

Development and challenges in the treatment of advanced gallbladder cancer (Review)

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Abstract. Gallbladder cancer (GBC) is a highly lethal disease and the most common cancer of the biliary tract. Numerous patients are diagnosed at an advanced stage, limiting surgical options and necessitating local or systemic treatment. Despite advancements in cancer treatment, 5-year survival rates remain low. Various therapeutic methods are available for the treatment of advanced GBC, including local therapy, chemo-radiotherapy, immunotherapy and targeted therapy. Although these treatments offer hope and broader prospects for patients, challenges persist. Through a systematic review of the literature from PubMed and Web of Science over the past decade, a summary and analysis of treatment trends, existing challenges and the latest research developments in advanced GBC were provided.

Contents

1. Introduction
2. Local treatment
3. Chemotherapy and radioembolization
4. Targeted therapy and immunotherapy
5. Adoptive immunotherapy
6. Tumor vaccine
7. Palliative treatment
8. Challenges and future prospects

1. Introduction

Gallbladder cancer (GBC) is a highly lethal disease and the most common malignancy of the biliary tract (1-3). The highest

incidence rates are observed in Chile and India, followed by Eastern Europe, Pakistan and Japan (4). In the United States, >1,000 new cases of GBC are diagnosed annually, with a mean age at diagnosis of 71 years (5). Women account for ~70% of GBC cases, with a female-to-male ratio of 2.41:1 (6). GBC is characterized by aggressive behavior, including local invasion, early lymph node metastasis and frequent distant metastasis. The initial stages of GBC are asymptomatic, leading to diagnoses at advanced stages (1,7,8). The median survival time is <1 year and the overall survival (OS) rate ranges from 17.8 to 21.7% (9). Although notable advancements have been made in the treatment of advanced GBC in recent years, their impact on patient prognosis remains limited. The present study aims to provide a comprehensive review of the latest treatment strategies and research progress in the management of advanced GBC.

2. Local treatment

Local therapies have proven effectiveness in prolonging patient survival and enhancing quality of life in advanced GBC. Transarterial hepatic embolization, transarterial chemoembolization (TACE), drug-eluting bead TACE (DEB-TACE) and hepatic arterial infusion chemotherapy (HAIC) have been well documented in the treatment of advanced GBC (10-12). These treatments selectively block the tumor arterial blood supply using various embolic agents, with or without local chemotherapeutic agents (13). In the literature, the most common adverse events of vascular interventional therapy included post-embolization syndrome, characterized by abdominal pain, fever and intestinal obstruction (14). Additionally, some cases of GBC were poorly responsive to treatment. A meta-analysis of different transarterial chemotherapy methods, such as TACE, HAIC and DEB-TACE, demonstrated an OS time of 15.7 months from the time of diagnosis. These findings suggest that transarterial chemotherapy-based treatment for cholangiocarcinoma (including GBC) is safe, well-tolerated and results in a survival benefit of 2-7 months compared with systemic treatments (15).

Other local treatment options for GBC include endoscopic radiofrequency ablation (RFA), radiotherapy (RT) and endoscopic photodynamic therapy (PDT) (16,17). RFA is increasingly being utilized for local tumor control (18). Biliary tract cancers (BTCs) (including GBC) may need higher doses in order to achieve better local control and maybe also a

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survival benefit, compared to other solid tumors. Concepts for safer dose escalation include the use of stereotactic body RT (SBRT), brachytherapy or proton beam RT (19-21). SBRT has been reported as a promising local treatment for cancer, providing effective local control (LC) and prolonging OS time. However, current guidelines recommend TACE as a primary treatment option for patients with early to intermediate-stage cancer, while SBRT is not included as a standard treatment (22). Compared with TACE, SBRT has demonstrated comparable OS time and improved LC across various stages of cancer, ranging from early to advanced stages, without causing serious adverse events. SBRT should be considered an effective treatment option for different stages of gallbladder cancer, as well as a comprehensive assessment of the patient's body. In one study, SBRT led to local control rates ranging from 65 to 100%, with OS time of 11-35.5 months (median, 15 months), in selected patients (23). RT is widely used to treat various cancer types, and while it can effectively control the local spread of GBC, it may not be sufficient on its own. To overcome the limitations of single-modality RT, combination chemotherapy is often administered concurrently.

