

Impressive Response of Advanced Hepatocellular Carcinoma to Cisplatin Combined with Sorafenib, Nivolumab, and PG2 Immunomodulatory Injection: A Case Report

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive tumor, and sorafenib is the only proven drug for treating advanced HCC with limited survival outcome. We present a case of severe right lower chest pain in a 54-year-old man. A computed tomography (CT) scan revealed liver cirrhosis and multiple HCCs with inferior vena cava invasion, regional nodal and right adrenal metastases, and hemoperitoneum. His hepatitis B virus (HBV) deoxyribonucleic acid (DNA) level and alpha-fetoprotein (AFP) remained high even after transcatheter arterial embolization for ruptured HCCs. He received combination therapy of entecavir, sorafenib, nivolumab, cisplatin, and PG2 injection. The follow-up positron emission tomography-CT confirmed no tumor in the liver, and alpha-fetoprotein and HBV DNA titers showed a promising decrease. This novel combination had encouraging therapeutic effects for advanced HCCs, which decreased viral replication without side effects.

Keywords: Carcinoma; Metastasis; Therapy; Replication

Introduction

Hepatocellular carcinoma (HCC) is one of the most lethal cancers with high recurrence rate and poor prognosis [1,2]. Surgical resection and liver transplantation are currently the most effective treatment options. However, the response rate is only 15% in HCC patients [3]. Although many researches attempted to improve diagnostic and treatment-related strategies, effective treatment options for HCC are limited [4]. Systemic chemotherapies may lead to treatment resistant and result in unsatisfactory responses [5]. Sorafenib, a multiple kinase inhibitor, remains the only approved targeted therapy for HCC [6].

Immunotherapies are considered to repress the tumor by regulating tumor immunosuppressive microenvironment and increasing T cell infiltration against cancer. However, the efficacy is limited, and severe side effects are experienced in patients [7]. Combination therapies that are considered as new approaches for immunotherapies, for example, combination of chemotherapy and immunotherapy, combination of targeted therapy and immunotherapy, or combination between immunotherapies, have exhibited some evidences with synergistic benefit [8]. Herein, we report a case of a patient with early cirrhosis, whose advanced HCCs and high viral replication regressed on simultaneous treatments with cisplatin, entecavir, nivolumab, sorafenib, and *Astragalus* polysaccharide injection.

Case Presentation

Herein, we report a case of a 54-year-old man who presented with a history of American Joint Committee on Cancer stage III (T4N1M1) and was diagnosed with Barcelona clinic liver cancer (BCLC) HCC in November 2016. Laboratory test results revealed leukocytosis (white blood cell count: 10.5 billion cells/L) and abnormal liver function (serum aspartate aminotransferase: 79 U/L and serum alanine aminotransferase: 136 U/L). The CA 19-9 level was 58.0 U/mL, and serum alpha-fetoprotein (AFP) level was 82,291 ng/mL. He had hepatitis B virus (HBV)-related liver cirrhosis with high HBV deoxyribonucleic acid (DNA) titer (59,376 IU/mL). Abdominal computed tomography (CT) scan revealed a large conglomerate hyper vascular tumor at the right hepatic lobe, predominantly in the superior segment. Infiltrative lesions at the inferior segment extended toward the inferior vena cava (IVC) and right atrium (RA) and formed large tumor thrombosis. Left

hepatic tumors interrupted the liver surface at segments V and VI, which indicated HCC rupture. Clinical presentation of hemoperitoneum with moderate ascites was found. Multiple HCCs with IVC invasion, regional nodal and right adrenal metastases, and hemoperitoneum were also found (Figure 1A).

Then, he was administered with entecavir 0.5 mg/day, sorafenib 100 mg twice daily, and intravenous nivolumab (0.6 mg/kg), cisplatin (30 mg/m²), and *Astragalus* polysaccharides (500 mg) triweekly.

