Excellent Response to Anti-PD1 therapy in a Patient with Hepatocellular Carcinoma: Case Report and Review of Literature

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Abstract:

Hepatocellular carcinoma (HCC) is an aggressive cancer associated with high mortality worldwide. HCC develops in the setting of underlying cirrhosis due to chronic liver disease. Surgery is usually considered the treatment of choice for early disease however most patients have locally advanced or metastatic HCC at diagnosis in which case treatments are limited. Immune checkpoint blockade of programmed death receptor-1 (PD-1) pathway offers a potential treatment strategy based on the encouraging results of the phase I/II trial of nivolumab (Checkmate 040 trial). This has led to the off-label use of nivolumab after failure of treatment with sorafenib either due to intolerance or progression of disease. Although rare (<5%), clinical response to anti-PD-1 antibody may be preceded by "pseudoprogression" – increase in the size and number of tumor lesions before actual tumor shrinkage. We report a case of pseudoprogression followed by excellent response in a HCC patient treated with nivolumab and review the literature for ongoing trials of immune checkpoint blockade in HCC. The pseudoprogression in our case is supported by both increase in tumor size as well as alpha-fetoprotein after four treatments with nivolumab however regression of tumor size and normalization of alpha-fetoprotein after subsequent treatments. To our knowledge, there are no reports of pseudoprogression in HCC although pseudoprogression has been well described in melanoma.

Introduction:

Hepatocellular carcinoma (HCC) is the primary malignancy of the liver that often occurs in the setting of underlying chronic liver disease and cirrhosis. It is the second leading cause of cancer related death worldwide (Jemal *et al.*, 2011). In the United States, annual incidence of HCC is 6 per 100,000 (El-Serag & Kanwal, 2014). Although the US is considered a low incidence area for HCC, the incidence has increased over the past two decades, likely due to a large cohort of people with chronic hepatitis C (Davila *et al.*, 2004). Other risk factors for HCC include chronic hepatitis B or C infection, and alcoholic liver disease. Nonalcoholic fatty liver disease (NAFLD)/ nonalcoholic steatohepatitis (NASH) is an emerging risk factor that is increasingly becoming more prevalent. Other less common risk factors are hereditary hemochromatosis, alpha 1- antitrypsin deficiency, autoimmune hepatitis, and Wilson's disease (El-Serag, 2011).

The treatment choice for HCC is predominantly driven by the extent of tumor and the degree of underlying liver dysfunction. Surgical resection or orthotopic liver transplant (OLT) offer the best chance of cure, however these treatments are applicable to a small minority of patients (Waller *et al.*, 2015). Liver directed therapies in the form of transarterial chemoembolization (TACE), or radiofrequency ablation (RFA) are frequently utilized for more advanced disease (Chok *et al.*, 2014). However, approximately 50% of patients are diagnosed with locally advanced or metastatic disease, and therefore, are not eligible for potentially curative treatments (SEER, 2017). Also, patients treated with locoregional therapy generally progress to disease that is too advanced for that modality. Being a relatively chemotherapy refractory tumor, the treatment options for advanced HCC are extremely limited. The only systemic treatment currently approved for the treatment of advanced disease is sorafenib, yielding a median overall survival of 6.5-10.7 months in patients with good liver function (Llovet *et al.*, 2008). Therefore, a search for novel therapeutic agents is necessary (Cheng *et al.*, 2009; Llovet *et al.*, 2008).

In recent years, immunotherapy in the form of immune checkpoint blockade has brought a paradigm shift in cancer treatment. Being an 'immune privileged' organ, the liver presents a unique opportunity to exploit modification of immune regulatory pathways as a potential therapeutic strategy for HCC (Flecken *et al.*, 2012). The liver confronts abundant exogenous antigens within blood from the gut via the portal vein. Specific mechanisms with regards to immune tolerance are activated to inhibit unneeded immune responses. Unfortunately, these mechanisms, such as recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells, and overexpression of inhibitory ligands such as programmed death ligand 1 (PD-L1), contribute to weakened anti-tumor immune responses and ultimately tumor progression (Hong *et al.*, 2015).

Blockade of immune checkpoint pathways such as the programmed death receptor – 1 (PD-1) pathway or the cytotoxic T lymphocyte antigen – 4 (CTLA-4) pathway can potentially offer a treatment strategy to reinstate host immune response against HCC and ultimately tumor regression. Encouraging results of a phase I/II trial of nivolumab (Checkmate 040 trial) (El-Khoueiry, 2016) has led many oncologists to use nivolumab for treating HCC patients especially in the second line setting (after sorafenib). Assessment of clinical efficacy for immune checkpoint inhibitors presents a unique challenge due to possibility of "pseudoprogression" – increase in the size and number of tumor lesions before tumor shrinkage (Chiou & Burotto, 2015; Hodi *et al.*, 2016). We report a case of HCC that had an excellent response to treatment with nivolumab after initial pseudoprogression.

