UDC: 616-006-085:615.277.3-37 DOI: 10.52532/2663-4864-2022-1-63-70-80

ADVANTAGES AND PROSPECTS OF TARGETED THERAPY IN ONCOLOGICAL PRACTICE: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Cancer is the second leading cause of death globally and is expected to be responsible for approximately 19.3 million new cases and 10 million deaths in 2022. With an unprecedented understanding of the molecular pathways that drive the development and progression of human cancers, novel targeted therapies have become an exciting new development for anticancer medicine. These targeted therapies, also known as biologic therapies, have become a primary treatment modality by blocking the growth of cancer cells by specifically targeting molecules required for cell growth and tumorigenesis. However, due to their specificity, these new therapies are expected to have better efficacy and limited adverse side effects than other treatment options, including hormonal and chemotherapy.*

The study aimed to *present an overview of the advantages and prospects of targeted therapy in oncological practice.*

Methods: *The search was carried out in the following databases: Scopus, Medline, Cochrane, PubMed, and Science Direct for 2016-2021. Sources were searched for the following keywords: clinical trials, immunotherapy, monoclonal antibodies, small molecular weight inhibitors, and targeted therapy.*

Results: *This review explores the clinical development, successes, and challenges facing targeted anticancer therapies, including small molecule inhibitors and antibody-targeted therapies. The authors describe targeted therapies to epidermal growth factor receptor, vascular endothelial growth factor, human epidermal growth factor receptor 2, anaplastic lymphoma kinase, BRAF, T-cell mediated immune response inhibitors, cytotoxic T-lymphocyte-associated protein 4, and programmed cell death protein-1/PD-1 ligand.*

Conclusion: *Over the past decade, there have been significant changes in cancer treatment, including targeted therapy, which has become more common. However, targeted drugs show low activity in monotherapy. In addition, the selection of patients for targeted therapy remains a difficult task since there are not enough reliable biomarkers to predict the action of most targeted agents. Therefore, it requires a deeper study of molecular biology, namely signaling pathways that determine the pathogenesis of cancers.*

Keywords: *clinical trials; immunotherapies; monoclonal antibodies; small molecule inhibitors; targeted therapies.*

Introduction: As of 2021, cancer incidence in the Republic of Kazakhstan amounted to 173.5 per 100 thousand population. The incidence decreased by 11.4%. In total, 32,526 new cases were registered. The contingent of cancer patients in 2021 amounted to 190,159 patients (in 2020 – 186,326 patients). About 80% of them required independent or adjuvant chemotherapy.

Chemotherapy is based on suppressing the fast-growing cell division characteristic of cancer cells. However, unfortunately, it also affects fast-growing normal cells such as hair follicles, bone marrow, and the gastrointestinal tract, causing the side effects of chemotherapy. In addition, the chaotic destruction of normal cells, the toxicity of conventional chemotherapy drugs, and the development of tolerance to most drugs confirm the need to find new effective targeted treatments based on changes in the molecular biology of tumor cells [1].

Recent advances in molecular biology have revealed the mechanisms of death and cell division, leading to the development of known molecular pathways, drugs called targeted therapies. In recent years, FDA-approved anticancer drugs have been blocking biological transduction pathways or specific cancer proteins, inducing tumor cell death by apoptosis and stimulating the immune system, or explicitly delivering chemotherapeutic agents to cancer cells, reducing unwanted side effects. Their advantage over traditional chemotherapy is that they target tumor cells instead of targeting both healthy and cancerous cells. Targeted therapy can be achieved directly by altering specific cell signaling via monoclonal antibodies or small molecule inhibitors. However, this review focuses on indirect targeted approaches that bring chemotherapeutic agents to molecular forms that overly suppress the surface of tumor cells. The article also reviews new targeted "designer" drugs that can be used with previous standard therapies as drug treatment progresses [2].

With our growing understanding of the molecular basis of carcinogenesis, several targeted agents have been developed that show promize in treating people with lung, colon, breast, or kidney cancer. Recent studies show that molecular targeted therapy can increase life expectancy. In addition, targeted therapies are being developed to complement traditional therapies to improve efficacy and reduce toxicity.

Most targeted drugs cannot kill or severely damage tumor cells (cytotoxic effect) but only have an inhibitory effect on proliferation or stimulate tumor cell differentiation, turning off the mechanisms responsible for forming a malignant phenotype (cytostatic effect). In this regard, the main effect of their use is not treatment but a long-term suppression of tumor growth or, at best, a decrease in tumor mass. This diminishes their potential importance since the transition of cancer to a state of chronic disease is a more attractive goal than achieving a complete cure [3].

However, the therapeutic benefit of this treatment is still debated. At the beginning of our millennium, an active study of the issues of chemotherapy optimization for malignant neoplasms, the choice of the best regimens and combinations continues. However, predicting chemotherapy sensitivity is a challenging trend.

The study aimed to provide a complete overview of the benefits and expectations of targeted therapies in oncology practice.

