hepatocellular carcinoma, sorafenib, nivolumab, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer related deaths worldwide. The occurrence of the disease is particularly high in East Asia and sub-Saharan Africa, and the rate is lower but the incidence is increasing in North America and most of Europe [1]. Although great efforts in fundamental and clinical research are devoted to HCC, its prognosis is still extremely poor, especially in advanced cases [2]. The incidence is increasing, with more than 600,000 new cases every year worldwide, most of whom die within a year [3]. Due to infection with the hepatitis B C viruses, about 55% HCC cases occur in China, and among them, 90% are diagnosed in the advanced stages [1, 4]. Patients with HCC usually have a long history of liver disease, which has impaired their liver function, and the prognosis of advanced-stage patients is gloomy due to a lack of effective therapies [4].

Nivolumab (Opdivo, Bristol-Myers Squibb), is a programmed cell death 1 monoclonal antibody.

It works as a checkpoint inhibitor, blocking a signal that would have prevented activated T cells from attacking the cancer [5]. It was approval by the FDA in 2017 as a second-line systemic treatment in HCC patients who have been treated with or who are intolerant to sorafenib. Only regorafenib, lenvatinib, and nivolumab are approved by the FDA to be a second-line treatment after progression on sorafenib, and they may produce clinical benefits to a limited extent. A phase 3 confirmatory study about using nivolumab with sorafenib is ongoing [6].

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals, Leverkusen, Germany), is a small-molecule inhibitor of several tyrosine protein kinases [vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)], and a RAF/MEK/ERK cascade inhibitor that inhibits cancer angiogenesis and cell proliferation [7]. It had prolonged patients' survival of HCC in the advanced stages around 3 months longer than the best supportive care, and

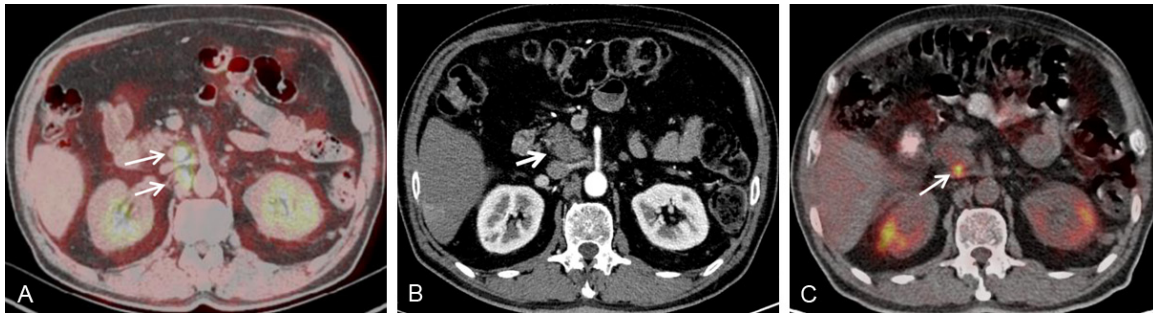


Figure 1. A. Positron emission tomography-computed tomography (PET-CT) scans showed retroperitoneal lymphadenopathy; the diameters were measured 2.5 × 2.2 cm and 1.5 × 1.1 cm respectively. B. CT scans with a control showed retroperitoneal lymph nodes slightly enlarged after sorafenib therapy; they measured 2.7 × 2.3 cm and 1.7 × 1.2 cm respectively. C. PET-CT scan showed retroperitoneal lymph nodes remarkably shrunk after nivolumab treatment. The residual one measured 0.8 × 0.5 cm. (The size of tumor was measured according to the response evaluation criteria in solid tumors (RECIST) evaluation criteria, and the efficacy was evaluated as partial remission (PR)).

it was approved by the FDA for first-line therapy in 2007 [2, 8]. In this case report, we present a patient with metastatic HCC, whose surgery, radiofrequency ablation, and trans-arterial chemoembolization all failed. After he failed systemic treatment with sorafenib, his disease responded to sorafenib combined with nivolumab. The patient's serum alpha-fetoprotein (AFP) level maintained a lower level, and his tumor reached a long time response duration.