PDT involves the intravenous injection of a photosensitive agent followed by irradiation with a specific wavelength of light to selectively target cancer cells and modulate the cancer microenvironment (24). However, the efficacy and safety of PDT for advanced GBC have not been fully evaluated. Further research is necessary to assess the role of PDT in combination with other therapies and its potential impact on the tumor microenvironment.

While there are various local treatment options for advanced GBC, each center may have different experiences and preferences with regard to selecting the most appropriate approach. Currently, there is no unified consensus on the optimal local treatment methods for advanced GBC.

3. Chemotherapy and radioembolization

GBC is known for its high rate of malignancy and multidrug resistance. Common chemical drugs used for the treatment of GBC include cisplatin (CDDP), gemcitabine (GEM), 5-fluorouracil (5-FU), epirubicin, oxaliplatin (OXA), S-1, capecitabine and irinotecan (25-28). The results of clinical trials showed that the response rates from combining these chemotherapy drug combinations were still low at 26.1, 15.5, 30.7, 14.3, and 29.8 for GEM + CDDP, GEM, GEM + OXA, 5-FU + folinic acid and GEM + S-1, respectively (29-31). The response rate of GEM + CDDP as a first-line chemotherapy regimen (26.1%) was 10.6% higher than that of GEM alone (15.5%) (29). Chemotherapy response remains suboptimal in patients with advanced GBC, often accompanied by high rates of chemotherapy resistance. Genetic testing of individual cancers that will be matched with known chemotherapy regimens or sensitizers will allow for individualized treatment based on the characteristics of specific tumor genes (32). A comprehensive list of clinical trials focusing on chemotherapy for patients with GBC was obtained from ClinicalTrials.gov and is detailed in Table I.

The GEM + CDDP regimen has served as the standard first-line treatment for GBC for over a decade, as demonstrated in the phase III clinical trial known as ABC-02 (29). However,

owing to the risk of renal dysfunction associated with CDDP, CDDP has been gradually replaced by OXA. A single-arm phase II trial (SWOG S0809), conducted in the United States and published in 2015, enrolled 79 patients with extrahepatic cholangiocarcinoma and GBC. The trial demonstrated the efficacy of adjuvant GEM + capecitabine chemotherapy, followed by capecitabine + RT. The results showed that the 2-year survival rate was 65% (95% CI, 53-74%), with mortality rates of 67 and 60% for R0 and R1 patients, respectively. The median OS time was 35 months (R0, 34 months; R1, 35 months) (33).

Second-line or subsequent systemic therapy regimens for GBC are similar to those employed in other gastrointestinal malignancies, including regimens such as 5-FU + leucovorin + OXA (also known as FOLFOX), 5-FU + leucovorin + irinotecan (also known as FOLFIRI) and nanoliposomal irinotecan + 5-FU + leucovorin (1,34). The 2015 prospective case series reported by Dodagoudar *et al* (35) utilized second-line agents, including folic acid, 5-FU and oxaliplatin (FOLFOX), demonstrating promising responses. The response rate was 24.2% (16/66), the disease control rate was 59.1% (39/66), the median time to progression was 3.9 months (95% CI, 3.1-4.7) and the median OS was 7.6 months (95% CI, 6.8-8.2). RT has proven effective for patients with advanced GBC. A Phase 2 clinical trial involving 41 patients with intrahepatic cholangiocarcinoma with selective radiotherapy combined with chemotherapy (cisplatin and gemcitabine) showed a 39% increase in response rate, a median progression-free survival (PFS) of 14 months and a median OS of 22 months (36).