The follow-up CT scan was performed every 2 months, and the results demonstrated partial therapeutic effects for multiple HCCs with extensive tumor necrosis and persistent venous thrombosis (Figure 1B). It also showed extensive necrotic changes possibly mixed with previous tumor hemorrhage related to resolving the hematoma in most pre-existing HCCs with metastatic small hyper vascular viable tumours in both lobes and partially improved venous tumoral thrombosis, particularly in the RA. The post-therapeutic findings of positron emission tomography-CT scan did not show any evidence of hypermetabolic lesions in the liver (Figure 1C). Follow-up AFP and HBV DNA titer showed promising decrease (Figure 1D). The lowest AFP level was 45.9 ng/mL (June 10, 2017). During treatment, nausea occurs initially, while no poor appetite, nausea, vomiting, oral ulceration, and dizziness were noted afterward.

Discussion

We reported the rare case of BCLC stage C HCC with venous thromboembolism and hypovolemic shock due to HCC rupture and no loco-regional treatment options with impressive tumor response. The current combination therapy by maximizing synergistic effects

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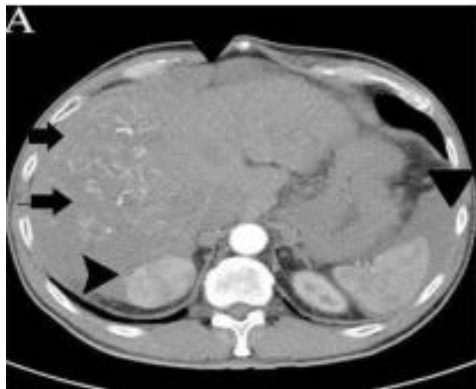


Figure 1A: Abdominal computed tomography (CT) of the patient (Initial examination).

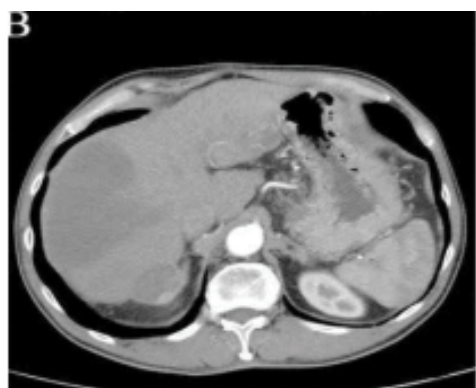


Figure 1B: Abdominal computed tomography (CT) of the patient (Follow-up examinations).

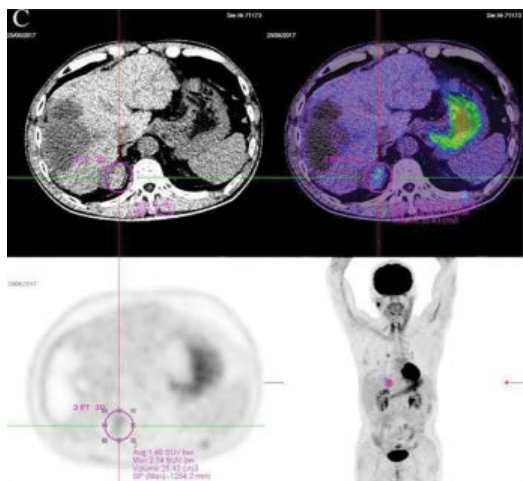


Figure 1C: Positron emission tomography-computed tomography (PET-CT) findings (4th month follow-up examination).

and minimizing treatment-related toxicities should be considered as a treatment approach.

