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Molecular Evaluation of BH3-mimics Inhibitor of Bladder Cancer as Targiting Chemotherapy (Review article)

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ABSTRACT

In Egypt, bladder cancer (BC) is considered the fourth most prevalent type of cancer. Bladder cancer is acknowledged as the seventh cause of mortality due to cancer among men. Researchers identified three different types of BC: squamous cell carcinoma (SCC), urothelial carcinoma (UC), and transitional cell carcinoma (TCC). BC accounts for around 31% of all cancer cases between Egyptian, making it a common form of cancer. Many research investigations have shown a relationship between BC incidence and schistosomiasis prevalence in endemic areas. This relationship includes SCC as well as UC, which is why this cancer is called schistosomal or bilharzial BC. A crucial element of the pro-apoptotic action is the BH3 domain. A class of compounds known as BH3 mimetic compounds has antagonistic effects of the BCL-2 family members, with anti-apoptotic effect, hence inducing apoptosis in cancer cells. Many BH3 mimics have been identified recently, and an increasing amount of research is showing how well they work to treat cancer. Evaluate the effect of BH3 mimics as inhibitor for targeting cancer specially bladder cancer. A thorough evaluation of relevant literature was done for the current investigation.

Key Words:

Bladder cancer; Bilharzia; Schistosoma; BH3 domain; BH3 mimics; Apoptosis.

1. INTRODUCTION

The frequency of BC is fourth among males, and it is the eighth leading cause of death from cancer among men. Almost four times as many males as women are diagnosed with this ailment, indicating a significant gender gap in the prevalence of this illness. What's more, people are often in their 70s when they get a diagnosis. In Egypt, around 31% of all cancer cases are diagnosed to be BC. BC is a prevalent malignancy in males, constituting around 16.2% of all cancer cases in men. The prevalence of cases among males residing in rural areas is approximately 32 per 100,000 individuals (Hameed et al., 2018).

TCC, UC, and SCC are the three subtypes of BC. Among BC, TCC is by far the most common. The first change occurs in the bladder's inner layer, where transitional cells reside. Transitional cells are able

to migrate out of a tissue without being damaged when it is stretched. Transitional cell cancer is the correct classification for UC of the bladder. SCC is classified as a non-urothelial malignancy. The main determinant(s) of risk for SCC are associated with infectious agents rather than exposure to environmental contaminants. The initiation of this process occurs when there is proliferation of thin, planar squamous cells inside the bladder, which may be attributed to the presence of a chronic infection or persistent irritation. Adenocarcinoma is a very uncommon malignancy that has a low incidence rate worldwide. It starts when glandular cells grow in the bladder as a result of chronic bladder irritation and inflammation (Moschini et al., 2017). Many researchers proved that the incidence of bladder carcinoma in schistosomiasis-endemic locations including both UC and SCC as schistosomiasis-associated carcinoma, and hence referred to it as schistosomal or bilharzial BC (Serag Eldien et al., 2021).

Like many types of cancer, treatment strategy of BC includes debulking surgery and chemo and/or radiotherapy (Miller et al., 2016). Immunotherapy is, sometimes, used in BC treatment regimen (Barani et al., 2021). It is used to enhance the body' innate ability to fight the disease. Management of BC hardly include radiation therapy alone, however combination of both chemotherapy and radiotherapy is common.

Cellular apoptosis is controlled by two main pathways, the first one involves the mitochondria (intrinsic pathway) and the other involves death receptors (extrinsic pathway) (Fletcher et al., 2020). Numerous anticancer medications use the Bcl-2 protein family to target mitochondrial-dependent apoptosis (Fletcher et al., 2020). Most people agree that the most effective way to treat a variety of cancer kinds is with chemotherapy. It has been studied a lot in clinical situations how tumor drugs like 5-fluorouracil, gemcitabine, gefitinib, and trastuzumab can become less effective over time (Feng et al., 2020).

Concurrently with the advancement of patient screening methodologies and investigations into the mechanisms underlying tumorigenesis, there has been a corresponding progression in the field of anti-cancer drug research. This progress has been marked by a shift away from chemotherapy-induced cytotoxic responses towards targeted therapies that selectively disrupt specific molecules associated with tumor growth (Ahn et al., 2019).

The field of mechanistic-based molecular-targeted medications for the treatment of human malignancies has seen substantial progress within a very little timeframe (Hallberg & Palmer, 2013). Pharmaceutical drugs derived from small molecules have been extensively used in the medical field to address many medical disorders, such as hypertension, infections, heart failure, diabetes, asthma, rhinitis, and malignancies, for a substantial duration of time. This category comprises about 75% of the anti-cancer drugs that were granted clearance by the Food and Drug Administration (FDA) over the period spanning from 1981 to 2014. In recent times, a multitude of small compounds have exhibited promising therapeutic efficacy in impeding the progression of tissue fibrosis and cancer inside experimental settings (Feng et al., 2020). These diminutive molecules selectively inhibit certain signaling pathways that are closely linked to the proliferation of tumors, and their efficacy in cancer therapy has been extensively verified (Hallberg & Palmer, 2013).

The amphipathic α-helix that makes up the pro-apoptotic BH3 domain interacts with the hydrophobic groove that contains the anti-apoptotic multidomain proteins BH1, -3, and -4. Sequestered pro-apoptotic proteins BAX, BAK, and activator type BH3-only proteins are released as a result of this interaction. The important factor in the start of apoptosis is the activation of released BAX and BAK, either by self-activation or by the act of released BH3-only proteins. This observation implies that therapeutic treatments targeting cancer could potentially utilize BH3 peptides or tiny molecules that possess structural similarities to the BH3 domain (Diepstraten et al., 2022).