Case presentation

A 68-year-old male patient with chronic hepatitis B virus (HBV) complained of right upper abdominal pain. A CT-scan showed a left hepatic mass that measured 1.7 × 3.0 cm. He underwent a left hepatic tumor resection in May 2005 and was confirmed to have hepatocellular carcinoma that was highly differentiated as confirmed by histology. After surgery, trans-arterial chemoembolization was given 4 times as a preventive measure.

In February 2011, the color Doppler ultrasound found that the size of the right liver mass was 2.9 × 3.2 cm. A core needle biopsy was performed, and histology confirmed well differentiated hepatocellular carcinoma. Considering that his tumor had recurred after surgery, an ultrasound-guided absolute ethyl alcohol injection to the right lobe recurring tumor was performed in July 2011. Microwave ablation of the right lobe tumor was also performed twice, once in March 2012 and once in March 2014. There was no abnormality in the AFP elevation during the period.

Beginning in July 2017, the patient started to complain of bilateral chest pains. The color doppler ultrasound showed a recurrence of the right lobe tumor, so trans-arterial chemoembolization treatment was given twice in that period. In September 2017, laboratory tests showed the patient's serum alpha-fetoprotein (AFP) level elevating to 195.2 ng/ml (reference range: 0-15 ng/ml), and sorafenib at a dose of 400 mg twice a day orally was initiated. In January 2018, positron emission tomography-computed tomography (PET-CT) scans revealed multiple retro-peritoneal lymphadenopathy (**Figure 1A**). Three months later, enhanced CT scans showed slightly enlarged retroperitoneal lymph nodes compared to 3 months earlier (**Figure 1B**). The serum AFP level further increased to 300 ng/ml. A genetic test with next generation sequencing (NGS) was done with the patient's blood; the results showed that the TMB was 16%, which is 93% higher than average. Nivolumab at a dose of 200 mg intravenous infusion, administered in 2-week cycles, was started two months later, after 4 cycles of nivolumab treatment, PET-CT scans revealed that the retroperitoneal lymph nodes were significantly shrunk (**Figure 1C**). Concurrently, the serum AFP level had reduced to 2.78 ng/ml. The patient's disease was stable at his last follow-up on September 6, 2018.

Discussion

Anti-PD1 therapy shows a satisfactory effect against multiple tumor types including melanoma, and non-small cell lung cancer (NSCLC) [9-11]. A programmed death ligand-1 could be a potential biomarker to predict the efficacy of

immune checkpoint inhibitors [12]. PD-L1 can be detected using several assays, and the definition of PD-L1 positivity and the methodology of measuring PD-L1 are needed to understand the role of PD-L1 in HCC. Nivolumab was approved by the FDA on September 22, 2017 as a second line systemic treatment in HCC patients who have been treated with or who are intolerant to sorafenib [12]. At present, an immune checkpoint blockade for HCC is being estimated in combination with other treatments, including TACE and ablation. However, no randomized studies on these combinations have been carried out [12]. Which therapeutic method can be combined with nivolumab to reach a superior and reliable curative effect remains unknown.

Immune checkpoint inhibitors combined with VEGF monoclonal antibodies have received considerable attention in recent years [13]. Factors that may contribute to the immunosuppressive hepatic environment include hepatic interstitial cells, such as Kupffer cells, dendritic cells, endothelial cells, and hepatic stellate cells, and immunosuppressive cytokines, such as interleukin (IL)-10 and transforming growth factor (TGF)- β , as well as the PD-1/ PD-L1 pathway [14]. This immunosuppressive environment may be inhibited by combinations of molecularly targeted agents and immune checkpoint inhibitors [15].

In the retrospective analysis CheckMate 040, PD-L1 was shown as biomarker that predicted the response to nivolumab in 174 out of 214 patients. The ORR was 26% vs 19% in patients with PD-L1 \geq 1% compared with PD-L1 < 1%, so it was suggested that PD-L1 could be a potential biomarker associated with nivolumab treatment [16].

In this case, a satisfactory effect was achieved in the patient who received sorafenib and nivolumab, and our retrospective study demonstrates the benefit of nivolumab in combination with sorafenib, a finding which needs additional studies to further confirm. However, on account of the positive results from this study, the application of nivolumab combined with other therapies should be further pursued.