Guiding Principles of the treatment method:

1. Interruption of chemical reactions that regulate the growth and division of atypical cells. The result of the process is the cessation of the development of neoplasia.

2. Targeted action on epidermal growth factors (EGFR) and vascular endothelial growth factor (VEGF) receptors.

3. Prevention of the formation of the vasculature that feeds cancer.

4. Activation of the body's immune resources to destroy degenerate cellular structures.

5. Destruction of tumor cells from the inside. The drug is made up of molecules. They have a toxic effect by binding to tumor cell receptors.

6. Inhibition of tyrosine kinase of the receptor intracellular domain leads to blockade of phosphorylation disrupts signal transmission from the receptor to molecules that carry out intracellular signal transmission.

7. It should provide intracellular inhibition of proteins that transmit intracellular signals [4].

Methods: The sources were searched in the following databases: Scopus, Medline, Cochrane, PubMed, ScienceDirect. The search depth was five years: the interval from 2016 to 2021. The study is based on published sources that have undergone a critical review process, research by scientists, articles in scientific journals of open access, evidence-based materials, abstracts and newspaper articles, and analysis of abstracts of reports at scientific forums. Sources were searched for the following keywords: clinical trials, immunotherapy, monoclonal antibodies, small molecular weight inhibitors, and targeted therapy.

Results:

Growth factor receptor inhibitors

Research on the epidermal growth factor (EGF) family and the receptor (EGFR) family has rapidly developed in recent years. New crystal structures of ectodomains with various ligands, activation of the kinase domain by oligomerization, and fluorescence techniques upon ligand binding revealed profound conformational changes. The control of cell signaling from the EGFR family is complex, with heterodimerization, ligand proximity, and opposing hindrances affecting cell outcomes. Some members of the EGFR family are overexpressed or mutated in cancer cells. Signaling disorders in the EGFR family drive the malignant phenotype of many cancers, and both inhibitors of these receptors and signaling antagonists have therapeutic effects in patients. The design of EGFR-family-targeted affinities, antibodies, small molecule inhibitors, and even immunotherapy has provided promising new approaches to improve outcomes for cancer patients. It has been shown that ionizing radiation is activated and interacts with the receptors of many growth factors and affects the tumor response to therapy. Among these receptor interactions, EGFR has been extensively studied in the last decade and received many clinical applications. The combination of radiation and EGFR targeting agents, using monoclonal antibodies (mAbs) or small molecule tyrosine kinase inhibitors (TKIs), provides a promising approach to improve tumor control over radiation alone. After combined treatment, several underlying mechanisms have been identified, enhancing antitumor activity. These include cell cycle propagation, apoptosis, tumor cell repopulation, DNA damage or repair, and the effect of the tumor on the vasculature. However, like virtually all anticancer drugs, patients who initially respond to EGFR-targeted drugs may develop resistance and indicate cancer progression. Several possible resistance mechanisms have been identified, including mutations in EGFR and downstream signaling molecules and activation of alternative tyrosine kinase receptors associated with organs bypassing EGFR signaling inhibition. Several strategies to overcome resistance in preclinical and clinical models are currently being studied, including agents, those targeting the t790 M EGFR stability mutation or targeting multiple members of the EGFR family, as well as agents targeting other receptor tyrosine kinases and areas of low signaling. Growth factor receptors are represented by a large group of different transmembrane proteins localized in cell surface membranes and have three receptor parts. Growth factor receptors are activated after binding to the ligand and receptor required, as well as by activating several special RAS/RAF/MAPK, STAT, and PI3K/AKT pathways to pass the mitogenic signal into the cell (Figure 1) [5, 6].