Radioembolization has emerged as a valuable and increasingly utilized treatment option for patients with advanced GBC. Although it is typically offered as a palliative treatment for liver tumors, ongoing advances are broadening the range of treatment options for patients with advanced GBC and offer a promising avenue for future research and clinical applications.

4. Targeted therapy and immunotherapy

Advanced sequencing technologies, such as next-generation sequencing (NGS), whole exome sequencing, RNA sequencing and single-cell analysis, have enabled the identification of genetic and epigenetic features, as well as key molecules that could serve as potential therapeutic targets for GBC (37-39). Kuipers *et al* (40) found that tumor protein p53 (TP53; ~57%), sonic hedgehog signaling molecule (~20%), E74-like ETS transcription factor 3 (~18.6%) and AT-rich interaction domain 1A (~14%) are among the most commonly mutated genes in GBC. Additionally, mothers against DPP homolog 4 (~13.1%), epidermal growth factor receptor (EGFR; also known as HER1/ERBB1; ~12%), erb-b2 receptor tyrosine kinase 2 (ERBB2; also known as HER2/NEU; ~10%), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (~14.6%) and KRAS proto-oncogene GTPase (KRAS; ~10.3%) were also identified (41-44). Ongoing clinical trials investigating targeted therapies and immunotherapy options for patients with GBC are summarized in Table II (45-48).

TP53. Mutations in the TP53 tumor suppressor gene are present in ~50% of all human cancer cases. TP53 acts as a transcription factor that directly regulates the expression of ~500 genes and blocks their tumor suppressive functions

Table I. Clinical trials of chemotherapy including GBC obtained from ClinicalTrials.gov.

NCT number	Year	Study phase	Condition	Study size, n	Treatment agents	Primary end point	Status
NCT02867865	2016-2027	II/III	GBC	314	RT + Gem + Cis vs. Gem + Cis	OS	Recruitment
NCT03473574	2018-2022	II	BTC (GBC)	128	Durvalumab + tremelimumab + Gem/Gem + Cis vs. Gem + Cis	ORR	None
NCT04362449	2019-2023	II	BTC (GBC)	30	Gem + Cis	OS	Recruitment
NCT05919095	2023-2025	II	GBC	37	Carrilizumab + GEMOX	OS, PFS	Recruitment
NCT05493956	2019-2023	III	GBC	120	Gem + Cis vs. Gem + Cis + CTRT	OS	Recruitment
NCT03768414	2019-2024	III	BTC (GBC)	452	Gem + Cis + nab-paclitaxel vs. Gem + Cis	OS	Recruitment
NCT04856761	2020-2024	II	BTC (GBC)	160	Capecitabine + S-1	PFS	Recruitment
NCT01470443	2011-2020	III	BTC (GBC)	240	GEMOX vs. XELOX	PFS	None
NCT05506943	2023-2024	II/III	BTC (GBC)	150	CTX-009 + paclitaxel vs. paclitaxel	ORR	Recruitment

NCT, National Clinical Trial; BTC, biliary tract cancer; Cis, cisplatin; GBC, gallbladder cancer; Gem, gemcitabine; GEMOX, gemcitabine plus oxaliplatin; XELOX, capecitabine plus oxaliplatin; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; RT, radiotherapy.

Table II. Main clinical trials of targeted therapy for gallbladder cancer.

