Case Report

Immunotherapy before liver transplant in unresectable hepatocellular carcinoma: a case report

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Background: Hepatocellular carcinoma (HCC) is a leading cause of global cancer mortality, with liver transplantation as the sole curative treatment. For advanced disease, first-line systemic therapies including immune checkpoint inhibitors (ICIs) have shown a survival benefit, but there is scarce data on clinical outcomes when used prior to transplantation.

Case Description: We present three case studies of patients who received immunotherapy with atezolizumab/bevacizumab or ipilimumab/nivolumab before liver transplant. We reviewed clinical outcomes including disease response, adverse events related to systemic therapy, as well as graft function post-operatively. One case demonstrated a 45% reduction in total HCC tumour burden whereas another showed stable disease with ICIs. No adverse clinical outcomes such as graft rejection or poor wound healing were noted post-transplant. Indeed, all three patients were successfully transplanted with excellent graft function at the last follow-up.

Conclusions: Our observations and data suggest ICIs are a viable option for treatment in the pre-transplant setting. It does not routinely lead to fatal graft rejection and may lengthen eligibility times until a donor organ is available.

Keywords: Hepatocellular carcinoma (HCC); liver transplant; immunotherapy; case report

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Introduction

Primary liver cancer is the second leading cause of cancer mortality worldwide (1). Hepatocellular carcinoma (HCC) makes up 72% of primary liver cancers (2). The incidence of liver cancer in Canada is rising, with an increase of 3.8% in men and 2.7% in women over the past 40 years (2).

Etiologies of HCC include non-alcoholic fatty liver disease, alcoholic liver disease, hepatitis B virus (HBV), hepatitis C virus (HCV), and aflatoxin B1 exposure (3). The Barcelona Clinic Liver Cancer (BCLC) staging system is used to determine treatment pathways for patients with HCC (3,4). BCLC A, or very early-stage disease, is treated with curative intent with resection, ablation, or liver transplantation. BCLC B is considered intermediate stage and includes patients with multinodular disease. These patients are treated with locoregional therapies. Individuals with portal vein invasion or metastases, well compensated liver function (Child-Pugh Class A), and performance status ≤2 are deemed to have unresectable advanced HCC and classified as BCLC C (3-5). Resection, ablation, or locoregional therapies are more difficult in these patients and they are treated with systemic methods. Patients with BCLC C disease have a poor prognosis with an estimated

5-year overall survival of 2 years (5).

In the unresectable HCC setting, the first-line systemic therapies that have shown survival benefit include monotherapy with sorafenib or lenvatinib, or doublet therapy combining atezolizumab and bevacizumab or durvalumab and tremelimumab (6-9). For HCC confined to the liver, a transplant is the ultimate curative treatment. The Milan criteria is primarily used to determine transplant eligibility, which predicts a low risk of recurrence in patients with a single tumour <5 cm in size or maximum three tumours all <3 cm in size, in addition to no macrovascular invasion (10). HCC beyond Milan criteria can be treated with locoregional and systemic therapies in an effort to down-stage, whereas those that do meet Milan criteria can receive the same treatments for disease control while waiting for an organ for transplant (11). Some studies suggest that a modest expansion of selection criteria may be warranted. Portal vein thrombosis is considered a relative contraindication to transplant, but in patients with a segmental portal vein thrombus, a significantly better oncological outcome has been noted with liver transplant compared to resection (12).

There is limited data on the outcomes of patients who receive systemic therapies, especially immune checkpoint inhibitors (ICIs), as bridging methods. A systematic review of immunotherapy in the treatment of HCC in 2021 identified only one patient who received nivolumab as a bridge to liver transplant. Successful downstaging of disease occurred, allowing for liver transplantation, but the patient experienced fatal graft rejection early in the post-operative period (13). A separate review paper by Gao *et al.* identified six case reports describing the use of immunotherapy in the pre-transplant setting. Patients were treated with a range of different agents including nivolumab, pembrolizumab, camrelizumab, toripalimab, or durvalumab. Outcomes varied among these 20 patients. Sixteen patients had successful transplants with no complications, two had mild rejection that was treated by adjusting the immunotherapy regimens, while two patients died secondary to liver failure (14). Further research into the risks, survival outcomes, and feasibility of using ICIs as a bridging treatment is needed given the overall paucity of data and increase in use of these agents in the HCC landscape.

