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Review

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Immune Checkpoint Inhibition for Hepatocellular Carcinoma, Cholangiocarcinoma, and Combined Hepatocellular-Cholangiocarcinoma

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Abstract

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary liver carcinoma that is composed of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). Given its low incidence, there is no standardized treatment protocol or systemic regimens. With the development of immune checkpoint inhibitors (ICIs), one of the immunotherapies that modulate the immune system by restoring antitumor immune response, studies have shown promising results for the use of ICI as systemic therapy for advanced solid tumors, including liver cancers. Moreover, prospective clinical studies displayed favorable outcomes of the use of ICIs in HCC and biliary tract cancers. Here, we review the recent evidence in application and comparison of ICIs for HCC, CCA, and cHCC-CCA as well as the future direction of systemic therapy for cHCC-CCA.

Keywords: Combined hepatocellular-cholangiocarcinoma; Hepatocellular carcinoma; Cholangiocarcinoma; Immune checkpoint inhibition

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary liver carcinoma with hepatocytic and cholangiocytic differentiations regardless of percentage of each component, diagnosed via routine histochemical stains [1, 2]. Since its first report in 1903, the terminology, definition, and classification of cHCC-CCA have undergone several modifications, likely contributing to its wide reported range of incidence from 0.4% to 14.2% [3-7]. The true incidence is also likely underestimated due to misdiagnosis as hepatocellular carcinoma (HCC) or cholangiocarcinoma (CCA) without tissue diagnosis if patients did not undergo surgical resection. The low incidence and rarity of the disease do not allow for standardization of treatment regimens, and clinicians rely on treatments used for HCC or CCA. Although resection is the only curative treatment, many are found to be unresectable at the time of diagnosis. Recurrence rate is high despite the use of adjuvant therapies. The prognosis of cHCC-CCA is known to be worse than that of HCC, and the 5-year overall survival (OS) is reported to be 20-30% [5, 8-10].

Immunotherapy using immune checkpoint inhibitors (ICIs) is a breakthrough in cancer treatment for many types of cancer [11-13]. Among ICIs, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade and programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) interaction disruption have demonstrated promising clinical outcomes in many cancers, including HCC and biliary tract cancers (BTCs) [14-16]. It is also known that microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) are predictive factors for higher response to ICIs in various cancers [17-19].

Here, we review the recent evidence of ICIs for cHCC-CCA in comparison to that of HCC and CCA.

Pembrolizumab

Pembrolizumab is a humanized immunoglobulin G4 monoclonal antibody that binds to the inhibitory immune checkpoint receptor PD-1 expressed on lymphocytes, blocking binding of its ligands, PD-L1 and programmed cell death-ligand 2 (PD-L2), and causes T-cell-mediated tumor destruction [20, 21]. It was first approved for unresectable or metastatic melanoma by the United States Food and Drug Administration (FDA) in 2014 [22] and currently used for various cancers, including MSI-H/dMMR solid tumor [19, 23], non-small cell lung can-

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cer [24], head and neck squamous cell carcinoma [25], gastric cancer [26], urothelial carcinoma [27], and triple-negative breast cancer [12].

