Journal of Infectious Diseases & Immune Therapies

Editorial A SCITECHNOL JOURNAL

Immune Checkpoint Inhibitors: The Emerging Cornerstone in Cholangiocarcinoma Therapy?

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Received date: 03 January, 2022; Manuscript No. JIDITH-22-57253;
Editor assigned date: 05 January, 2022; PreQC No. JIDITH-22-57253(PQ);
Reviewed date: 17 January, 2022; QC No JIDITH-22-57253;
Revised date: 27 January, 2022; Manuscript No. JIDITH-22-57253(R);
Published date: 03 February, 2022; DOI: 10.4172/jidith.1000140.

Introduction

Cholangiocarcinoma (CCA) is a term used to describe a category of biliary malignant tumors that have a poor prognosis. Different cells inside the peribiliary glands, such as hepatic stem/progenitors cells, cholangiocytes, hepatocytes, and/or multipotent stem cells, are vulnerable to neoplastic transformation, which helps to explain the great variety of these tumors. CCAs are characterized as Intrahepatic Cholangiocarcinoma (iCCA), Perihilar Cholangiocarcinoma (pCCA), and Distal Cholangiocarcinoma (dCCA) based on where they grow anatomically (dCCA). CCA is the second most prevalent primary liver neoplasm after Hepatocellular Carcinoma (HCC), accounting for 15% and 3% of all primary hepatic malignancies and gastrointestinal cancers, respectively, over the past few decades.

Because the aetiology of CCA is largely unknown, it's possible that rising incidence patterns are due to new and yet-to-be-identified etiological causes. In this regard, several conditions have been identified as increasing the risk of cholangio carcinogenesis, including primary sclerosing cholangitis, cirrhosis, viral and parasitic infections, type 2 diabetes mellitus, and genetic landscape, while the role of others, such as non-alcoholic fatty liver disease and alcohol/tobacco consumption, is still debated. Furthermore, the lacks of symptomatology in the early stages of the disease, as well as the lack of specific screening tools, make it difficult to diagnose CCA early. As a result, most patients are discovered at an advanced stage when the cancer has already spread, reducing the efficacy of curative therapeutic options and ultimately leading to a poor prognosis and short life expectancy.

Surgical excision of the tumor is now the only potentially curative therapy for people with CCA. However, due to late detection, only 20% of patients are suitable for surgery, and even when curative resection is achieved, relapse has been observed in 60%-70% of patients, regardless of CCA subtype. Patients with unrespectable, metastatic, or recurring malignancies can only get palliative chemotherapy as a result. The GemCis (gemcitabine plus cisplatin) combination is now widely acknowledged as the first-line standard of therapy. However, several attempts have been undertaken to develop more effective first-line therapy regimens by mixing other substances with the gold standard of care, with no definitive results thus far.

The development of second-line treatment strategies (*i.e.*, folinic acid + fluorouracil + oxaliplatin) for a non-negligible minority of CCA patients who progress after first-line regimens has been prompted by the existence of diverse and complex mechanisms of chemoresistance in tumor cells and the microenvironment, which has led to the development of second-line treatment strategies (*i.e.*, folinic acid + fluorouracil + o Furthermore, the CCA subtype influences the application of various therapeutic techniques, such as loco-regional operations or liver transplantation, and their benefits must be demonstrated.

The development of novel and tailored therapies based on the mutational status of CCA driver genes (primarily isocitrate dehydrogenase1/2 mutations and fibroblast growth factor receptor 2 gene fusions) and the immunological tumor microenvironment has benefited from a better understanding of the molecular biology driving biliary tract malignancies. Modulation of immunological checkpoints has gained importance in clinical oncology, and is now being investigated as a viable method for the treatment of a variety of malignancies. We present a current state-of-the-art review that focuses on the clinical importance of immune checkpoints in CCA as well as current and emerging therapeutic options aimed at modulating the immunological tumor microenvironment in this malignancy.

Local and Systemic Therapies Combined with ICIs for CCA Treatment

Combination of radiotherapy and ICIs

Radiation's usefulness in CCA is still debated today. It was recently evaluated in four patients with advanced iCCA in combination with pembrolizumab or nivolumab in four patients with advanced iCCA (anti-PD-1 inhibitors). Despite the fact that none of them met the criteria for receiving this immunotherapy set forth by the national comprehensive cancer network, the combination of both therapeutic strategies (*i.e.*, radiotherapy + ICI) either achieved PR with a reduction in the sum of lesion diameters or maintained Complete Response (CR) for 11 and 26 months [1]. The radiotherapy's potential to sensitize the tumor to ICIs by boosting the presentation of tumor-associated antigens and increasing PD-L1 expression in tumor cells could explain this unexpectedly favorable anticancer effect of immunotherapy combined with radiotherapy in iCCA. However, because the only data available is sourced from case reports, more research is needed to substantiate this statement.

Combination of ablative therapy and ICIs

Tumor ablation procedures may also boost the anticancer immune response by enhancing the effects of ICIs. As a result, one of the arms (arm E) of a phase I/II clinical trial (NCT01853618) coupled microwave ablation with tremelimumab (anti-CTLA4 mAb) for the treatment of 20 patients iCCA (n=12), eCCA (n=6), and GBC (n=2) are advanced BTCs. Only two responsive individuals (*i.e.*, 12.5%; all eCCA) were identified out of a total of 16 patients with lesions that could be evaluated for response [2]. Furthermore, 37.5% of patients (6/16) had Stable Disease (SD) for up to 6.2 months, whereas the remaining 50% (8/16) had disease progression. Overall, medication was well tolerated by the majority of patients, with only 10% of them experiencing severe Adverse Events (AEs), however all research participants suffered some low-grade treatment-related AEs. The authors also discovered that tremelimumab caused a considerable increase in CD8 + T cell activation. However, as compared to the other arms of the clinical trial, when tremelimumab was paired with Radiofrequency Ablation (RFA) and other ablative therapy, this arm

had the lowest mOS and mPFS (*i.e.*, 6 months and 3.4 months, respectively). This could be one of the reasons why a pilot research (NCT02821754) is presently underway to assess the efficacy of RFA or cry ablation in combination with tremelimumab and durvalumab (anti-PD-L1 mAb) in a similar but bigger cohort of BTC patients [3].

