PD-1 Blockade in a Liver Transplant Recipient With Microsatellite Unstable Metastatic Colorectal Cancer and Hepatic Impairment

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ABSTRACT

Immune checkpoint inhibitors represent a newly established standard of care in patients with refractory metastatic colorectal cancer with mismatch repair deficiency and microsatellite instability. However, the use of immunotherapy is unclear in recipients of liver transplants with or without concurrent liver function abnormalities. Clinical trials investigating immunotherapy have mostly excluded liver transplant recipients and patients with abnormal liver function. This report presents the first case, to our knowledge, of a liver transplant patient with mismatch repair-deficient colon adenocarcinoma with liver metastases and concurrent abnormal liver function who safely responded to immunotherapy. We also review the literature on checkpoint inhibitor use in patients with other metastatic solid tumors after liver transplant and those with baseline liver function abnormalities. An increasing body of evidence supports the safety of checkpoint inhibition in patients with cancer and solid organ transplants, but further prospective studies are warranted. Use of immunotherapy in liver transplant recipients who have metastatic colorectal cancer with microsatellite instability is feasible but should be performed in a multidisciplinary team setting.

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Immune checkpoint inhibitors (ICIs) now represent standard-of-care options in refractory metastatic colorectal tumors with microsatellite instability (MSI) or mismatch repair deficiency caused by loss of or defective DNA mismatch repair proteins, such as MLH1, MSH2, MSH6, and PMS2.^{1,2} However, most large, prospective clinical trials investigating checkpoint blockade in MSI metastatic colorectal cancer (mCRC) have excluded patients who received a liver transplant.^{1,3} The safety and efficacy of ICIs in patients with cancer and solid organ transplants remain unclear given the possibility of graft rejection. This report presents the first case, to our knowledge, of a liver transplant recipient who developed mCRC with MSI and was safely and effectively treated with an ICI. We also review the literature on immunotherapy use in patients with other metastatic solid tumors after liver transplant and those with baseline liver function abnormalities.

Case Presentation

A 61-year-old man with a history of alcoholic cirrhosis underwent liver transplantation in November 2014. His postoperative course was complicated by tacrolimus neurotoxicity, and thus his immunosuppressive regimen was transiently modified to mycophenolate mofetil and everolimus. He was doing well until October 2016 when a screening colonoscopy discovered a moderately differentiated colon adenocarcinoma of the ascending colon with MSI on immunohistochemical staining (deficient MLH1 and PMS2 with intact MSH2 and MSH6) and *RAS/BRAF* wild-type status. FoundationOne test results (Foundation Medicine, Inc.) of the primary tumor revealed a tumor mutational burden (TMB) of 40 mutations per megabase (Mb). CT scans of the chest, abdomen, and pelvis showed no evidence of metastatic disease; he underwent a right hemicolectomy on January 2017 and his tumor was assigned a pathologic stage of pT3N2b (stage IIIC). In May 2017, a new segment 7 liver lesion

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Figure 1. (A) CEA levels and (B) results of liver function tests during pembrolizumab therapy.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen.

was noted, with biopsy results showing metastatic colon cancer.

He was treated initially with FOLFOX (5-FU/leucovorin/oxaliplatin). However, response imaging after 7 cycles showed progressive disease with new liver and lung metastases. He subsequently received 5 cycles of irinotecan and cetuximab but developed a small bowel obstruction in the setting of further progressive disease.

After a thorough discussion of risks and benefits with the patient, a decision was made to pursue ICI therapy with pembrolizumab, 200 mg every 3 weeks, starting June 2018. In conjunction with his transplant hepatologist, prednisone was given at 60 mg (1 mg/kg) on days of immunotherapy infusion, and at 10 mg daily throughout the remainder of each cycle for 3 months. Adjunctive corticosteroids were discontinued after evidence of normalization in liver enzymes. Mycophenolate mofetil was discontinued when corticosteroids were started, and tacrolimus was maintained with a goal trough of 3 to 5 ng/mL. Before initiation of pembrolizumab, his total bilirubin level was 3.0 mg/dL, alkaline phosphatase (ALP) was 369 U/L, aspartate aminotransferase (AST) was 53 U/L, and alanine aminotransferase (ALT) was 52 U/L. Hepatic impairment was attributed to the interval development of innumerable hepatic metastases. His carcinoembryonic

antigen (CEA) level was 36.8 ng/mL 21 days before his first dose of pembrolizumab, peaked at 88.7 ng/mL 4 days after his first dose of pembrolizumab, and nadired to 19 ng/mL before plateauing (Figure 1A). His bowel obstruction resolved after 2 cycles of pembrolizumab. At the time of writing, he had completed 15 cycles of pembrolizumab and his liver function tests normalized after cycle 3, although they initially increased during the first 2 cycles (Figure 1B). Surveillance imaging after cycle 12 showed a sustained partial response (Figure 2).