NCT ID or first author, year	Year	Phase	Targeted therapy	Treatment regimens	Primary end point	Status	(Refs.)
NCT05512377	2022-	II	TP53	Brigimadlin (BI 907828)	None	Ongoing	-
Kim <i>et al</i> , 2020	2014-2017	II	EGFR and VEGF pathways	Regorafenib	OS, 6.7 months	Complete	(45)
Lee <i>et al</i> , 2023	2020-2023	II	ERBB2 (human/neu)	Trastuzumab + FOLFOX	ORR, 29.4% (95% CI, 16.7-46.3)	Complete	(46)
Costello <i>et al</i> , 2014	2009-2012	I	PI3K/AKT/mTOR pathway	Gemcitabine and cisplatin	CR, 2 (7.4%); PR, 3 (11.1%)	Complete	(47)
Bekaii-Saab <i>et al</i> , 2023	2020-2022	II	KRASG12C	Adagrasib	DOR, 5.3 months (95% CI, 2.8-7.3); PFS, 7.4 months (95% CI, 5.3-8.6)	Complete	(48)

NCT ID, National Clinical Trial identification; OR, objective response; OS, overall survival; ORR, objective response rate; CR, complete response; PR, partial response; DOR, duration of response; PFS, progression-free survival; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; TP53, tumor protein p53; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; ERBB2, erb-b2 receptor tyrosine kinase 2; KRAS, KRAS proto-oncogene GTPase.

by preventing them from binding to target DNA sequences. TP53 also upregulates genes involved in cellular processes, such as apoptosis, cell cycle arrest and senescence, which are key mechanisms that prevent tumorigenesis (49-51). The frequency of TP53 mutations varies notably across different tumor types. TP53 mutations are present in >90% of ovarian cancer cases, whereas <15% of cases of acute myeloid leukemia exhibit TP53 mutations. This disparity suggests the possibility of tissue-specific factors influencing the loss of

wild-type TP53 function or the gain of function in mutated p53 (52). The expression and accumulation levels of p53 increase from precancerous lesions (dysplasia) to aggressive GBC (53-55). Detection of p53 protein upregulation can be a valuable diagnostic tool for accurate cancer identification. Stancu *et al* (56) found that p53 is upregulated in 30% of papillary regions, 30-50% of undifferentiated adenocarcinomas and 80-100% of highly differentiated adenocarcinomas, particularly in the context of chronic cholecystitis (56). In

general, TP53 represents a promising therapeutic target, and with the advancement of p53-targeted therapies, personalized treatment plans based on specific p53 mutations are becoming increasingly feasible.

A phase IIa/IIb, open-label, single-arm, multicenter trial of brigimadlin (BI 907828) is currently ongoing in patients with locally advanced/metastatic, mouse double minute 2-amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma and other selected solid tumors. The study aims to assess the efficacy of BI 907828 in treating cancers affecting the biliary tract, pancreas, lungs or bladder (57).

TP53 mutations have significant effects on several aspects of the immune system; they can promote immune evasion and cancer progression by regulating exosomes, growth factors, cytokines and chemokines (58). These mutations can alter the immune recognition of tumor cells and, through mechanisms such as reduced infiltration, decrease the cytotoxicity and activity of immune cells, thereby promoting the recruitment of immune-suppressive cells (59,60).

EGFR and vascular endothelial growth factor (VEGF) pathways. Both EGFR and VEGFR activate signaling pathways that regulate cell growth and proliferation (9,61). Additionally, the simultaneous inhibition of both EGFR and VEGFR may enhance antitumor effects (62). Studies on GBC have shown that overexpression of VEGF-A plays a crucial role in angiogenesis and serves as an independent prognostic factor associated with reduced survival (63). VEGF overexpression in GBC cells promotes angiogenesis, cell proliferation and metastasis (64,65). Up to 48% of patients with GBC exhibit elevated VEGF-A expression, potentially benefiting from anti-angiogenic drugs (63). Research has proved the efficacy of drugs targeting tumor angiogenesis via the VEGF/VEGFR pathway (66,67).

