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Review Article

Advancements in Immunotherapy for Biliary Tract Cancers: Current Perspectives and Future Directions

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Abstract

Biliary tract cancer is a heterogenous group of malignancy which comprises of carcinoma gall bladder, intrahepatic and extra hepatic cholangiocarcinoma. Management of BTC is challenging and there are very limited treatment options. Surgical treatment is the only curative treatment option but most of the patients present with advanced disease which are not amenable to surgery. For decades the combination of gemcitabine plus cisplatin has been the only treatment option in locally advanced or metastatic BTCs, with limited efficacy. Extensive research and development have happened in field of immunotherapy (IO) in last decade, especially for solid tumours. Immunotherapy alone has limited role in BTC but in combination with standard of care chemotherapy it has provided overall survival benefit. Recently molecular profiling of tumor resulted in identification of new targets like IDH 1, MAP, HER-2, FGFR. Various trials are exploring the role of targeted therapies to improve survival. Antiangiogenics, cancer vaccines, IO in combination with radiotherapy are the other options under exploration. This article provides an overview of literature on the above recent advances.

Keywords: Immunotherapy; Biliary Tract Cancer; Check Point Inhibitors; Targeted Therapy; Cholangiocarcinoma; Gall Bladder Cancer; Recent Advancements; Combination Therapy.

Introduction

Brief Overview of Biliary Tract Cancers (BTCs) and Their Global Incidence

Biliary tract cancers (BTCs) include malignancies arising from the biliary epithelium and encompass intrahepatic, perihilar, distal cholangiocarcinoma, and gallbladder cancers [1].These cancers are relatively rare but are particularly aggressive, with the incidence varying significantly worldwide [2, 3]. For example, regions such as Southeast Asia exhibit higher rates due to endemic factors like liver fluke infections, water pollution, obesity, consumption of chilly, and adulterated oil [4-12].

Challenges in Treating BTCs

The treatment of BTCs remains challenging due to factors such as late diagnosis, as early-stage BTCs often lack specific symptoms. Furthermore, BTCs are characterized by complex molecular heterogeneity, including diverse genetic and epigenetic alterations that contribute to drug resistance and a generally poor prognosis [13]. Surgery is the only potentially curative treatment modality; however, only a minority of patients are eligible, leaving most patients to rely on systemic therapies, which have shown limited efficacy [14]. At present standard of care chemotherapeutic option is gemcitabine plus cisplatin with a progression free survival of 8 months [15]. To improve survival newer therapeutic options are being explored. A phase III study evaluated the role of addition of nab paclitaxel to standard of care gemcitabine plus cisplatin [16]. It showed non-statistically significant numerical benefit in progression free survival with higher toxicity.

Introduction to Immunotherapy and Its Emerging Role in Oncology

Immunotherapy, an innovative treatment approach that leverages the self-immune system to target and kill cancer cells and it has transformed the oncology landscape over recent years. By targeting immune checkpoints or enhancing T-cell responses, immunotherapy has demonstrated success in many solid tumors, including melanoma and lung malignancy, and is now being

investigated for its potential in BTCs [17]. Recently TOPAZ-1 study confirmed the benefit of addition of durvalumab to gemcitabine plus cisplatin in the first-line management of advanced BTCs [18]. Given BTCs' resistance to conventional treatments, there is a rising interest in applying immunotherapeutic strategies to improve patient outcomes.

Aim of the Review

This review aims to explore recent advancements in immunotherapy for BTCs, examine current perspectives on available and emerging therapies, and discuss the future directions for optimizing immunotherapeutic approaches in these cancers. By assessing the progress and identifying challenges, this review provides insights into how immunotherapy could reshape BTC treatment paradigms, potentially improving the prognosis for affected patients.

Pathophysiology of Biliary Tract Cancers and Immunogenicity

Molecular and Genetic Landscape Relevant to Immunotherapy

The genetic and molecular landscape of BTCs is complex and includes a variety of mutations and expression patterns that influence disease progression and response to therapies. Gene mutations such as IDH1/2, FGFR2, and KRAS are frequently found in BTCs, and while some may influence targeted therapies, they also affect tumor immune dynamics [13]. The tumor mutation burden (TMB) in BTCs is generally low, suggesting limited neoantigen production. However, PD-L1 expression, a critical immune checkpoint marker, varies across BTC subtypes and can be present in up to 10-20% of cases, potentially enabling BTCs to evade immune detection and creating a target for checkpoint inhibitors [19].