Pembrolizumab for HCC

Pembrolizumab was first evaluated as a monotherapy for advanced HCC previously treated with sorafenib in the nonrandomized, open-label, phase II KEYNOTE-224 trial, which included 104 patients across 47 medical centers in 10 countries [28]. It demonstrated a 17% objective response rate (ORR) (95% confidence interval (CI): 11-26%). Of the patients, 25% and 1% had a grade 3-4 or grade 5 treatment-related adverse events, respectively [28]. The FDA granted accelerated approval for pembrolizumab for HCC with previous history of sorafenib treatment based on the result of this study. The phase III KEYNOTE-240 trial comparing pembrolizumab to a placebo as second-line treatment for HCC was then conducted, consisting of 413 patients from 119 medical centers in 27 countries [29]. Although this trial did not meet its primary endpoints, OS, progression-free survival (PFS), ORR, and duration of response (DOR) were favorable to pembrolizumab group [29]. The median OS with pembrolizumab versus placebo was 13.9 versus 10.6 months, respectively (hazard ratio (HR): 0.771; 95% CI: 0.617 - 0.964), and the median PFS was 3.0 versus 2.8 months, respectively (HR: 0.718; 95% CI: 0.571 - 0.903). Grade 3 or 4 adverse events were reported for 53.4% of patients on pembrolizumab and for 46.3% of patients on placebo. Pembrolizumab was also assessed in the paralleled phase III KEYNOTE-394 trial in Asian countries, consisting of patients with advanced HCC with progression on or after intolerance to sorafenib or oxaliplatin-based chemotherapy in mainland China, Hong Kong, Republic of Korea, Malaysia, and Taiwan [30]. Pembrolizumab showed statistically significant improvement in OS, PFS, and ORR compared with placebo [30]. Median OS with pembrolizumab or placebo were 14.6 and 13.0 months, respectively (HR for death: 0.79; 95% CI: 0.63 - 0.99; P = 0.0180). Median PFS were 2.6 and 2.3 months, respectively (HR for progression or death: 0.74; 95% CI: 0.60 - 0.92; P = 0.0032). ORR was 12.7% (95% CI: 9.1-17.0%) with pembrolizumab, which was greater than in the placebo group (1.3%, 95% CI: 0.2-4.6%; P < 0.0001). KEYNOTE-240 and KEYNOTE-394 had similar OS HRs (0.78, 95% CI: 0.61 - 1.0; 0.79, 95% CI: 0.63 - 0.99, respectively). PFS HRs were also comparable (KEYNOTE-240 (final analysis): 0.72, 95% CI: 0.57 - 0.90 and KEYNOTE-394 (second interim analysis): 0.74, 95% CI: 0.60 - 0.92). ORR with pembrolizumab versus placebo also demonstrated a similar trend (KEYNOTE-240, 13.8%; KEYNOTE-394, 11.4%) [29, 30].

Pembrolizumab was also evaluated as a first-line monotherapy for patients with advanced HCC from cohort 2 data in phase II KEYNOTE-224 trial [31]. Fifty-one patients were allocated to cohort 2. ORR was 16% (95% CI: 7-29%) with a median DOR of 16 months (range, 3 to 24+ months). Median PFS was 4 months (95% CI: 2 - 8), and an estimated PFS rate at 12 months was 28%. Of the participants, 16% experienced more than grade 3 treatment-related adverse events. The authors concluded that pembrolizumab showed durable antitumor activity, promising OS, and safe profile for patients with advanced HCC with no prior systemic therapy. Currently, National Comprehensive Cancer Network (NCCN) 2024 recommends pembrolizumab as one of other recommended regimens for first-line (category B2) and subsequent-line systemic therapy [32].

Pembrolizumab for CCA

KEYNOTE-158 is a nonrandomized, open-label, multisite phase II study of pembrolizumab monotherapy for MSI-H/dMMR advanced non-colorectal cancer as second-line therapy [18]. A total of 233 patients with MSI-H/dMMR non-colorectal cancer from 18 countries, including 22 (9.4%) patients with CCA, were enrolled. Median follow-up was 13.4 months. Radiographic ORR was 34.3% (95% CI: 28.3-40.8%) with median PFS of 4.1 months (95% CI: 2.4 - 4.9 months). Median OS was 23.5 months (95% CI: 13.5 months - not reached). Of the patients, 14.6% had more than grade 3 treatment-related adverse events. Subgroup analysis of 22 patients with CCA demonstrated an ORR of 40.9% (95% CI: 20.7-63.6%) with a median PFS and OS of 4.2 months (95% CI: 2.1 months - not reached) and 24.3 months (95% CI: 6.5 months - not reached), respectively. In the updated analysis of KEYNOTE-158 with a median follow-up of 37.5 months, 30.8% of 351 patients (95% CI: 25.8-36.2%) achieved an overall response [33]. The median PFS, median OS, and median DOR were 3.5 months (95% CI: 2.3 - 4.2 months), 20.1 months (95% CI: 14.1 - 27.1 months), and 47.5 months (95% CI: 2.1+ months to 51.1+ months), respectively. Subgroup analysis of the same 22 patients showed a median PFS of 4.2 months (95% CI: 2.1 - 24.9 months) and a median OS of 19.4 months (95% CI: 6.5 months - not reached). The ORR was the same as previously reported in KEYNOTE-158. Based on the results of KEYNOTE-158, the FDA approved pembrolizumab monotherapy for patients with unresectable, metastatic MSI-H or dMMR solid tumors that failed previous treatment and lacked alternative treatment options.

