



Case Report

Immune Checkpoint Inhibitor and Salvage Dendritic Cell-Immunotherapy for Advanced Hepatocellular Carcinoma-A Case Report

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Abstract

Advanced hepatocellular carcinoma (HCC) is a complicated malignancy with poor prognosis. Herein, we reported a 40-year-old male patient with a 16 cm HCC and a 9 cm peritoneal seeding tumor due to previous tumor rupture. Immune checkpoint inhibitor, Nivolumab, was given once and discontinued due to grade III adverse effects of hepatitis and life-threatening myocarditis. Subsequently, he received 3 doses of autologous dendritic cell infusion, followed by one hepatic arterial embolization. The main and seeding tumors were significantly shrunken, became operable, and were excised. The pathological figures showed massive tumor necrosis surrounded by CD3+CD8+ lymphocytes. Currently, the patient is freed from tumor for two years. In conclusion, sequential treatments with immune checkpoint inhibitor and salvage dendritic cell-immunotherapy boosted by hepatic artery embolization can create a curative opportunity for advanced HCC patients.

Keywords: Hepatocellular Carcinoma; Dendritic Cell; Immune Checkpoint Inhibitor; Cell Therapy; Liver Resection

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy in the liver. Unless the liver tumors are screened regularly, many HCCs are already at large sizes or even at late stage when they are found. While the tumors are at late stage, curative treatments are almost impossible for the patients. According to the last update of the Barcelona Clinic Liver Cancer prognosis and treatment strategy [1], the suggested treatment for advanced HCC will be systemic treatment with immune checkpoint inhibitors and molecular targeting agents. Sorafenib is the first molecular targeting agent proved to have efficacy in treating advanced HCC

since 2008 [2] until regorafenib, lenvatinib, cabozantinib, and ramucirumab are approved recently [3-5]. Although patients' survival is prolonged with these molecular targeting agents, the objective response rate is only 2-11% and complete response rate is less than 1%. Immune checkpoint inhibitors (ICI) are emerging agents to undergo immunotherapy for advanced HCC with 16-19% of objective response rate [6]. But, the complete response was only 1%. Recently, combination of atezolizumab and bevacizumab for advanced HCC treatment is exciting and can yield 33% of objective response rate with 10.2% of complete response according to modified Response Evaluation Criteria in Solid Tumors [7]. Nevertheless, majority of the advanced HCC patients still can not be cured. Sequential multimodality-treatment or cocktail therapy served as curative treatment is desired. Dendritic cell (DC) is the

most potent antigen-presenting cell to promote antigen-specific cytotoxicity. DC has been applied to treat advanced-stage cancers with promising effects. However, this personalized medicine is still limited due to high requirement of technique and facilities. The Healthy Welfare Department in Taiwan opens the cell therapy to clinic for advanced cancer under a special regulation. Herein, we reported an advanced HCC patient received ICI, salvage DC-immunotherapy, transcatheter arterial embolization, and liver resection to cure of advanced HCC.