Discussion

Immunotherapy in Solid Organ Transplant Recipients

Recipients of solid organ transplants are at high risk of developing a broad spectrum of malignancies, which is at least partly due to immunosuppression.⁴ The risk of CRC in the setting of liver transplant is unclear and may be related to inflammatory bowel disease.⁵ In one case report, a liver transplant recipient on chronic immunosuppression developed CRC with MSI, progressed to metastatic disease despite initial surgical resection, and died shortly after starting systemic 5-FU-based chemotherapy.⁶

Figure 2. Axial CT imaging of 2 dominant liver lesions prior to pembrolizumab therapy, performed in the setting of (A, B) acute complete mechanical small bowel obstruction and (C, D) after 12 cycles of pembrolizumab.

Table 1. Literature Review of Liver Transplant Recipients Treated With ICIs

Publication	Malignancy	Time From Transplant to Malignancy (y)	ICI	Immunosuppression	Response	PFS (mo)	ICI Duration (mo)	OS (mo)	Graft Rejection
Morales et al, ¹⁰ 2015	Melanoma	1	Ipilimumab	Rapamycin	Response	>10	2.5	>10	No
Ranganath et al, ¹¹ 2015	Melanoma	7	Ipilimumab	Tacrolimus	Progression	8	2	>4	No
De Toni et al, ¹² 2017	HCC	0.9	Nivolumab	Tacrolimus	Progression, then mixed	3.5	7	10	No
Dueland et al, ¹³ 2017	Melanoma	1.5	Ipilimumab	Prednisolone, 10 mg/d	Rejection	—	0.75	5	Yes
Friend et al, ¹⁴ 2017	HCC	3	Nivolumab	Sirolimus	Rejection	—	0.5	4.25	Yes
	HCC	1	Nivolumab	Tacrolimus	Rejection	—	0.25	1	Yes
Schvartzman et al, ¹⁵ 2017	Melanoma	>20	Pembrolizumab	—	Response, HCV reactivation	>6	1	>6	No
Varkaris et al, ¹⁶ 2017	HCC	6	Pembrolizumab	Tacrolimus	Progression	3	—	3.33	No
Biondani et al, ¹⁷ 2018	NSCLC (SCC)	12	Nivolumab	Prednisone, 60 mg/d, taper to 5 mg/d, tacrolimus, everolimus	Progression	2.1	2.1	12	No
DeLeon et al, ¹⁸ 2018	HCC	2.7	Nivolumab	Tacrolimus	Progression	2.2 ^a	1.2	1.2	No
	Melanoma	5.5	Pembrolizumab	MMF, everolimus	Response	>21.1	9.5	>21.1	No
	HCC	7.8	Nivolumab	MMF, sirolimus	Progression	0.7	1.1	1.1	No
	HCC	3.7	Nivolumab	Tacrolimus	Progression	1.3	1.3	1.3	No
	HCC	1.2	Nivolumab	Tacrolimus	Multiorgan failure	—	0.3	0.3	No
	HCC	1.1	Nivolumab	Sirolimus	Rejection	—	0.9	0.9	Yes
	Melanoma	3.1	Pembrolizumab	MMF, prednisone	Rejection	—	0.7	>0.7	Yes
Gassmann et al, ¹⁹ 2018	HCC	2	Nivolumab	MMF, everolimus	Rejection	—	0.83	0.38	Yes
Kuo et al, ²⁰ 2018	Melanoma	4.5	Ipilimumab, pembrolizumab ^a	MMF, sirolimus	Progression, response ^a	3, >24 ^a	3, 17.5 ^a	>24	No
Rammohan et al, ²¹ 2018	HCC	3	Pembrolizumab (with sorafenib)	MMF, steroids, tacrolimus	Response	>10	>10	>10	No
Tio et al, ²² 2018	Melanoma	—	Pembrolizumab	Cyclosporine	Rejection	—	0.27	0.27	Yes

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; MMF, mycophenolate mofetil; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

^aPatient initially experienced disease progression on ipilimumab, and experienced response after switching to pembrolizumab.