The standard first-line regimen for advanced biliary tumor is the combination of gemcitabine and cisplatin, which acts to upregulate the immune system via several mechanisms, such as the recruitment of immune effector cells, enhancement of antigenicity, and downregulation of the immunosuppressive microenvironment [34-36]. The phase III randomized KEYNOTE-966 trial investigated the effect of the combination of pembrolizumab with gemcitabine and cisplatin on advanced BTC by looking at 1,069 patients with unresectable, locally advanced or metastatic BTC, in which 59% had intrahepatic CCA [37]. Of note, eight patients (2%) in the pembrolizumab group and five patients (1%) in the placebo group had cHCC-CCA. In the intention-to-treat population, median OS in the treatment group showed significant improvement compared to the control group (12.7 vs. 10.9 months, HR: 0.83; 95% CI: 0.72 - 0.95; one-sided P = 0.0034) as well as a trend towards improved benefit to add pembrolizumab in patients with intrahepatic CCA. Currently, the NCCN 2024 guideline recom-

mends pembrolizumab in addition to gemcitabine plus cisplatin as category 1 preferred recommendations for the first-line systemic treatment of unresectable or metastatic BTCs [38].

Pembrolizumab for cHCC-CCA

Although prospective data to determine the systemic therapy for cHCC-CCA are insufficient, NCCN 2024 guideline comments that gemcitabine plus cisplatin chemotherapy combined with pembrolizumab or durvalumab is an appropriate choice for first-line therapy based on the data for HCC and CCA [38]. The subjects in the phase III KEYNOTE-966 trial that evaluated the efficacy of combination of pembrolizumab with gemcitabine and cisplatin for unresectable biliary tumors included eight cHCC-CCA patients in the pembrolizumab group and five cHCC-CCA patients in the placebo group [37]. Furthermore, case series from Korea evaluated clinical outcomes for 25 patients with advanced cHCC-CCA who were treated with pembrolizumab [39]. The median follow-up was 20.1 months (95% CI: 4.9 - 35.2 months). The median PFS was 3.5 months (95% CI: 2.4 - 4.8 months), and the median OS was 8.3 months (95% CI: 6.8 - 9.8 months). The ORR was 20.0%, meaning one out of five patients responded to pembrolizumab.