Three patients treated at a single academic institute in Alberta, Canada with unresectable HCC who received ICIs followed by liver transplantation from 2020–2021 were retrospectively selected for review. The cases were non-consecutive. Follow-up extended for up to 30 months since initiation of systemic treatment and primarily involved chart review of vital status, physician notes, and liver function tests. To our knowledge, this is the first case report from a Canadian institute. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-634/rc).

Highlight box

Key findings

- Systemic treatment of unresectable hepatocellular carcinoma (HCC) with immune checkpoint inhibitor (ICI) pre-transplant did not lead to poor post-operative outcomes with respect to graft function and wound healing.

What is known and what is new?

- In unresectable HCC, systemic treatment with oral tyrosine kinase inhibitors or ICI improves overall survival.
- Systemic treatments including ICIs may be able to control and/or downstage disease and extend patient eligibility for a liver transplant, the ultimate curative treatment.

What is the implication, and what should change now?

- Further research into treatment responses, transplant outcomes, and toxicity must be conducted to determine whether ICIs should be routinely used as a bridge to liver transplantation.

Cases presentation

Case 1

A 68-year-old male was diagnosed with decompensated cirrhosis in the setting of new jaundice and ascites. A screening magnetic resonance (MR) abdomen with contrast was done, revealing numerous lesions up to 2.5 cm in size in the right lobe consistent with HCC. He had active HCV at the time of diagnosis, with a longstanding alcohol use history. His HCV was successfully treated with sofosbuvir/velpatasvir. Repeat MR abdomen one year later showed progression with enlargement of existing nodules and the interval development of five more lesions. His liver function declined, and his ascites became refractory to diuretic treatment, necessitating paracentesis every 2 weeks. He started systemic treatment with atezolizumab and bevacizumab as an Eastern Cooperative Oncology Group (ECOG) status 0, alpha-fetoprotein (AFP) 3, and Child-Pugh Class B. The immunotherapy agents were obtained through a compassionate access program. He completed 7 cycles, and in conjunction with a change in diuretic

Table 1 Graft outcomes at most recent follow-up.

Pt. case	Age, year	Time since transplant	Bilirubin (μmol/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	Hb (g/L)	Platelet (10^9/L)	INR	Albumin (g/L)
1	68	24 months	14	14	10	87	145	175	1.1	38
2	58	23 months	7	14	14	64	135	187	1.1	37
3	37	18 months	21	42	52	74	150	119	1.0	43

Pt., patient; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; Hb, hemoglobin; INR, international normalized ratio.

Table 2 Characteristics of patients, cancer stage, and systemic treatment regimens.

Pt. case	Sex	Age, year	Line of Tx	ICI	Regimen	Cycles	Time between LT and ICI (days)	Pathologic stage
1	M	68	1st	Atezo/bev	1,200 mg atezo + 15 mg/kg bev IV every 3 weeks	7	229	pT2N0
2	M	58	1st	Ipi/nivo then nivo alone	3 mg/kg ipi + 1 mg/kg nivo IV every 3 weeks followed by 480 mg nivo IV every 4 weeks	4+3	2	pT2N0
3	M	37	1st	Atezo/bev	1,200 mg atezo + 15 mg/kg bev IV every 3 weeks	6	7	pT0N0 (no residual tumour)

Pt., patient; Tx, treatment; ICI, immune checkpoint inhibitor; LT, liver transplant; M, male; atezo, atezolizumab; bev, bevacizumab; ipi, ipilimumab; nivo, nivolumab.

from amiloride to spironolactone, showed significant improvement in liver function and resolution of ascites. He did not have any ICI-associated side effects. Unfortunately, his overall tumour burden increased on imaging, but as his ascites had resolved, he was then deemed eligible for local control with Y90 radiotherapy. The glass microspheres were injected into segment VIII, at the location of the largest lesion of 4.6 cm. Despite locoregional therapy there was recurrence of the tumour in segment VIII within a year and he underwent a neurologically determined deceased (NDD) liver transplant. He suffered no post-operative complications. He is now 24 months since his liver transplant with excellent graft function and no episodes of rejection or failure (*Table 1*).