Many small molecule inhibitors with anticancer efficacy that target members of the Bcl-2 family have recently been developed by many research (Mongre et al., 2019). Polypyrrole compounds, such as the synthetic prodigine, Obatoclax "GX15-070" (GX15), is one of these inhibitors proposed as an option

used in management of some types of solid tumors (Sulkshane & Teni, 2017). Unlike previous Bcl-2 inhibitors, this GX15 has stable binding properties to all anti-apoptotic Bcl-2 family members. Therefore, GX15, which is not FDA approved yet, may help in the treatment of many cancers. However, many studies are still needed on the preclinical and clinical levels to test such inhibitor in different cancers.

2. BLADDER CANCER

BC is the tenth most common cancer form worldwide (Lenis et al., 2020). According to projections, there was around 573,000 new cases of BC in 2020. It ranks as the thirteenth most significant contributor to cancer-related deaths, resulting in about 212,000 fatalities worldwide. This is compared with BC ranks as the fourth most prevalent cancer among males in the United States and is the eighth primary contributor to cancer-related deaths (Lenis et al., 2020). After prostate cancer, BC is the second most frequent cancer in the urinary system.

Roughly 90% of BC cases are TCC, commonly referred to as UC. SCC represents approximately 5% of cases, whereas adenocarcinoma accounts for less than 2% of all BC cases (Saginala et al., 2020). A small proportion of breast cancer cases are attributed to less prevalent histopathological types.

It's well acknowledged that smoking plays a significant role in the development of breast cancer. An increased risk of bladder SCC has been linked to chronic bladder irritation and infection, which includes diseases like bladder stones, the need for a long-term indwelling bladder catheter, and schistosomiasis (a disease primarily found in Africa and the Middle East). UC is a distinct form of BC that does not originate from the urothelial lining. The present condition is characterized by the development of an adenocarcinoma within the urachal remnant (Moreira et al., 2021).

Upper tract urothelial carcinoma (UTUC) exhibits histological characteristics that are comparable to those observed in urothelial BC. On the contrary, UTUC exhibits a range of different clinical, biochemical, and molecular features (Green et al., 2013). UC affecting the main upper urinary system, including the ureter, renal pelvis, and renal calyces, is an uncommon tumor that accounts for around 5% to 10% of all cases of UC (Zhao et al., 2021).

3. CLASSIFICATION OF BC

The European Association of Urology has established recommendations that divide BC into two primary categories: muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC). There are three different types of BC: adenocarcinoma, squamous epithelial carcinoma, and UC. Of these, nearly 90% of diagnosed cases are UC, making them the most common kind (Bonkat et al., 2018).

3.1 Based on the tumor cells' morphology as seen under a microscope.

There are three main types of BC: (S. Zhu et al., 2020)

3.1.1. Urothelial Carcinoma

Approximately 90% of all BC are attributed to urothelial carcinoma, or UCC. Additionally, it is responsible for approximately 10% to 15% of diagnosis of kidney cancer in adults. The initiation of the process occurs within the urothelial cells of the urinary system. The term "urothelial carcinoma," which was once known as "transitional cell cancer" (TCC), is now used to describe this cancer.

3.1.2. Squamous Cell Carcinoma

Squamous cells are generated within the lining of the bladder as a result of irritation and inflammation. Over time, these cells have the potential to change into cancerous forms. Roughly 4 percent of BC cases are SCC.

3.1.3. Adenocarcinoma

This kind, which develops from glandular cells, makes for around 2% of BC. Micropapillary, plasmacytoid, sarcomatoid, and SCC of the bladder are among the other, less common types of BC.

Sarcomas of the bladder usually originate in the layers of muscle or fat. One rare kind of BC that may spread to other parts of the body is small cell BC.

3.2 According to How Far They Have Migrated into The Bladder Wall:

3.2.1. Noninvasive Bladder Cancer

There are two forms of noninvasive bladder cancer: carcinoma in situ and papillary carcinoma. Noninvasive papillary carcinoma is a benign tumor that may be easily removed and develops on a small patch of tissue. Stage Ta is the name given to this. Stage Tis refers to cancer that is only seen on or around the bladder's surface (Cassell et al., 2019).

3.2.2. Non-Muscle Invasive Bladder Cancer (NMIBC)

The chances of NMIBCs developing into muscle invasive bladder cancers (MIBCs) and their susceptibility to current first intravesical therapy vary. Transurethral resection of bladder tumors (TURBT) is the current standard treatment for NMIBC. This procedure may be done with or without intravesical chemotherapy, utilizing drugs such gemcitabine with docetaxel, Bacillus Calmette-Guérin (BCG), or mitomycin C. BCG is regarded as the recommended treatment among these alternatives for high-risk NMIBC. Despite the relatively high initial response rates of 70%, the issue of recurrence remains a significant concern among patients. A significant proportion of patients develop BCG-resistant illness, for which the current guidelines prescribe either radical cystectomy or trimodal therapy with maximal TURBT in conjunction with chemotherapy and radiation. As of right now, there are no predictive markers available to determine an individual's reaction to BCG. Consequently, in order to evaluate the heterogeneity of NMIBC, researchers are conducting extensive genomic studies. Consequently, NMIBCs have been and are now undergoing comprehensive investigation of mRNA expression across the whole transcriptome, as well as molecular subtype characterization. This endeavor aims to identify biomarkers associated with the various clinical outcomes observed in NMIBC (Fong et al., 2020).

