Editorial

The upward trend in the immunotherapy utilization for hepatobiliary cancers

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Hepatobiliary cancers (HBCs) include those of the liver [mainly hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma] and biliary tract (extrahepatic cholangiocarcinoma and gallbladder cancer). Based on the 2020 global cancer statistics, liver cancer ranks seventh in incidence and third in mortality among all malignant tumors, while gallbladder cancer ranks 25th in incidence and 21st in mortality (1). Due to the lack of typical symptoms and signs at the early stages, HBCs are often diagnosed at intermediate or advanced stages, and thus the opportunity of curative surgical interventions is missed (2). Therefore, most patients with HBC can only be treated with noncurative treatments, including immunotherapy. Several immunotherapeutic approaches have been attempted for HBCs, including oncolytic viruses, tumor vaccines, adoptive immunotherapy, and immune checkpoint inhibitors (ICIs; *Figure 1*). Of them, only ICIs, a promising group of agents that have been used in several malignancies in the past decade, have been used in clinical practice to prolong survival, and thus represent a new era in the treatment of HBCs. ICIs disrupt the tumor's immune tolerance, causing reactivation of the host's immune system against the cancer cells. Common ICIs include inhibitors of programmed cell death protein-1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4). The use of immunotherapy may vary widely among different parts of the world and even among patient subgroups in the same country or area.

In one study, Sahara *et al*. (3) used the National Cancer Database to investigate the use of immunotherapy for HBC as well as factors affecting such use in USA. The most important finding was that the overall use of immunotherapy in US patients with HBCs was rather low but increased over time, while HCC, especially at the advanced stage, was the most frequent indication for the use of immunotherapy (3). These findings reflect the recent developments in immunotherapy for the management of HBCs. In 2017, based on the results of the CheckMate040 trial, the US Food and Drug Administration (FDA) approved the first ICI, nivolumab, as a second-line treatment option for patients with advanced or metastatic HCC (4). Following this, several trials were conducted that assessed the safety and efficacy of ICIs, given with or without tyrosine kinase inhibitors, as first-line (e.g., lenvatinib plus pembrolizumab, atezolizumab plus bevacizumab, sintilimab plus bevacizumab) or second-line therapy (e.g., pembrolizumab, nivolumab plus ipilimumab) in patients with advanced HCC (*Table 1*) (5-8). Further trials and retrospective studies have evaluated the efficacy of ICIs in patients with advanced HCC (9,10). Currently, several ICIs have been approved by the FDA and included in the scientific guidelines, and their clinical use is being expanded to patients with HCC.

The more frequent use of immunotherapy in patients

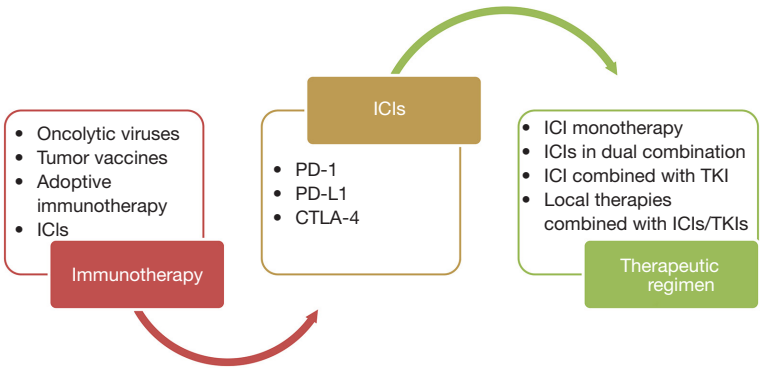

Figure 1 ICIs are the main immunotherapy drug for hepatobiliary cancer. CTLA-4, cytotoxic T lymphocyte–associated antigen-4; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor.

Table 1 Summary of data from published trials of immune checkpoint inhibitors in hepatocellular carcinoma