Case 2

A 58-year-old male with previous history of HCC secondary to HCV was diagnosed with recurrence on surveillance ultrasound. His initial disease was successfully treated with a limited left lobectomy in addition to interferon, ribavirin, and sofosbuvir for the HCV infection. Six years later, the ultrasound revealed a hypoechoic lesion in the left lobe of the liver. Subsequent MR abdomen with contrast confirmed HCC and revealed multifocal bi-lobar disease with at least 9 lesions, the largest measuring up to 2.2 cm in size. At this time access to atezolizumab and bevacizumab was limited due to closure of the compassionate access program. Thus, he started systemic therapy with ipilimumab and nivolumab as part of a clinical trial. His ECOG status was 0, AFP 8, and Child-Pugh Class A. He received a total of four cycles. He subsequently developed hypothyroidism and central adrenal insufficiency secondary to the immunotherapy, requiring daily levothyroxine and hydrocortisone. He resumed treatment with single-agent nivolumab and received a total of 3 cycles until his NDD liver transplant. Throughout the duration of immunotherapy, his HCC demonstrated stable disease with no evidence of new or enlarging lesions. His last treatment with nivolumab was two days prior to his transplant. The donor's liver was HCV positive and at the time of transplant, the patient was found to have a positive HBV core. He was treated for both HCV and HBV after graft stabilization. Currently he is 22 months post-transplant. His graft function is excellent with no signs

of acute liver failure, thrombosis, or rejection (*Table 2*).

Case 3

A 37-year-old male developed HCC in context of HBV cirrhosis. He was treated for HBV with tenofovir. He was initially diagnosed with early-stage HCC with a small tumour in segment II. He underwent open partial liver resection and cholecystectomy. The tumour size was 1.4 cm with positive margins, requiring revision surgery. He subsequently underwent a magnetic resonance imaging (MRI) of the abdomen with contrast six months later which revealed a new 3.75 cm mass in segment V of the liver. This was confirmed with a positron emission tomography (PET). He started immunotherapy with atezolizumab and bevacizumab through a compassionate access program while awaiting a liver transplant. At that time, his ECOG status was 0, AFP 2,143, and Child-Pugh Class B. He received a total of 6 cycles with no adverse events. A follow-up MRI revealed an interval decrease in size from 3.5 cm × 3.2 cm × 3.3 cm to 1.9 cm × 2.2 cm × 1.9 cm. He further underwent stereotactic body radiotherapy treatment with 50 Gy in 5 fractions over two weeks to this lesion. He underwent an NDD liver transplant seven days following his final ICI treatment. He maintains excellent graft function 18 months post-liver transplant (*Table 1*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The above cases demonstrate the novel treatment approach of immunotherapy as a bridge to liver transplantation. Disease staging, treatment approach, and timelines are depicted in *Table 2*. Neither case 1 or case 2 would have qualified for liver transplant based on Milan criteria before initiation of systemic treatment. ICIs led to disease control in case 2, whereas in case 1 there was an overall increase in tumour burden. Given the variability in response, additional cases are needed to determine whether systemic immunotherapy could potentially downstage disease and change a transplant-ineligible HCC into an operable one.

In contrast, case 3 did meet Milan criteria for liver transplant upfront. Systemic ICIs were initiated for the purposes of disease control while waiting for a donor. This patient demonstrated the best response to immunotherapy with a 45% objective reduction in tumour size following six cycles of atezolizumab/bevacizumab. Often the rate-limiting factor for liver transplant is not patient eligibility but organ availability. This case demonstrates that ICIs can be used as a tool for disease control in transplant-eligible HCC until a donor is secured.