Bevacizumab is a humanized monoclonal antibody targeting VEGFA, while ramucirumab regulates VEGFR-2 specifically (68). Regorafenib, a novel oral multikinase inhibitor, blocks various vasogenic and stromal receptor tyrosine kinases (FGFR1, PDGFR-OMAN, TIE2, VEGFR1, VEGFR2 and VEGFR3) and downstream cellular signaling pathways (RAS/LUR/MEK/ERK and PI3K/PTEN/AKT) (69-71). In a multi-center, open-label, single-arm phase 2 trial evaluating regorafenib efficacy in refractory BTC, 33 patients treated for at least 3 weeks. The results showed a median PFS time of 3.9 months and an OS time of 6.7 months. The target response rate was 9.1%, with a disease control rate of 63.6% (45).

ERBB2. The receptor tyrosine protein kinase ERBB2, also known as HER2, is a member of the receptor tyrosine kinase EGFR family. Heterodimerization of this receptor with other members of the EGFR family leads to the self-phosphorylation of tyrosine residues in the heterodimeric cytoplasmic domain and initiates multiple signaling pathways, leading to cell proliferation and tumorigenesis (72). ERBB2 upregulation has been observed in several solid tumors, such as breast cancer, gastroesophageal junction cancer and BTC (73-77). Nam *et al* (78) found that in patients with gallbladder cancer ($N=21$), the proportion of HER2-positive disease was 28.6%.

A phase 2 clinical trial, which was investigator-initiated, open-label, non-randomized and multi-institutional, evaluated the efficacy of treatment in patients aged ≥ 19 years with ERBB2-positive BTC (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and GBC) that had progressed despite GEM and CDDP chemotherapy (79). The trial reported an overall response rate of 29.4% (95% CI, 16.7-46.3) and a disease control rate of 79.4% (95% CI, 62.9-89.9). The median PFS time was 5.1 months (95% CI, 3.6-6.7), while the median OS time was 10.7 months (95% CI, 7.9-not reached) (46).

PI3K/AKT/mTOR pathway. The PI3K-AKT-mTOR signaling pathway is a critical pathway involved in drug resistance and malignant processes in patients with solid cancer, with dysregulation potentially leading to various human cancers (79-82). This pathway is increasingly being recognized as a promising target in cancer and related diseases, such as hepatocellular carcinoma and colon cancer (83). Abnormal activation of the PI3K-AKT-mTOR pathway has been observed in GBC and in other malignancies, such as prostate, breast and endometrial cancer (42). Activation of this pathway promotes increased cell proliferation and growth, and plays a key role in angiogenesis. The pathway is also involved in numerous cellular processes, including proliferation, invasion, migration, apoptosis and metabolism (84-86). Targeting the PI3K/AKT-mTOR pathway in combination with chemotherapy or other targeted therapies can help inhibit tumor progression (87).

In a phase I trial, a chemotherapy regimen combining everolimus, an mTOR inhibitor, with GEM and CDDP resulted in stable disease in 6 out of 10 patients with BTC, suggesting a potential therapeutic benefit (47).

KRAS. KRAS, a member of the RAS oncogene family, was first identified in the 1980's by Barbacid (88) in a human bladder cancer cell line. This gene, also known as HRAS, is a homolog located on chromosome 11 (11p15.1-11p15.3) (88). KRAS is the best-known oncogene, the most common driver of numerous cancer types, with relatively high mutation rates in various cancers, such as non-small cell lung cancer, colorectal cancer and pancreatic ductal adenocarcinoma (89,90). Numerous studies have demonstrated the biochemical heterogeneity of KRAS mutations across various aspects, including intrinsic GTPase activity and affinities for effectors and binding sites. For instance, alterations in codons 12, 13 and 61 typically result in impaired intrinsic GTPase activity in KRAS, unlike the mutations KRAS G12D, KRAS G12C and KRAS G13D (91,92). The simultaneous activation of KRAS and the typical Wnt pathway induces BTC (93). Initial clinical reports for KRASG12C-mutated BTC showed a limited clinical response to sotorasib and GDC-6036 (48), and secondary mutations in the KRAS gene conferred acquired resistance to KRASG12C inhibitors. A phase II cohort of the KRYSTAL-1 study (ClinicalTrials.gov identifier: NCT03785249) was begun to evaluate adagrasib (600 mg orally twice daily) in patients with KRASG12C-mutated advanced solid tumors (excluding non-small cell lung cancer and colorectal cancer). As of October 1, 2022, 64 patients with KRASG12C-mutated solid tumors were enrolled and 63 patients treated (median follow-up, 16.8 months). Among 57 patients with measurable disease at