Immune Evasion Mechanisms in BTCs

BTCs exhibit several immune evasion mechanisms, making them challenging to treat with immunotherapies. One well-known method is the production of immune checkpoint proteins like PD-L1, which attaches to T-cell PD-1 to prevent T-cell activity and enable cancer cells to avoid immune surveillance [17]. Additionally, BTCs often create an immunosuppressive tumor microenvironment (TME), populated with myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), which collectively dampen the immune activity. More than 70% of BTC tissues are enriched in immune cells, as per Cancer Genome Atlas (TCGA), the prognosis of cancer patients is strongly correlated with the extent of particular immune cell infiltration [20]. One study suggests, for instance, that the OS of BTC patients has been considerably extended by the enhanced infiltration of CD4+ and CD8+ T cells. Conversely, the more tumor-associated neutrophils and regulatory T cells (Tregs) infiltrate ECC, the worst will be prognosis [21]. This immunosuppressive milieu presents a significant barrier to effective immunotherapy.

The Potential for Immunogenicity in BTCs: Challenges and Opportunities

While BTCs typically have low immunogenicity due to their low TMB and immunosuppressive TME, certain characteristics suggest potential immunotherapy targets. For instance, studies have shown that BTCs with higher PD-L1 expression and specific genetic mutations may respond better to checkpoint inhibitors [22]. Immune checkpoint inhibitors are the class of drugs that blocks inhibitory pathways on immune cells, allowing T-lymphocytes to mount a stronger response against tumor cells. The two main checkpoints targeted in BTC immunotherapy are PD-1/PD-L1 and CTLA-4. The PD-1 is a receptor on T-cells that, when bound by PD-L1 present on cancer cells, suppresses the host immune response [17]. Binding of PD-1 inhibits T-cell proliferation, production of interleukin-2, interferon-alpha (INF-α), TNF-a, and decrease T-cell survival. The binding of CTLA-4 to its ligands B7-1 and B7-2 results in apoptosis and T-cell anergy, simultaneously preventing CD28 co-stimulation [23]. So blockade of PD-L1 and CTLA-4 can enhance immune responses against tumors [24].

Moreover, ongoing research is exploring combination strategies, such as pairing checkpoint inhibitors with other agents that modulate the immune environment, to increase BTCs' immunogenicity and enhance treatment efficacy. However, achieving durable responses remains a challenge, necessitating further studies to refine therapeutic strategies and identify predictive biomarkers [25].

Current Immunotherapeutic Approaches in BTCs

Checkpoint Inhibitors Monotherapy

Several trials (table 01) have assessed the effectiveness of PD-1 and PD-L1 inhibitors in biliary tract cancers (BTCs). In the Keynote-028 trial, only patients with PD-L1 positivity (defined as membranous PD-L1 expression in at least 1% of tumor and associated inflammatory cells or positive staining in the stroma) were enrolled. This study included 24 patients, and after a median follow-up of 6.5 months, the objective response rate (ORR) was 13%. The median overall survival (OS) was 6.2 months (range 3.8–10.3), with a 12-month OS rate of 27.6%. Grade 3 to 5 adverse events (AEs) occurred in 16.7% of participants [26].

NCT number	Trail name	Treatment given	Prim. End point	ORR	OS (mo)	PFS (mo)
NCT02054806	KEYNOTE-028	Pembrolizumab	ORR	13.00%	5.7	1.8
NCT02628067	KEYNOTE-158	Pembrolizumab	ORR	5.80%	7.4	2
NCT02829918	-	Nivolumab	ORR	10.9	14.2	3.7
NCT02923934	CA209-538	Ipilimumab/nivolumab	DCR	23.10%	5.7	2.9
NCT03704480	IMMUNO-BIL/ PRODIGE 57	Durvalumab/tremelimumab	OS (6 mo)	9.70%	8	2.5
ORR- objective response rate, OS- overall survival, PFS- progression free survival, mo- months, DCR- disease control rate, DLT-dose limiting toxicity.						

Table 1: Immune check point inhibitors in BTC.

In the Keynote-158 trial, 104 patients with advanced BTC whose disease had progressed after any line of systemic treatment were treated with pembrolizumab. PD-L1 positivity was not a required inclusion criterion in this study; 61 patients had PD-L1 combined positive scores (CPS) of = 1, while 34 were PD-L1 non-expressers. The overall response rate was 5.8% (range 2.1–12.1), with six patients demonstrating partial responses. Among PD-L1 positive patients, the ORR was 6.6% (range 1.8–15.9), compared to 2.9% (range 0.1–15.3) in PD-L1 non-expressers. When comparing median OS for patients with PD-L1 CPS = 1 versus < 1, the results were 7.2 months (range 5.3–11.0) versus 9.6 months (range 5.4–12.8), respectively. Overall, 13% of patients experienced grade = 3 AEs [26].