Sorafenib is known as a multiple tyrosine kinase inhibitor that inhibits tumor growth, reduces tumor angiogenesis, and induces tumor cell apoptosis by inhibiting the Raf/MAPK pathway [9]. Although

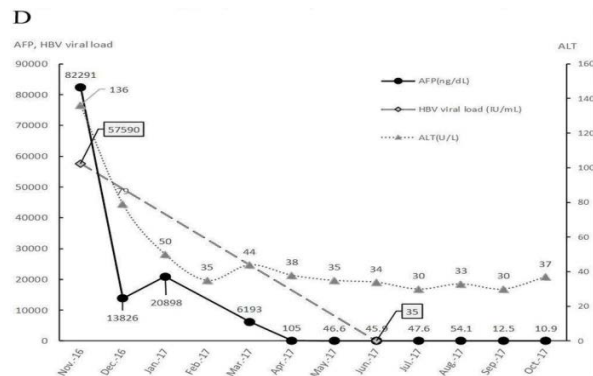


Figure 1D: Serum AFP level and HBV DNA titer of the patient from Dec 2016 to Jun 2017.

sorafenib has been proven to have survival benefits in patients with HCC according to SHARP and the Asia-Pacific trials [10,11], frequent dose adjustment is usually required due to high occurrence of adverse events, such as fatigue, diarrhea, and hand-foot skin reaction, which can lead to treatment discontinuation [12].

Recent updates in the clinical trials used immune checkpoint inhibitors in patients with advanced HCC. Notably, the result reported that nivolumab treatment might provide efficacy without new safety concerns [9]. The overexpression of PD-1 and PD-L1 in HCCs showed poor prognosis. A phase I/II trial of nivolumab revealed tolerable side effects and reliable objective responses for advanced HCCs but only for HBV viral load below 100 IU/mL [13].

The anti-PD-1 combinations for advanced HCC are limited, except for a complete response of metastatic HCC after a pembrolizumab and sorafenib treatment in a decompensated cirrhotic patient [14]. The rationale of this combination was based on inducing effective natural killer cells against HCC [15] or the immunomodulatory effect of sorafenib [16]. Platinum-based chemotherapy could also possibly enhance the anti-tumor effects of immunotherapy by eliminating immunosuppressive cells.

One concurrent treatment additionally considered is PG2 injection, which contains a mixture of extracted, isolated, and purified polysaccharides from *Astragalus membranaceus*. PG2 injection has been clinically proven to relieve fatigue among patients with advanced cancer [17] and approved as a prescription drug for alleviating cancer-related fatigue by the Taiwan Food and Drug Administration. Combination of PG2 injection and chemotherapies has also been proven to significantly improve the quality of life and reduce treatment-related toxicities among cancer patients [18].

Fatigue remains a prominent adverse effect of current treatment with entecavir, cisplatin, sorafenib, and nivolumab. The findings in this case showed that almost no treatment-related adverse event was reported, and good compliance of cancer treatment was achieved. The effects of PG2 injection in reducing adverse event could also play a role. In previous pre-clinical researches, PG2 injection showed immunomodulatory activity by inducing dendritic cell (DC) maturation and stimulating T lymphocyte growth and differentiation [19]. It can also regulate CD4+CD25+ Treg cells [20]. Furthermore, an *in vitro* study demonstrated that PG2 injection has an anti-inflammatory effect by inhibiting LPS-induced TNF- α and IL-1 β production in the THP-1 cell [21]. These studies provided supportive evidence on the combination of PG2 injection and other therapeutic

agents to modulate immunosuppressive tumor microenvironment and reduce drug resistance.

Moreover, PG2 injection showed anti-fibrotic effects in an *in vitro* study with hepatic stellate cell line, LX2. PG2 injection inhibited LX2 cell growth and induced LX2 cell apoptosis [22]. The supportive role of PG2 injection in the liver is also suggested in our study.

Conclusion

In this early cirrhotic patient, simultaneous cisplatin, entecavir, nivolumab, sorafenib, and PG2 injection had encouraging therapeutic effects for advanced HCCs that decreased viral replication with no side effects. Thus, these combinations possibly increased the therapeutic responses for advanced HCC and viral replication. Future studies are warranted to assess the safety and efficacy of these combinations for high viral replicative advanced HCCs.

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