baseline, the median duration of response was 5.3 months (95% CI, 2.8-7.3) and the median PFS time was 7.4 months (95% CI, 5.3-8.6) (48). KRAS mutant tumors exhibit significant heterogeneity, highlighting the urgent need for selective inhibitors that target specific KRAS mutations. Notable progress has been made in targeting KRAS, particularly KRASG12C. New approaches, including NMR-based fragment screening, drug teaming and computational drug design, have been employed to discover novel compounds that bind directly to KRAS (92). However, achieving effective KRAS targeting is still a considerable challenge. Such treatments are essential to effectively inhibit the function of various KRAS mutants, aligning with the goals of precision oncology (92).

Immune checkpoint inhibitors. Chemotherapy primarily delays tumor growth by inhibiting DNA replication, blocking the cell cycle and interfering with cellular metabolism (94). Additionally, some cytotoxic chemotherapy agents, such as anthracyclines and OXA, can induce immunogenic cell death and stimulate antitumor immune responses (95,96). Therefore, for chemotherapy-based immunotherapy with antibodies targeting programmed cell death protein 1/programmed death ligand 1 (anti-PD-1/PD-L1) may serve as a suitable partner to enhance the ability of chemotherapy to control tumor growth (97).

Currently, the common immune checkpoints of GBC include PD-1/PD-L1 and cytotoxic T-lymphocyte protein 4 (CTLA-4), and monoclonal antibodies targeting these targets have also been tested in clinical trials (98-100). PD-1 serves as a well-known immunosuppressive checkpoint, whereas PD-L1 acts as its ligand (101). PD-L1 is a biomarker for patient prognosis and susceptibility to PD-1/PD-L1 inhibitors. PD-L1 is expressed mainly in tumor cells, tumor-infiltrating cells and antigen-presenting cells in a number of cancer types, such as breast and bone cancer (102). Numerous studies have affirmed the clinical importance of PD-1/PD-L1 antibodies in influencing the prognosis of human cancer (97,103-105). Based on the immense success of clinical trials, ten anti-PD-1 antibodies (nivolumab, pembrolizumab, cemiplimab, sintilimab, camrelizumab, toripalimab, tislelizumab, zimberelimab, prolgolimab and dostarlimab) and three anti-PD-L1 antibodies (atezolizumab, durvalumab and avelumab) have been approved for the treatment of various types of cancer, including pancreatic and gastric cancer (106).

A multicenter phase II study involving 54 patients assessed the effectiveness and safety of nivolumab monotherapy in patients with advanced cholangiocarcinoma who had undergone first to third-line treatment. The study found that PD-L1 upregulation was significantly associated with worse OS times (hazard ratio, 1.58; 95% CI, 1.30-1.92; $P < 0.001$) (107). However, serious challenges remain, such as limited beneficiaries, high drug resistance, lack of predictive and prognostic biomarkers, and treatment-related adverse reactions (108). Moreover, few predictive biomarkers can identify the types of patients who will benefit from treatment (109). Nevertheless, PD-1/PD-L1 immune checkpoint inhibitors have wide application prospects and clinical value for the treatment of cancer in humans.

CTLA-4, a receptor found on activated T cells, has been the focus of numerous clinical trials on combination therapies. The use of both CTLA-4 and PD-1 inhibitors has shown

effectiveness in enhancing the response rates and survival of patients with various cancer types, including pancreatic and gastric cancer (110,111). However, combination therapy may also increase the risk of adverse events (112). A recent phase I clinical trial (NCT01938612) revealed that treatment with durvalumab and tremelimumab in patients with BTC led to a median OS time of 10.1 months (95% CI, 6.5-11.6) compared with 8.1 months (95% CI, 5.6-10.1) in patients with durvalumab monotherapy (113).

