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Research Article

Targeted Anticancer Therapy as a New Strategy of Treatment: Current and Future Scenery

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Abstract

Cancer is a disease with high incidence. Other therapies as surgery and radiotherapy are also used in the treatment of this disease. However, the effect adverse and the metastasis limited the use of these therapies. Target anticancer Targeted cancer treatment is an attractive approach where drugs or other substances which targets specific molecules to block the growth and spread of cancer cells. Identification of targets is essential for a successful development of molecular targeted therapies in cancer. This review summarizes current knowledge on the molecules target and the up to date of drugs in clinic assays as Targeted Anticancer Therapies.

Keywords: Cancer; Therapeutics; Drugs; Oncogene addiction; Pharmacology; Immunotherapy; Small inhibitor

Abbreviations

AKT: Ribosomal Protein S6 Kinase Beta-1; 4EBP1: Eukaryotic Translation Initiation Factor Binding Protein 1; HER2: Human Epidermal Growth Factor Receptor 2; DLT: Dose Limiting Toxicity; PFS: Progression-Free Survival; HIF: Hypoxia-Induced Factor; NF-KB: Nuclear Transcription Factor Kappa B; CAFs: Cancer-Associated Fibroblasts; Bcl-2: B-Cell Lymphoma 2; Mcl-1 Myeloid: Cell Leukemia 1; Bcl-xL: B-Cell Lymphoma XL; Bak Bcl-2: Homologous Antagonist/Killer; lncRNAs: Long Non-Coding RNA; miRNAs: Micro RNA; ADCC: Antibody-Dependent Cellular Cytotoxicity; ADCP: Antibody-Dependent Cellular Phagocytosis; PARP: Poly-(ADP-Ribose) Polymerase; DNA: Deoxyribonucleic Acid; BRCA: Breast Cancer; ATP: Adenosine 5'-triphosphate; ROS: Reactive Oxygen Species; MTH1: Mutt-Type Nudix Hydrolase 1; NUDT1: Nudix Hydrolase 1; TAMs: Tumour-Associated; MDSC: Myeloid-Derived Suppressor Cells; STAT1: Signal Transducer and Activator of Transcription 1; STAT6: Signal Transducer and Activator of Transcription 6

Cancer Disease and Treatment

Cancer is currently one of the main causes of death worldwide and it is estimated that the number of deaths will reach 13.1 million in 2030. The incidence and mortality provider of website GLOBOCAN estimates 2.3 million new cases (11.7% of total case) of breast cancer, lung (11.4%), colorectal (10.0 %), prostate (7.3%), and stomach (5.6%) cancers. Therapeutic strategies are determined by early diagnosis, which guarantees surgery as the best therapeutic option, as well as the application of chemotherapy and/or radiotherapy regimens in more advanced stages of the disease. Despite the existence of multiple therapeutic modalities for the treatment of this disease, they have only resulted in discreet increases in survival. On the other hand, the toxicity events associated with the use of conventional chemotherapy regimens deteriorate the quality of life of the patient, constituting a limitation for its use, in addition to the development of resistance, mutagenicity and teratogenicity [1].

Target anticancer therapy as a new alternative to treatment of cancer

New findings in the study of cancer biology and the discovery of new genes or proteins related to cancer cell survival have allowed the identification of targets for the development of new drugs in cancer therapy. These target molecules are involved in important signaling pathways for the cancer cell: apoptosis, tumor growth, angiogenesis, (receptors, growth factors, kinase cascades). The objective of this new therapy is to affect specific targets that affect excessive cell growth of cancer and prevent the formation of metastases [2]. In addition, the main objective of these drugs is to reduce unwanted effects in non-tumor tissues and improve the patient's quality of life. Figure 1 shows the cancer hallmark-related proteins or genes that are targets of drugs that are from preclinical studies, clinical studies, or that are approved for cancer therapy [3-5].

