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Immune Checkpoint Inhibitor Therapy Before Liver Transplantation – Case and Literature Review

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INTRODUCTION

Immune checkpoint inhibitors (ICI) have transformed cancer management. Nivolumab, a monoclonal antibody that blocks the programmed cell death protein 1 pathway (PD-1/PD-L1) has been shown to produce meaningful improvements in survival when compared with sorafenib for patients with advanced hepatocellular carcinoma (HCC). Despite the promising benefits associated with ICI use, the safety and efficacy of their use in the pretransplant setting is unknown. There is trepidation surrounding concomitant use of ICI and posttransplant immunosuppression because of their opposing effects on the immune system and fear of rejection, liver failure, and graft loss.

Herein, we describe the case of a 64-y-old male with cirrhosis and advanced HCC who was treated with nivolumab and successfully went on to receive a liver transplant (LT) with early T cell-mediated rejection (TCMR), which was successfully treated. This case highlights the potential feasibility and safety of LT after pretransplant immunotherapy for malignancy.

MATERIALS AND METHODS

This case report was approved by the institutional review board at the University of Minnesota. Written consent was obtained for this case report.

Case Report

A 64-y-old male with compensated cirrhosis secondary to hepatitis C virus (HCV) and advanced HCC, with 3 lesions

(2.0, 2.4, and 2.4 cm) along with a malignant portal vein (PV) thrombus, was referred for LT. He underwent HCV treatment with ledipasvir and sofosbuvir and achieved sustained virologic response. Initially, he was deemed not an LT candidate given that the tumor-associated PV thrombosis placed him outside Milan and University of California San Francisco (UCSF) criteria for LT. His HCC was treated with radioembolization, chemoembolization, microwave ablation, and sorafenib, with a peak serum alpha fetoprotein (AFP) of 6323.0 ng/mL. Due to disease progression and intolerance to sorafenib, he was started on nivolumab. After 8 cycles of nivolumab, he had no active disease, and his AFP was 2.3 ng/mL (Figure 1). He remained without active disease on imaging in the liver or extrahepatic for 1 y before transplant. He received a total of 23 cycles of nivolumab, 480 mg dosed every 4 wks. Nivolumab was intended as destination therapy; however, given his excellent response, he was reevaluated for LT. Given that the patient did not meet typical criteria for initial Model for End-Stage Liver Disease (MELD) exception points for HCC, the transplant team applied for HCC exception points, which were approved by the National HCC MELD Exception Committee. Once he was considered an appropriate transplant candidate, stopping nivolumab was felt to increase his risk of disease recurrence and potentially jeopardize his LT candidacy. His last infusion of nivolumab was 16 d before LT.

The patient underwent deceased donor LT with a liver from a donation after brain death donor with an end-to-end choledochocholedochostomy. His native MELD-Na at the time of transplant was 7. Back-table biopsy of the donor liver showed mild macroscopic steatosis. The hepatic artery and bile duct were considered small. Cold and warm ischemia times were 289 and 35 min, respectively. Two units of packed red blood cells and no other blood products were given during the surgery. The liver explant showed no viable HCC, no evidence of vascular invasion, and no transcapsular extrahepatic tumor extension. The liver was cirrhotic without evidence of active viral hepatitis or alcoholic liver disease.

For induction immunosuppression, he received mycophenolate mofetil, tacrolimus, and prednisone. On postoperative day 5, he developed a rising serum bilirubin. Magnetic resonance cholangiopancreatography was notable for minimal narrowing at the choledochocholedochostomy without a significant anastomotic stenosis or biliary leak. Endoscopic retrograde cholangiopancreatography on postoperative day 8 was notable for bile duct stent displacement and a mild stricture at the surgical anastomosis without upstream dilation. The patient underwent sphincterotomy, and a biliary stent was placed. Liver biopsy on day 9 showed acute cellular rejection (ACR)