Atezolizumab and Bevacizumab

Angiogenesis plays a key role in tumor progression process and crosstalk between angiogenesis and immune regulation in the tumor microenvironment and has gained increasing attention over the recent years [40]. Rapid tumor growth leads to hypoxia, which stimulates hypoxia-inducible factor 1 (HIF-1) and promotes vascular endothelial growth factor (VEGF)-mediated tumor angiogenesis [40, 41]. Endothelial cells of pathological vasculature have immunosuppressive features such as PD-L1 expression, which promotes T-cell exhaustion [40]. VEGF also plays immunosuppressive roles by suppressing dendric cell maturation, resulting in the interruption of T-cell priming [42], inducing exhaustion of $CD8^+$ T cells [43], accumulating regulatory T cells (Tregs), which are the most abundant immune suppressive cells, and repolarizing tumor-associated macrophages (TAMs) to M2-like phenotypes from M1-like phenotypes [44, 45]. Meanwhile, immune cells also modulate tumor angiogenesis. Tumor-promoting cells such as Tregs enhance angiogenesis via secretion of VEGF and recruitment of endothelial cells [46]. Interestingly, Tregs express immune checkpoint molecules, such as CTLA4 and PD-1 [47]. PD-1 blockade upregulates Treg activation while CTLA4 blockage downregulates it [48]. On the other hand, tumor-suppressing cells, such as mDC, M1-like TAMs, $CD8^+$ cells, and T helper-1 cells suppress angiogenesis [49-51]. Understanding the interactions between tumor immunity and angiogenesis has led to the exploration of combination therapy involving immunotherapy and vascular-targeting therapy. For example, preclinical studies in various cancer models showed that anti-VEGFR2 treatment upregulates the expression of PD-L1 [52, 53]. Shigeta et al reported the use of combination therapy with anti-VEGFR2 and anti-PD-1 and observed the promotion of vascular normalization and increased accumulation of tumor-suppressive CTLs and M1-like TAMs in murine HCC model [53].

Atezolizumab is a monoclonal antibody which selectively targets PD-L1, preventing interaction with receptors, PD-1 and B7-1, and reverses T-cell suppression against cancer immunity [54]. Bevacizumab is a monoclonal antibody that targets VEGF [55] and has been used for many advanced cancers in combination with chemotherapy [56, 57]. Liver is known to have a higher VEGF level compared to other organs due to hypervascularity [58], and overexpression of VEGF has been linked to the development and progression of liver cancer [59, 60]. While clinical trials combining anti-angiogenic therapy with PD-1/PD-L1 inhibitors have shown promising outcomes in non-squamous non-small cell lung cancer, renal cell carcinoma, and endometrial cancer [61-64], the combination of atezolizumab and bevacizumab has yielded the most successful results in HCC.

Atezolizumab and bevacizumab for HCC

IMbrave150 is a global, open-label, phase III trial, assessing the efficacy of combination of atezolizumab and bevacizumab for unresectable HCC as first-line treatment, which showed that the combination had better OS and PFS outcomes compared to sorafenib [65]. In this study, 501 patients at 111 sites across 17 countries were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. The median follow-up time was 8.6 months. The HR for death comparing the atezolizumab plus bevacizumab group to the sorafenib group was 0.58 (95% CI: 0.42 - 0.79; $P < 0.001$), and OS at 12 months was 67.2% (95% CI: 61.3-73.1%) for atezolizumab plus bevacizumab and 54.6% (95% CI: 45.2-64.0%) for sorafenib. Updated analysis with a median follow-up of 15.6 months showed a median OS of 19.2 months (95% CI: 17.0 - 23.7) with atezolizumab plus bevacizumab and 13.4 months (95% CI: 11.4 - 16.9) with sorafenib (HR: 0.66; 95% CI: 0.52 - 0.85; descriptive $P < 0.001$) [66]. The median PFS was 6.9 months (95% CI: 5.7 - 8.6 months) for the atezolizumab plus bevacizumab group and 4.3 months (95% CI: 4.0 - 5.6 months) for the sorafenib group (HR: 0.65; 95% CI: 0.53 - 0.81; descriptive $P < 0.001$). Following this study, the 2024 NCCN guideline recommends the combination of atezolizumab and bevacizumab as the first-line systemic therapy for advanced HCC as a category 1 recommendation [32].