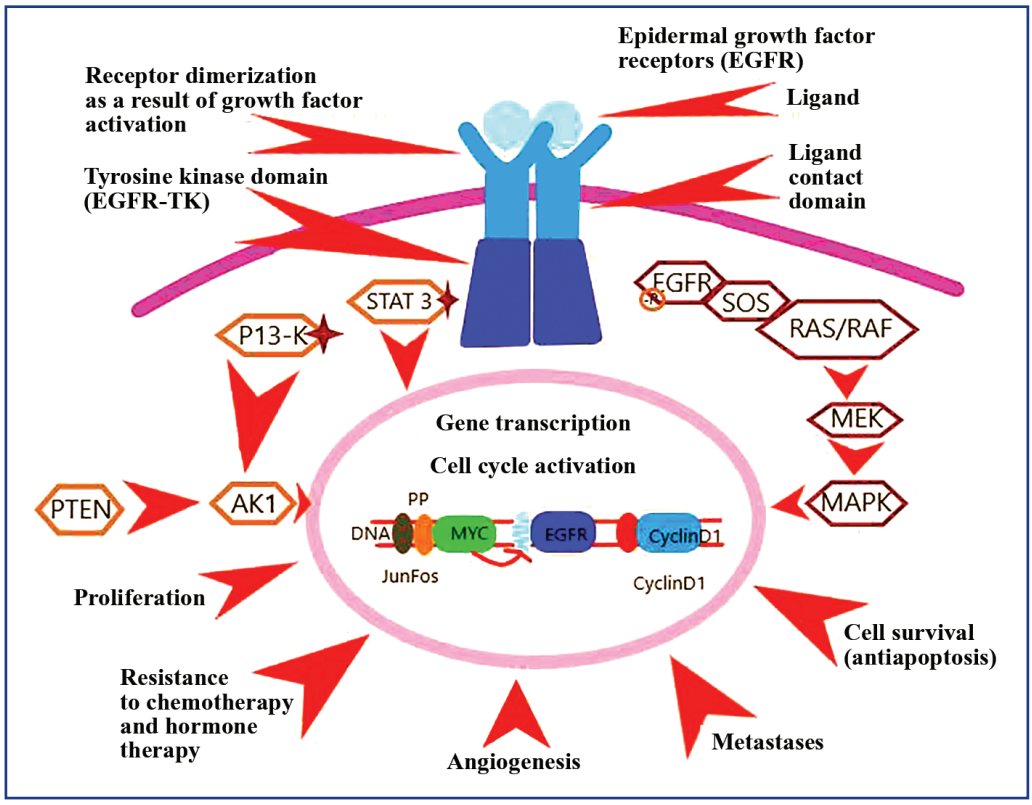

Figure 1 – Method of binding EGFR receptors with ligands and corresponding receptors [6]

The VEGF signal is activated in endothelial cells by binding VEGF receptors to tyrosine kinases (VEGFR1-3). In tumors, hyperactivity of the signal from these receptors is often noted. This phenomenon results from several factors, particularly persistent active overexpression due to excessive amounts of ligand caused by tumors and receptor mutations and independent contact with the ligand [7].

Angiogenesis and the role of VEGF as a therapeutic target in cancer

Cancer cells are radically different from normal cells in that they have unique features that ensure the growth and development of the tumor. Due to high metabolic demands, growing solid tumors require nutrients and oxygen associated with vascularity and remove metabolic products. Vascularisation can promote angiogenesis, that is, the formation of new blood vessels by sprouting from existing blood vessels. Angiogenesis plays a vital role in forming new vessels during embryogenesis in normal physiology. However, it is primarily dormant during wound healing that is temporarily activated in adults and during the female reproductive cycle. Although angiogenesis is tightly controlled by a complex interplay of PRO and anti-angiogenic factors, it can be activated with the growth of solid tumors; this "angiogenic connector" is recognized as a feature of solid tumors. Among the pro-angiogenic factors secreted by the tumor, VEGFs, in particular VEGF-a, have been identified as the main factors in the induction of tumor angiogenesis. Activates the VEGF signal in endothelial cells by binding VEGF receptors to tyrosine kinases (VEGFR1-3). Thus, VEGF stimulates the reproduction and survival of endothelial cells and increases vascular permeability, thereby supporting the metabolic needs of a growing tumor. Given the importance of angiogenesis in tumor biology, drug development efforts in recent decades have been directed against angiogenesis with VEGF-A as a therapeutic goal of inhibiting angiogenesis and normalizing the tumor vasculature. The validity of this approach is confirmed by in vivo studies in several tumor models that inhibiting angiogenesis by monoclonal antibodies to VEGF also inhibited tumor growth. The influence of VEGF is significant; it is considered a "direct stimulator" of angiogenesis. High levels of vascular endothelial growth factor are found in many tumors (colon cancer, breast cancer, stomach cancer, lung cancer). Finally, hypoxia and oxidative stress conditions are characteristic of the tumor [8].

The role of VEGF, independent of angiogenesis, in the development and progression of cancer

A tumor has a complex and interactive microenvironment composed of various cells, including endothelial cells, pericytes, immune cells, fibroblasts, and an extracellular matrix. Cancer cells impact their microenviron-

ment by releasing extracellular signals to induce tumor angiogenesis, stimulate tumor cell proliferation, and increase immune endurance to prevent immune system recognition.

Recent studies have shown that VEGF signaling, in particular VEGF-α signaling, plays an additional role, independent of angiogenesis, in supporting tumor development, e.g., vascular endothelial (VEGFR) 1, tumor stem cells; VEGFA/stem stimulation by neuropilin-1 pathway activation and self-renewal by VEGFR2/STAT3 signaling, immune cells; immune suppression in a small tumor environment by VEGFR signaling in hematopoietic cells (VEGFR1), dendritic cells (VEGFR3), macrophages (VEGFR1 and VEGFR3), t cells (VEGFR-1 and VEGFR-2), and regulatory t cells (VEGFR1, VEGFR1, and VEGFR2). In particular, VEGF signaling suppresses the immune system through many mechanisms, including aberrant hematopoiesis, impaired maturation and function of dendritic cells and T cells, inhibition of the transport and survival of activated T cells, and stimulation of the activity of immunosuppressive cells such as regulatory T cells and myeloid suppressor cells. Given its role in enhancing immune resistance to cancer, VEGF/VEGFR has been recognized as a method to enhance immunity to cancer, especially in combination with cancer immunotherapy that has been recognized in dendritic cells (VEGFR3), macrophages (VEGFR1 and VEGFR3), T cells (VEGFR-1 and VEGFR-2) and regulatory T cells (Vegfr1, VEGFR1, and VEGFR2) immune suppression in a small tumor environment by VEGFR signaling [9].