3.2.3. Muscle-Invasive Bladder Cancer (MIBC)

A thorough analysis of tumors diagnosed with MIBC revealed discrete basal and luminal molecular groupings, each distinguished by unique gene expression patterns and clinical characteristics (Robertson et al., 2017; Sjödahl et al., 2017). Numerous organizations have reported varying numbers of molecular subtypes, ranging from k=2 to k=5, including Lund, UNC, MDA, and TCGA. The expression of basal cell markers, such as KRT5/6 and KRT14, as well as the appearance of squamous and sarcomatoid characteristics, were used to distinguish between basal and SCCL-like cancers. Uroplakins, KRT20, ERBB2, and luminal differentiation markers such as forkhead box A1 (FOXA1), GATA-binding protein 3 (GATA3), tripartite motif-containing protein 24 (TRIM24), and peroxisome proliferator-activated receptor (PPAR) were all expressed at higher levels in luminal malignancies (Fong et al., 2020).

The molecular subtypes demonstrated an inclination for basal and luminal indicators to be expressed in an antagonistic fashion, hence indicating the possibility of several indicators serving as possible therapeutic targets. GU tumors, urobasal A/luminal papillary, and infiltrated/p53-like cancers are the three different types of luminal malignancies. Cancer-associated fibroblasts (CAFs) and extracellular matrix (ECM) markers were more abundant in the infiltrated/p53-like subtype, although cell cycle and proliferation markers were less expressed. Activating FGFR3 mutations, FGFR3-related mRNA signatures, and papillary histopathological characteristics were more common in uro-basal/luminal papillary malignancies than in GU tumors. On the other hand, GU tumors showed greater tumor mutational burdens (TMBs) and a decreased prevalence of FGFR3 mutations (Kamoun et al., 2020; Mariathasan et al., 2018).

4. SCHISTOSOMIASIS-RELATED BLADDER CANCER

An infection with Schistosoma haematobium, similar to other species within the Schistosoma genus, gives rise to schistosomiasis, a debilitating condition that afflicts a population exceeding 200 million individuals (Gryseels et al., 2006). Praziquantel is the principal therapeutic intervention, whereas

diagnostic methods encompass the identification of schistosome eggs in fecal or urinary samples, as well as the detection of schistosome antigens by blood analysis. It is noteworthy that prevalence estimations relying on egg identification may potentially underestimate the actual occurrence, which raises concerns. This is due to the fact that parasitological tests, while exhibiting excellent specificity, demonstrate limited sensitivity in comparison to blood testing (Colley et al., 2017).

Unlike the more researched Schistosoma mansoni and Schistosoma japonicum, which are linked to hepatosplenic and intestinal disorders, Schistosoma haematobium is known to produce illness in the bladder. study on the carcinogenicity of other schistosome species is lacking, but over the course of many years, a great deal of study has been done to determine and investigate the link between S. haematobium infection and BC (IARC, 2012; Salem et al., 2011). Research with a sample size of around 10,000 patients was carried out in Egypt between 1970 and 2007. The results of this study showed that S. haematobium infections are becoming less common. Furthermore, there was a discernible decline in the frequency of squamous cell carcinoma, concomitant with a rise in urothelial cell cancer. Additionally, the research noted an increase in the median age of the patients who were being studied (Gouda et al., 2007).

In addition to the infection caused by S. haematobium, numerous investigations have indicated the utilization of cigarettes as a significant risk factor (Zheng et al., 2012). Schistosoma haematobium is a member of Group 1, which includes specific biological carcinogens, along with Opisthorchis viverrini and Clonorchis sinensis. Numerous parasitic genera have also been linked to the emergence of cancer, including Echinococcus, Strongyloides, Fasciola, Heterakis, Platynosomum, and Trichuris (Machicado & Marcos, 2016).

5. POSSIBLE MECHANISM OF SCHISTOSOMAL BLADDER CANCER

There exists a prevailing opinion among the scientific community about the involvement of urogenital schistosomiasis in the pathogenesis of cancer. Nevertheless, it is important to note that this parasitic infection is not regarded as the only determinant in the process of oncogenesis. The accelerated advancement of schistosomal BC may be influenced by the simultaneous presence of supplementary carcinogens, including environmental exposures such as the ingestion of nitrosamine compounds through smoking or diet, genetic predisposition characterized by the presence of mutations leading to the impairment of tumor suppressor gene function or the acquisition of oncogene function, as well as other infections such as uropathogenic E. coli and HPV (Honeycutt et al., 2014). Nevertheless, current research is now in its nascent phase, with a primary emphasis on examining the distinct elements of S. haematobium infection that contribute to the progression of BC.