Inflammatory scenery

There is a strong relationship between inflammation and cancer. The tumor microenvironment is an important component in the cancer niche and contributes to the activation of genes related to angiogenesis, cell crime, modulation of genes that are linked to cancer progression, and cell growth. During an inflammatory process, the cells of the immune system predominate and are the main component in the tumor. The tumor-associated macrophage has been the major component of the leukocyte infiltrate. These cells secrete pro-inflammatory cytokines that stimulate other cells of the immune system and strengthen the inflammatory microenvironment [6]. Interferon, Tumor Necrosis Factor, IL6 and IL17 are some of the cytokines that also cause the activation of transcription factors with NFkB, STAT1, and STAT6 that regulate genes involved in apoptosis, metastasis, and cell proliferation. On the other hand, as an art of the

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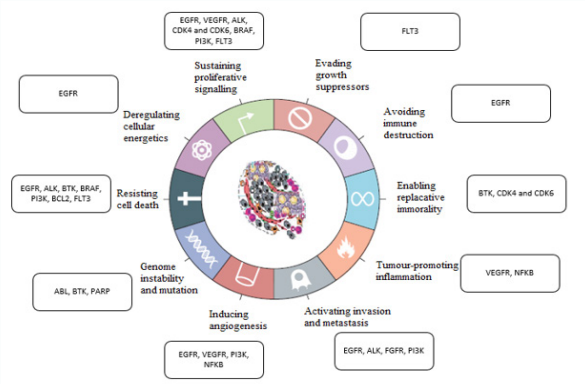

Figure 1: Inflammatory changes and bowel wall thickening centred.

inflammatory microenvironment, cancer stem cells are an essential component in the tumor, since they are capable of maintaining the growth and differentiation properties of the cells. Therefore, its presence in the tumor is related to tumorigenesis, metastasis and tumor progression. The most abundant lymphoid cells in the tumor are TAM and MDSC, whose presence in the tumor favors tumor immunosuppression and strengthens the cancer stem cell phenotype. All these factors of the tumor environment are targets for cancer therapies. These strategies could eliminate the functions of the TAMs, reactivate the antitumor functions of the macrophage (ADCC, ADCP, and M1 like phenotypes) and the elimination of cancer stem cells [7,8], a new quote from the photo.

Cancer-associated fibroblasts

The tumor microenvironment is made up of cells of the immune system (macrophages, lymphocytes), tumor cells, stromal cells (endothelial cells, stromal fibroblasts) and non-cellular components such as hyaluronan, fibronectin, laminin, among others. These components stimulate cancer cell diversity, increase drug resistance, progression and metastasis. Cancer-Associated Fibroblasts (CAFs) play a very important role in the interaction of cancer cells with the microenvironment, since it favors the reduction of apoptosis, increases the proliferation, migration and survival of the cancer cell. Therefore, CAFs is an attractive target to anticancer therapies [9,10].

Apoptosis and metabolic stress

Mitochondrial apoptosis is a cascade of signals whose end is the death of the cell. Therefore, it is a highly regulated cascade to maintain the homeostasis of the organism. A number of proteins positively and negatively regulate this pathway (pro-apoptotic and antiapoptotic proteins). Cancer cells escape cell apoptosis through low expression of pro-apoptotic proteins or overexpression of anti-apoptotic proteins or transcription factors that favor the activation of genes that keep this pathway inhibited. The Bcl2 protein is the most frequently over expressed protein in tumors, being highly important in leukemia due to its function in leukogenesis. On the other hand, Mcl-1 is over expressed in acute myeloid leukemia and its function is very important for the development and maintenance of B and T lymphocytes, it is also of great importance in the survival of leukemia cells, being very important in AML. Therefore, both Bcl2 and Mcl-1 are attractive targets for cancer therapy in AML. Due to its role in tumors, the expression of these proteins exists in several drugs in preclinical studies [11].

On the other hand, the fatty acid synthesis, glutamine metabolism and aerobic glycolysis are other pathways that are failing in cancer cells to increase energy consumption. These aspects of metabolism favor cell growth, survival and exacerbated growth [12-14]. Various mechanisms of the normal cell, the cancer cell regulates, such as glucose transporters, increases glycolysis, lipid metabolism among other pathways to provide NADPH and other molecules that participate in aerobic glycolysis. In addition, a hypoxic niche originates in the tumor, in which glucose transporters and the enzymes that participate in glycolysis are exacerbated. All these irregularities in glucose metabolism allow the cancer cell to evade apoptosis, favor metastasis and resistance to therapies. For this reason, the glycolysis pathway and the factors that favor this pathway are targets for the development of drugs against cancer [15-18].