Development of Bevacizumab as first-line therapy targeting VEGF

The first anti-angiogenic drug available is a humanized monoclonal antibody, Bevacizumab (Avastin), which binds to all circulating soluble isoforms of VEGF-A. Bevacizumab is a recombinant humanized monoclonal antibody against VEGF. By binding to VEGF-A, Bevacizumab prevents the interaction of VEGF-A with VEGFR and thereby blocks the activation of VEGF signaling pathways that contribute to neovascularisation (Fig. 2). In vivo studies have shown that Bevacizumab slows vascular growth, induces regression of newly formed vessels, normalizes the vasculature to facilitate the delivery of cytotoxic chemotherapy, and directly affects tumor cells. Based on its mode of action, the clinical development of Bevacizumab is directed at the types of tumors caused by angiogenesis. In particular, the vital role of VEGF in cancer progression has been confirmed by the association of intrapunctural manifestations of VEGF with poor prognosis or an aggressive disease in several types of solid tumors, including metastatic colorectal cancer, small-cell lung cancer, metastatic breast cancer, glioblastoma multiforme, and ovarian cancer. In addition, renal cell carcinoma is recognized as a high vascular cancer with hypoxia-induced factor dysregulation, resulting in a higher VEGF expression. Initially approved for the treatment of metastatic colorectal cancer combined with chemotherapy, its indications now include metastatic breast cancer, non-small-cell lung cancer, glioblastoma, renal cell carcinoma, and ovarian and cervical cancer.

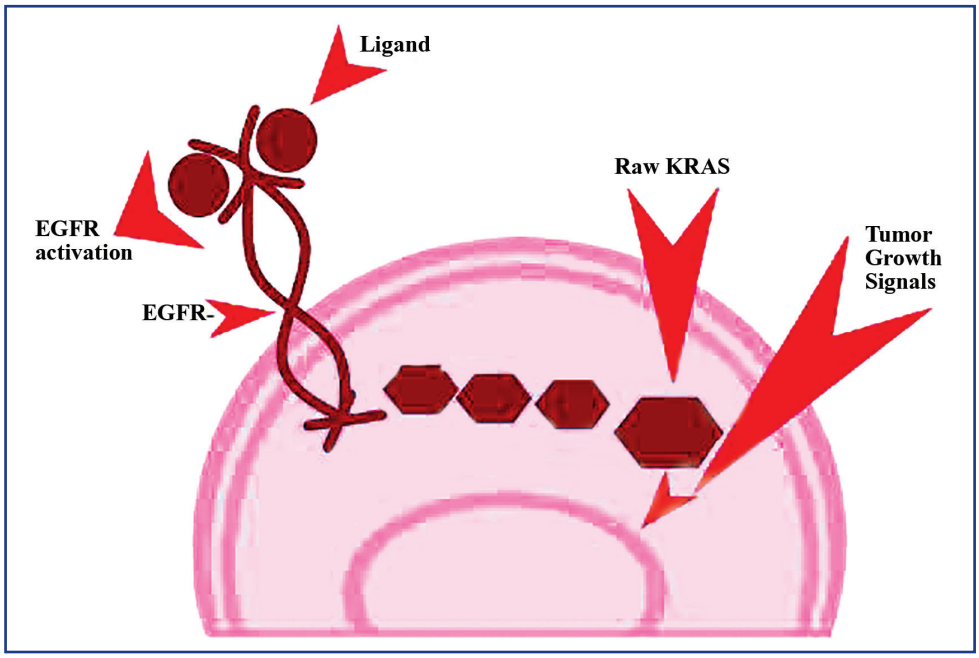

Figure 2 – Myogenic signal transmission and interruption in contact with EGFR [10]

Over the past 15 years, our understanding of the VEGF's role in the tumor microenvironment has changed. We know that VEGF plays a vital role in controlling blood vessel formation and modulates tumor-induced immunosuppression. The immunomodulatory properties of Bevacizumab have opened up new perspectives for combination therapy approaches being explored in clinical trials. In particular, the combination of Bevacizumab with cancer immunotherapy has recently been approved for the treatment of non-cellular lung cancer, and clinical benefit has also been demonstrated for hepatocellular carcinoma treatment. However, despite intensive research, reliable and validated biomarkers that allow Bevacizumab to be used alone remain difficult. Overall, Bevacizumab is expected to remain the mainstay of cancer therapy [12].