The occurrence of S. haematobium infection leads to the deposition of eggs in the bladder wall. Some of these eggs can produce detrimental effects by traversing the urothelium and reaching the lumen of the bladder. The eggs that do not migrate across the host's tissues elicit a sustained inflammatory response by interacting with the immune cells of the host, leading to the formation of granulomas over time (Grech et al., 2022). The bladder's urothelium is composed of many layers of distinct cell types, which effectively augment its generally modest rate of cellular turnover in response to damage (Wang et al., 2017). The Virchow posited during the mid-19th century that regions characterized by inflammation could potentially give rise to cancerous conditions (Ishida & Hsieh, 2018), and recently, there has been a proposition suggesting that dysbiosis in the microbiome may serve as a risk factor (Francescone et al., 2014; Shirazi et al., 2020). The extant literature on the urine microbiome of individuals, particularly those afflicted with schistosome infection and bladder disease, has effectively elucidated the occurrence and distribution of microbiota species in each unique instance. Nevertheless, doing future research might potentially augment our comprehension by integrating supplementary factors, such as the severity of bladder disease and the prevalence of parasite infection, in order to build more thorough correlations.
The etiology of schistosomal BC is believed to be connected with the activation of cellular proliferation and injury repair pathways in response to urothelial damage caused by the traversal of schistosome eggs.

The potential cause for the observed rise in chromosomal damage among persons affected by urogenital schistosomiasis may be linked to the concurrent presence of inflammation and the existence of parasite molecules that possess the ability to initiate genetic changes (Nesi et al., 2015). As mentioned earlier, it has been observed that metabolites similar to estrogen, which are produced by schistosomes, have the potential to enhance the frequency of genetic mutations by forming adducts with DNA (Vale et al., 2017). Through multiple cellular generations, the gradual accumulation of these potentially mutagenic occurrences may ultimately result in the development of faulty or even cancerous cells (Vale et al., 2017). Through successive cell divisions, the gradual accumulation of these potentially mutagenic occurrences may ultimately lead to the development of faulty or cancerous cells.

Furthermore, it should be noted that the secretions of S. haematobium eggs has the capability to stimulate an increase in the proliferation of urothelial cells, in addition to their reaction to physical stress. The enhancement of cell proliferation in endothelial cells has been proven by both soluble egg antigen and IPSE, a prominent constituent of soluble egg antigen. This finding suggests a correlation between angiogenesis and the formation of egg granulomas, further supporting the hypothesis that angiogenesis could serve as a potential mechanism connecting schistosome infection and BC (Dematei et al., 2017). Vascular endothelial growth factor (VEGF) was expressed more when human umbilical vein endothelial cells were exposed to the soluble egg antigen from S. mansoni (Kifle et al., 2020), This result is consistent with the disruption of VEGF pathway that was seen after injecting S. haematobium eggs into the mice's bladder walls and the increased vascularization of the vaginal mucosa of infected women compared to uninfected individuals (Costain et al., 2018). Given the proliferation-promoting properties of IPSE, future studies clarifying its host gene targets may reveal its regulatory effect on VEGF expression in addition to its effect on genes related to other cellular pathways, including Hedgehog (Hh) and Wingless (Wnt), which are both known to promote cell division (Wang et al., 2017).

6. BLADDER CANCER TREATMENT

Cytotoxic therapy has been widely accepted as the conventional treatment for advanced breast cancer, encompassing both local invasiveness and metastasis. One common first treatment strategy for individuals with advanced breast cancer is the administration of platinum-based cytotoxic chemotherapy (Figure 1). Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has been a commonly used chemotherapy combination since 1980 (Sternberg et al., 1989). The patients in the group with metastatic illness who received MVAC therapy had a 13-month median survival time (Scher et al., 1993; Sternberg et al., 1989). Gemcitabine and cisplatin (GC) have been used together since the late 1990s (Cassell et al., 2019). However, the administration of GC therapy did not yield a significant improvement in survival outcomes; nevertheless, it exhibited a lower level of toxicity compared to MVAC. There was no significant disparity observed in pathological full response and overall response rates when comparing dose-dense (dd) MVAC to conventional MVAC. However, a notable enhancement in overall survival was observed with the utilization of dd-MVAC (C. Zhu et al., 2017). It is important to note that immune checkpoint inhibitors (ICIs), fibroblast growth factor receptor (FGFR) inhibitors, and antibody-drug conjugates (ADCs) have become viable salvage therapy in the setting of metastatic illness.