Despite observing variable effectiveness of ICIs with respect to overall tumour burden, all three cases demonstrated minimal complications and good graft outcomes post-transplant. There were no issues related to wound healing. Overall, these cases demonstrate that ICIs can be safely used in the pre-transplant setting.

The rate of adverse side effects from doublet immunotherapy in HCC can occur in up to 90% of patients (11). Out of the three cases, case 2 demonstrates autoimmune-mediated toxicities such as irreversible endocrinopathy. The patient now requires a lifetime of levothyroxine for hypothyroidism and hydrocortisone for central adrenal insufficiency. The risk and benefits of ICIs needs to be constantly evaluated while the patient is undergoing therapy such that these complications do not limit their eligibility for transplant.

The patients in our case report had highly variable washout periods ranging from two to 229 days. No firm guidelines exist on the time required from cessation of immunotherapy to surgery. The duration is often determined based on rough estimates of the half-life of the ICI (14). However, the half-life rarely correlates with elimination of programmed cell death 1 (PD-1) occupancy in tissues. For example, nivolumab has a half-life of 12–20 days, but can occupy up to 70% of PD-1 receptors in T cells two months following initial infusion (15). In the case of treatment with atezolizumab-bevacizumab, a washout period for bevacizumab is also of clinical relevance. Bevacizumab has been associated with multiple surgical complications including wound dehiscence, ecchymosis, and surgical site bleeding and the recommendation is to wait 6–8 weeks after cessation of therapy before proceeding with surgery (16). Further research into the optimal timing of surgery following immunotherapy is needed.

The advent of ICI has led to prolonged survival in patients with unresectable disease. With increasingly effective systemic therapies, one questions the utility of a liver transplant, which comes with associated risks for infection and bile duct complications. Based on the

HIMALAYA randomized clinical trial, median overall survival is roughly 14 months with sorafenib but up to 16 months with durvalumab and tremelimumab combination therapy (9). In contrast, the median overall survival following liver transplant is 158 months (17). Even in patients with resectable HCC, improved overall survival and disease-free survival is seen with liver transplant compared to liver resection (18). Liver transplantation, therefore, remains the gold standard for HCC.

Our case report adds to the limited yet growing body of evidence that suggests immunotherapy may be a safe and effective method to control or downstage disease prior to liver transplantation. A 16-month follow-up of nine patients who received nivolumab prior to liver transplant, with most receiving the last dose <4 weeks prior to the operation, revealed no severe allograft rejections, tumour recurrences, or death (19). A retrospective cohort study of HCC patients treated with the programmed death-ligand 1 (PD-L1) inhibitors pembrolizumab and camrelizumab revealed a response rate of 71% with a biopsy-proven rejection rate of only 14.3% (20). More recently, Abdelrahim *et al.* reported on the successful transplant outcomes in an HCC patient treated with neoadjuvant atezolizumab-bevacizumab (21).

Limitations of the study include small sample size and a heterogenous group of patients with differing disease stages. The case report includes only male patients, and females may exhibit differing treatment outcomes. The duration of treatment and immunotherapy washout periods were varied, with some receiving treatment up to transplant while others had 6 months or more between the last treatment cycle and the transplant. Finally, the follow-up period post-transplant differed for each case but was less than two years, which may fail to capture the rejections and complications that occur later.

Despite this, our study provides valuable insight into how ICIs may be safely used in patients prior to transplant. As more ICIs are approved for use in the HCC landscape, these medications may be used frequently as bridging treatments.

Conclusions

The only curative treatment for patients with unresectable HCC is liver transplantation. In many patients listed for transplant, drop-out rates are high due to disease progression. Our study describes the successful use ICIs in the pre-transplant setting to downstage or control disease before a liver transplant. There were no episodes of acute rejection or graft failure. Further research in the form of retrospective or prospective cohort studies are needed to better elucidate the degree of HCC response, transplant outcomes, and associated toxicities when ICIs are used as a bridging method.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-634/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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