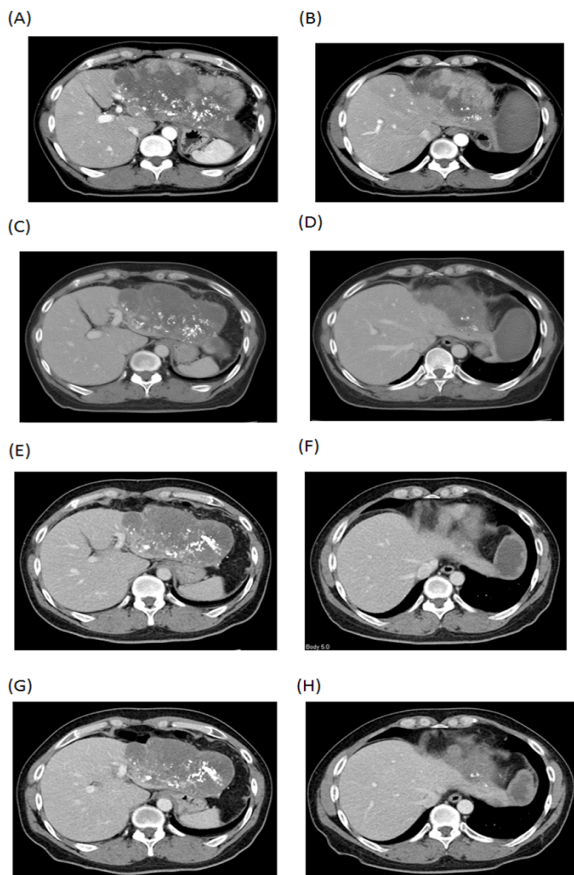


Figure 1: The representative figures of CT at different treatment stages. Before receiving any treatment at our hospital, liver tumor was 162.5 mm in diameter with a 90.3 mm seeding tumor on left hemidiaphragm (A & B). The main tumor was reduced to 138.0 mm and seeding tumor was reduced to 77.1 mm at two months after one dose of nivolumab (C and D). The main tumor was further reduced to 132.3 mm and the seeding tumor was reduced to 60.1 mm at one month after 3 doses of DC treatment (E & F). The main tumor was further reduced to 128.6 mm and the seeding tumor was reduced to 48.3 mm at one month after TAE (G & H).

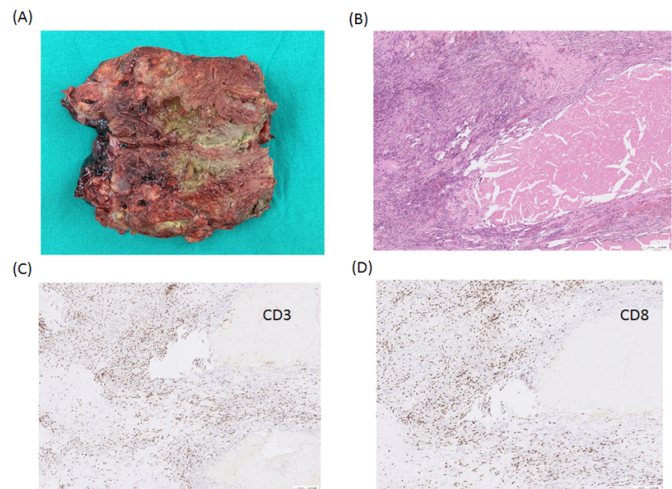


Figure 2: Gross and microscopic figures of the tumor. The surgical specimen showed that the tumor was marked necrotic grossly (A). Microscopically, the cancer cells were necrotic and surrounded with a thick layer of lymphocytes (B). These lymphocytes were positive for CD3 (C) and CD8 (D).

Case Presentation

A 40-year-old hepatitis B patient had sudden onset of abdominal pain with hypotension on July 20, 2020, and was sent to the emergency room of a local hospital. Computed tomography (CT) showed a huge liver tumor in left lateral segment with enlarged peri-aortic lymph nodes. Hepatocellular carcinoma rupture with internal bleeding was the impression and emergent transcatheter arterial embolization (TAE) was performed to stop the bleeding. Later on, he was transferred to our hospital. CT was repeated and revealed that liver tumor was 162.5 mm in diameter with a 90.3 mm seeding tumor on left hemidiaphragm (Figure 1A & B). Combination of nivolumab (3mg/kg) and sorafenib (200mg, bid) was administered on Sep. 2, 2020. Ten days later, he visited our emergency room due to high fever (39.6°C), skin rashes, and hand-foot reaction. Laboratory test showed that aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated to 526U/L and 692U/L, respectively. Nivolumab-related grade III adverse effect of hepatitis were the impression and prednisolone (0.5mg/kg) was given. Liver function was improving gradually. However, the patient had dizziness, short of breath, cold sweating, chest tightness and hypotension in the evening of Sep. 24. Breath sound revealed bilateral rales. Laboratory data showed 10.146 ng/ml of Troponin-I, 35.5 ng/ml of CK-MB and 2306 pg/ml of N terminal pro B type natriuretic peptide (NT-ProBNP). Cardiac catheterization was performed. Coronary arteries were patent, but the ejection fraction was only 35%. Nivolumab-related