Nevertheless, immune-checkpoint blocking antibodies are effective in many types of cancers, so immune mediated adverse events

should not be ignored. These events include common side-effects, for instance, atypical pneumonia, colitis, hepatitis, rash and endocrinopathies [9, 16]. Moreover, there are unusual side-effects, such as cardiotoxicity, vision and hearing loss, and lupus nephritis [17]. Severe nivolumab-related side effects were not observed in this patient. This result indicated that nivolumab might be a relatively safe and effective drug for the treatment of metastatic hepatocellular cancer. Nivolumab combined with sorafenib may have a synergetic effect, and more patients enrolling in more studies are needed in the future.

Conclusions

Nivolumab in combination with sorafenib was effective and safe in the treatment of metastatic HCC. More patients are required to be enrolled in studies to further confirm the results of combination therapy in advanced HCC.

Disclosure of conflict of interest

None.

Address correspondences to: Lan-Qiu Wang, Department of Radiotherapy, Qingdao Cancer Hospital, 127 Si Liu South Road, Qingdao, Shandong, China. Tel: (86) 18660221960; E-mail: wlq130@126.com

References

- [1] Venook A, Papandreou C, Furuse J, Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist* 2010; 15: 5-13.
- [2] Llovet M, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J and Oliveira A. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378-390.
- [3] Ji YX, Zhang ZF, Lan KT, Nie KK, Geng CX, Liu SC, Zhang L, Zhuang XJ, Zou X, Sun L, Zhang ZC. Sorafenib in liver function impaired advanced hepatocellular carcinoma. *Chin Med Sci J* 2014; 29: 7-14.
- [4] Bruix J, Raoul J, Sherman M, Mazzaferro V, Bolondi L, Craxi A and Galle P. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepa* 2012; 57: 821-829.
- [5] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010; 236: 219-242.
- [6] Contratto M, Wu J. Targeted therapy or immunotherapy? Optimal treatment in hepatocellu-

Nivolumab and sorafenib treats hepatocellular carcinoma

- lar carcinoma. *World J Gastrointest Oncol* 2018; 5: 108-114.
- [7] Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D and Wilhelm S. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006; 66: 11851-11858.
- [8] Cheng A, Kang Y, Chen Z, Tsao C, Qin S, Kim J and Luo R. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 25-34.
- [9] Sekulovic LK, Peris K, Hauschild A, Stratigos A, Grob JJ, Nathan P and Dummer R. Science direct more than 5000 patients with metastatic melanoma in Europe per year do not have access to recommended first-line innovative treatments. *E J Cancer* 2017; 75: 313-322.
- [10] Remon J, Pardo N, Cedrés S, Martinez A, Navarro A and Felip E. Lung Cancer Immune-checkpoint inhibition in first-line treatment of advanced non-small cell lung cancer patients: Current status and future approaches. *Lung Can* 2017; 106: 70-75.
- [11] Postow MA, Harding MJ, Wolchok JD. Releasing the restraints on anti-tumor immunity for patients with melanoma. *Cancer J* 2012; 18: 153-159.
- [12] Pinter M, Peck-radosavljevic M. Review article: systemic treatment of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2018; 48: 598-609.
- [13] Kudo M. Molecular targeted therapy for hepatocellular carcinoma: where are we now? *Liver Cancer* 2015; 4: I-IV.
- [14] Zhang B, Finn RS. Personalized clinical trials in hepatocellular carcinoma based on biomarkerselection. *Liver Cancer* 2016; 5: 221-232.
- [15] Kudo M. Immuno-oncology in hepatocellular carcinoma: 2017 update. *Oncology* 2017; 93: 147-159.
- [16] El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C and Kim TY. Nivolumab in patients with advanced hepatocellular carcinoma (checkmate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; 389: 2492-2502.
- [17] Hamid O, Robert C, Ph D, Daud A, Hodi FS, Hwu WJ and Kefford R. Safety and tumor responses with lambrolizumab (Anti-PD-1) in Melanoma. *N Engl J Med* 2013; 7: 134-144.