PERSPECTIVE

The numerous effects and alterations that targeted therapy has on gallbladder cancer

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ABSTRACT

The rarest and most dangerous type of biliary tract malignancy is Gall Bladder cancer (GBC). Sadly, only a small percentage of cancer patients can successfully undergo surgical resection, the current standard of care; as a result, the high mortality rate has remained constant for years. Due to the development of cutting-edge technological tools (such as next-generation sequencing, transcriptomics, and proteomics), a number of therapeutic strategies—including targeted therapy, immunotherapy, and nanoparticle-based delivery systems—have been vigorously innovated in order to significantly avoid the stagnant scenario. In this review, we largely concentrate on targeted therapies that can effectively block particular critical molecules that control abnormal signalling cascades in GBC. Updated global clinical trials for GBC focused therapy may provide significant benefit for new pathological and therapeutic insights.

Key Words: *Surgical resection; Malignancy; Transcriptomics; Chemotherapy*

INTRODUCTION

The most prevalent malignancy of the biliary tract system and one of the top six gastrointestinal tract neoplasms globally is Gallbladder Cancer (GBC). Although the incidence rate of GBC varies greatly, many locations have a distinctive pattern of distribution, with Chile, India, several other Asian nations, Eastern European nations, and Latin American nations reporting more cases per year than the rest of the world combined. This geographic distribution profile, which is likely related to variations in genetic vulnerability, raises the risk of GBC. The other factors, such as hepatobiliary stones, liver flukes, and Clostridium often found in these locations, which are linked to chronic inflammation and disease pathogenesis, also make up the additional high-risk factors of Bile Tract Cancer (BTC), including GBC 7 In addition to these regionally specific risk factors, numerous universal risk factors have been identified and taken into consideration globally. These include gallstones, gender, age, obesity, reproductive factors, race, primary sclerosis cholangitis, gallbladder polyps, congenital biliary cysts, typhoid, Helicobacter pylori infection, alcohol intake, smoking, fatty liver disease, unhealthy diet, and exposure to specific chemicals in the environment. Since early protection against carcinogenesis has been made mandatory in clinical practice, only 1.2% of all cancers diagnosed globally are caused by this condition.

Chemotherapy, which has been widely utilized in the treatment of a variety of cancers, involves medicines used for non-specific reduction of tumor cell growth typically via blocking of DNA synthesis. The National Comprehensive Cancer Network offers two treatment choices for GBC: a multiagent regimen that combines oxaliplatin, cisplatin, and capecitabine, and single-agent therapy that uses fluoropyrimidine or gemcitabine as its foundation. The combined therapy regimens of FOLFOX (5-Fluorouracil and Oxaliplatin), CAPOX (Capecitabine And Oxaliplatin), GC (Gemcitabine And Cisplatin), and GEMOX (Gemcitabine and Oxaliplatin), still represent the standard chemotherapy programmers in clinical trials, despite the lack of data to define a standard regimen or unambiguous benefit. It is noteworthy that several clinical trials have demonstrated that Fluorouracil, Leucovorin, Irinotecan, and Oxaliplatin (FOLFIRINOX) combination chemotherapy produces positive outcomes in BTC. Since unforeseen reactions such systemic toxicity, inadequate therapeutic responses, and drug resistance were purposefully taken into account, none of the single programmers have, however, been extensively made available. As a result, numerous preclinical and clinical studies are currently making considerable efforts to define the overall benefit of pharmacological treatment—even in the face of antagonistic responses, which can otherwise be controlled at a low level. To examine individual drug sensitivity and

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choose more efficient drugs from combined agent trials for the direction of clinic drug-selective treatment in the patient, for instance, one method is to transplant freshly removed patient tissue of GBC into mice as a Mini Patient-Derived Xenograft (mini-PDX) model. They experimented with irinotecan, nanoparticle albumin-bound nab-paclitaxel, gemcitabine, oxaliplatin, and 5 fluorouracil. and discovered that patients in the PDX-guided chemotherapy group had significantly longer median overall survival.