Nivolumab a PD-1 inhibitor has been evaluated in several studies. It has been used as monotherapy in patients with advanced biliary tract cancers who had progressive disease on prior lines of chemotherapy [27]. The evaluated objective response rate (ORR) to nivolumab for unresectable or metastatic BTC who had progressed on more than first line but no more than three lines of systemic therapy was 22% (10/46) and disease control rate (DCR) was 59%. On central independent review response rate dropped to 11% and DCR to 50% (n = 23). The median follow-up was 12.4 months, the median progression free survival was 3.68 months (95% CI, ranges 2.30-5.69 months) and median overall survival was 14.24 months (95% CI, 5.98 months to not reached). Grade 3/4 adverse events (AE) occurred in 17% patients but there was no grade 5 toxicity. Immune mediated AEs occurred in almost half of the patients (n = 28, 52%) most common being elevated AST (n = 11, 20%), increased ALT (n = 9, 17%), loose stools (n = 6, 11%), rashes (n=5, 9%), infusion-related reaction (n=4, 7%]), and pruritus (n=4, 7%]. The toxicity was manageable, similar to previous studies with immunotherapies, and did not include any unexpected toxicity. However other studies evaluating role of durvalumab and nivolumab as monotherapy had different results. Objective response rate (ORR) was 4.8% with durvalumab and 3.3% with nivolumab monotherapy [28, 29].

Checkpoint Inhibitors Combinations

A promising approach to improve tumor response is combining anti-PD-1/PD-L1 therapies with CTLA-4 inhibitors, a strategy that has demonstrated clinical benefits in other cancer types [30-32]. In the CA209-538 trial, a phase 2, nonrandomized study, patients with advanced biliary tract cancers received four doses of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) every three weeks [33]. This was followed by a maintenance dose of nivolumab (3 mg/kg) administered every two weeks for up to 96 weeks or until disease progression or unacceptable toxicity occurred. The overall response rate (ORR) was 23% (n = 9), with a disease control rate (DCR) of 44% (n = 17). Median progression-free survival (PFS) was 2.9 months (95% CI, 2.2–4.6), and overall survival (OS) was 5.7 months (95% CI, 2.7–11.9). Immune-related adverse events occurred in 49% of patients (n = 19), with 15% (n = 6) experiencing grade 3 or 4 events. Another study evaluated combination of durvalumab plus tremelimumab (durvalumab 20 mg/kg every four weeks [Q4W] plus tremelimumab 1 mg/kg Q4W for four doses, followed by durvalumab 20 mg/kg Q4W). ORR was 10.8% in patients of BTC with median DOR of 8.4 months. The median progression free survival was only 1.6 months (95% CI, 1.4–2.8) with a median overall survival of 10.1 months (95% CI, 6.5–11.6). Toxicities were consistent with prior studies, though treatment-related serious AEs were reported in nine (13.8%) patients with BTC. Treatment related grade 3 or more toxicity were reported in 23.1% of patients. The combination therapy of durvalumab plus tremelimumab has acceptable safety profiles consistent with published literature, and also demonstrated clinical benefits [34]. Another study The IMMUNOBIL GERCOR D18-1 PRODIGE-57 evaluated combination of durvalumab (1500

mg Q4 weeks) and tremelimumab (75 mg Q4 weeks X4 cycles) with or without paclitaxel for recurrent and advanced platinum failed BTCs [35]. Due to dose limiting toxicity paclitaxel arm was closed early. The interim analysis shows ORR of 9.7% (including 2 complete responses) and a disease control rate of 40.8% and the median progression free survival was 2.5 months and median overall survival was 8.0 months. These combinations did not yield a profound benefit and needed further exploration.

Adoptive Cell Therapy (ACT)

Types of ACT (TILs, CAR-T Cells) Adoptive cell therapy involves collecting and re-engineering a patient's immune cells to recognize and attack cancer cells. Two main types are Tumor-Infiltrating Lymphocytes (TILs) and Chimeric Antigen Receptor T-cell (CAR-T) therapies. TILs are harvested from tumor samples, expanded ex vivo, and reinfused into patients, while CAR-T cells are genetically engineered T-cells that express a receptor specific to cancer antigens [36].

Challenges and Recent Developments in ACT for BTCs ACT faces significant challenges in BTCs, including the low immunogenicity of tumors and difficulties in targeting specific tumor antigens. Recent advances have focused on engineering CAR-T cells to target specific BTC markers, such as mesothelin and HER2, which have shown preclinical efficacy but limited clinical success thus far due to toxicity and limited efficacy [36]. Research into combining ACT with immune checkpoint inhibitors is ongoing to potentially overcome these barriers.

Cancer Vaccines

Cancer vaccines aim to stimulate the immune system to recognize and target tumor antigens. Peptide-based vaccines use short protein fragments from the tumor to trigger an immune response. Whole-cell vaccines contain inactivated tumor cells, while dendritic cell vaccines involve loading dendritic cells with tumor antigens to boost T-cell responses [37].

