Anti-Programmed Cell Death Protein 1 (PD-1) Immunotherapy for Metastatic Hepatocellular Carcinoma After Liver Transplantation: A Report of Three Cases

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Abstract

The treatment of recurrent hepatocellular carcinoma (HCC) after liver transplantation is difficult due to the lack of effective treatment options. The available evidence on the emerging immunotherapy in liver transplantation is based on anecdotal experiences and requires additional investigations. To determine the efficacy and safety of immunotherapy in liver transplant recipients, we report three cases of recurrent metastatic HCC after liver transplantation who were treated with nivolumab as off-label salvage therapy.

Introduction

Hepatocellular carcinoma (HCC) is ranked first among primary hepatic cancers, involving more than half a million patients per year [1]. Several early-phase clinical trials have investigated the value of immunotherapy in advanced HCC, as it represents the example of inflammation-induced cancers [2]. Liver transplantation is the treatment of choice for localized HCC in the absence of contraindications [3]. The recurrence rate after liver transplantation for HCC, despite the strict eligibility criteria, is high, varying between 6% to 18% [4]. The treatment of recurrent HCC after liver transplantation is a real challenge for the clinical practice, given the absence of any therapeutic standards [5]. The principle of immunotherapy consists of the induction of an anti-tumor immune response using monoclonal antibodies targeting immune checkpoints present on the surface of T-cells. Immune-checkpoint inhibitors include two major families of antibodies targeting either the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or the programmed cell death protein 1 (PD-1) [6]. Nivolumab is the first recombinant human monoclonal antibody developed in the world that targets PD-1 [7]. The response rate with this molecule reached 20% with two complete responses in phase I/II trial (CheckMate-040 trial) in advanced HCC. These results seemed extremely promising for the advanced stage of this malignancy known by its poor survival [8]. Nivolumab is also characterized by its persistent effect in responders, which encouraged scientists-clinicians to continue patients’ enrollment for this setting. At the Congress of the American Society of Clinical Oncology (ASCO) in 2017, the updated data of this study confirmed satisfactory results for overall survival (OS) with a median of 28.6 months in the first line of treatment and 15.6 months in the second line [9]. The nivolumab positioning in the first-line versus sorafenib is under investigation in phase III [10].

It is actually known that the tolerance of transplant organs involves the modulation of cell-mediated immunity [11-12] and that the transplant rejection’s risk may be caused by the deregulation of these processes [13]. The fear of transplant rejection leads to the exclusion of the recipient’s solid organ transplant from the clinical trials of immune checkpoints inhibitors [14]. The current data on immunotherapy after hepatic transplantation are lacking and are limited to case reports and small published series [15-16].

In this paper, we describe three cases of recurrent metastatic HCC after liver transplantation in whom nivolumab was used as off-label salvage treatment.

Case Presentation

Case reports

Case 1

A 70-year-old male with a personal history of nonalcoholic steatohepatitis presented with multifocal HCC that was diagnosed at the age of 64. No regional lymph node or distal metastasis was found, classified as...
Therefore, to define the feasibility of immunotherapy in hepatic transplants for HCC, clinical trials including current data but medicine is one of the most evolving areas where the guidelines change overnight. Overall, the use of immunotherapy in HCC recurrent after liver transplantation is not recommended in light of the efficacy of immunotherapy in hepatic transplant patients. Further studies with a large patient cohort are awaited.

**Conclusions**

Overall, the use of immunotherapy in HCC recurrent after liver transplantation is not recommended in light of current data but medicine is one of the most evolving areas where the guidelines change overnight. Therefore, to define the feasibility of immunotherapy in hepatic transplants for HCC, clinical trials including...
Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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