Thyrone kinase inhibitors form a highly active chemical p210bcr/ABL that leads to the formation of a protein in hematopoietic progenitor cells that disrupt the normal functioning of the cell and its malignant cells changes. Over time, cells with p210bcr/ABL cancer crowd out normal stem cells, resulting in a clinical and hematological picture of chronic myelogenous leukemia. Imatinib was created as a drug for this disease treatment since it has a high inhibitory activity against p210 protein tyrosine kinase [13].

Imatinib, a small molecule tyrosine kinase inhibitor, was found to inhibit the tyrosine kinase of several receptors, particularly the c-kit stem cell receptor, during drug research. The functions of the c-kit are similar to those of other growth factor receptors - regulation of proliferation, differentiation, cell adhesion, and apoptosis [14].

In the late 1990s, a mutant c-kit oncoprotein appeared on the surface of stromal tumor cells of the gastrointestinal tract, which led to the uncontrolled proliferation of these tumor cells. Mutated c-kit occurs in 85-90% of gastrointestinal stromal tumors. These data formed the basis for the study and subsequent introduction of the efficacy of imatinib for the treatment of stromal tumors of the gastrointestinal tract [15].

Targeted drugs that inhibit proteins that support mitogenic signaling

mTOR is an intracellular protein called serine-threonine kinase. Downstream signaling integrator. Dysregulation of mTOR leads to various diseases, including various types of cancer. The mTOR signaling pathway plays a vital role in the pathogenesis of kidney cell cancer (PKR) [16].

The following groups of targeted drugs are used in cancers:

1. Monoclonal antibodies are protein structures produced by immune cells that block receptors that control tumor growth. For drug production, genetic engineering technologies are used. The choice of the treatment regimen is determined by the results of immunohistochemical and molecular genetic analyses. The prominent representatives of the group are Cetuximab, Panitumumab, and Trastuzumab [17].

2. Small molecule inhibitor. The drug is synthesized in the laboratory and penetrates the cell, neutralizing the mechanisms of cell division or protein synthesis. Imatinib, Dabrafenib, and Sunitinib [18].

Table 1 describes the targeted drugs used in clinical practice.

Table 1 – Targeted drugs used in clinical practice [19]

Medicines	Target	Antitumor effect (spectrum)
Monoclonal antibodies to growth factors and their receptors		
Trastuzumab (Herceptin)	HER2 (EGFR2)	Breast cancer (HER2+), stomach cancer (HER2+)
Pertuzumab (Perjeta)	HER2 (EGFR2)	Breast cancer (HER2+)
Cetuximab (Erbitux)	EGFR1	Colorectal malignancies, head and neck tumors
Panitumumab (Vectibix)	EGFR	Colorectal malignant tumors
Bevacizumab (Avastin)	VEGF	CMT, non-cellular lung cancer, kidney cancer, glioblastoma
Aflibercept (Zaltrap)	VEGF(VEGF-A, VEGF-B, PIGF)	CMT
Monoclonal antibodies to non-receptor antigens (phenotypically oriented)		
Rituximab (MabThera)	CD20	B-cell non-Hodgkin's lymphomas, chronic lymphocytic leukemia
Alemtuzumab (Campas)	CD52 B and T cells	B-cell CLL. T-cell proliferative LL
Ofatumumab (Arzerra)	CD20 B cells	CLL, CD20, B-cell non-Hodgkin's lymphomas
Ibritumomab (Zevalin)	CD20	B-cell non-Hodgkin's lymphomas
Ipilimumab (Yervoy)	CTLA-4	Melanoma
Denosumab (Exgiva)	RANK-L	Large cell bone cancer
Small molecule kinase inhibitors (signaling inhibitors)		
Erlotinib (Tarceva)	TK EGFR1	Non-small-cell lung cancer (with a mutation in the EGFR gene), pancreatic cancer
Gefitinib (Iressa)	TK EGFR1	Non-small-cell lung cancer (with a mutation in the EGFR gene)
Afatinib (Giotrif)	EGFR1	Non-small-cell lung cancer (with a mutation in the EGFR gene)
Lapatinib (Tyverb)	HER2 (EGFR2) EGFR1	Breast cancer (HER2+)

