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Case Report

Long-term Remission by Nivolumab Monotherapy for Sorafenib-refractory Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is considered to be a relatively chemotherapy-resistant tumor. There was no standard systemic therapy for patients with metastatic HCC until 2007 when sorafenib was demonstrated to be superior to supportive care. Lenvatinib has also been used as a first-line choice since a randomized phase III noninferiority trial was conducted in 2018. In the second-line setting, regorafenib was the first drug to be approved for sorafenib-refractory advanced HCC. Other drugs such as cabozantinib and ramucirumab have also shown benefits in a second-line setting. Immunotherapy is another novel and well-tolerated treatment option for patients who are refractory to tyrosine kinase inhibitors. Here, we present a patient with HCC which progressed after sorafenib treatment, and who subsequently achieved a nearly complete remission after nivolumab monotherapy. Maintenance therapy with nivolumab every 2–3 months was prescribed to sustain the good response based on a previous study that used rituximab maintenance therapy in a patient with follicular lymphoma.

Keywords: Hepatocellular carcinoma, maintenance, nivolumab, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide. Despite the decreased incidence of hepatitis B after the implementation of vaccination programs, liver cancer (HCC along with biliary tract malignancies) was still the second leading cause of cancer-related mortality in Taiwan in 2017. Sorafenib, an oral multikinase inhibitor, has been shown to significantly prolong the survival time of patients with advanced HCC, with a reported median overall survival of 10.7 months for those treated with sorafenib versus 7.9 months for those treated with placebo (hazard ratio: 0.69; 95% confidence interval [CI], 0.55–0.87; $P < 0.001$).[1] Lenvatinib was subsequently shown to be noninferior to sorafenib in overall survival in patients with untreated advanced HCC in a phase III study.[2] For the patients with sorafenib-refractory HCC, regorafenib, cabozantinib, and ramucirumab have been shown to be beneficial in phase III studies[3-5] and are approved by the Food and Drug Administration (FDA).

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Nivolumab and pembrolizumab, both immune checkpoint inhibitors, are approved in the United States as a second-line choice for advanced HCC through phase II studies with promising survival and response outcomes.[6,7] However, the application of advanced immune checkpoint inhibitors for patients with HCC has been hampered by the results of a phase III trial.[8] Nevertheless, recent studies have still shown the promising and important role of immunotherapy in advanced HCC.

Here, we present a patient with sorafenib-refractory HCC who received nivolumab monotherapy. The patient obtained a nearly complete response of the tumor for 6 years under maintenance doses of nivolumab without immunotherapy-related adverse events.

Case Report

A 56-year-old woman without systemic disease had been diagnosed with HCC 6 years previously, and presented with abdominal fullness for 2 months. The computer tomography (CT) showed a huge, ruptured hepatoma at S4 and S5, and the staging was cT4N0M0 by TNM staging system, the score is 4 by the Cancer of the Liver Italian Program (CLIP), and stage B by the Barcelona Clinic Liver Cancer (BCLC) staging system. Laboratory data showed no hepatitis B or C, and the Child–Pugh score was 6, A. She received transcatheter arterial embolization first, followed by extended right lobectomy. Her alpha-fetoprotein (AFP) level was 2484 ng/mL at that time. After R0 resection, she was regularly followed at our outpatient department, and her AFP dropped to the normal range with no evidence of tumor recurrence via sonography.

Six months later, a gradual increase in her AFP level was noted, and follow-up CT showed several nodules in the peritoneum, and thus, she was started on sorafenib. However, after 2 months of sorafenib treatment, her AFP level doubled, and CT showed increased size and number of seeding nodules in the peritoneum and liver surface, with two nodules in the left upper lobe of the lung. After discussion, immunotherapy with biweekly nivolumab 3 mg/kg was administered. After two cycles of nivolumab, her AFP level dropped dramatically from 10046 to 2936 ng/mL, and after six cycles, it dropped to the normal range (<9 ng/mL). The trend of AFP level with the course of nivolumab is illustrated in Figure 1. CT also showed no obvious viable tumors in the liver, a decrease in the size of seeding tumors in the peritoneum and liver surface [Figure 2], and a marked decrease in the size of left lung metastasis [Figure 3].