BRCA-PARP

Healthy cells in the human body managed to cope with genomic mutations through different mechanisms of repairing damage or variations in the DNA molecule. These mechanisms are Non-Homologous End Joining (NHEJ), Homologous Recombination (HR), and base excision repair. Cells became more dependent on some of these pathways for their survival once one of them loses its activity. Under this principle, specific therapies have been developed that take into account synthetic lethality in two DNA repair pathways. This treatment is currently being considered in BRCA-deficient breast and ovarian cancer. Treatment consists of the administration of inhibitors of the enzyme (poly ADP ribose polymerase) that cancel the NHEJ pathway. Therefore, tumor cells with DNA damage will resort to alternative repair mechanisms, in this case BRCA1 or BRCA2. By not finding these genes available in these types of cancer, an accumulation of unrepaired DNA will occur and this will ultimately lead to specific cell death in these tumors [19].

Oxidative stress

Oxidative stress is a predominant feature in cancer cells and not so in normal cells [20]. The main cause of this stress may be due to oncogenic signaling, which leads to a greater generation of Reactive Oxygen Species (ROS) [21,22]. DNA mutations that cause genomic instability are part of the damage caused by ROS to cell biomolecules [23]. Previous studies have shown the important role that the removal of oxidized nucleotides from available free nucleotides plays in the survival of tumor cells. The *NVDT1* gene participates in reducing the damage to free nucleotides caused by oxidative stress. It was shown that the activity of this gene is essential for the survival of these cells with abnormal growth. This fact was verified with gene inhibitors, which caused the selective death of cancer cells. An alternative for cancer therapy is the induction of high levels of ROS from the inhibition of antioxidant proteins. This treatment model has obtained positive results in the preclinical setting where agents such as piperlongumine, dichloroacetate and beta-phenylethyl isothiocyanate have shown potent antitumor effects. These studies show that a good strategy to fight cancer may be the imbalance in the levels of oxidative stress [24,25].

Target anticancer agents

Several types of cancer affect the world population. For the treatment of this disease, a group of drugs for the treatment with targeted activity has been developed and is being investigated. These are defined and grouped as monoclonal antibodies, small molecules, and gene therapy [26]. The promotion of cell death, the interruption of

the cell division process, and the inhibition of signals that participate in the growth and development of cancer cells are some of the events that are part of the mechanism of action of these drugs with antitumor activity [1].

Immunotherapeutic drugs

An alternative of great value in targeted molecular therapy against cancer are monoclonal antibodies. These perform their function through direct and indirect mechanisms. The direct mechanism is due to the effect of cell death by the binding of monoclonal antibodies conjugated to a drug with antitumor activity to biological structures such as cell receptors and membrane-bound proteins in the tumor microenvironment [27]. On the other hand, the indirect mechanism is based on the effect or activity of specific cells for this purpose such as NK killer cells and the Complement System, as well as through the phagocytosis process, after a group of cellular signals given by the interaction of cell-specific antigens with monoclonal antibodies [28]. Several monoclonal antibodies have been registered and approved for the treatment of cancer and others are still in clinical studies (Table 1).

Trastuzumab Mertansine (T-DM1) is an antibody-drug conjugate consisting of trastuzumab bound to the cytotoxic agent mertansine (DM1). This drug works by interrupting the cellular development of cancer cells by interacting with HER2, a human epidermal growth factor, and then mertansine is internalized inside the cells and induces their death by binding to tubulin and inhibiting the assembly of structural microtubules. Clinical studies have demonstrated the effectiveness of this therapeutic agent in comparison with combination therapies of other drugs such as lapatinib and capecitabine; where T-DM1 has an improvement of 5.8 months in patient survival. For treatment with T-DM1, those treated must have previously received therapy for the disease [37].