Case Presentation:

A 79-year-old man with diabetes mellitus, hypertension, hyperlipidemia, and hypothyroidism presented with worsening back pain and found to have large heterogeneous irregular mass within the right hepatic lobe on CT imaging. A subsequent MRI abdomen showed

at least 2 hepatic lesions with the largest measuring up to 7.9 x 7.6 cm in dimension with nonspecific imaging characteristics. Serum alpha-fetoprotein (AFP) was 117 ng/mL at that time. Because of the lack of characteristic radiologic appearance of the liver lesions for HCC (hyperenhancement during arterial phase and delayed washout in venous phase), he underwent ultrasound guided core needle biopsy of the lesion in segment 8 which confirmed the diagnosis of well differentiated hepatocellular carcinoma in a background of cirrhosis secondary to hemochromatosis and NASH **(Figure 1A)**. Viral infection was ruled out. He was initially treated with sorafenib and ipafricept on a clinical trial due to multifocal disease and good liver function (Child-Pugh class A cirrhosis). Ipafricept is a fusion protein comprised of the cysteine-rich domain of frizzled family receptor 8 (Fzd8) fused to the human immunoglobulin Fc domain with potential antineoplastic activity. Despite doing clinically well, he had radiographic progression of disease after 4 months of treatment.

Due to lack of an available clinical trial, he was started on off-label nivolumab (3 mg/kg IV every 2 weeks) based on the phase II data mentioned above (El-Khoueiry *et al.*, 2015). Baseline computed tomography (CT) showed two large liver lesions but no extrahepatic disease (Figure 1 A). Restaging CT after 4 cycles of nivolumab showed increase in the size of the liver lesions but no new lesions (Figure 1 B). At this time, his alpha-fetoprotein (AFP) also increased to 3,246 ng/mL as compared to 1,232 ng/mL before nivolumab was started. The patient was continued on nivolumab due to lack of any other effective treatments, clinical stability, and possibility of pseudoprogression. Repeat imaging after 8 cycles of nivolumab (4 months) showed significant decrease in the size of the liver lesions and AFP decline to 68 ng/mL. The patient remained on biweekly treatments with bimonthly restaging scans. His tumor size continued to decrease until cycle 12 of nivolumab, and remained stable thereafter until last restaging after cycle 19 (9 months) of nivolumab. Similarly, his AFP continued to decrease until cycle 12 of nivolumab, and become normal (< 25 ng/ml) thereafter until last restaging after cycle 19 (9 months) of nivolumab.

Discussion:

We report a case of HCC in the setting of cirrhosis from hemochromatosis and NASH that had an excellent response to off-label use nivolumab and take this opportunity to review the literature for anti-PD1 therapy in HCC and highlight a key observation in this regard – pseudoprogression. Although HCC is the second most frequent cause of cancer mortality worldwide, sorafenib remains the only chemotherapy option for the treatment of advanced HCC. Notably, sorafenib has shown an improvement in median OS in phase III placebo-controlled trial from 7.9 months to 10.7 months however the objective response rate is low (2.2%) and treatment is often complicated by underlying liver dysfunction requiring dose reduction to avoid treatment related toxicity (Llovet *et al.*, 2008).

In recent years, immune checkpoint blockade has brought a paradigm shift in the treatment of a number of malignancies. Various immune checkpoint blocking agents are being tested for their efficacy in HCC. There are several ongoing trials with immune checkpoint blockade in HCC **(Table 1)**. The PD-1/PD-L1 pathway downregulates the immune response by suppressing antigen-specific T cell activation. PD-1 receptors are expressed on several immune cells including B cells, myeloid cell, T cells and NK cells. The PD-L2 is only expressed on dendritic cells whereas PD-L1 is expressed on dendritic cells, blood vessels, myocardium, lung, and placenta. Similarly, the CTLA-4 pathway also downregulates T-cell immune responses by regulating the proliferation of T lymphocytes however CTLA-4 is mainly expressed on Tregs and the CTLA-4 pathway functions solely within the lymph nodes (Kudo, 2017).

We conducted a thorough English literature search on PubMed using the search terms ‘anti-PD1’, ‘pembrolizumab’ or ‘nivolumab’ and ‘hepatocellular cancer’, ‘HCC’ or ‘hepatoma’. There are no published data from randomized controlled trial of checkpoint inhibitors in HCC, however, results of a phase I/II trial of nivolumab (CheckMate 040) in patients with HCC have

generated significant excitement (El-Khoueiry *et al.*, 2015; Sangro, 2016). Besides the CheckMate 040 trial, we only found a case report of a metastatic HCC patient successfully treated with pembrolizumab after progression on sorafenib (Truong *et al.*, 2016). Notably, there are many ongoing trials evaluating the safety and efficacy of checkpoint inhibitors in HCC **(Table 1).**