Atezolizumab and bevacizumab for cHCC-CCA

Several published studies suggest the utility of the combination of atezolizumab and bevacizumab for cHCC-CCA. A retrospective, multicentric study from France demonstrated antitumor efficacy of the combination therapy of atezolizumab and bevacizumab in patients with unresectable or metastatic cHCC-CCA [67]. In this study, 16 patients with unresectable or metastatic cHCC-CCA from seven centers were included. Nine patients received atezolizumab and bevacizumab as a

first-line systemic therapy and seven patients as a second line or more. The first-line therapy group had a median OS of 13 months and a median PFS of 3 months. Among the seven patients receiving this combination therapy as a second line or more, four patients had stable disease, two had a partial response, and one had progressive disease. Saito et al reported a case of the use of atezolizumab plus bevacizumab for distant lymph node recurrence of cHCC-CCA after surgical resection [68]. The patient developed distant lymph node metastases after right hepatic lobectomy and adjuvant chemotherapy with titanium silicate (TS)-1 for cHCC-CCA. The patient initially received gemcitabine and cisplatin, but was discontinued due to severe rash. The patient then subsequently received lenvatinib, but it was also discontinued due to grade 3 adverse event, and the decision was made to switch to atezolizumab and bevacizumab. The patient achieved 7.5 months of PFS before ultimate progression of disease.

Nivolumab

Nivolumab is a human immunoglobulin G4 monoclonal antibody targeting PD-1 and blocks the interaction between PD-1 expressed on T cells and PD-L1 expressed on tumor cells, modulating T-cell-modulated immune response [69, 70]. Nivolumab initially showed efficacy for melanoma [71, 72] and has been extensively studied for multiple cancers.

Nivolumab for HCC

CheckMate 459 is a randomized phase III trial, comparing nivolumab monotherapy to sorafenib as the frontline treatment for advanced HCC [73]. A total of 743 patients from 22 countries and territories in Asia, Australasia, Europe, and North America were randomly assigned to treatment. Median OS was 16.4 months (95% CI: 13.9 - 18.4) with nivolumab and 14.7 months (11.9 - 17.2) with sorafenib (HR: 0.85; 95% CI: 0.72 - 1.02; P = 0.075; minimum follow-up 22.8 months), but the protocol-defined significance level (P = 0.0419) was not reached in this trial. The study displayed the favorable efficiency and safety of nivolumab monotherapy, but it did not demonstrate a statistically significant OS compared to sorafenib. Although nivolumab monotherapy was removed from the recommendations as the first-line therapy for advanced HCC in version 1 of NCCN 2024 guideline, it is recommended as subsequent-line systemic therapy in certain circumstances [32]. Nivolumab has been also studied in combination with ipilimumab, a CTLA-4 ICI. Although PD-1 and CTLA-4 both inhibit T-cell activation, they act on different phases of the cancer immunity cycle. PD-1 is a major regulator of T-cell exhaustion in the tumor microenvironment while CTLA-4 mainly inhibits activated and regulatory T cells in the lymphoid organs [74, 75]. In CheckMate 040, a multicenter, open-label, multicohort, phase I/II study, efficacy of the combination therapy with nivolumab and ipilimumab was studied [76]. In this study, a total of 148 patients with advanced HCC previously treated with sorafenib from 31 centers in 10 territories in Asia, Europe, and North America were randomized across three dosing arms. The median follow-up was 30.7 months, and investigator-assessed ORR was greater than 30% across treatment arms. The arm A regimen (four doses nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks then nivolumab 240 mg every 2 weeks) had the highest complete response rate, promising median OS of 22.8 months, 12-month survival rates of 61%, 24-month survival rates of 48%, and 30-month OS rates of 44%, receiving accelerated approval in the USA. Currently, NCCN 2024 guideline recommends the combination of nivolumab plus ipilimumab as second-line therapy for HCC [32].