End of Table 1

Crizotinib (Xalkori)	RTKsALK,c-MET, RON	Non-small-cell lung cancer with ALK dislocation
Imatinib (Filachromin)	BCR-ABL, PDGFR, c-kit	CML Ph+, GIST
Dasatinib (Sprycel)	BCR-ABL, PDGF	CML Ph+
Nilotinib (Tasigna)	BCR-ABL	CML Ph+
Sorafenib (Nexavar)	RAF/MEK/ERR,VEGFR2, PDGFR	Renal cancer, hepatocellular carcinoma
Sunitinib (Sutent)	VEGFR, PDGFR, c-kit	GIST, pancreatic NET, kidney cancer
Pazopanib (Votrient)	VEGFR, PDGFR	Kidney cancer, soft tissue sarcoma
Axitinib (Inlyta)	VEGFR1, VEGF2, VEGFR	Renal cell carcinoma
Vandetanib (Caprelsa)	EGFR,VEGF,RET	Medullary thyroid cancer
Regorafenib (Stivarga)	VEGFR 1,2,3; PDGFRα,β; TIE 2, c-kit, RET, RAF, BRAT; FGFR 1.2; DDR2TrLA, Eph2A, SAPK2; PTR2; ABL.	Colorectal malignancies, GIST
Temsirolimus (Torizel)	mTOR	kidney cancer
Cabozantinib (Comometric)	TKs, RET, MET, VEGF 1,2,3; KIT, FLT3,AXL, TIE-2.	Medullary thyroid cancer
Dabrafenib (Tafinlar)	BRAF	Melanoma BRAFV 600E with mutation
Vemurafenib (Zelboraf)	BRAF V600E	Melanoma BRAFV 600E with mutation
Everolimus (Afinitor)	mTOR	Giant cell astrocytoma, kidney cancer, SBO, (pancreatic NET) PNET
Vismodegib (Erivedge)	Hedgehog signal-ing path-way protein	Basal cell carcinoma
Proteas Inhibitors		
Bortezomib (Bar-tizarBoramilan, Velcade)	Proteasome 26S	Multiple myelomas, lymphomas
Carfilzomib (Kyprolis)	Proteasome 26S	Multiple myelomas, lymphomas

Targeted therapy for breast cancer

Anti-HER/2 drugs - qualitative (mutations) or quantitative (overexpression, amplification) changes in the HER/2 epidermal growth factor receptor family are among the most unfavorable breast cancer molecular biological characteristics. It was observed in 20-30% of cases of invasive breast cancer that it causes a significant deterioration in the relapse-free and general life of patients and the worst efficiency of standard therapy [20].

The use of trastuzumab (monoclonal antibodies to the extracellular domain her/2) for the first time in the last 30-40 years has significantly increased the overall survival of patients with metastatic breast cancer. When used adjuvantly in early-form and HER/2-positive breast cancer patients, trastuzumab halved the relative risk of disease recurrence. Unfortunately, some trastuzumab patients have primary or acquired tumor resistance to ongoing anti-HER/2 therapy. Primary resistance is usually understood as the primary lack of effect, and acquired resistance develops during therapy or after its completion. The main mechanisms for the development of resistance to trastuzumab are a structural change in the extracellular domain of the HER 2 receptor that occurred in the primary or therapeutic process. [21].

The creation of Lapatinib, a small molecule that inhibits the tyrosine kinase of two types of EGFR receptors (her/1 and her/2), was determined by the following theoretical assumptions: the use of drugs that target several targets at once is preferable, as it can prevent or delay the emergence of resistance. The HER-2 encapsulation strategy has been so successful that it is currently the most actively studied area in breast cancer. The idea of dual blockade of the HER/2 receptor (extracellular domain and tyrosine kinase domain) was reflected in the awe-inspiring results of the combination of trastuzumab and Lapatinib. Considering that other EGF family receptors (except HER/2) are involved in the mechanisms of breast cancer progression, the efficacy of neratinib, an irreversible inhibitor of pan-HER tyrosine kinase, is currently being studied. Unlike some other multitargeted tyrosine kinase inhibitors, Neratinib is effective in monotherapy in patients who have not previously received trastuzumab and in patients progressing during treatment with Trastuzumab [22].

One of the reasons why tumor cells are resistant to chemotherapy is their ability to repair DNA damage caused by chemotherapy. The suppression of the ability to repair the damage is based on the mechanism of a new class of anticancer drugs, the PARP inhibitor. By inhibiting the activity of PARP (an enzyme responsible for the repair of single-strand breaks in DNA), in preclinical studies, they significantly increased the cytotoxicity of chemicals. Anti-angiogenic therapy for breast cancer. One of the ways to treat breast cancer does not affect tumor cells but the process of neovascularization in the tumor - angiogenesis. So far, only one drug with this mechanism of action, Bevacizumab, has been registered for breast cancer treatment [23].

Targeted therapy in the treatment of lung cancer

In the structure of male diseases in the country, lung cancer consistently ranks first. In addition, in 60-70% of cases, the disease is more common at diagnosis (IIIb-IV-sat). Chemotherapy increases patient survival by only 2-3 months compared to maintenance therapy. The response rate decreases with each successive chemotherapy regimen in small-cell lung cancer. Lung cancer is the leading cause of cancer death. It is divided into various histological subtypes, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma (commonly referred to as non-small cell lung carcinoma), and small cell lung carcinoma. In addition, comprehensive molecular characterization of lung cancer has expanded our understanding of the cellular origin and molecular pathways that affect each of these subtypes.

