Immunotherapy as a Neoadjuvant Treatment in Liver Transplant Recipients with Cholangiocarcinoma

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Background

Cholangiocarcinoma (CCA) is an aggressive malignancy arising from the biliary epithelium. It is the second most common primary liver cancer after hepatocellular carcinoma (HCC), and it remains challenging to treat due to delayed diagnosis and limited effective systemic therapies. The treatment of CCA depends on the stage of the disease at the time of diagnosis, which includes surgical resection, orthotopic liver transplantation (OLT), chemotherapy and radiotherapy. However, combination systemic therapy with gemcitabine plus cisplatin continues to be the standard treatment for advanced stage patients. Immunotherapies as neoadjuvant setting are now being actively investigated in the transplant oncology era to enhance outcomes in patients with CCA. This study reports our institutional experience in patients with CCA who received Immune Checkpoint Inhibitors (ICPIs) prior to curative OLT.

Methods

This retrospective cohort included eight patients with CCA (seven with intrahepatic cholangiocarcinoma (IHCCA), and one with perihilar cholangiocarcinoma (PCCA) who received ICPI prior to OLT at a single institution from December 2022 to January 2025. Graft rejection was assessed and reported along with the type of ICPI, tumor features, locoregional therapies (LRTs), and the timing of ICPI in association with OLT.

Results

Eight patients with CCA underwent OLT after receiving neoadjuvant ICPI. Five patients were male and three were female with a median age of 49.5 (interquartile range: 40–63) years at OLT. Etiologies included chronic cholecystitis (N = 2), primary sclerosing cholangitis (PSC) (N = 1), and unknown (N = 5). Tumor focality was unifocal in five patients and multifocal in three. Lymphovascular invasion was identified in four patients while perineural invasion was noted in two patients. All patients received ICPI, including PD-L1 inhibitors. Liver-directed/ locoregional therapies were utilized in half of the cases, including transarterial chemoembolization (TACE), Yttrium-90 (Y90), and stereotactic body radiotherapy (SBRT). The median washout period (WOP) was 8.25 months. All patients responded to ICPI and achieved a safe and successful OLT. Most patients received tacrolimus, prednisone and mycophenolate as immunosuppressant (IS) therapy post-OLT with two patients requiring additional IS, including everolimus. Rejection was observed in two out of eight patients (25%) during the first year post-transplant. Both patients had IHCCA.

Conclusion

Our study highlights the potential of ICPI to achieve tumor downstaging prior to OLT in patients with CCA when given as a neoadjuvant therapy. In addition, this study illustrated the importance of timing for the administration of ICPI before OLT.

Figures

ID	Age (years)	Sex	Type of cholangiocarcinoma (CCA)	ICPI Agent	Locoregional Therapy	WOP (months)	AFP before OLT	Rejection	IS Agents after OLT
1	36	Male	Intrahepatic CCA	Durvalumab	SBRT / Proton	0.5	7.8 ng/mL	Yes	Mycophenolate, Prednisone, Tacrolimus
2	37	Male	Perihilar CCA	Durvalumab	None	6.5	3.3 ng/mL	No	Prednisone, Tacrolimus, Everolimus
3	54	Female	Intrahepatic CCA	Durvalumab	Y90	10	5.7 ng/mL	No	Mycophenolate, Prednisone, Tacrolimus
4	63	Male	Intrahepatic CCA	Durvalumab	XRT	16	3.1 ng/mL	No	Mycophenolate, Prednisone, Tacrolimus
5	43	Female	Intrahepatic CCA	Durvalumab	Ablation, Y-90, TACE	18	5.2 ng/mL	No	Mycophenolate, Prednisone, Tacrolimus
6	45	Female	Intrahepatic CCA	Durvalumab	None	2	2.7 ng/mL	Yes	Mycophenolate, Prednisone, Tacrolimus
7	66	Female	Intrahepatic CCA	Durvalumab	None	14	17.5 ng/mL	No	Mycophenolate, Prednisone, Tacrolimus
8	63	Male	Intrahepatic CCA	Durvalumab	None	5	2 ng/mL	No	Prednisone, Tacrolimus, Everolimus

Table 1. Characteristics and outcomes of patients receiving liver transplants after treatment with immune checkpoint inhibitors (ICPIs). ICPI: Immune Checkpoint Inhibitors, PDL-1: Programmed death-ligand 1, Y90: Yttrium-90, XRT: external radiation therapy, OLT: Orthotopic liver transplantation, TACE: Transarterial Chemoembolization, CCA: cholangiocarcinoma, IS: Immunosuppressant, WOP: Washout period, AFP: Alpha-fetoprotein, ng/mL: Nanograms per milli