Nivolumab for CCA

Nivolumab monotherapy for advanced BTC was evaluated in a multicenter, phase II trial with 54 patients [77]. In this study, patients with advanced BTCs with disease progression after treatment with at least one line but no more than three lines of systemic therapy were included. The inclusion criteria comprised patients with advanced BTCs who had experienced disease progression while undergoing treatment using at least one line but no more than three lines of systemic therapy. The study showed ORRs of 22% by investigator review and 11% by central review, and DOR of 59% by investigator review and 50% by central review per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. In the intention-to-treat population, the median PFS and median OS were 3.7 months (95% CI: 2.3 - 5.7 months) and 14.2 months (95% CI: 6.0 months - not reached), respectively. Of note, PD-L1 expression was associated with prolonged PFS but was not significantly associated with OS (HR: 0.23; 95% CI: 0.10 - 0.51; P < 0.001). Current NCCN 2024 guideline recommends nivolumab as category 2B, useful in certain circumstances as a subsequent-line systemic therapy option for unresectable or metastatic progressive CCA without prior history of a checkpoint inhibitor use [38].

In terms of combination therapy with other ICIs, the combination of nivolumab plus ipilimumab was evaluated in the CheckMate 848 trial [78]. In this randomized, open-label, phase II clinical trial, 201 patients with advanced or metastatic solid tumors of high tumor mutational burden (TMB) were randomized 2:1 to receive the combination of nivolumab plus ipilimumab or nivolumab monotherapy. TMB is defined as the total number of somatic mutations in the tumor genome and high tissue TMB (tTMB) or high blood TMB (bTMB) tumors are thought to be more responsive to immunotherapies compared to low TMB tumors [79, 80]. Indeed, it has been shown that TMB is a predictive biomarker for response to immunotherapies in solid tumors [81, 82]. In the high tTMB cohort of this study, ORR was 38.6% (95% CI: 28.4-49.6%) with nivolumab and ipilimumab and 29.8% (95% CI: 17.3-44.9%) with nivolumab monotherapy. In the high bTMB cohort, ORR was 22.5% (95% CI: 13.9-33.2%) with nivolumab and ipilimumab and 15.6% (95% CI: 6.5-29.5%) with nivolumab monotherapy. Median OS with high tTMB was 15.0 (95% CI: 10.2 - 29.8) and 14.6 (95% CI: 7.7 - 20.7) months in the nivolumab plus ipilimumab, and nivolumab monotherapy arms, respec-

tively; in patients with high bTMB, median OS was 8.1 (95% CI: 5.8 - 10.5) and 11.2 (95% CI: 5.3 - 19.0) months, respectively. Based on this study, NCCN 2024 recommends the combination of nivolumab and ipilimumab as first and second line for advanced BTC with high TMB [38].

Nivolumab for cHCC-CCA

NCCN 2024 guideline recommends the combination of nivolumab plus ipilimumab as a reasonable treatment based on the evidence extrapolated from treatment efficacy on both HCC and CCA [38]. Jang et al published a case series of 25 patients who received ICIs for unresectable or metastatic cHCC-CCA [39]. Seventeen patients (68%) received nivolumab. All patients, except one, had previously received systemic therapy. Median PFS was 3.5 months, median OS was 8.3 months, and ORR was 20.0%.

Durvalumab

Durvalumab is an IgG1 monoclonal antibody that has high-affinity binding to PD-L1 receptor and was first approved by FDA for urothelial carcinoma in 2017 [83]. Durvalumab has been used alone or with combination of other ICIs including CTLA-4 inhibitors in various cancers. Of note, while the PD-1 pathway regulates T-cell activation in peripheral tissues, CTLA-4 is thought to regulate T-cell proliferation in lymph nodes [84-86]. It has been shown that CTLA-4 blockage enhances the efficacy of PD-1 inhibitors [87, 88].

Durvalumab for HCC

In the phase III HIMALAYA trial, comparison was made between tremelimumab, a CTLA-4 inhibitor, plus durvalumab, durvalumab monotherapy, and sorafenib as the first-line therapy for unresectable HCC [89]. Compared to sorafenib, the combination treatment significantly improved OS, and durvalumab monotherapy was noninferior to sorafenib. Based on the result of this study, NCCN 2024 guideline recommends the combination of tremelimumab plus durvalumab as the preferred regimen (category 1) and durvalumab monotherapy as one of the other recommended regimens (category 1) for first-line therapy [32]. This STRIDE regimen has gained approval internationally as first-line treatment for unresectable HCC, and durvalumab monotherapy has also been approved in Japan and the European Union.