Clinical trials investigating cancer vaccines in BTCs are in the early stages. For example, a peptide-based vaccine targeting the WT1 protein, a tumor-associated antigen expressed in BTCs, demonstrated safety and preliminary immune responses in a phase I trial [38]. However, response rates remain low, and further studies are exploring combination strategies with checkpoint inhibitors to improve efficacy.

Oncolytic Viruses

Oncolytic viruses are genetically engineered or naturally occurring viruses that selectively infect and kill cancer cells while sparing normal cells. These viruses can also trigger an immune response against tumor cells by releasing tumor-associated antigens as the infected cells lyse [39]. In BTCs, oncolytic viruses such as engineered adenoviruses and herpes simplex virus (HSV) derivatives have been explored. Early-phase studies have shown that oncolytic viruses can induce immune responses and improve tumor control in some patients with BTCs [40]. However, challenges remain in ensuring selective infection of BTC cells and avoiding off-target effects. Furthermore, the immunosuppressive tumor microenvironment in BTCs can limit the effectiveness of oncolytic viruses, and combining these therapies with checkpoint inhibitors or ACT may help overcome these challenges.

Combination Therapies in BTCs

Checkpoint Inhibitors with Chemotherapy

Combining checkpoint inhibitors with chemotherapy is a promising strategy in BTCs, as chemotherapy can promote immunogenic cell death, releasing tumor antigens that activate immune responses. Additionally, chemotherapy may modulate the tumor microenvironment, potentially increasing tumor cell susceptibility to immune attack [30]. Several preclinical studies have shown synergy between cytotoxic chemotherapy and immunotherapy [41,42].

BilT-01, A phase II study randomised Patients in Arm A with nivolumab along with gemcitabine and cisplatin for 6 months followed by nivolumab and in Arm B patients received nivolumab and ipilimumab. The addition of nivolumab and ipilimumab did not improved PFS compared to conventional chemotherapy while immunotherapy only arm was inferior but there was OS benefit at 2 years in chemoimmunotherapy arm [43]. Another phase II study enrolled 128 patients in three different configurations. In first group 32 patients received chemotherapy followed by chemotherapy plus durvalumab and tremelimumab. In second group 49 patients recieved chemotherapy plus durvalumab and in third group 47 patients received chemotherapy plus durvalumab and tremelimumab. Primary end point of the study was objective response rate. The objective response rates were 50%, 72% and 70% in group 1, 2, and 3 respectively. There was no statistical comparison between the groups. The most common grade 3 and 4 toxicity were neutropenia (53%), decrease haemoglobin (40%) and thrombocytopenia (19%), with no unexpected safety events. No discontinuation of treatment or death occurred due to adverse events. Immunotherapy in combination with Gemcitabine and cisplatin showed promising efficacy with acceptable toxicity in patients with advanced BTC [22]. These excellent results from this study thus laid the foundation for the phase III TOPAZ-1 trial, which adopted the combination of chemotherapy with durvalumab regimen from this trial.

TOPAZ-1 is a phase 3 study (table 02) conducted in unresectable, locally advanced, or metastatic biliary tract cancer. Patients were randomly assigned to 8 cycles of durvalumab plus gemcitabine–

cisplatin combination or placebo plus gemcitabine–cisplatin combination [22]. Patients received gemcitabine-cisplatin plus durvalumab or gemcitabine- cisplatin eight cycles followed by durvalumab or placebo until disease progression or other discontinuation criteria were met. Overall survival was primary end point. Secondary end points were progression-free survival, objective response rate, duration of response, and disease control rate and efficacy by PD-L1 expression. With median follow-up of 16.8 months in the durvalumab group and 15.9 months in placebo group the median OS was 12.8 months (95% CI, 11.1 to 14.0) in the durvalumab arm and 11.5 months (95% CI, 10.1 to 12.5) in the placebo treatment arm (subsequently updated to 12.9 and 11.3 months, (hazard ratio, 0.80; 95% CI, 0.66 to 0.97; P=0.021) respectively. Though the difference is not numerically and clinically significant its usage have been widely recommended in major oncology guidelines. The cost benefit ratio poses a challenge specially in low- and middle-income countries which highlights the need for further optimization of treatment paradigms for BTC. The overall survival hazard ratio was 0.91 (95% CI, 0.66 to 1.26) up to 6 months and 0.74 (95% CI, 0.58 to 0.94) after 6 months. This showed that there was no separation of OS and PFS curves until the 6-month mark, while the subsequent advantage of gemcitabine -cisplatin plus durvalumab persisted thereafter. Median duration of PFS was 7.2 months (95% CI, 6.7 to 7.4) with durvalumab and 5.7 months (95% CI, 5.6 to 6.7) with placebo. The ORR was 26.7% (n=341) and 18.7% (n=343) in the durvalumab and placebo group respectively which is similar to ABC02 trial of gemcitabine-cisplatin arm but lower than phase II studies discussed above. The grade 3 or 4 adverse events were similar in both arm, 75.7% in durvalumab group versus 77.8% in placebo group. anemia, nausea, and neutropenia were the most frequent AE, and they were comparable across treatment groups. In the durvalumab group, the rate of immune-related adverse events was 12.7%, while in the placebo group, it was 4.7%. Similar advantages were observed in both populations when patients with a PD-L1 tumor area positivity of =1% (PD-L1-positive) or <1% (PD-L1-negative) were sub grouped. This indicates that baseline PD-L1 status may not be a reliable biomarker for predicting how well immunotherapy will work. Although adding durvalumab increased OS and PFS, it's unclear if using durvalumab for the first six months of treatment has any therapeutic benefits.