The idea of specific chemicals that may eradicate some germs in the early 1900s served as the foundation for the development of targeted therapy for cancer in 1988. Since then, a great deal of research has been done on the effectiveness of targeted therapy in treating various cancers to specifically block a number of molecular targets that are closely linked to tumour cell proliferation, differentiation, migration, cancer stemness, vascular angiogenesis, and antitumor immune responses. The majority of the medications developed for targeted therapy are tiny compounds and antibodies that have been vaccinated. Small molecules with a molecular weight of less than 900 Da can easily enter cells to deactivate particular proteins or enzymes, which inhibits the growth of tumour cells, while therapeutic antibodies specifically bind to cell membrane receptors or their ligands to inhibit the growth of tumour cells. either growth or apoptosis. As a result, tumour growth, angiogenesis, and metastasis are inhibited by several medications that target extracellular molecules that promote angiogenesis or immune response in the tumour microenvironment. We updated these targeted therapies on specific signalling pathways, such as the Human Epidermal Growth Factor Receptor 2 (HER2), Growth Factor Receptor Tyrosine Kinases (RTKs) (EGFR), Vascular Endothelial Growth Factor Receptor (VEGFR)), and programmed death receptor 1 (PD-1)/programmed death ligand 1 in light of recent intensive clinical research on a variety of specific agents that intervene intracellular signalling pathways dysfunctional in GBC.

The VEGF/VEGFR axis is crucial for both normal and abnormal vascularization in conditions like tumour angiogenesis. In a mammal, the VEGF family consists of five different members: VEGF-A (commonly known as VEGF), VEGF-B, VEGF-C, VEGF-D, and Placenta Growth Factor (PLGF). The RTK members VEGFR1, VEGFR2, and VEGFR3 as well as the non-tyrosine kinase co-receptors Neuropilin-1 (NP-1) and NP-2 make up the VEGFR family. vascular smooth muscle cells and endothelial cells. The lymphoendothelium-expressed VEGFR3 has a high affinity for VEGF-C and VEGF-D, which promotes lymphangiogenesis.

Numerous cell types, including endothelial, epithelial, inflammatory, and cancerous cells, expressed VEGFR1. Interestingly, VEGFR1 appears to control epithelial cell differentiation and migration but not endothelial cell migration or proliferation. VEGFR1 is known to work in endothelial cells as a pawn to control free VEGF-A by binding to and activating VEGFR2.VEGFR2 is phosphorylated at Tyr951 and Tyr1175 as a result of the interaction of VEGF, with Tyr951 regulating vascular permeability through the activation of SRC tyrosine kinase80 and Tyr1175 recruiting Phospholipase C-(PLC-) and activating downstream of both MAPK cascades.

Endothelial cell proliferation and survival are promoted by the MAPK cascade and PI3K/AKT pathway. Induced by activated VEGFR3, the RAS/MAPK/ERK and PI3K-AKT/PKB pathways promote lymphatic endothelial cell differentiation, migration, proliferation, and survival. It's interesting to note that VEGFR3 has been shown to fenestrate VEGF-A/VEGFR2 signalling and contribute to angiogenesis.

Along with the extensive body of research demonstrating the VEGF-VEGFR axis' regulatory function, the cooperative or independent effects of the axis-associated chemicals on GBC have also been concurrently investigated. For instance, it was discovered that HIF-1 promoted tumour cell motility in GBC by upregulating VEGF-A; metformin prevented this effect. Lymphangiogenesis and lymphatic metastasis of GBC are caused by ERK1/2-AP-1 pathway-dependent transcriptional activation of VEGF-D caused by Tumour Necrosis Factor (TNF). The multifunctional protein receptor-interacting protein 1, which is part of the TNF-signalling system, which was significantly expressed in GBC and stimulated the transcription of VEGF-C by nuclear factor-B, enhanced lymphangiogenesis and lymph node metastasis. In a mouse model of GBC, Dual-Specificity Map Kinase Phosphatase 1 (DUSP1/MKP1) inhibited VEGF expression and prevented angiogenesis. Additionally, miR-1 overexpression in GBC cells reduced VEGF-A mRNA expression.