Cetuximab is a monoclonal antibody against cancer that works by blocking the Epidermal Growth Factor Receptor (EGFR), thereby interrupting cell signaling that induces its proliferation and slows down tumor growth. It is indicated as therapy for head and neck Squamous Cell Carcinoma (SCC) in conjunction with radiation therapy; Metastatic head and neck SCC plus 5-fluorouracil. EGFR mutations and overexpression are common in patients with Colorectal Cancer (CRC). This monoclonal antibody in clinical studies showed a significant antitumor effect in people with CRC as single therapy with an objective response rate of 10.8%, a progression-free survival of 1.5 months, and an overall survival of 6.9 months. While treatment together with irinotecan resulted in a 22.9% response rate, 4.6 months of stability until disease progression, and 8.6 months of overall survival [38]. In other clinical studies for patients with CRC, cetuximab was applied as a combination treatment with FOLFIRI; the latter is a chemotherapy that includes folinic acid, fluorouracil and irinotecan. These trials performed better in terms of disease progression than FOLFIRI as single therapy [39].

Panitumumab is a humanized IgG 2 type monoclonal antibody. It works by binding to EGFR and blocking its activity during cell growth. Its mechanism of action is therefore similar to that of cetuximab. This medicine is indicated in the CCR as main therapy together with FOLFOX; the latter is the combination of the drugs folinic acid, fluorouracil, and oxaliplatin. In addition, it is used as a treatment in pancreatic cancer as second-line therapy and in gastric cancer as palliative therapy [40].

Small molecule drugs

Small molecules are defined as relatively low molecular weight compounds (<900 daltons) that can penetrate cells to target specific proteins within cells [41]. Many known small molecule inhibitors focus on inactivating kinases and disrupting signaling pathways that are dysregulated during carcinogenesis. In addition, small molecules can be used to target proteasomes, Cyclin-Dependent Kinases (CDKs), and inhibitors of poly ADP-Ribose Polymerase (PARP) to activate the cell cycle checkpoint, trigger apoptosis, and coordinate cell production DNA repair [42] (Table 2).

One of the critical pathways in cancer is the Phosphatidylinositol 3-Kinase (PI3K) signaling pathway that has an impact on survival, growth, metabolism, motility, and cancer progression [69]. The PI3K family catalyzes the phosphorylation of phosphatidylinositols at its third position and is organized into class I, class II, and class III. Only class IA signaling changes are involved in human cancers [70]. Dactolisib, also known as BEZ235, is a drug with an antitumor effect that acts as a specific inhibitor of PI3K and TORC1/2. This intervenes in the G1 phase of the cell cycle, affecting consequently the processes of cell proliferation; furthermore, it inhibits the activity of AKT, S6K and 4EBP1. Dactolisib is indicated to combat breast and colorectal cancer. This therapeutic agent has been evaluated in phase I and II clinical trials with patients presenting with advanced cancer. Therapy in the dactolisib trials was combined with other drugs such as trastuzumab and paclitaxel [71]. Specifically, in a phase IB study in 15 patients with breast cancer, dactolisib was administered in combination with trastuzumab, the results were a tolerable treatment for the patients, and 40% of them managed to maintain the disease stable [68].

One of the most attractive biological targets for the development of new antitumor agents is the epidermal growth factor receptor. The epidermal growth factor binds to its receptor, favoring the formation of dimers and cell signals through the enzyme tyrosine kinase. This mechanism involves important events such as cell survival and proliferation, and metastasis development of cancer cells [72]. Afatinib is an oral drug that is a specific EGFR inhibitor. This drug has been evaluated in conjunction with pemetrexed in people with lung

Table 1: List of monoclonal antibodies that act on critical cancer targets.

Monoclonal Antibody	Targets	Cancer types	References
Brentuximab vedotin	CD30	Hodgkin's Lymphoma (HL) and systemic Anaplastic Large Cell Lymphoma (ALCL)	[29]
Ado trastuzumab emtansine	HER2+	HER2-positive Metastatic Breast Cancer (MBC)	[30]
Y-Ibritumomab tiuxetan	CD20	non-Hodgkin's lymphoma (NHL)	[31,29]
Bevacizumab	VEGF	Metastatic Colorectal Cancer (mCRC), non-squamous, Non-Small Cell Lung Cancer (NSCLC) glioblastoma, and metastatic renal cell carcinoma.	[32]
Alemtuzumab	CD52	Chronic Lymphocytic Leukemia (CLL)	[33]
Ofatumumab	CD20	Chronic Lymphocytic Leukemia (CLL)	[34]
Nivolumab	PD-L1	NSCLC, RCC, Hepatocellular Carcinoma (HCC)	[35]
Gemtuzumab ozogamicin	CD33	Acute myeloid leukemia	[36]