Durvalumab for CCA

The TOPAZ-1 trial is a double-blind, placebo-controlled, phase III study for the addition of durvalumab to gemcitabine plus cisplatin for advanced BTC as first-line therapy [90]. A total of 685 patients including 383 (55.9%) intrahepatic CCA were randomly assigned to treatment. Median OS was 12.8 months (95% CI: 11.1 - 14.0) in the durvalumab group and 11.5 months (95% CI: 10.1 - 12.5) in the placebo group. Durvalumab significantly improved OS compared to placebo (HR: 0.80; 95% CI: 0.66 - 0.97; P = 0.021). Of note, HRs of OS and PFS for intrahepatic CCA were 0.76 (95% CI: 0.58 - 0.98) and 0.79 (95% CI: 0.64 - 0.99), respectively. NCCN 2024 guideline recommends the combination of durvalumab, gemcitabine plus cisplatin as primary treatment for unresectable and metastatic disease (category 1) [38]. This regimen is also recommended as an option for patients with recurrent disease more than 6 months after surgery or completion of adjuvant therapy.

Durvalumab for cHCC-CCA

NCCN 2024 guideline recommends the regimen of gemcitabine plus cisplatin chemotherapy with either durvalumab or pembrolizumab immunotherapy as an appropriate choice for first-line therapy [38]. Unome et al reported the use of the STRIDE regimen for unresectable cHCC-CCA based on the HIMALAYA study [89] and the TOPAZ-1 trial [90, 91]. In this study, a grade 3 maculopapular rash developed 25 days after the initiation of durvalumab and tremelimumab combination therapy, requiring steroid therapy. Rapid tumor growth was noted after two cycles.

Toripalimab

Toripalimab is a humanized IgG4 monoclonal antibody targeting PD-1 and has been approved by FDA and China's National Medical Products Administration (NMPA). It has shown promising efficacy and safety profiles for urologic cancer [92], melanoma [92], and gastric cancer [93]. Lenvatinib is a multikinase inhibitor that targets vascular endothelial growth factor receptors (VEGFRs) 1 to 3, fibroblast growth factor receptors (FGFRs) 1 to 4, platelet-derived growth factor receptor-α (PDGFRα), rearranged during transfection (RET), and stem cell factor receptor (KIT). Like many other tyrosine kinase inhibitors (TKIs), lenvatinib is known for its antitumor immunomodulatory effects. Experimental studies on mice have been shown that lenvatinib modulates antitumor immunity by decreasing TAMs and increasing cytotoxic $CD8^+$ T cells, which are the major effectors in the antitumor immunity and enhance antitumor activity of anti-PD-1 antibody [94-96]. In fact, the combination of PD-1 inhibitor with lenvatinib is reported to be useful in several cancer types [97-100].

Toripalimab for HCC

Multiple phase II trials using the combination of TKI and toripalimab for HCC have been published. He et al reported the results of a phase II trial looking at the efficacy of the combination of lenvatinib, toripalimab plus folinic acid, fluorouracil, and oxaliplatin (FOLFOX) for HCC with extrahepatic metastasis [101]. Thirty patients were included in this study, which demonstrated 6-month PFS rate of 66.7%, with a me-

dian PFS of 9.73 months, and a median OS of 14.63 months (95% CI: 11.77 - 17.50) with ORR of 43.3%. Zhang et al reported a prospective, multicenter, phase II study assessing the efficacy of a combination of anlotinib and toripalimab as first-line therapy for unresectable HCC [102]. Thirty-one patients from two centers in China were enrolled. ORR was 29.0% by immune-related RECIST (irRECIST)/RECIST v1.1, and 32.3% by modified RECIST (mRECIST) criteria. Median PFS was 11.0 months, and median OS was 18.2 months. The most recent phase 2 trial is a multicenter trial that used the combination of toripalimab and bevacizumab as first-line treatment for advanced HCC [103]. Fifty-four patients were enrolled in this trial. ORR was 31.5% (RECIST v1.1) and 46.3% (mRECIST). Median PFS was 8.5 months (RECIST v1.1) and 9.8 months (mRECIST). The 12-month and 24-month OS rates were 77.3% and 63.5%, respectively.