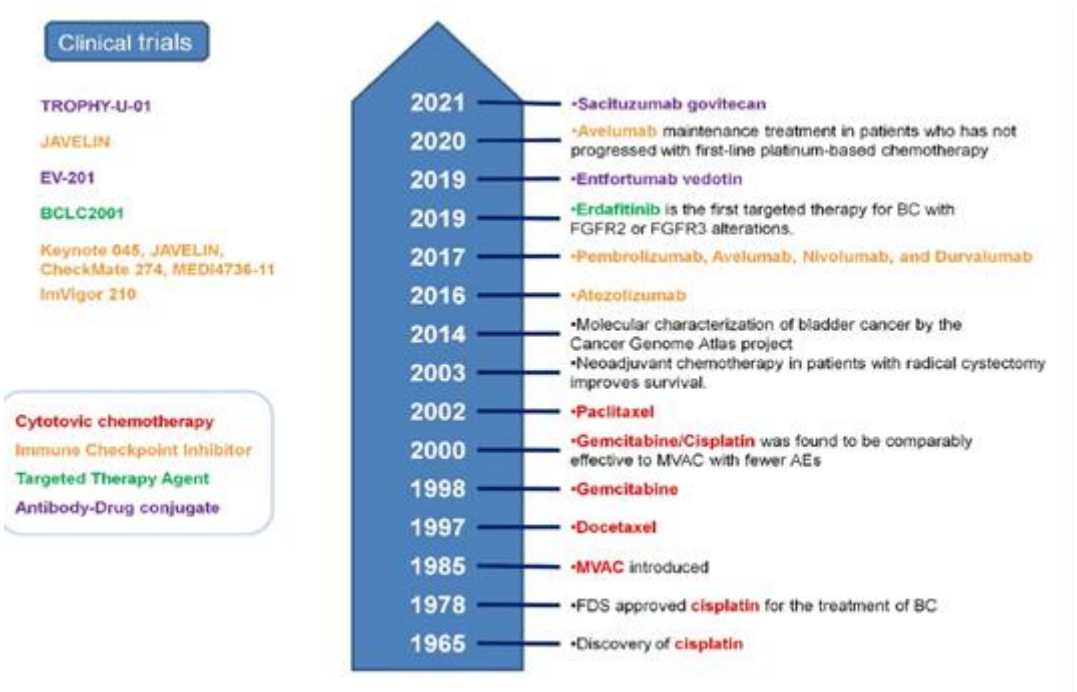

Figure 1: Meta analysis of BC clinical trials and FDA approval. (Bilim et al., 2022)

7. TARGETED THERAPY FOR BLADDER CANCER

A novel treatment strategy known as "targeted therapy" prevents malignant cells from proliferating, spreading, and growing by interfering with certain biochemical pathways. The treatment approach has shown promising outcomes in the treatment of several tumors, including colon and breast cancer (Lee et al., 2018). The therapeutic options for managing ulcerative colitis are somewhat limited owing to their diminished effectiveness and the possibility of treatment-related harm.

Currently, the incorporation of targeted therapies into the core treatment regimen for BC has not been implemented. Significant genetic abnormalities have been found when a broad range of MIBC samples (131–412) were analyzed. These include mutations in the PI3K/AKT pathway, FGFR3, DNA repair, p53, and the cell cycle, as well as alterations in the Peroxisome proliferator-activated receptors (PPAR) gene (Robertson et al., 2017; Weinstein et al., 2014). The United States FDA authorized erdafitinib as a pan-FGFR-targeting drug to be taken orally in April 2019 for patients with metastatic UC who also have vulnerable FGFR3 or FGFR2 mutations. While obstacles including genetic instability, molecular heterogeneity, and route redundancy continue to impede BC targeted treatment, researchers are continuously developing ways to improve its effectiveness. Here, we clarify the consequences of combining targeted treatments with other medications in preclinical settings (Figure 2).

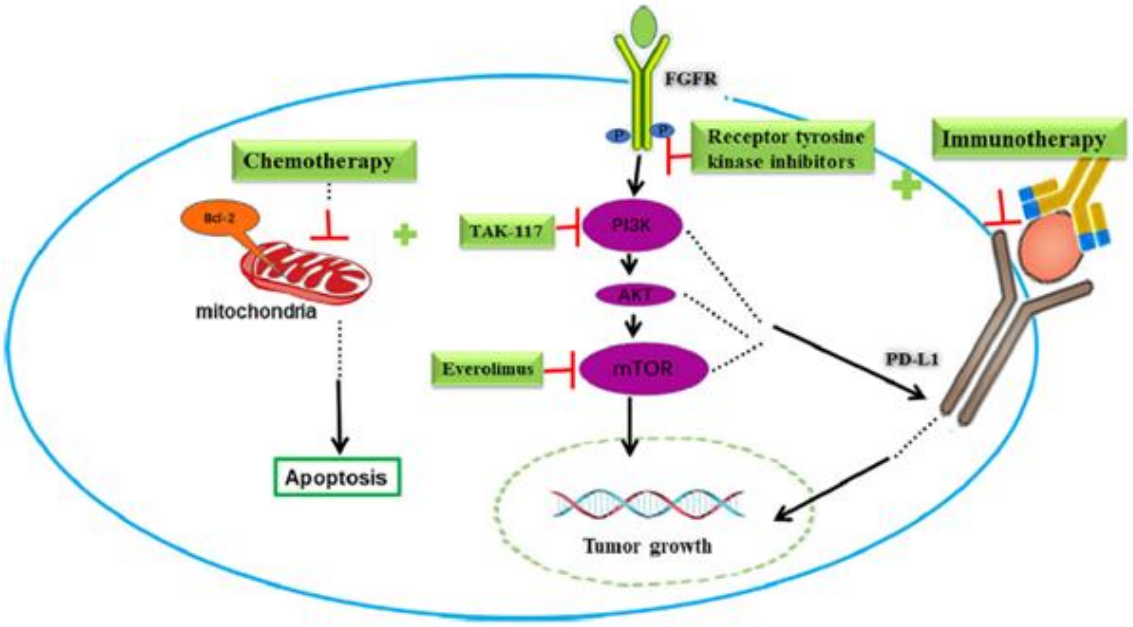

Figure 2: The concurrent utilization of targeted therapy in conjunction with immunotherapy or chemotherapy has demonstrated a synergistic effect in the management of BC.

Potential targets for BC therapy have been discovered, including the FGFR and PI3K/AKT/mTOR signaling pathways. The suppression of the FGFR or PI3K/AKT/mTOR pathways resulted in a decrease in PD-L1 levels and an increase in the responsiveness to immunotherapy. In contrast, these specific pharmaceutical interventions enhanced the pro-apoptotic and cytotoxic properties of chemotherapeutic drugs (Peng et al., 2021).