CD: Cluster of Differentiation; HER2: Human Epidermal Growth Factor Receptor 2; PD-L1: Programmed Death-Ligand

Table 2: List of FDA approved drugs used in the clinic.

Drugs	Targets	Cancer types	References
Gefitinib	EGFR	Non-Small Cell Lung Cancer (NSCLC)	[43]
Lapatinib	EGFR/ERBB2	EGFR/ERBB2 ERBB2-positive breast cancer	[43]
Sorafenib	VEGFR kinase, RAF, PDGFR	Renal cancer, Hepatocellular carcinoma	[43,44]
Crizotinib	ALK kinase	NSCLC	[45]
Sunitinib	VEGF, PDGFR, SCF	Gastrointestinal Stromal Tumour (GIST)	[46]
		Advanced Renal Cell Carcinoma (RCC)	
		Advanced Pancreatic Neuroendocrine Tumours (pNET)	
Pazopanib	VEGFR, PDGFR, FGFR, SCF, Itk, Lck	Advanced Soft Tissue Sarcoma (STT),	[26]
		Advanced Renal Cell Carcinoma (RCC)	
Imatinib	PDGFR, ABL kinase	Chronic mylogenous leukemia, Gastrointestinal stromal tumours	[47]
Acalabrutinib	BTK inhibitor	Mantle cell lymphoma	[48]
Ibrutinib		Chronic Lymphocytic Leukemia (CLL)	
Carfilzomib	Proteasome	Multiple Myeloma	[49]
Bortezomib			
Ixazomib			
Ribociclib	CDK4, CDK6	Metastatic breast cancer	[50,51]
Palbociclib			
Rucaparib	PARP	BRCA-positive ovarian cancer	[52]
Olaparib	PARP	gBRCA-mutated advanced ovarian cancer	[53]
Niraparib	PARP	Epithelial ovarian, fallopian tube, or primary peritoneal cancer	[54]
Alectinib	ALK	Non-small-lung cell carcinoma	[55,56]
Brigatinib			
Encorafenib	BRAF	Melanoma	[57]
Alpelisib	PI3K	Breast cancer	[58]
Duvelisib	PI3K	Chronic lymphocytic leukemia and small lymphocytic lymphoma,	[59,60]
Idelalisib			
Venetoclax	BCL2	Chronic myeloid leukemia, acute myeloid leukemia	[61]
Afatinib	EGFR	Non-small-lung cell carcinoma	[62]
Erlotinib	EGFR	Non-small-lung cell carcinoma, pancreatic cancer	[63]
Midostaurin	FLT3	Acute myeloid leukemia	[64]
Talazoparib	PARP1 and PARP2	Breast cancer	[65]
Cabozantinib	VEGFR	Medullary thyroid, hepatocellular carcinoma, and renal cell cancer	[66]
CIGB552 peptide	NFKB	Advanced solid tumors	[67]
BEZ235	PI3K	Melanoma, breast, and colorectal cancer and sarcoma	[68]

EGFR: Epidermal Growth Factor Receptor; ERBB, VEGFR: Endothelial Growth Factor Receptor; PDGFR: Platelet-Derived Growth Factor Receptors; SCF: Stem-Cell Factor Receptor; ALK: Anaplastic Lymphoma Kinase; FGFR: Fibroblast Growth Factor Receptors; Itk: Interleukin-2 Receptor-Inducible T-Cell Kinase; Lck: Leukocyte-Specific Protein Tyrosine Kinase; BTK: Bruton's Tyrosine Kinase; BRCA: Breast Cancer Gene; CDK: Cyclin-Dependent Kinases; PARP: Poly (ADP-ribose) Polymerase; BRAF: gene that codes for the receptor for Epidermal Growth Factor; PI3K: Phosphoinositol 3-kinase; FLT3: Tyrosine Kinase Factor 3 Gene; BCL2: B-cell Lymphoma 2

adenocarcinoma in phase III clinical trials. In relation to the results in comparison with standard chemotherapy, a greater progression-free survival was evidenced in treatment with afatinib. Another drug that acts on this pathway is lapatinib, indicated for breast cancer with an overexpression of HER2, a growth receptor. This treatment is applied together with capecitabine. Cetuximab, panitumumab, and erlotinib are other drugs with antitumor activity that target EGFR as their biological target [73].