Combination of chemotherapy and ICIs

Of date, the clinical response to CCA treatment that is only based on chemotherapy has been disappointing. Treatment with gemcitabine and other chemotherapeutic drugs, on the other hand, was found to boost PD-L1 expression, hence increasing PD-1/PD-L1 axis signaling. As a result, combining chemotherapy with ICIs to improve therapeutic efficacy is a good concept. In this context, 32 patients with unrespectable or metastatic BTCs (*i.e.*, iCCA (n=11), pCCA (n= 6), dCCA (n=9), and GBC (n = 6)) were examined in a phase II linical trial (NCT03311789) that combined GemCis with nivolumab (*i.e.*, anti-PD-1 mAb). Unfortunately, 5 patients were removed from the study due to rapid deterioration as a result of tumor-related problems (n=4) and Adverse Events (AEs) unrelated to the study medicines (n=1) [4]. With a mOS and a mPFS of 8.5 months and 6.1 months, respectively, response-evaluable patients had an ORR of 55.6% (5 patients with CR and 10 patients with PR). In addition, six patients who had previously been determined to be resistant to GemCis-based therapy were included in the study to see if the combination of ICIs and chemotherapy could re-sensitize BTCs.

Surprisingly, one of these patients was able to obtain CR, while the other had PR. In patients with non-respectable CCA, a Japanese study (JapicCTI-153098) used the similar therapy approach (GemCis + nivolumab). Those treated with the combination therapy exhibited a significant increase in mOS, mPFS, and response rate (*i.e.*, 15.4 months, 4.2 months, and 36.7%, respectively) when compared to patients treated with nivolumab as monotherapy. However, the number of patients experiencing significant AEs as a result of their treatment increased [5]. The NCT03101566 is an ongoing clinical experiment that shares many parallels with the aforementioned study, although it is being conducted in a western population.

In contrast, a phase II (NCT03046862) investigation of CCA and GBC patients found no significant changes in mOS (*i.e.*, 18.1 months *vs.* 20.7 months, respectively), mPFS (*i.e.*, 11.0 *vs.* 11.9 months, respectively), or ORR between GemCis + durvalumab and GemCis + durvalumab + tremelimumab schemes (*i.e.*, 73.4% *vs.* 73.3% , respectively). Nonetheless, when both ICIs were coupled with standard of care chemotherapy and provided after 1 cycle of GemCis, both treatment regimens enhanced the mOS and ORR (*i.e.*, 15.0 months and 50.0% , respectively) [6]. The combination of GemCis + durvalumab versus GemCis + placebo is being studied in a phase III clinical trial based on these promising results (NCT03875235). Other clinical trials are currently examining potential therapeutic combinations of ICIs with various chemotherapeutic drugs as both first- and second-line treatments, but no results have been reported thus far [7].

Combination of other therapies and ICIs

For CCA therapy, the therapeutic potential of a combination of ICIs and targeted therapies or epigenetic modulators is being investigated. In this vein, an observational research combining lenvatinib (a VEGF 1–3 and fibroblast growth factor receptor 1–4 inhibitor) with pembrolizumab or nivolumab (anti-PD-1 mAbs) showed encouraging results in patients with iCCA who had previously failed two or more anticancer treatments. As a result, 3 of the 14 patients participated in the study attained PR after treatment, with a median PFS of 5.9 months [8]. The DCR and clinical benefit rate (*i.e.*, ORR + SD 5 months) were 92.9% and 64.3%, respectively. According to these findings, an Asian phase II clinical trial (NCT04550624) utilizing the aforementioned antigenic inhibitor in combination with pembrolizumab was just initiated in a population with similar characteristics. Intriguingly, another vascular endothelial growth factor inhibitor, bevacizumab, has been combined with atezolizumab (*i.e.*, anti-PD-L1 mAb), yielding promising results for the treatment of patients with unrespectable HCC and spurring the development of a phase II clinical trial (NCT04677504) to assess the safety and efficacy of bevacizumab in combination with atezolizumab and GemC [9]. M7824, a fusion protein containing the human transforming growth factor receptor II extracellular domain and an IgG1 anti-PD-L1 antibody, was recently created and tested in a phase I trial for metastatic or locally advanced solid cancers (NCT02699515). The ORR, mPFS, and mOS of this trial's expansion group of 30 Asian BTC patients were 20%, 2.5 months, and 12.7 months, respectively. Importantly, therapy response was independent of PD-L1 expression and was long-lasting, with 83% of patients still responding at the data cutoff (12.5-14.5 months).

Based on these findings, phase II/III (NCT04066491) and phase II (NCT03833661) clinical trials for locally advanced or metastatic BTC patients are being developed to see if M7824 can be used as a first-line treatment in combination with GemCis or as a second-line treatment after chemotherapy failure [10]. ICIs have also been explored in combination with epigenetic modulators such entinostat, a histone deacetylase inhibitor that has been shown to enhance both MHC class II expression and Trig function. As a result, an ongoing phase II clinical trial (NCT03250273) is exploring the combination of nivolumab and entinostat for the treatment of unrespectable or metastatic CCA and pancreatic adenocarcinoma in patients with unrespectable or metastatic CCA and pancreatic adenocarcinoma.

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