Immunotherapy has rapidly become a mainstay of therapy for a variety of malignancies but is generally contraindicated in the setting of liver transplant due to fear of graft rejection and need for systemically active doses of immunosuppressants. Transplant rejection in patients receiving ICIs is infrequently reported in literature. PD-L1 has been previously established to modulate graft tolerance in cardiac transplant mouse models, and blockade of PD-L1 was associated with graft rejection.⁷ This is mediated by increased activity of IFN- γ -producing T-helper cells and cytotoxic CD8⁺ T cells, with decreased activity of T-regulatory cells.⁸ Similar results have been seen in mouse liver transplant models, whereby interruption of PD-1 is associated with acute rejection.⁹

To date, only 20 cases of immunotherapy given in the setting of liver transplant have been reported (Table 1)^{10–22}; 11 patients had hepatocellular carcinoma (HCC), 9 had melanoma, and 1 had squamous non-small cell lung cancer. Outcomes in these cases ranged from fatal graft rejection (7/20 or 35% rejection rate) to treatment response and prolonged survival over 20 months.^{10–18,20,23} When graft rejection occurred, most cases occurred within 1 month of starting ICI therapy. Most primary cancers in these cases were either HCC or melanoma, for which immunotherapy consisted of ipilimumab, nivolumab, or pembrolizumab.

Nearly all of those cases were treated with concurrent immunosuppressive regimens. For our case, we initially used higher-dose prednisone on infusion days and then a lower maintenance level thereafter in combination with the calcineurin inhibitor tacrolimus. A similar strategy in conjunction with everolimus was reported previously without graft rejection, although the patient experienced disease progression after 2 months of therapy.¹⁷ Evidence showing the effect of immunosuppressants, including corticosteroids, on the efficacy of ICI is mixed. In a study examining corticosteroid use during nivolumab therapy in non-small cell lung cancer, exposure to corticosteroids in the first cycle corresponded to less total cycles of nivolumab and lower median overall survival.²⁴ In contrast, a study of patients with melanoma treated with ipilimumab and immunosuppression for immune-related adverse events did not show differences in overall survival or time to treatment failure.²⁵ Corticosteroids are first-line therapy for treating immune-related adverse events; however, it remains unclear whether responses to ICIs in mCRC with MSI are diminished with doses of concurrent immunosuppressants. It is similarly unclear whether the degree of immunosuppression required for maintenance of liver transplants, including medications such as mycophenolate mofetil, mTOR inhibitors, and calcineurin

inhibitors, alters the efficacy of immunotherapy. The mTOR pathway is implicated in PD-L1 expression, and calcineurin inhibitors have been suggested to downregulate PD-L1 expression.²⁶ This issue requires further consideration in future studies of ideally prospective design.

Immunotherapy in Patients With Abnormal Liver Function

As the use of ICIs becomes more prevalent, their role in patients with baseline abnormal liver function remains unclear. According to manufacturers' package inserts, there is insufficient information to suggest whether clinically significant differences exist in the clearance of pembrolizumab in patients with moderate-to-severe hepatic impairment, whereas no dosage adjustments for nivolumab are recommended in patients with baseline mild-to-moderate hepatic impairment.²⁷ There are no definitive guidelines regarding use of ICIs in patients with baseline abnormal liver function.

Few cases have been reported in which ICIs were used in patients with hepatic impairment.^{28,29} In these cases, patients had evidence of cirrhosis on imaging or AST, ALT, total bilirubin, or ALP levels >3 times the upper limit of normal. Hepatic impairment was due to cirrhosis from alcohol ingestion or hepatitis and metastatic disease. Primary neoplasms in these patients included Hodgkin lymphoma,²⁹ melanoma, renal cell carcinoma, small cell and non-small lung cancers, and urothelial carcinoma,²⁸ and patients received either single-agent pembrolizumab or nivolumab. In 2 patients with abnormal liver function and concomitant abnormal renal or cardiac function, worsening edema (grade 1) and volume overload (grade 3) were seen, respectively.²⁸ Among patients with baseline organ dysfunction treated with ICIs in a prior review,²⁸ immune-related adverse events were generally tolerable and evidence of at least stable disease was seen in more than half of these cases. Our patient had a bilirubin level of 3.0 mg/dL at treatment initiation, which was attributed to disease burden and eventually improved to normal limits on continued therapy.

Conclusions

CRC with MSI in the general population can have durable responses to ICI; however, its use in liver transplant recipients is less clear due to risk of graft rejection. This report presents a patient who was safely treated with pembrolizumab together with an immunosuppressive regimen of tacrolimus and prednisone at 1 mg/kg at the time of infusion and at maintenance dosage thereafter. Prospective trials examining the safety and efficacy of ICIs in organ transplant recipients would

be ideal; however, this may be difficult given the rarity of concurrent organ transplantation and immunotherapy-sensitive malignancies. Thus, reports such as this highlight the potential for immunotherapy to be safely and effectively administered in this unique patient population. A thorough discussion of risks and benefits with the patient and shared decision-making are critical before pursuing immunotherapy in transplant recipients. A clear need exists for more rigorous examination of the safety and efficacy of immunotherapy in patients on immunosuppressive

regimens that prevent graft rejection and in those with abnormal liver function at baseline.