Anaplastic lymphoma kinase is a protein involved in cell cycle control. It originates from the *Anaplastic Lymphoma Kinase (ALK)* gene. This gene presents modifications in some cancers such as non-small cell lung cancer. Several drugs have been developed that inhibit ALK. Crizotinib is one of them and as the main treatment during therapy, it presented less toxicity and higher progression-free survival compared to chemotherapy. Ceritinib is another ALK inhibitor that has shown greater antitumor effect in clinical trials than crizotinib. This type of treatment is proposed to patients after they have been previously treated with crizotinib. In phase I clinical studies, the objective response rate was 58% and progression-free survival of 7 months. Ongoing studies are comparing ceritinib treatment with chemotherapy in people with non-small cell lung cancer. Others are investigating ceritinib as a single therapy in bile duct and thyroid cancer. Another ALK inhibitor is alectinib, a second-generation drug that has been evaluated in phase I/II clinical trials in treatment-naïve patients with non-small cell lung cancer; the results of these studies were encouraging with a response rate of 93.5% [74].

In the relentless search for an effective therapy against cancer, antitumor peptides have become attractive agents due to their high specificity, small molecular weight, and low tissue toxicity relative to traditional therapies. CIGB552 is a second-generation synthetic peptide with antitumor activity that arose from structural modifications to the L-2 peptide. The latter owes its origin to changes made with the aim of obtaining greater anticancer activity in the primary structure of the CIGB550 peptide designed from the 31-52 sequence of a protein from the limulus polyfermous horseshoe crab. The anticancer peptide CIGB-552 interacts with the intracellular protein COMMD1 and increases its protein levels in tumor cells. Upregulation of the COMMD1 protein supports the ubiquitination and degradation of NF-κB, a transcription factor that stimulates the expression of oncogenes, angiogenesis, and cell proliferation proteins [75]. COMMD1 also regulates HIF-1, which has a key role in cell survival in areas of hypoxia, a common feature of tumors [76]. In preclinical studies of this drug, it's *in vitro* cytotoxicity has been demonstrated in several cell lines of colon cancer and lung cancer [77,78]. *In vivo* antitumor activity was also demonstrated in a mouse model inducing solid tumors of carcinoma of murine colon CT-26 and HT-29 originating in the human colon [79], and in dog solid tumor models with evidence of regression in tumor size [80].

CIGB552 is already in the stage of clinical studies, a phase I clinical trial was carried out where safety, pharmacokinetic profile, evaluation of CD4+ and CD8+ lymphocytes and preliminary activity in patients with advanced tumors were evaluated. Stable disease was observed in a significant number of patients, including two metastatic soft sarcomas. CIGB-552 at a dose of 4.7 mg was defined to be well tolerated with no significant adverse effects and appeared to provide some clinical benefit [67]. Studies of the antiproliferative activity of the peptide and in combination with other traditional chemotherapeutic drugs in lung cancer cells were also carried out. CIGB552 and cisplatin were evaluated as pretreatment and concomitantly at different concentrations. These assays were performed in the NCI-H460, A549 cell line and in mouse models of lung cancer. The results showed an effective antitumor response with the drug combination, without adverse effects and signs of deterioration.

Target-directed therapy is emerging as an alternative for cancer treatment. Researchers and clinicians must work together for the development of novel, tumor-selective and effective drugs. Combination therapy it has become the most effective modality for the treatment of cancer. Targeted drugs and standard therapy allow increasing the effectiveness of the treatments and increasing the survival of the patients. In addition, this form of treatment decreases the adverse effects and the effect on normal cell.

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