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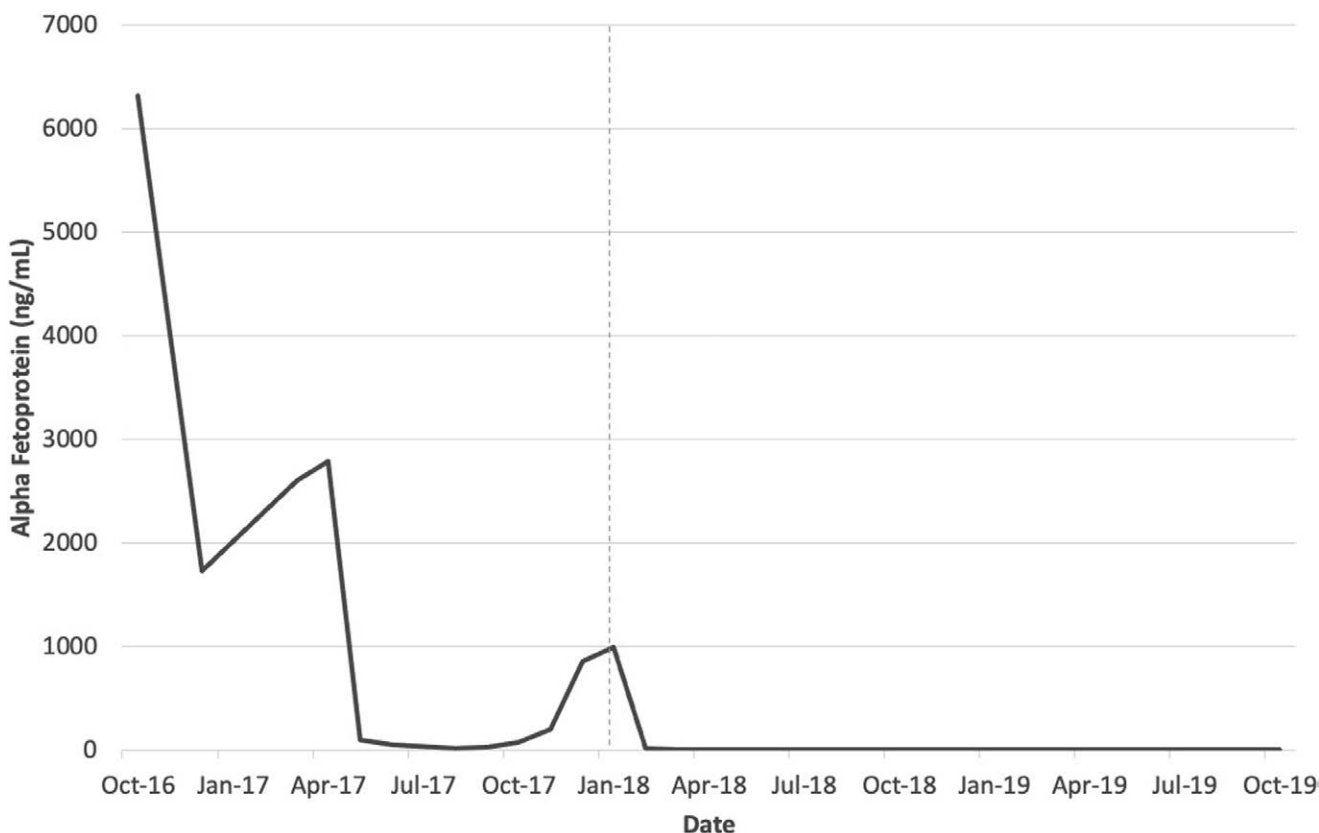


FIGURE 1. Alpha fetoprotein trend before liver transplantation in November 2019. Dashed line indicates nivolumab initiation.

with a Banff rejection activity index of 7 out of 9. The patient was treated with high-dose solumedrol (a total of 1600 mg) followed by thymoglobulin 100 mg IV daily for 4 d. Repeat liver biopsy 8 d following the initiation of treatment showed no evidence of ACR. The patient was discharged on maintenance immunosuppression—mycophenolate mofetil, tacrolimus, and prednisone. The patient is well 16 mo post-LT with normal liver chemistries and no additional episodes of rejection.

DISCUSSION

The impact of pretransplant immunotherapy for cancer has not been well described in patients after LT. Clinical trials investigating immunotherapy have excluded pre- and post-LT patients. This report describes a patient who successfully underwent LT for HCV cirrhosis and advanced HCC treated with immunotherapy.