8. SMALL MOLECULES IN TARGETED CANCER THERAPY

The principal modalities for cancer treatment encompass pharmacotherapy, surgical intervention, radiation therapy, and biotherapeutics. For a considerable period, chemotherapy served as the exclusive modality for cancer drug treatment, employing chemical drugs to eliminate tumor cells or impede their growth and multiplication. Chemotherapy's inability to discriminate between diseased and healthy cells is one of its most notable features, which may result in high toxicity and a variety of adverse effects. The manner that cancer is treated has changed significantly over the last 20 years, shifting from the use of broad-spectrum cytotoxic medications to more individualized therapeutic approaches (Bedard et al., 2020). In contrast to conventional chemotherapy regimens, targeted drugs exhibit the ability to selectively target cancerous cells, therefore minimizing harm to healthy cells. This focused strategy lowers the likelihood of side effects while increasing treatment effectiveness. The FDA's 2001 approval of imatinib, the first small-molecule tyrosine kinase inhibitor (TKI), gave the drug's clinical use a boost (Savage & Antman, 2002), the development of targeted medicines has advanced quickly, and it is presently experiencing a highly fruitful period of growth. The number of FDA-approved cancer therapy medications that are intended to selectively target cancer cells has increased significantly during the last 20 years.

Small molecules and macromolecules are the two basic categories into which targeted medications may be divided. Monoclonal antibodies, polypeptides, antibody-drug conjugates, and nucleic acids are a few examples of macromolecules (Lee et al., 2018; Wilkes, 2018). When comparing small-molecule targeted therapeutics to macromolecule medications, there are several benefits, including affordability, patient adherence, pharmacokinetic (PK) features, and drug storage and transportation. In spite of the current obstacles posed by macromolecule pharmaceuticals, particularly monoclonal antibodies, the

progress of small-molecule targeted treatments remains swift. Up to now, China and the United States have approved 89 small compounds that have anti-cancer qualities. As of 2001, the FDA and China's National Medical Products Administration have granted approval for small-molecule anti-cancer drugs. These medications target a diverse array of biological entities, including but not limited to kinases, epigenetic regulatory proteins, DNA damage repair enzymes, and proteasomes. Among the many obstacles facing the development of small molecule targeted anti-cancer medications are inadequate response rates and the rise in drug resistance.

To further progress these therapies, a thorough evaluation of small molecule targeted anti-cancer medications will be carried out. The inclusion of protein targets of authorized medications can serve as a valuable tip to facilitate the description process. The presentation will cover the marketed small-molecule drugs as well as the primary therapeutic candidates now undergoing clinical development for each specific target.

9. BCL-2 INHIBITORS

Approximately twenty members of the protein family B-cell lymphoma 2 (BCL-2) regulate the intrinsic apoptotic pathway. These members are categorized into three subfamilies according to their structure and function: cell death mediators, proapoptotic proteins, and anti-apoptotic proteins (Knight et al., 2019). Cell survival is enhanced by the presence of four successive BCL-2 homology (BH) domains in anti-apoptotic proteins, including BCL-2 and its closely related counterparts BCL-XL, BCL-W, MCL-1, and A1/BFL-1. In response to diverse physiological stressors, pro-apoptotic effector proteins that are restricted to BCL-2 homology 3 (BH3) and multi-regional proteins, such as BAX and BAK, contribute to the activation of cell death. By altering the permeabilization of the outer membrane of mitochondria (MOMP), these proteins facilitate the release of cytochrome C from the mitochondria (Figure 3) (Huang et al., 2019; Warren et al., 2019). The BCL-2 protein family's pro- and anti-apoptotic members interact reciprocally to control the process of programmed cell death. Hematologic cancers in particular often exhibit dysregulation of the apoptotic pathway (Fabregat, 2009; Schattenberg et al., 2011). Since BCL-2 has been identified as a suppressor of apoptotic cell death, more research has been done on this molecular target, which has advanced the development and use of BCL-2 inhibitors in the treatment of cancer (Choueiri et al., 2016).

The therapy of hematological malignancies has shown the effectiveness of BCL-2 family inhibitors, indicating the possibility of focused intervention of protein-protein interactions. Even if these inhibitors provide positive results, there are still many obstacles to overcome, including the need to determine trustworthy response markers and understand the processes behind resistance to BCL-2 inhibition. According to sampling research from individuals treated with venetoclax for chronic lymphocytic leukemia (CLL), neither the TP53 status nor an in vitro cell sensitivity test showed any predictive power for the antitumor response to venetoclax. As a possible solution to this problem (Thomas et al., 2013), The article discussed the use of BH3 profiling, an in vitro method for assessing tumor response to specific anti-apoptotic proteins (Thomas et al., 2013). However, since there are so many factors that affect how effective BCL-2 inhibitors are, further confirmation via rigorous clinical studies is necessary to confirm the validity of this discovery. Research has consistently shown that cancer cells are capable of becoming resistant to targeted treatment; this also applies to cancers that depend on the BCL-2 apoptotic pathway.

Resistance mechanisms include the overexpression of BCL-XL and MCL-1, which are antiapoptotic members of the BCL-2 family; BCL-2 mutations or phosphorylation; loss-of-function mutations in pro-apoptotic proteins; and sometimes, downregulation of the proapoptotic BAX or BAK. This phenomenon is observed in cancers that rely on the BCL-2 apoptotic pathway. The use of combination therapy, which involves administering several anti-apoptotic BCL-2 family inhibitors or a combination of BCL-2 family inhibitors and traditional chemotherapy, is now the main approach for treating resistant cancer.