Nivolumab is a fully humanized IgG4 monoclonal antibody to programmed cell death receptor-1 (PD-1) that has shown apparent efficacy in HCC (Sangro, 2016). In the CheckMate 040 trial, a total of 214 advanced HCC patients with Child-Pugh score ≤ 6 were treated into 3 separate expansion cohorts: HCV-infected, HBV-infected and uninfected (sorafenib naïve/intolerant and sorafenib progressors). Objective responses were seen in 35 of 214 (16%) including 2 complete responses (CR) and 33 partial responses (PR) regardless of the etiologic subtype, PD-L1 status or cohort (El-Khoueiry *et al.*, 2015; Sangro, 2016). Responses were durable, lasting for 14–17+ months for CR and up to 8 months for PR. Time to tumor response was 3 months, however the median duration of response has not yet been reached. The overall survival rate for all patients combined together was 82.5% and 70.8% at 6 and 9 months, respectively.

Treatment related grade 3 or 4 adverse events were seen in 18% patients; most commonly an asymptomatic elevation in AST and ALT (Sangro, 2016). Based on the encouraging results of Checkmate 040, a multinational phase III randomized controlled trial, (CheckMate 459) (NCT02576509) (NCT02576509) is currently ongoing with a primary endpoint of overall survival and time to tumor progression. The trial will randomize (1:1) systemic therapy naive HCC patients to either sorafenib or nivolumab (3 mg/kg Q 2 weekly) with a planned enrollment of 726 patients.

It is not surprising to see clinical benefit with immune checkpoint blockade in infected HCC (those with hepatitis B or C infection), since both these infections are associated hepatic inflammation and upregulation of PD-1 (Barathan *et al.*, 2015; Xu *et al.*, 2014). Interestingly, in

CheckMate 040, about a third of the patients were uninfected and both CRs were seen in uninfected patients. In addition, both these patients had longer than median duration of response.

Our case highlights some important aspects of use of nivolumab in HCC. Firstly, we observed pseudoprogression followed by excellent and durable response to anti-PD1 therapy. Pseudoprogression has not been described in HCC. Although the overall incidence of pseudoprogression is low (< 5%) even in melanoma (Hodi *et al.*, 2016), oncologists treating HCC patients with immune checkpoint blockade therapy should be aware of the possibility of pseudoprogression, which may manifest as increase in AFP as well as tumor size. While the mechanism of pseudoprogression is not fully elucidated, transient increase in tumor size is believed to be secondary to immune cell infiltration and necrosis (Chiou & Burotto, 2015). The case may assist in clinical decision making especially for oncologists not familiar with Immune-Related Response Criteria. Secondly, unlike chronic hepatitis, uninfected HCC (such as, induced by hemochromatosis and NASH) is not known to be associated with upregulation of PD-1 or PDL-1, yet treatment with nivolumab in this setting seems to be beneficial. Notably, our patient's tumor lacked expression of PD-L1 **(Figure 1B)** but still had good response raising question about the value of PD-L1 testing as a biomarker in HCC.

In summary, we present a case of uninfected HCC treated successfully with anti-PD1 antibody (nivolumab) after pseudoprogression. The results from Checkmate 049 will add to our knowledge of anti-PD1 therapy in the treatment of HCC and provide more information about the phenomenon of pseudoprogression.

Table 1: Ongoing clinical trials with immune checkpoint blockade in HCC.

Agent	N	Trial Phase	Line of Therapy	Primary Endpoint	Status
Anti PD-1 Ab					
Nivolumab (NCT01658878) *CheckMate 040*	576 + Cohort 5	I/II	First and Second	DLT, MTD and ORR	Recruiting
Nivolumab (NCT02576509) *CheckMate459*	726	III	First	OS and TTP	Recruiting
Nivolumab and CC-122 (NCT02859324)	50	I/II	First	DLT, AE and ORR	Recruiting
Pembrolizumab (NCT02702414) *KEYNOTE-224*	100	II	Second	ORR	Completed
Pembrolizumab (NCT02940496)	15	I/II	Second	Predictive Biomarkers	Recruiting
Pembrolizumab (NCT02658019)	28	II	Second	DCR and AE	Recruiting
Pembrolizumab (NCT02702401) *KEYNOTE-224*	408	III	Second	PFS and OS	Recruiting
Pembrolizumab (NCT03062358) KEYNOTE-394	330 Asian Subjects	III	Second	OS	Recruiting
Pembrolizumab and Lenvatinib (NCT03006926)	30	Ib	First	DLT and AE	Recruiting
Anti PD-L1 Ab					
Durvalumab (MEDI4736) and Tremelimumab (NCT02519348)	144	II	First and Second	Safety and Tolerability	Recruiting
Durvalumab (MEDI4736) and Tremelimumab (NCT02572687)	114	I	Second	DLT	Recruiting
Anti CTLA-4 Ab					
CP-675,206 (NCT01008358)	20	II	Second	Tumor response	Completed

Abbreviations: ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression Free Survival; DLT, Dose Limiting Toxicity; AE, Adverse Effect; DCR, Disease Control Rate; BSC, Best Supportive Care.

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