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References

- Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; 357:409–413.
- Benson AB III, Venook AP, Al-Hawary MM, et al. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 1.2019. To view the most recent version, visit NCCN.org. Accessed April 21, 2019.
- Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018;36:773–779.
- Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* 2011;306:1891–1901.
- Rompianesi G, Ravikumar R, Jose S, et al. Incidence and outcome of colorectal cancer in liver transplant recipients: a national, multicentre analysis on 8115 patients. *Liver Int* 2019;39:353–360.
- Wassano NS, Sergi F, Ferro G, et al. Rapid disease progression of liver metastases following resection in a liver-transplanted patient with probable Lynch syndrome – a case report and review of the literature. *Case Rep Oncol* 2017;10:244–251.
- Ito T, Ueno T, Clarkson MR, et al. Analysis of the role of negative T cell costimulatory pathways in CD4 and CD8 T cell-mediated alloimmune responses in vivo. *J Immunol* 2005;174:6648–6656.
- Tanaka K, Albin MJ, Yuan X, et al. PDL1 is required for peripheral transplantation tolerance and protection from chronic allograft rejection. *J Immunol* 2007;179:5204–5210.
- Morita M, Fujino M, Jiang G, et al. PD-1/B7-H1 interaction contribute to the spontaneous acceptance of mouse liver allograft. *Am J Transplant* 2010;10:40–46.
- Morales RE, Shoushtari AN, Walsh MM, et al. Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation. *J Immunother Cancer* 2015;3:22.
- Ranganath HA, Panella TJ. Administration of ipilimumab to a liver transplant recipient with unresectable metastatic melanoma. *J Immunother* 2015;38:211.
- De Toni EN, Gerbes AL. Tapering of immunosuppression and sustained treatment with nivolumab in a liver transplant recipient. *Gastroenterology* 2017;152:1631–1633.
- Dueland S, Guren TK, Boberg KM, et al. Acute liver graft rejection after ipilimumab therapy. *Ann Oncol* 2017;28:2619–2620.
- Friend BD, Venick RS, McDiarmid SV, et al. Fatal orthotopic liver transplant organ rejection induced by a checkpoint inhibitor in two patients with refractory, metastatic hepatocellular carcinoma. *Pediatr Blood Cancer* 2017;64:e26682.
- Schvartsman G, Perez K, Sood G, et al. Immune checkpoint inhibitor therapy in a liver transplant recipient with melanoma. *Ann Intern Med* 2017;167:361–362.
- Varkaris A, Lewis DW, Nugent FW. Preserved liver transplant after PD-1 pathway inhibitor for hepatocellular carcinoma. *Am J Gastroenterol* 2017; 112:1895–1896.
- Biondani P, De Martin E, Samuel D. Safety of an anti-PD-1 immune checkpoint inhibitor in a liver transplant recipient. *Ann Oncol* 2018;29:286–287.
- DeLeon TT, Salomao MA, Aqel BA, et al. Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: the Mayo Clinic experience. *J Gastrointest Oncol* 2018;9:1054–1062.
- Gassmann D, Weiler S, Mertens JC, et al. Liver allograft failure after nivolumab treatment: a case report with systematic literature research. *Transplant Direct* 2018;4:e376.
- Kuo JC, Lilly LB, Hogg D. Immune checkpoint inhibitor therapy in a liver transplant recipient with a rare subtype of melanoma: a case report and literature review. *Melanoma Res* 2018;28:61–64.
- Rammohan A, Reddy MS, Farouk M, et al. Pembrolizumab for metastatic hepatocellular carcinoma following live donor liver transplantation: the silver bullet? *Hepatology* 2018;67:1166–1168.
- Tio M, Rai R, Ezeoke OM, et al. Anti-PD-1/PD-L1 immunotherapy in patients with solid organ transplant, HIV or hepatitis B/C infection. *Eur J Cancer* 2018;104:137–144.
- Munker S, De Toni EN. Use of checkpoint inhibitors in liver transplant recipients. *United European Gastroenterol J* 2018;6:970–973.
- Scott SC, Pennell NA. Early use of systemic corticosteroids in patients with advanced NSCLC treated with nivolumab. *J Thorac Oncol* 2018;13:1771–1775.
- Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol* 2015;33: 3193–3198.
- Dong Y, Sun Q, Zhang X. PD-1 and its ligands are important immune checkpoints in cancer. *Oncotarget* 2017;8:2171–2186.
- KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2018.
- Kanz BA, Pollack MH, Johnpulle R, et al. Safety and efficacy of anti-PD-1 in patients with baseline cardiac, renal, or hepatic dysfunction. *J Immunother Cancer* 2016;4:60.
- Sandoval-Sus JD, Mogollon-Duffo F, Patel A, et al. Nivolumab as salvage treatment in a patient with HIV-related relapsed/refractory Hodgkin lymphoma and liver failure with encephalopathy. *J Immunother Cancer* 2017;5:49.