Toripalimab for CCA

A phase II study of combination of toripalimab, lenvatinib, and gemcitabine and oxaliplatin (GEMOX) for advanced intrahepatic CCA as first-line therapy was published in 2023 from China [104]. Thirty patients with advanced intrahepatic CCA from a single center were enrolled. The median follow-up time was 23.5 months, and the ORR was 80%. Twenty-three patients achieved partial response, and one achieved complete response. The median OS, PFS, and DOR were 22.5, 10.2, and 11.0 months, respectively. Another study using the combination of toripalimab and a multi-targeted TKI is a phase II study of the combination of anlotinib (multi-targeted TKI) and toripalimab for advanced BTC [105]. In this study, 15 BTC patients, including nine ICC, three HCCA, and three gallbladder cancers, were enrolled. Among 15 patients, four (26.7%) received anlotinib plus toripalimab as the first-line therapy due to intolerability to chemotherapy, and 11 patients (73.3%) received the combination as second-line therapy. The first-line treatment group achieved an ORR of 50% and a disease control rate (DCR) of 100%. The second-line treatment group had an ORR of 18.2% and a DCR of 81.8%. There was no report of serious immune-related adverse events.

Toripalimab for cHCC-CCA

Xu et al reported a case of a patient who received the combination of toripalimab and lenvatinib as second-line therapy for abdominal lymph node metastasis after radical resection and adjuvant therapy with capecitabine for cHCC-CCA [106]. The patient was still undergoing treatment and PFS exceeded 27.2 months.

Conclusions

cHCC-CCA is a rare liver cancer without standardized systemic therapy for advanced or recurrent disease. The use of ICIs, which has effect on both HCC and CCA, has been reported for cHCC-CCA, showing encouraging outcomes. Given the rareness of cHCC-CCA, prospective clinical trials for this condition may not be feasible, and one may need to rely on available data such as this narrative review.

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Conflict of Interest

The authors have no potential conflict of interest to disclose.

Author Contributions

Conceptualization: K. Shichiri and K. Takabe. Writing - original draft preparation: K. Shichiri. Writing - review and editing: K. Tung, K. Takabe, and D. Bartlett. Supervision: K. Takabe and D. Bartlett. Funding acquisition: K. Takabe.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

BSC: best supportive care; BTC: biliary tract cancer; bTMB: blood tumor mutational burden; CCA: cholangiocarcinoma; cHCC-CCA: combined hepatocellular-cholangiocarcinoma; CI: confidence interval; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; DCR: disease control rate; DOR: duration of response; FDA: Food and Drug Administration; FGFR: fibroblast growth factor receptor; HR: hazard ratio; HCC: hepatocellular carcinoma; ICI: immune checkpoint inhibitor; MSI-H: microsatellite instability-high; MSI-H/dMMR: microsatellite instability-high/mismatch repair deficiency; MMR: mismatch repair; NCCN: National Comprehensive Cancer Network; NMPA: National Medical Products Administration; ORR: objective response rate; OS: overall survival; PD-1: programmed cell death-1; PDGFRα: platelet-derived growth factor receptor-α; PD-L1: programmed cell death-ligand 1; PD-L2: programmed cell death-ligand 2; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid

Tumors; SEER: Surveillance, Epidemiology, and End Results; TS: titanium silicate; TKI: tyrosine kinase inhibitor; TMB: tumor mutational burden; tTMB: tissue tumor mutational burden; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; WHO: World Health Organization

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