Numerous clinical studies have been undertaken to examine the impacts of the planned combination treatment (Lok et al., 2019; Tahir et al., 2017). Researchers are currently faced with new challenges pertaining to the selection of synergistic drugs, while also mitigating the risk of potential adverse effects. Thorough and discerning assessments are necessary when many phase I trials yield findings pertaining to combination therapy.

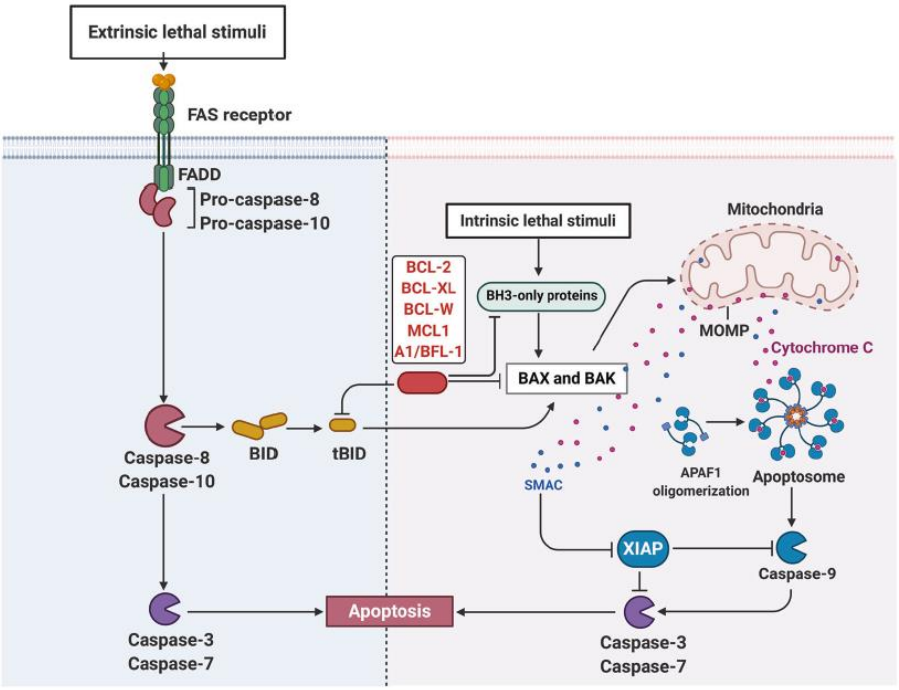

Figure 3: Extrinsic and Intrinsic Pathways of Apoptosis' Schematic Illustration (Zhong et al., 2021)**.**

The triggering of apoptosis by BH3 mimics is shown in Figure 4. The anti-apoptotic members of the Bcl-2 family serve as buffers, mitigating the apoptotic signals induced by the uncontrolled proliferation of cancer cells. Apoptosis is induced by BH3 mimics by their specific attachment to the hydrophobic groove of anti-apoptotic BCL-2 proteins, leading to the displacement of the associated activator BH3-only proteins. This relocation makes it easier for BAXand/or BAK to activate, which triggers further downstream apoptotic signaling (Chonghaile & Letai, 2008).

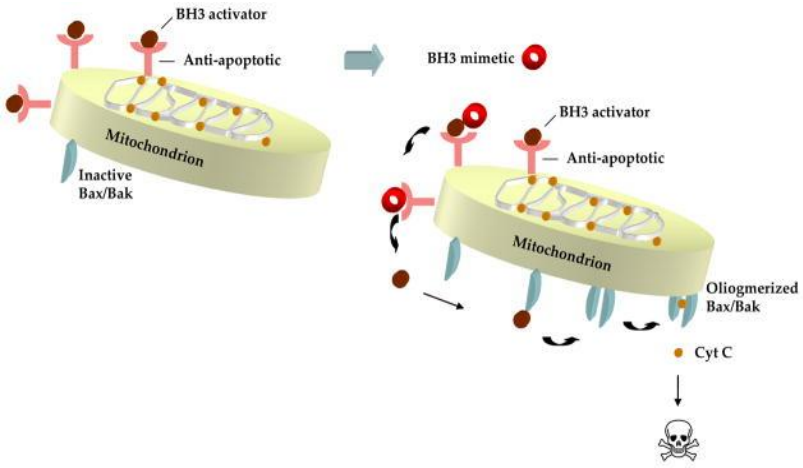

Figure 4: BH3 mimetic-induced apoptosis signaling (Chonghaile & Letai, 2008)**.**