Gefitinib (Iressa) is widely used to treat local or metastatic non-cellular lung cancer. Some studies have been reported on its pharmacokinetic profiles, especially metabolism. Overall, Gefitinib rapidly reached peak plasma levels and was widely adopted. It underwent wide biotransformation and was excreted mainly with feces, less than 7% – with urine. CYP450 enzymes play a critical role in the metabolism of Gefitinib. The main enzyme involved in metabolism was CYP3A4, while other CYP450 enzymes played a minor role. High clearance of Gefitinib may lead to drug resistance due to decreased drug concentrations. Improved fluidity and reduced uptake of vectors were essential mechanisms for resistance. Carriers involved in the pharmacokinetics of Gefitinib consist of an ATP-binding cassette and a superfamily of dissolved carriers. Understanding the pharmacokinetic properties of Gefitinib can provide valuable and new information to combat drug resistance and personalized therapy concerning their variability [25].

Gefitinib is an EGFR inhibitor resistant to chemotherapy (Figure 3). Gefitinib is well-tolerated and active in patients with small-cell lung cancer. On the other hand, Gefitinib is an interstitial lung disease in less than 2% of untreated patients. Given these circumstances, it is essential to evaluate this drug and determine its clinical use. However, we do not currently have sufficient data to evaluate Gefitinib. This evaluation requires a trial of maintenance therapy using phase III of the second and third route or Gefitinib. The development of individual therapy with Gefitinib may also be required [26].

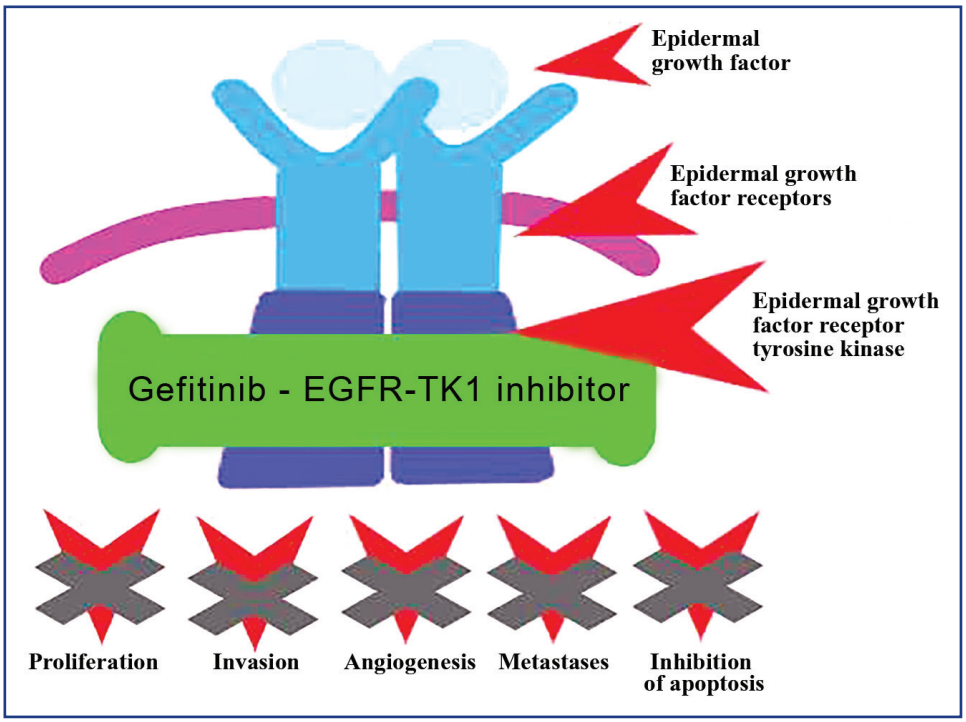

Figure 3 – Gefitinib mechanism of action [27]

Erlotinib (Tarceva) has similar effects. US FDA recommends Erlotinib (OSI-774), marketed as Tarceva, as a drug for treating non-cellular lung cancer and pancreatic cancer. Erlotinib inhibits EGFR, which represses tumor cell division, induces cell cycle arrest, and initiates programmed cell death in human tumor cells [28].

Ways to use targeted therapy for tumors of the gastrointestinal tract

Despite progress in treating many solid tumors, the success of medical treatment of gastrointestinal tumors does not always matter. Chemotherapy for many tumors has peaked, and targeted therapy may be used to improve treatment in the future.

Despite recent advances in the treatment of colorectal cancer, metastatic disease remains challenging, and patients are rarely treated. However, a good understanding of the pathways involved in cancer cell evolution and reproduction has led to the development of targeted treatments, which opened the way to recognizing agents whose activity is directed along these pathways. This approach is more characteristic of cells because pathways, such as EGFR, are very active and contradict the relatively undetermined mechanism by which cytotoxic chemotherapy affects rapidly dividing cells, regardless of their role. Patient-specific factors such as the location of the primary tumor (unilaterality) or the presence of mutations that provide stability may limit the use of these agents. However, targeted therapy is now part of the metastatic colorectal cancer treatment paradigm, significantly improving survival outcomes. The mechanism of action of drugs is the same. By binding to the extracellular domain of EGFR, they prevent its binding to the natural ligand and thereby prevent receptor dimerization and subsequent autophosphorylation of intracellular receptor domain tyrosine kinases. As a result, there is no activation of the proteins included in the signaling cascade, the cell does not receive a proliferative signal, does not split, and ultimately apoptosis occurs [29].