5. Adoptive immunotherapy

Immunotherapy has recently revolutionized cancer treatment and constitutes the fourth cornerstone of cancer therapy following surgery, RT and chemotherapy. To date, >700 clinical trials of CAR-T therapy have been registered at clinicaltrials.gov, with a number focusing on solid tumors. CAR-T cell immunotherapy has achieved marked success in the treatment of hematological malignancies. However, only six chimeric antigen receptor T-cell (CAR-T) cell products approved by the US Food and Drug Administration (FDA) for the treatment of R/R B cell malignancies, including tisagenlecleucel (Kymriah; Novartis), axicabtagene ciloleucel (Yescarta; Gilead), brexucabtagene autoleucel (Tecartus; Gilead), lisocabtagene maraleucel (Breyanzi; Bristol Myers Squibb), idecabtagene vicleucel (Abecma; Bristol Myers Squibb and Bluebird Bio), and ciltacabtagene autoleucel (Carvykti; Legend and Janssen) (114). There are currently six commercial CAR-T products that have been FDA approved for diseases such as B-acute lymphoblastic leukemia, large B-cell lymphoma, mantle cell lymphoma (MCL), follicular lymphoma, multiple myeloma and chronic lymphocytic leukemia/small lymphocytic lymphoma (115). In a single-arm, open-label, first-in-human phase I pilot study (NCT03159819), patients aged 18-70 years with confirmed CLDN18.2-positive advanced gastric or pancreatic cancer received one or more cycles of CAR-CLDN18.2 T cell infusion following lymphocyte pretreatment, until disease progression or the onset of intolerable toxicity. At a median follow-up of 14.3 months after infusion, the estimates for 6- and 12-month PFS rates were 69% (95% CI, 61-75) and 59% (95% CI, 51-66), respectively (116). Brexucabtagene autoleucel (brexu-cel) is an autologous CD19-directed CAR T-cell therapy approved for relapsed/refractory MCL. Patients who underwent leukapheresis between August 1, 2020, and December 31, 2021, at 16 US institutions, with an intent to manufacture commercial brexu-cel for relapsed/refractory MCL, were included. Of 189 patients who underwent leukapheresis, 168 (89%) received brexu-cel infusion. At a median follow-up of 14.3 months after infusion, the estimates for 6- and 12-month PFS rates were 69% (95% CI, 61-75) and 59% (95% CI, 51-66), respectively (117). However, due to the complexity of solid tumors and their unique anatomical locations, treating solid tumors with CAR-T cells presents numerous challenges, such as the lack of cancer-specific antigens, inefficient transport and migration of CAR-T cells to the tumor site. Consequently, the immunosuppressive tumor microenvironment (TME) and CAR-T therapy for solid tumors remain underdeveloped (114,118,119). As a result, CAR-T therapy for solid tumors is still in its developmental stages (120). However, clinical studies have

demonstrated promising antitumor efficacy of CAR-T therapy, and the potential remains.

In recent years, various strategies have been developed to enhance the efficacy and safety of CAR-T cell therapies for solid tumors, primarily by addressing challenges posed by the unique characteristics of T cells and the TME. Companion diagnostics, such as immunohistochemistry and circulating tumor cell detection assays, can play a crucial role in improving the treatment of solid tumors with CAR-T cells (121).

6. Tumor vaccine

There are four types of cancer vaccines: Tumor- or immune cell-based vaccines, peptide-based vaccines, viral vector-based vaccines and nucleic acid-based vaccines (122). Vaccines based on nucleic acids (DNA or RNA) show great promise. mRNA cancer vaccines stand out due to their efficiency, safe management, rapid development potential and cost-effectiveness. Clinical trials have demonstrated positive results for over two dozen mRNA-based immunotherapies in treating solid tumors. Notably, a 3-year phase 1 follow-up from BioNTech's neoantigen individualized mRNA vaccine [autogene cevumeran (BNT122, RO7198457)] clinical study for patients after complete resection of pancreatic ductal adenocarcinoma has shown promising results (123).