ICIs have revolutionized cancer management. They include antibodies that block cytotoxic T lymphocyte-associated antigen 4 and the PD-1/PD-L1 pathway, which consequently augment cell-mediated immunity and antigen recognition and lead to an enhanced antitumor response.

Although ICIs have been approved to treat a variety of cancer types, their role in the treatment of HCC is evolving. Pembrolizumab, a PD-1 inhibitor, has been compared with placebo for second-line treatment in those with advanced HCC and found to have significant survival benefit in an Asian trial¹ but no benefit in terms of overall survival in a Western trial.²

Despite the potential benefits of ICIs, all ICI can simultaneously result in an array of immune-related toxicity, including allograft rejection, because of the accelerated immune

response. Given that allograft rejection remains an important problem following LT, all patients receive immunosuppressive therapy to dampen the immune response and promote allograft acceptance. Even though the incidence of TCMR has been reduced in the setting of modern immunosuppression regimens, TCMR still occurs and typically develops in the first 6 wks following LT. Given the concern for an increased risk of rejection post-LT, there is apprehension surrounding concomitant use of ICI and posttransplant immunosuppression because of their opposing effects on the immune system.

PD-L1 expression plays a critical role in the prevention of in situ graft pathology and chronic rejection given its ability to alter the balance between pathogenic and regulatory T cells.³ PD-1 is expressed on allograft-infiltrating cells, and PD-L1 is expressed by hepatocytes and cholangiocytes and along the sinusoids in posttransplant liver grafts; thus, when PD-1/PD-L1 blockade occurs, there is increased allogeneic proliferative responses of graft-infiltrating T cells, which can predispose post-LT patients to rejection.^{4,5} In mouse LT models, similar effects have been seen where acute rejection has been associated with disruption of PD-1.⁶

Previous published reports in humans suggest that organ rejection can occur in the setting of ICI following LT.⁷⁻¹² In a systematic literature research of ICI in solid organ recipients, 3 of 5 case of LT recipients who were treated with nivolumab developed cellular rejection.¹³ The use of ICI following solid organ transplantation is associated with rejection in 35% to 36% of patients with a median time to rejection of 10 d.^{12,14} Despite emerging data on the impact of ICI use post-transplant, there is a paucity of data surrounding the impact of ICI use pretransplant.

The initial case report of ICI use in the immediate pretransplant was concerning. The first report of a case of fatal hepatic necrosis after nivolumab use in the pre-LT setting was published in 2019.¹⁵ The patient was treated with nivolumab pre-LT for advanced HCC, with the last dose given 8 d before LT. Following LT, he developed acute hepatic necrosis in the early postoperative setting as corticosteroids were tapered. Another recent case report described a young male with hepatitis B viral infection and HCC treated with lenvatinib and toripalimab, a PD-1 receptor antibody, with the last dose of toripalimab 93 d before LT. Unfortunately, the patient suffered fatal acute hepatic necrosis and died within 72 h of transplant.¹⁶

Despite initial concerns regarding ICI use pre-LT, a case report of successful ICI use as a downstaging therapy pre-LT was published in 2020. A 62-y-old male with advanced HCC was down staged to within Milan criteria using nivolumab and underwent LT, with a unifocal, poorly differentiated, 42-mm HCC noted in the explant.¹⁷ Nivolumab was stopped 15 wks before activation on the waiting list. In the year post-LT, he had no evidence of tumor recurrence or allograft rejection.

A recent publication describes the largest series of patients with advanced HCC who were treated with nivolumab before LT.¹⁸ A total of 9 patients at a single center underwent LT following nivolumab with no episodes of severe allograft rejection/loss, tumor recurrence, or death. A third of patients were outside of Milan criteria but within UCSF criteria. No patients had PV invasion. The last dose of nivolumab was given within 4 wks pre-LT in 89% of patients, with a range of nivolumab use 1 to 253 d pre-LT.

A summary of published reports on pre-LT ICI use and the associated post-LT outcomes can be found in Table 1.