NCT number	TRIAL name	Treatment given	Prim. End point	ORR	OS (mo)	PFS(mo)
NCT03101566	BilT-01	Gem/cis + nivolumab		22.9	10.6	6.6
		Ipilimumab/nivolumab	PFS	3	8.2	3.9
NCT03875235	TOPAZ-1	Gem/cis + durvalumab		26.7	12.8	7.2
		Gem/cis	OS	18.7	11.5	5.7
NCT04003636	KEYNOTE-966	Gem/cis + pembrolizumab		28.7	12.7	6.5
		Gem/cis	OS	28.5	10.9	5.6
ORR- objective response rate, OS- overall survival, PFS- progression free survival, mo- months, DCR- disease control rate, DLT- dose limiting toxicity						

Table 2: Combination of immunotherapy with chemotherapy.

In patients with treatment-naïve metastatic or unresectable BTC, KEYNOTE-966, a randomised, double-blind phase III trial, examined the safety and effectiveness of gemcitabine and cisplatin with or without pembrolizumab, a PD-1 inhibitor [44]. With a median OS of 12.7 months with chemoimmunotherapy compared to 10.9 months in the standard-of-care arm, KEYNOTE-966 achieved its primary end point; the effect was comparable for PD-L1-negative and -positive cases, which were defined as having a CPS of less than 1% or greater than 1%, respectively. Regardless of PD-L1 status, TOPAZ-1 and KEYNOTE-966 together established the importance of immune checkpoint inhibition in conjunction with chemotherapy as a first-line treatment approach for advanced BTCs.

In conclusion, the addition of immunotherapy (durvalumab or pembrolizumab) to conventional first-line chemotherapy has been proven to be beneficial in two phase III trials, encouraging this strategy as the new standard of care. Currently there is no study which directly compared pembrolizumab and durvalumab. Last but not least, more investigation is required on the function of immunotherapy after progression on first-line chemoimmunotherapy.

Checkpoint Inhibitors with Targeted Therapy

Checkpoint inhibitors have also been studied in combination with targeted therapies that inhibit specific oncogenic pathways in BTCs. For instance, fibroblast growth factor receptor (FGFR) inhibitors and isocitrate dehydrogenase (IDH) inhibitors have shown activity in subsets of BTCs with FGFR2 fusions or IDH1 mutations, respectively [45]. The rationale for combining these inhibitors with checkpoint blockade lies in potentially overcoming immune resistance linked to tumor-specific mutations. Trials, such as those investigating pembrolizumab with FGFR inhibitors, are ongoing to evaluate efficacy in patients with specific BTC subtypes [25]. A phase 3 study evaluated patients with advanced, IDH1-mutant cholangiocarcinoma who had progressed on previous therapy and had received at least two regimens [46]. Patients were randomised to receive either ivosidenib (IDH1 inhibitor) or placebo. PFS was 2.7 month with ivosidenib versus 1.4 months in placebo arm. Grade 3/4 toxicity were reported in 30% of patients receiving ivosidenib and 22% of patients receiving placebo. A single arm prospective study evaluated role of triplet therapy [47]. It included patients with local advanced or metastatic BTCs and evaluated standard GemOX plus sintilimab and Lenvatinib (no targetable gene alterations present) or targeted therapy based on next generation sequencing (Olaparib for BRCA1/2 mutation, dasatinib for IDH1/2 mutation, afatinib for EGFR amplification, Lenvatinib for PDGFR and KIT mutation, or FGFR/KIT mutation. ORR was 45.5%, and the disease control rate was 86.4%. treatment related grade 3 or 4 AE were 9.09%. The combination of GemOX plus sintilimab and Lenvatinib or NGS-guided targeted therapy showed promising ORR and DCR. Another study evaluated Apatinib plus Camrelizumab in patients with Previously treated advanced biliary tract cancer [48]. Patients in this study received apatinib orally at 250 mg per a day and camrelizumab intravenously at 200 mg Q3W until disease progression or intolerable adverse events occurred. The DCR was 71.4%, the OS was 13.1 months and the median progression-free survival was 4.4 months. The grade 3 or 4 AEs occurred in 63.6% of patients.