myocarditis and heart failure was the impression. Intravenous solumedrol 250mg followed by 40mg every 6 hours and oral mycophenolate mofetil 500mg every 12 hours were given. The patient's condition was improved and cardiac ejection fraction went back to 60% 2 weeks later. Although the severe form of adverse effects of nivolumab occurred, therapeutic effect presented as reduction of main tumor size from 162.5 to 138.0 mm and seeding tumor from 90.3 to 77.1 mm (Figure 1 C and D). Because of life threatening adverse effects of ICI, DC pulsed with autologous tumor lysate salvaged the treatment [8]. Three courses of DC (37.46×10^6 cells in total) were administered intravenously. CT showed the main tumor was further reduced to 132.3mm and the seeding tumor was reduced to 60.1mm one month later (Figure 1 E & F). The percentage of CD8+ T-cells among T-lymphocytes was 39.41% prior to nivolumab treatment, 37.97% prior to DC-immunotherapy, and increased to 44.82% after DC-immunotherapy in his peripheral blood. TAE was performed on Dec. 28, 2020, to induce cancer cell necrosis and boost tumor antigens. The main tumor was further reduced to 128.6mm and the seeding tumor was reduced to 48.3 mm at one month after TAE (Figure 1 G & H). Thereafter, surgical resection was arranged to excise the main and diaphragmatic seeding tumors on Feb. 20, 2021. Grossly, the tumor was marked necrotic (Figure 2A). Microscopically, the cancer cells were necrotic and surrounded with a thick layer of lymphocytes (Figure 2B) which were positive for CD3 and CD8 (Figure 2 C & D). Now, he was regularly followed up at outpatient clinic and cancer-free for more than 2 years.

Discussion

Advanced HCC is a critical situation and difficult to be treated. Curative treatment for advanced HCC patients is not expected. In this case presentation, we showed application of sequential ICI, DC, TAE and surgery to cure a patient with advanced HCC. For advanced HCC, a single treatment modality to cure the patients is almost impossible. To our knowledge, a malignant liver tumor progressive to advanced HCC is a complicated process including cell transformation, microenvironment change, dysfunctional hosts' immunity, etc. Under such a complicated interaction between cancer cells and hosts' immunity, it is not surprised that a single treatment modality will fail to treat an advanced HCC. Sequential multimodality or cocktail treatment may be the solution for advanced stage HCC. Currently, combination of atezolizumab and bevacizumab can yield around 30% of objective response rate for advanced HCC and progression-free survival was 6.8 months [7]. Except the 8-10% of the patients with complete response, the tumors will regrow eventually, additional therapy shall be added. DC pulsed tumor antigens can proceed antigen-specific cytotoxicity. DC following ICI may be a good strategy to treat advanced HCC since ICI can reactive T-cells and decreased immunosuppressive cells, and DC can re-direct cytotoxic T-cells to

kill cancer cells [9]. In this case, ICI already triggers off treatment response and DC-immunotherapy can further induce anti-cancer effect. TAE can induce tumor cell necrosis by blocking oxygen and nutrition supply to cancer cells, and release tumor antigen to recall memory T-cells which are induced by DC-immunotherapy [10,11]. In this case, the tumor was further shrunken by TAE and let the surgical treatment became feasible. Finally, this patient could receive a curative surgery. Until now, the patient is free from HCC for more than 2 years. In conclusion, advanced HCC is a complicated malignancy with poor prognosis, and it is not possible to be cured by a single treatment modality. Immunotherapy with sequential ICI and DC is one of prompt options to create an opportunity to cure patients of advanced HCC.

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Conflict of interest: There is no conflict of interest among authors.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

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