In our case, the patient developed moderate to severe ACR within the first 2 wks following transplant and was promptly treated with high-dose glucocorticoids followed by thymoglobulin with resolution of rejection on follow-up liver biopsy. Given that the patient's ACR was detected early and treated adequately, there was no adverse impact on this patient's allograft survival in the year following LT. Long-term immunologic and tumor outcomes, however, are unknown.

The "safe" interval between ICI treatment and LT remains unknown. Some authors postulate that ICI within a short period pre-LT predisposes recipients to fatal rejection post-LT. Given the 4-wk half-life of nivolumab, Schwacha-Eipper et al propose that ICIs should not be used 6 wks before activation on the waiting list¹⁷; however, the case series by Tabrizian et al included 8 patients who received nivolumab within 30 d of transplant and 3 patients who received nivolumab within 1 wk of transplant without any fatal rejection.¹⁸ One case of mild rejection occurred in a patient who had received nivolumab 22 d before LT, and it was in the setting of low-tacrolimus levels.¹⁸ Given that these data are only from small case series, further work is needed to better understand appropriate timing of ICI use before LT. At this time, the timing of stopping ICI use pre-LT must be determined based on a case-by-cases basis in the setting of risk factors for post-LT rejection and poor outcomes.

Our case adds to the growing body of literature about ICI for advanced HCC and may serve as a bridge therapy to LT in select cases. Moreover, we believe that our case adds to the published literature given that our case initially presented with HCC outside of Milan and UCSF criteria given the tumor-related PV thrombosis and was then down staged within Milan criteria. In addition, our patient had an AFP over

TABLE 1. Summary of prior studies—impact of pretransplant ICI on posttransplant outcomes

Authors	Number of patients	Max tumor diameter, cm	Max pre-LT AFP, ng/mL	Number of LRT	ICI	Cycles of ICI pre-LT	ICI use pre-LT, d	LDLT, n (%)	Immunosuppression	Complications	Rejection, n (%)	Recurrence	Follow-up post-LT, mo
Tabrizian et al ¹⁸	9	2.0–21.0	3–1493	0–7	Nivolumab	2–32	1–253	1 (11.1%)	Tacrolimus, mycophenolate mofetil, steroids	Bile leak—1 (11.1)	Mild—1 (11.1)	None	8–23
Qiao et al ¹⁴	7	Unk	Unk	Unk	Pembrolizumab or camrelizumab with lenvatinib	1–5	Average: 39	Unk	Combination or separate use of steroids, a calcineurin inhibitor (cyclosporine or tacrolimus), sirolimus, and mycophenolate mofetil	Unk	1 (14.3)	71% partial remission	Unk
Nordness et al ¹⁵	1	5.5	2500	2	Nivolumab	Unk	8	0	Tacrolimus, mycophenolate mofetil, steroids	Death 10 d post-LT due acute hepatic necrosis	N/A	N/A	N/A
Chen et al ¹⁶	1	6.0	Unk	3	Toripalimab	10	93	0	Tacrolimus, steroids	Death 3 d post-LT due to acute hepatic necrosis	N/A	N/A	N/A
Schwacha-Eipper et al ¹⁷	1	6.4	Unk	0	Nivolumab	34	105	Unk	Unk	None	None	None	12

Milan criteria: single hepatocellular carcinoma <5cm or up to 3 nodules <3cm. University of California San Francisco criteria: a maximum tumor size of 6.5 cm or 2 lesions ≤4.5 cm in diameter with a total tumor diameter of ≤8 cm. Max tumor diameter: diameter of largest single tumor. AFP, alpha fetoprotein; ICI, immune checkpoint inhibitor; LDLT, living donor liver transplant; LRT, locoregional therapy (chemo/radioembolization, ablation, radiation); LT, liver transplantation; N/A, not applicable; Unk, unknown.

6000—portending a worse prognosis. Finally, our case adds to the literature regarding ICI within 4 wks pre-LT with good posttransplant outcomes.

CONCLUSIONS

This case report and literature review are the basis for optimism that in carefully selected patients, ICI use may serve as a bridge to LT. It must be acknowledged that this case report and literature review represent <20 successful cases of ICI use pre-LT, and therefore, further investigation is needed regarding the risk of rejection and long-term immunologic and tumor outcomes following ICI use pre-LT.

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