Immunotherapy with Radiation Therapy

Radiation therapy can induce immunogenic cell death, releasing tumor-associated antigens and promoting an anti-tumor immune response. This “abscopal effect,” where localized radiation enhances systemic anti-tumor immunity, has been observed in several cancer types and may be beneficial in BTCs when combined with immunotherapy [49]. Clinical trials are evaluating combinations of immune checkpoint inhibitors with radiation therapy to leverage this immune modulation, especially in patients with limited systemic disease who may benefit from localized treatments. The combination of immunotherapy with radiation therapy was evaluated by Chen et al [50]. They prospectively observed 117 participants with unresectable BTC either at initial diagnosis or at first recurrence. Patients were given either RT + IO or standard of care chemotherapy (gemcitabine plus Cisplatin). Primary end points were OS and DFS. The OS was 17 months in RT/IO vs 11.5 months in chemotherapy arm. DFS was 12.5 vs 7.9 months in RT/IO and chemotherapy group respectively. Adverse events (grade =3 AEs) were higher in the CT group (79.4% vs 7.7%, $P < .001$). RT combined with anti-PD-1 IO may be well tolerated and associated with an improved response rate, DFS, and OS compared with CT alone in patients with unresectable BTC but further research is needed in this field.

Immunotherapy with Anti-VEGF Agents

Rationale and Current Research Outcomes Anti-VEGF agents, such as bevacizumab, inhibit vascular endothelial growth factor (VEGF), which is involved in tumor angiogenesis and immune suppression within the tumor microenvironment. VEGF inhibition may normalize the vasculature, improve immune cell infiltration, and enhance the efficacy of immunotherapies [51]. Combining anti-VEGF agents with checkpoint inhibitors has shown efficacy in several cancers, and research in BTCs, such as the combination of atezolizumab (PD-L1 inhibitor) with bevacizumab, is ongoing to determine whether these therapies can improve clinical outcomes in BTC patients. Lenvatinib plus pembrolizumab combination has been evaluated in patients with previously treated biliary tract cancers [52]. Patients received lenvatinib 20 mg once daily along with pembrolizumab 200 mg every 21 days for up to 35 cycles (approximately 2 years) or until confirmed disease progression,

unacceptable adverse effect. ORR was the primary endpoint. Secondary endpoints was disease control rate. The primary endpoint of objective response rate was 10%, including all partial responses, while the disease control rate was 68%. JVDF phase I study (table 03) evaluated ramucirumab plus pembrolizumab in patients with previously treated advanced or metastatic BTC [53]. Safety and tolerability were primary end point while secondary end points were ORR, PFS, OS. ORR was 4%, median PFS and OS were 1.6 months and 6.4 months, respectively. Most common side effect was hypertension. REGOMUNE is a phase II trial evaluated regorafenib-avelumab combination in patients with biliary tract cancer [54]. The primary end-point was confirmed ORR and the secondary end-points were 1-year non-progression rate; progression-free survival (PFS) and overall survival. ORR was 13.8% and the DCR was 51.7%, median PFS was 2.5 months and median OS was 11.9 months. The most common grade 3 or 4 clinical AEs observed were hypertension (17.6%), fatigue (14.7%) and maculopapular rash (11.8%). The authors concluded that regorafenib combined with avelumab has antitumour activity in a subset of heavily pretreated biliary tract cancer population.

NCT number	TRIAL name	Treatment given	Prim. End point	ORR	OS (mo)	PFS (mo)
NCT04642664.	-	Apatinib plus camrelizumab	ORR	19%	13.1	4.4
NCT02989857.	ClarIDHy	Ivosidenib	PFS	2%	10.8	2.7
NCT03475953	Regume	Regorafenib + avelumab	ORR	13.80%	11.9	2.5
NCT02443324	JVFD	Ramucirumab + pembrolizumab	DLT	3.80%	6.4	1.6
ORR- objective response rate, OS- overall survival, PFS- progression free survival, mo- months, DCR- disease control rate, DLT-dose limiting toxicity						

Table 3: Immunotherapy with targeted and antiangiogenic therapy.

Future Potential for Multi-Modal Combinations

The future of BTC treatment may involve multi-modal combinations, including checkpoint inhibitors, targeted therapies, chemotherapy, radiation, and anti-angiogenic agents. Such combinations aim to address the heterogeneous and often immunosuppressive nature of BTCs more comprehensively. Multi-modal strategies can potentially enhance the immunogenicity of BTCs and offer tailored approaches for patients based on tumor biology and genetic profiles. Ongoing trials are exploring innovative combinations to refine and expand the therapeutic landscape for BTCs [3].