Since certain anti-angiogenic inhibitors, including as antibodies and small compounds, were regularly used in patients with different types of cancer, these inhibitors have also been used more frequently in clinical settings for GBC patients. Bevacizumab, a VEGF antibody, was combined with gemcitabine and oxaliplatin in an advanced BTC single-arm phase II investigation, which showed that the response rate was 40%, the Median Progression-Free Survival (mPFS) was 7 months, and the Overall Survival (OS) was 12.7 months. A comparable single-arm phase II trial (NCT00356889) in patients with unresectable BTC showed a response rate of 18.4%, mOS of 9.9 months, and Time To Progression (TTP) of 4.4 months when bevacizumab was used with erlotinib but without conventional cytotoxic treatments. In addition, bevacizumab in combination with atrial of multicenter phase II research (NCT01007552), 10.2 months of mOS. A phase II research (NCT02053376) showed promising efficacy of regorafenib (inhibitor of VEGFR1-3) in chemotherapy-refractory advanced/metastatic BTC, with mPFS of 15.6 weeks, mOS of 31.8 weeks, PR of 11%, stable disease of 44%, and disease control rate of 56%. The following adverse responses occurred throughout the course of these clinical trials: hypertension (23%), hyperbilirubinemia (26%), hypophosphatemia (40%), and hand-foot skin reaction (7%). A few trial failure incidents were also recorded. In a non-randomized phase II clinical trial, sorafenib, a multi-kinase inhibitor of VEGFR2/3, B-Raf, PDGFR-, and C-Raf, demonstrated minimal drug efficacy in advanced BTC with an ORR of 2%, a rate of stable disease at 12 weeks of 32.6%, a PFS of 2.3 months (range: 0month-12 months), and a PFS of 2.3 months. and 4.4 months for the mOS (range: 0month–22 months). This study's findings are supported by a multicenter, international phase II study (NCT01082809) that found sunitinib, an inhibitor of several RTKs including VEGFR, to be only moderately effective in treating metastatic BTC patients. The disease control rate was 50.0%, the ORR was 8.9%, and the median TTP was 1.7 months. In a phase II trial, the VEGFR2 antagonist vandetanib monotherapy or chemotherapy combinations failed to significantly improve PFS in advanced BTC (NCT00753675). Furthermore, a phase I trial (NCT02443324) of the completely humanised monoclonal VEGFR2-

targeted IgG antibody ramucirumab revealed an OR rate of 4% and mPFS and mOS of 1.6 months and 6.4 months in advanced BTC, respectively. Ramucirumab's new phase II study in individuals with advanced BTC is comparable. Although the mechanism underlying the divergence between these separate clinical studies on angiogenic blockage is yet unknown, there are a number of probable considerations that could be taken into consideration. First, compared to small-molecule inhibitors, which have a broader binding ability to block many proteins/kinases and may cause off-target events, monoclonal antibodies (such as bevacizumab) often have higher selectivity to bind to single proteins. Second, some forms of individual drug resistance cannot be ignored since they may quickly manifest in some individuals whose treatment-related dynamic changes in the expression of targeted receptors or molecules were not promptly assessed. In addition, the susceptibility to certain blockers should be assessed in relation to the different amounts of VEGF/VEGFR expression and/or polymorphisms in GBC. Lastly, highly longitudinal case-control studies involving sizable cohorts may chemotherapeutic drug uses, and diminished or absent responses abe necessary to prove the advantages of anti-angiogenic blockers. However, the combined regimen including angiogenic-targeted antibodies and additional chemotherapeutic drugs now provides the most effective way to treat GBC. s a result of fast resistance development. Additionally, other possibilities that might normally cooperatively avoid the targeted therapy cannot be overlooked include individual genetic variation, tumour gene alterations, and tumour heterogeneity. The therapeutic effectiveness of intriguing medication candidates as well as any potential negative effects should therefore be carefully considered. Combination targeted therapies that target many critical pathways behind cancer metastasis are highly advised in order to obtain overall benefits as they are believed to produce synergistic efficacy with minimum side effects. Notably, the recently developed tumour models, such as PDX/PDTX and patient-derived organoids, transplanted directly with patient-derived malignancies have offered a great deal of promise.