Table 1. BH3 mimetics and their action

BH3 mimetics	Target	Targeting apoptosis in cancer chemotherapy
ABT-737	BCL-2, BCL-XL, BCL-W	ABT-737 exhibits primary efficacy in hematological malignancies, while demonstrating comparatively reduced efficacy in solid tumors. In particular, a number of small cell lung cancer (SCLC) cell lines show a significant level of sensitivity.
ABT-263 (Navitoclax)	BCL-2, BCL-XL, BCL-W	ABT-263 exhibits primary efficacy in hematological malignancies, while demonstrating comparatively reduced efficacy in solid tumors. When treating advanced and recurrent small cell lung cancer (SCLC), ABT-263 has little success.
ABT-199	BCL-2	ABT-199 effectively triggers programmed cell death in hematological malignancies that rely on BCL2 for survival, while avoiding the adverse effect of thrombocytopenia.
WEHI-539	BCL-XL	It has been discovered that the substance WEHI-539 increases the susceptibility of colon cancer stem cells to chemotherapeutic treatments.
BXI-61, BXI-72	BCL-XL	Using xenograft animal models, the research investigated the effects on lung cancer cell lines and showed the inhibition of tumor cell growth both in vitro and in vivo.
GX15-070 (Obatoclax)	All of the anti-apoptotic BCL-2 family proteins	Because of its ability to bind to MCL-1 so well, obatoclax has a great deal of promise for treating solid cancers. Thus, in small cell lung cancer (SCLC) clinical trials, the treatment's efficacy was investigated.
S1	BCL-2, MCL-1	The mouse liver carcinoma xenograft model demonstrated the anti-tumor efficacy of S1.
JY-1-106	BCL-XL, MCL-1	JY-1-106, an investigational chemical, shown the capacity to suppress tumor growth in a lung cancer xenograft model.
Apogossypolone (ApoG2)	BCL-2, MCL-1	ApoG2 inhibited the development of nasopharyngeal carcinoma (NPC) cells in a dose-dependent manner.
BI97C1 (sabutoclax)	BCL-2, BCL-XL, BCL-2A1, MCL-1	In cultivated cells, the BI97C1 molecule induces programmed cell death, or apoptosis, by a process that depends on the activation of caspase-9 and the presence of BAX/BAK proteins.
TW-37	MCL-1, weekly BCL-2	The presence of an effect has been

	and BCL-XL	observed in cells associated with prostate and pancreatic cancer.
MIM1	MCL-1	When MIM1 was administered to a leukemia cell line that depends on MCL-1, apoptosis was induced.
MS1 (MCL-1-specific peptide)	MCL-1	The delivery of MS1 caused triple-negative breast cancer cells, which are reliant on the MCL-1 protein, to undergo apoptosis.
BH3I-1 and its structural derivatives	MCL-1	N.D.
UMI-77	MCL-1	It has been discovered that the substance UMI-77 efficiently inhibits the growth of pancreatic cancer cells and initiates intrinsic apoptotic pathways.
Compounds from Takeda Pharmaceutical Company	MCL-1, BCL-XL (MCL-1/BCL-XL dual inhibitor)	N.D.
University of Michigan Compounds	MCL-1	The substance caused caspase-3 to become activated and showed a dose-dependent suppression of cell proliferation.
Marinopyrrole A (Maritoclax)	MCL-1	It has been shown that the chemical Marinopyrrole A causes leukemia and melanoma cells to undergo apoptosis, or programmed cell death. Cells that depend on the protein MCL-1 for life are the only ones that show this impact; cells that depend on the proteins BCL-2 and BCL-XL do not show the same reaction.
Compounds from Eutropics Pharmaceuticals	MCL-1 and weekly BCL-XL	The identified compounds were seen to elicit a dose-dependent release of cytochrome c and exhibit antiproliferative effects on various cell lines that rely on MCL-1 for survival.
AbbVie Compounds	MCL-1	N.D.
Vanderbilt University Compounds	MCL-1	N.D.
ABT-737	BCL-2, BCL-XL, BCL-W	ABT-737 exhibits primary efficacy in hematological malignancies, while demonstrating comparatively reduced efficacy in solid tumors. Specifically, several cell lines of small cell lung cancer (SCLC) exhibit a high degree of sensitivity.

According to the data presented in Table 1, many BH3 mimics were identified and subjected to analysis in order to assess their impact on cancer cells. Among the substances examined, ABT-263 (navitoclax), a derivative of ABT-737 that may be taken orally, has demonstrated notable efficacy in the majority of individuals with CLL, or chronic lymphocytic leukemia in clinical trials. Furthermore, ABT-199 (venetoclax) has been beneficial for CLL patients who have relapsed or are resistant (Nakajima & & Tanaka, 2016).

Bcl2 inhibitors were utilized in several trials to treat BC. Lobaplatin (LBP) is a third-generation platinum-based drug. LBP inhibits the growth and migration of T24 and 5637 BC cells both in vivo and in vitro. It may also be able to trigger apoptosis in BC cells by means of the PI3K/Akt pathway. Cell apoptosis mediated by LBP was shown by an increase in the expression of proapoptotic proteins Bax and cleaved caspase-3 and a reduction in the expression of antiapoptotic proteins Bcl-2 (Yu et al., 2023). A new target, miR-21, causes the cytotoxicity and death of BC cells and is the target of resveratrol. By inhibiting the synthesis of miR-21, resveratrol inhibits Akt activity and Bcl-2 expression (ZHOU et al., 2014). Triterpene Xanthoceraside was isolated from the husk of Xanthoceras sorbifolia. Stack (Chi et al., 2013), With regard to BC, xanthoceraside shown anti-tumor properties. Additionally, in human BC cell lines, xanthoceraside causes cell death by downregulating the PI3K/Akt/Bcl-2/Bax signaling pathway (Chai et al., 2021).

Conclusions: A class of compounds known as BH3 mimetic compounds has antagonistic effects of the BCL-2 family members, with anti-apoptotic effect, hence inducing apoptosis in cancer cells. Many BH3 mimics have been identified recently, and an increasing amount of research is showing how well they work to treat cancer.

Recommendations: We therefore recommend more further studies to investigate the potential biological impact of theBH3 targeting specially in bladder cancer management.

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