Biomarkers and Predictive Indicators in Immunotherapy for BTCs

PD-L1 Expression:

Programmed death-ligand 1 (PD-L1) expression on tumor cells or immune cells has been associated with response to PD-1/PD-L1 checkpoint inhibitors across several cancer types, including BTCs. While PD-L1 expression is detected in a subset of BTC cases, its predictive value for immunotherapy response remains variable, as not all PD-L1 positive BTCs respond to checkpoint inhibition [55]. Studies suggest that PD-L1 expression could serve as a preliminary screening tool for potential responders in BTC immunotherapy, although its utility as a standalone marker is limited.

Microsatellite Instability (MSI):

MSI-high status is characterized by defects in the DNA mismatch repair system, leading to high mutational loads and potential neoantigen formation that can stimulate immune responses. In BTCs, MSI-high status is relatively rare but has been associated with improved responses to PD-1 inhibitors, such as pembrolizumab, in select cases [56]. Consequently, MSI testing is often considered for BTC patients when evaluating eligibility for immunotherapy, as it can indicate likely benefit from PD-1 blockade.

Tumor Mutation Burden (TMB):

High TMB, which correlates with neoantigen burden, has shown predictive value in various cancers for response to checkpoint inhibitors. In BTCs, however, TMB is typically low, which may partially account for the modest response rates to immunotherapy [19]. Still, emerging studies suggest that BTC cases with higher TMB may be more responsive to immunotherapy, and TMB testing could help identify such cases.

Emerging Biomarkers and Their Implications

Tumor-Infiltrating Lymphocytes (TILs):

The presence and density of TILs in the tumor microenvironment has been linked with immunotherapy response, as they may indicate an active immune response against the tumor. Studies show that higher TIL levels in BTCs are associated with improved survival and potential responsiveness to checkpoint inhibitors. Further research is needed to validate TILs as a predictive biomarker, but they represent a promising indicator of BTC immunogenicity.

FGFR2 Fusions and IDH1 Mutations:

Specific genetic alterations, such as FGFR2 fusions and IDH1 mutations, common in subsets of BTCs, have potential implications for immunotherapy. For instance, FGFR2 fusions may contribute to an immunosuppressive tumour environment, and ongoing studies are examining whether targeting these mutations in combination with immunotherapy could enhance treatment outcomes [57]. IDH1 mutations may similarly impact immune pathways and are the subject of current research to evaluate their predictive value.

Inflammatory Markers and Cytokine Profiles:

Circulating inflammatory markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP), are being explored for their potential to predict immunotherapy response. In BTCs, elevated levels of certain cytokines have been associated with poor prognosis but may provide insights into immunotherapy responsiveness [58]. As research progresses, integrating cytokine profiles with other biomarkers could improve patient stratification.

Challenges in Identifying Reliable Predictive Markers for BTC Patients

Identifying reliable predictive biomarkers for BTC immunotherapy remains challenging due to the cancer's molecular heterogeneity and generally low immunogenicity. While current markers like PD-L1, MSI, and TMB offer some predictive insights, they often lack specificity and sensitivity in BTCs, leading to variability in treatment responses. Additionally, emerging biomarkers require rigorous validation across larger BTC cohorts to confirm their utility.

Another challenge is the limited availability of tissue samples in BTCs, which complicates comprehensive biomarker analysis. Liquid biopsy approaches, which analyze circulating tumor DNA or immune cells in the blood, offer a minimally invasive alternative but are still under development and need further standardization [44]. Finally, the dynamic nature of the immune response and tumor evolution in BTCs necessitates serial biomarker assessments to optimize predictive accuracy over time, a complex and resource-intensive requirement in clinical practice.

Challenges and Limitations of Immunotherapy in BTCs

Intrinsic Resistance and Low Immunogenicity of BTCs

Biliary tract cancers (BTCs) are characterized by low immunogenicity, partly due to their generally low tumor mutation burden (TMB), which limits neoantigen presentation and reduces immune system recognition [19]. This intrinsic resistance presents a significant barrier to effective immunotherapy. Additionally, the immunosuppressive tumor microenvironment (TME) in BTCs, often enriched with regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), further hinders immune response activation [59]. The combination of low TMB and an immunosuppressive TME leads to limited efficacy of checkpoint inhibitors in many BTC patients, prompting ongoing research to find methods to enhance the immunogenicity of BTCs.

Heterogeneity within BTC Subtypes Impacting Therapy Response

BTCs comprise a heterogeneous group of cancers, including intrahepatic, perihilar, distal cholangiocarcinoma, and gallbladder cancer, each with distinct molecular and genetic profiles [2]. This heterogeneity influences treatment response, as mutations, such as FGFR2 fusions and IDH1/2 mutations, are present in specific subtypes and may affect the efficacy of immunotherapy. Consequently, response rates to immunotherapy vary across BTC subtypes, complicating the ability to generalize treatment approaches [44]. Tailoring immunotherapy based on molecular subtypes and predictive biomarkers is essential, yet these differences within BTCs make it challenging to develop a universally effective treatment strategy.