Cancer vaccines are an effective treatment option as they stimulate a durable immune response that targets and eliminates tumor cells. However, the complexity of the immune system makes the development of effective cancer vaccines challenging. In particular, the heterogeneity of solid tumors may require different vaccinations. With the promising results from multiple clinical trials involving mRNA cancer vaccines against aggressive solid tumors, rapid advancements in mRNA vaccine technology can be anticipated for cancer immunotherapy in the near future (124).

7. Palliative treatment

The goal of palliative care for patients with GBC is to ensure unobstructed biliary drainage and provide nutritional support. Biliary drainage can be achieved using percutaneous catheterization or endoscopic biliary stenting to alleviate biliary obstruction, relieve liver cholestasis and enhance liver function. A multicenter retrospective analysis was performed of all cases of consecutive endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) with lumen-apposing metal stents (LAMSs) used as a rescue treatment for patients with distal malignant biliary obstruction (DMBO) in 14 Italian centers between June 2015 and June 2020. The study showed that EUS-GBD with LAMSs used as a rescue treatment for patients affected by DMBO represents a valuable option in terms of technical and clinical success rates, with an acceptable adverse event rate (5 patients; 10.4%) (125).

Tumors often compress the stomach or duodenum. In situations where the tumor compresses the stomach or duodenum, various interventions, such as nasoenteral nutrition tubes, gastrojejunal bypass therapy and peripheral nutrition support, can be employed to improve the patient's nutritional status (126). In addition to prolonging life, effective relief

of symptoms is also of utmost importance for two reasons: i) Relief of physical suffering is desirable and can improve quality of life; and ii) effective symptom control translates into improved existential well-being (127). As advanced tumors often involve tumor spread or metastasis, a single treatment approach is often insufficient to achieve optimal treatment results. Therefore, palliative care also requires the collaboration of experts from multiple disciplinary fields to develop and implement individualized treatment programs aimed at improving patient outcomes and quality of life (128). At the same time, psychological intervention and symptomatic treatment should be carried out for patients. Psychosocial care for advanced cancer encompasses a wide range of interventions that help patients make life-changing decisions, relieve patient suffering, confront impending mortality and improve other patient outcomes (129). Cancer care guidelines also recommend distress screening for patients with cancer and the provision of psychological support when necessary, although a number of patients decline such support when offered.

Tondorf *et al* (130) conducted a prospective observational study to assess distress, the intention to utilize psycho-oncology support, and the acceptance of psycho-oncology services. Of the 333 patients assessed (mean age, 61 years; 55% male; 54% distress thermometer ≥ 5), 25% intended to use the psycho-oncology service (yes), 33% were ambivalent (maybe) and 42% reported no intention (no). Overall, 23% had attended the psycho-oncology service 4 months later.

8. Challenges and future prospects

The treatment of GBC, the most common malignancy of BTC, has progressed over the past 20 years. However, the treatment of advanced GBC remains challenging due to chemotherapy resistance and tumor heterogeneity due to mutations of genes such as KRAS and TP53. Given the improving understanding of the unique tumor biology of GBC, treatments for advanced GBC have changed markedly. The treatment options are no longer limited to single chemotherapy or local treatment, and the application of combination therapy can improve the prognosis of patients with advanced GBC. NGS of genes, related molecular genetic analysis and biomarker studies will aid the development of effective targets and drugs for GBC therapy, improve patient prognosis and improve therapeutic effectiveness.

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Authors' contributions

GC conceived and designed the study, SRZ carried out the data collection and BZ wrote the manuscript. All authors contributed to the revision of the manuscript and have read and approved the final version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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