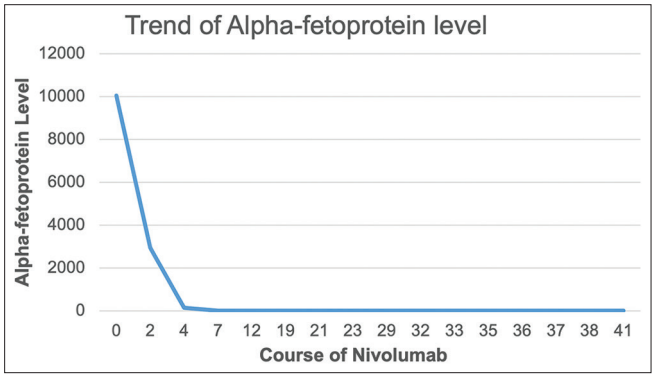

Figure 1: The level of alpha-fetoprotein decreased dramatically after 2 courses of nivolumab, and nearly normal after six cycles

We retrospectively checked for PD-L1 (by immunohistochemical staining using Dako clone 22C3 pharmDx), which showed completely negative membranous staining in the tumor cells (tumor proportion score TPS = 0% and negative for PD-L1 expression; tumor volume: 70%). However, due to the good response, we gradually prolonged the duration of nivolumab from 2 weeks to 3 weeks after the 11th dose, then 4 weeks after the 21st dose, 8 weeks after the 31st dose, and then 3 months after the 40th dose until now. Currently, after 4 years, she remains in complete remission without any side effects from the immunotherapy.

Interestingly, her laboratory data showed a change in lymphocyte-to-monocyte ratio (LMR) from 1.98 before to 4.01 after 4 weeks of nivolumab therapy, and a change in neutrophil-lymphocyte ratio (NLR) from 6.08 to 1.66.

Discussion

HCC is primarily induced by chronic hepatitis B and C viral infection, alcoholic or nonalcoholic fatty liver disease, and it is considered to be an immunogenic tumor by pathogenetic mechanisms such as chronic inflammation and an intrahepatic immunosuppressive microenvironment. These mechanisms accompanied with underlying cirrhosis make it resistant to and difficult to treat with chemotherapy. Thus, besides tyrosine kinase inhibitors (TKIs), immunotherapy provides a new therapeutic opportunity for patients with inoperable HCC.

In a sorafenib-refractory setting, several agents have been shown to be beneficial. Regorafenib has been shown to improves overall survival with a median survival of 10.6 months compared to 7.8 months with placebo treatment, with a hazard ratio of 0.63 in a phase III study.[5] Cabozantinib,

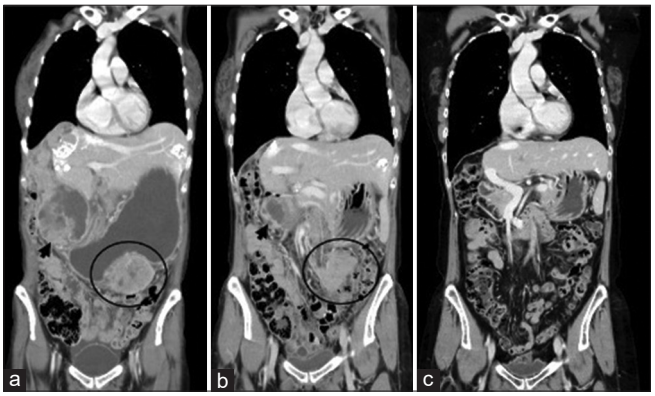

Figure 2: (a) Before nivolumab, there's a peritoneum tumor measuring 8.2 cm in largest diameter. (b) The mass shrank to 6.1 cm after six cycles of nivolumab. (c) The mass became invisible after 4 years of nivolumab monotherapy