Financial Burden and Accessibility in Different Healthcare Settings

Immunotherapy is often expensive, creating a substantial financial burden for patients and healthcare systems. Many BTC patients require long-term treatment, further increasing costs. In low- and middle-income countries, where BTC incidence is often higher, financial barriers limit access to these therapies, making it difficult for patients to benefit from the latest advancements [3]. Furthermore, the cost of biomarker testing, essential for identifying suitable candidates for immunotherapy, adds to the financial strain. Ensuring wider access to affordable immunotherapy and companion diagnostics remains a significant challenge in global healthcare, particularly in resource-limited settings.

Future Directions in Immunotherapy for BTCs

Exploration of New Immunotherapy Agents and Combination Strategies

As BTCs exhibit intrinsic resistance to monotherapy with immune checkpoint inhibitors, future efforts are focused on developing novel agents and combination strategies to improve efficacy. Combining immunotherapies, such as PD-1/PD-L1 inhibitors with new checkpoint targets (e.g., LAG-3, TIGIT), or integrating with traditional modalities like chemotherapy, targeted therapy, or radiation, is being explored to enhance anti-tumor immune responses [60]. Ongoing trials are also investigating the efficacy of agents like bispecific antibodies and immune-stimulating cytokines in BTC, aiming to bypass immune resistance mechanisms and increase treatment responses.

Development of Personalized Immunotherapy Approaches Based on Genetic and Molecular Profiling

Personalized medicine has the potential to transform BTC treatment by tailoring therapies to the unique genetic and molecular profiles of each patient's tumor. Advances in genomic sequencing and biomarker identification allow for the selection of patients likely to respond to specific immunotherapies based on mutations, such as FGFR2 fusions or IDH1 mutations [44]. Future strategies may incorporate multi-omic profiling to understand the complex interaction between tumor genomics, immune responses, and therapeutic responses, allowing clinicians to optimize immunotherapy combinations and predict outcomes more accurately [3].

Potential for Microbiome Modulation in Enhancing Immune Response

Emerging research suggests that the gut microbiome can influence the efficacy of immunotherapies, including checkpoint inhibitors, by modulating systemic immune responses. Alterations in gut microbiota composition have been linked to response variability in cancer immunotherapy, and studies are now exploring the potential of microbiome modulation through diet, prebiotics, or probiotics to enhance immune responses in BTC patients [60]. While these approaches are still in the experimental phase, the microbiome represents a promising avenue to potentially improve immunotherapy outcomes by enhancing immune activation and reducing immunosuppression.

Leveraging Artificial Intelligence in Predicting Patient Response to Immunotherapy

Artificial intelligence (AI) is increasingly utilized in oncology to analyse complex data and predict treatment responses. In BTCs, AI algorithms could help integrate diverse data sources such as genomic profiles, biomarker levels, imaging findings, and clinical histories to predict which patients are most likely to respond to specific immunotherapies [60]. Machine learning models can assist in biomarker discovery, outcome prediction, and treatment optimization, paving the way for more precise and effective use of immunotherapies in BTCs. This approach could improve patient stratification, minimize unnecessary side effects, and reduce healthcare costs by identifying the most effective therapies for each individual.

Conclusions

Immunotherapy for biliary tract cancers (BTCs) has seen significant advancements, particularly with the introduction of checkpoint inhibitors like PD-1/PD-L1 inhibitors, which have demonstrated promising responses in some BTC patients. While these therapies alone have shown limited efficacy due to the low immunogenicity and intrinsic resistance of BTCs, combination strategies-integrating checkpoint inhibitors with chemotherapy, targeted therapy, radiation, and anti-angiogenic agents-are offering new avenues to enhance treatment responses. Current research is also identifying potential biomarkers, such as PD-L1, MSI status, and TMB, to better select patients who are likely to respond to immunotherapy, while emerging insights into tumor genetics and the microbiome may further refine these approaches.

Looking ahead, the future of BTC immunotherapy lies in the development of personalized treatment strategies. Advances in genetic and molecular profiling, combined with artificial intelligence, hold promise for tailoring immunotherapy based on individual tumor characteristics, improving both response rates and patient outcomes. Additionally, the potential for microbiome modulation and innovative multi-modal approaches highlights the expanding landscape of immunotherapy in BTC treatment.

Despite these advances, there remains an urgent need for further research to optimize immunotherapy approaches and to address the unique challenges of BTC, including tumor heterogeneity, immunosuppressive microenvironments, and adverse effects. Continued clinical trials and translational research will be essential to overcome these obstacles and to provide BTC patients with more effective, accessible, and durable treatment options. Through these efforts, the goal is to ultimately improve survival rates and quality of life for individuals affected by this challenging disease.

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