Trials	Treatment and sample size	Phase	ORR according to RECIST 1.1, %	Median PFS time, months	HR (95% CI) of PFS	Median survival time, months	HR (95% CI) of OS	PMID
First-line								
CheckMate 040	Nivolumab dose-expansion (n=214) *vs.* dose-escalation phase (n=48)	I/II	19.6 *vs.* 14.6	4.0 *vs.* 3.4	–	Not reached *vs.* 15	–	28434648
KEYNOTE 524	Lenvatinib plus pembrolizumab (n=100)	Ib	36.0	9.3	–	22.0	–	32716739
GO30140	Atezolizumab plus bevacizumab (n=104) *vs.* atezolizumab plus bevacizumab (n=60) *vs.* atezolizumab (n=59)	Ib	32.7 *vs.* 13.3 *vs.* 8.5	7.4 *vs.* 5.7 *vs.* 2.0	–	17.1 *vs.* not reached *vs.* not reached	–	32502443
RESCUE	Camrelizumab plus apatinib (n=70)	II	46.0	5.7	–	20.1	–	33087333
CheckMate 459	Nivolumab (n=371) *vs.* sorafenib (n=372)	III	15.4 *vs.* 7.0	3.7 *vs.* 3.8	–	16.4 *vs.* 14.7	0.85 (0.72–1.02)	–
IMbrave 150	Atezolizumab plus bevacizumab (n=336) *vs.* sorafenib (n=165)	III	27.3 *vs.* 11.9	6.8 *vs.* 4.3	0.59 (0.47–0.76)	19.2 *vs.* 13.4	0.66 (0.54–0.85)	32402160
ORIENT-32	Sintilimab plus bevacizumab (n=380) *vs.* sorafenib (n=191)	III	19.6 *vs.* 2.9	4.6 *vs.* 2.8	0.56 (0.46–0.70)	15* *vs.* 10.4	0.57 (0.43–0.75)	34143971
Second-line								
CheckMate 040	Nivolumab plus ipilimumab (group A, n=50; group B, n=49; group C, n=49)	I/II	32.0 *vs.* 26.5 *vs.* 28.6	–	–	22.8 *vs.* 12.5 *vs.* 12.7	–	33001135
RESCUE	Camrelizumab plus apatinib (n=120)	II	25	5.5	–	21.8	–	33087333
KEYNOTE-224	Pembrolizumab (n=104)	II	17.3	4.9	–	12.9	–	29875066
KEYNOTE-240	Pembrolizumab (n=278) *vs.* placebo (n=135)	III	18.3 *vs.* 4.4	3.0 *vs.* 2.8	0.72 (0.57–0.90)	13.9 *vs.* 10.6	0.78 (0.61–0.99)	31790344

*, estimated from Kaplan–Meier survival curve. CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

with HCC and subsequent cholangiocarcinoma reflects the higher incidence of these cancers compared to gall bladder cancer. HCC is therefore more attractive for the development of clinical trials and thus more conducive to the clinical application of new therapies including immunotherapy. Cholangiocarcinoma is a less frequent cancer compared to HCC, but ICIs have also been explored in this highly heterogeneous malignancy, offering varying rates of efficacy. Notable results have only been observed with pembrolizumab for patients with cholangiocarcinoma and microsatellite instability–high or mismatch repair–deficient status (11). No trial of ICIs in the treatment of patients with gallbladder cancer has been reported to date, which explains the minimal use of immunotherapy in this setting.

Another interesting finding of the Sahara *et al.* (3) study was the independent association of socioeconomic factors, particularly of patients' median income, with the probability of using immunotherapy. These types of associations can be expected in expensive treatment options, especially in countries without total national health coverage for the population. Similar associations between the patients' income and the likelihood of immunotherapy use have been reported in US patients with other malignancies (12). In general, patients in the advanced stages of any cancer and with high income are more likely to receive new, expensive therapeutic regimens, such as immunotherapy, for several reasons that include the affordability of the treatment cost and the greater frequency of management by experts disposed to using novel agents. The increasing popularity and use of ICIs over time are expected to gradually reduce the disparity in access to immunotherapy of patients of different socioeconomic status.

The third finding of the study by Sahara *et al.* (3) was the independent association of immunotherapy use with more frequent prior receipt of cytotoxic chemotherapy. Although the details concerning cytotoxic chemotherapy were not provided, it is anticipated that the more difficult-to-treat patients with HBC who have received several pre-existing treatment options will be the candidates and will eventually be treated with immunotherapy. The safety and efficacy of several combinations of ICIs with other type of agents or locoregional therapies in patients with HBCs are currently being investigated in phase II and phase III trials.

Although immunotherapy has revolutionized the treatment of HBCs over the last decade and its indications are constantly expanding, the identification of patients who will receive the best survival benefit and of those biomarkers that could drive personalized treatment decisions are lacking. A recent meta-analysis of 3 randomized trials (CheckMate 459, KEYNOTE-240, IMbrave150) suggested that ICI-inclusive regimens do not improve the survival of patients with nonviral HCC (13). This finding was confirmed in 2 additional cohorts of patients with nonalcoholic steatohepatitis-related HCC who had reduced overall survival after ICI therapy compared to patients with HCC related to other etiologies (13). The better stratification of patients with HBCs in relation to their response to immunotherapy and the identification of reliable biomarkers for a personalized approach could lead to more frequent and more effective use of such innovative treatment options for HBCs.

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Footnote

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