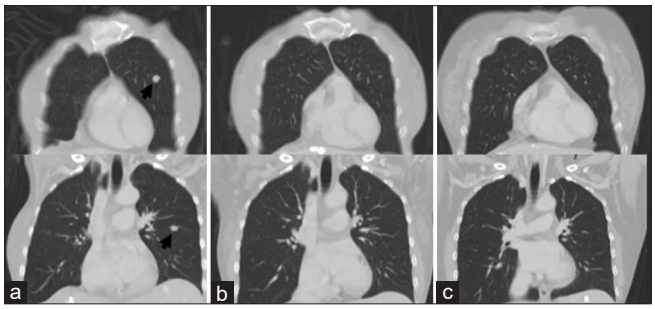

Figure 3: (a) Before nivolumab, there are two nodules in the left lungs. (b) The nodules markedly decreased in size. (c) The noduled became invisible after 4-year follow-up

another TKI, has also shown longer overall survival than placebo with median overall survival of 10.2 versus 8.0 months and median progression-free survival of 5.3 versus 1.9 months, significantly.[3] Ramucirumab, a vascular endothelial growth factor inhibitor, has shown a significant survival benefit, with a reduction in the risk of death (29%) in patients with HCC and AFP ≥ 400 ng/mL who progressed on or were intolerant to sorafenib.[4]

Immunotherapy such as nivolumab, ipilimumab and pembrolizumab, either monotherapy or combination, have shown promising response in patients with sorafenib-refractory or intolerable HCC. Nivolumab monotherapy was shown to have an objective response rate of 20% (95% CI: 15–26) in the dose-expansion phase and 15% (95% CI 6–28) in the dose-escalation phase in a phase I/II study,[6] while when combined with ipilimumab, the objective response rate was 32% with median (range) duration of response not yet reached.[9] Pembrolizumab, on the other hand, had shown an objective response of 17% in a phase II study.[7]

Based on these results, the FDA gave approval for nivolumab, either alone or combination with ipilimumab and pembrolizumab for patients with HCC who progressed on or after sorafenib. However, these indications were reassessed by the FDA in April 2021 because nivolumab lacked sufficient data in a phase III study and pembrolizumab did not reach statistical significance in OS or PFS in a phase III study.[8]

Of note, our patient received maintenance nivolumab therapy for 4 years after achieving a complete remission. Data of initial immunotherapy followed by maintenance immunotherapy are still insufficient. According to the biology and durable responses of immunotherapy,[10] a subset of patients with advanced cancer can be maintained for several years even after stopping the treatment. A similar concept was seen in patients with follicular lymphoma who received rituximab maintenance for 2 years after first-line treatment (rituximab plus chemotherapy), with a median PFS of 10.5 years in the rituximab maintenance arm compared with 4.1 years in the observation arm.[11]

There are currently no standard biomarkers to predict the response of immunotherapy in patients with advanced HCC. Although PD-L1 protein expression may predict a better response to immune checkpoint inhibitors, a minority of patients with advanced HCC without PD-L1 expression still have a durable response of up to 30%.[12] There are several possible explanations for this finding, including tumor heterogeneity, the proportion of immune cells expressed in immunohistochemistry, and differences in detection modality. Other biomarkers beside PD-L1 have been reported, such as tumor mutation burden, tumor-infiltrating lymphocytes, and microsatellite instability. However, these are either technically difficult or costly. Previous studies have reported relationships between NLR, LMR, and the outcomes of patients using PD-1 inhibitors. One retrospective study analyzed 101 patients with advanced NSCLC treated with nivolumab and found improved median PFS rates from 2.1 and 2 to both 5.3 months in patients with an NLR ≥3 and <3 at 2 weeks and 4 weeks after treatment, respectively.[13] Another retrospective study also found that the increase (≥10%) in the LMR at 4 weeks after the start of nivolumab monotherapy relative to the pretreatment LMR was positively correlated with an objective response, PFS and OS.[14] The NLR of our patient at 4 weeks after nivolumab treatment was 1.66, and her LMR had increased by >10% at that time, which suggests that peripheral white cell ratio changes may be a surrogate marker to predict the response.

In conclusion, patients with sorafenib-refractory HCCs may choose another TKI or immunotherapy as subsequent treatment. Immunotherapy shows a durable response in a minority of patients. Further prospective studies are needed to identify the factors that can predict the outcomes of patients with HCC using immunotherapy.

Research involving human participants and/or animals

We obtained the appropriate patient consent forms. In the form, the patient provided her consent for her clinical information to be reported in the journal. The patient understands that her 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.

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