Clinical studies have shown that Cetuximab and panitumumab are effective in only 10-30% of colorectal cancer patients, despite EGFR overexpression found in 70-75% of colon tumors. In a particular clinical study, it was found that Cetuximab does not depend on the number of cells responsible for therapy nor the distribution density of these receptors in the membrane. The study of the causes of this phenomenon made it possible to establish that it is associated with an activating mutation of the Ras proto-oncogene located on the 12th chromosome and the formation of a mutated KRAS protein in the cell. In addition, activated KRAS transmits mitogenic signals by turning on various signaling lines. When EGFR interacts, instead of the usual ligand, Kras with the antibody is not activated, so the cell does not receive the necessary signal that is achieved by suppressing proliferation and apoptosis (Figure 2) [30].

In the treatment of colorectal cancer, another targeted drug is Bevacizumab (Avastin), an inhibitor of neoangiogenesis and, therefore, inhibits the formation of new blood vessels that are very important for tumor growth [31].

Targeted therapy for kidney cancer

The problem of treating common forms of kidney cell cancer is significant in clinical oncology. Regarding the growth of cancers in Kazakhstan, kidney cancer consistently ranks third, and in 50% of all cases, the disease becomes metastatic. The standard of living of patients with metastases is also disappointing: the median overall survival and the level of 5-year survival do not exceed 12 months and 5%, respectively [31]. However, until recently, non-specific immunotherapy using alpha interferons and interleukin-2, both in single regimens and in combinations, was the standard for disseminated drug treatment by only 15% with a relatively low average frequency of objective effects. In addition, the emergence of new knowledge in molecular biology has revealed the involvement of some signaling pathways in the development and pathogenesis of kidney cell cancer [32].

Over the past 12 years, kidney cancer treatment has shifted from a non-specific immune approach (in the era of cytokines) to targeted therapy against VEGF, and today – to new immunotherapy agents. After the VHL mutations and the activation of VEGF, PDGF, and other genes involved in angiogenesis, cell growth, and survival were discovered, several targeted therapies have been successfully developed to improve clinical outcomes in patients with multi-target small molecule TKIs against mpkr/VEGF receptors (VEGFR), PDGF receptors (PDGFR) and other kinases (sunitinib and pazopanib); VEGF (VEGFR) inhibitory monoclonal antibody (VEGF) Bevacizumab). New options were suggested for patients not treated with temsirolimus, a low-risk mTOR inhibitor with mostly mild cellular histology. All treatments were compared to the standard of care over time, except for Pazopanib, since placebo turned out to be a preferred option compared to sunitinib in a Phase II study. Pazopanib was as effective as sunitinib, and quality of life data favored pazopanib. A study showed a significant patient benefit of Pazopanib over Sunitinib, and quality and safety of life were identified as critical influencing factors [33].

Despite the different mechanisms of action, the toxicity of these treatments shared some common symptoms: fatigue, asthenia, anorexia, nausea, and diarrhea. Medullary toxicity, including anemia, leukopenia, and thrombocytopenia, is familiar with Sunitinib/pazopanib; Bleeding was common with Bevacizumab, and frequent rash and shortness of breath with temsirolimus. Hypertension has been frequently observed with all VEGF inhibitors.

Another tyrosine kinase inhibitor, Sorafenib, should be used as a second line of treatment for kidney cell cancer. Sorafenib is a multipurpose tyrosine kinase inhibitor used primarily to treat advanced hepatocellular carcinoma and renal cancer. However, hand and foot skin reactions (HFSR), as one of the most common ad-

verse reactions, preclude the long-term clinical use of Sorafenib. Currently, the mechanism of its occurrence is not clearly understood, leading to the lack of adequate means of intervention. This article reviews the known mechanisms and treatments for sorafenib-induced HFSR. When the mechanism of HFSR is not understood, the most common sorafenib-induced clinical treatment is dose reduction or discontinuation of treatment that affects the efficacy and even survival [34].

Discussion: Targeted therapy is a treatment with drugs that inhibit the growth and spread of tumor cells by acting on specific molecules involved in the growth and development of tumor cells. This type of treatment can be much more effective than many other cancer therapies, including chemotherapy and radiation therapy because targeted therapy targets specific molecules in a cancer cell. Another essential feature is that targeted therapy has little effect on healthy cells in the body.

Like other body cells, tumor cells need oxygen to survive and reproduce, and targeted drugs prevent their access to tumor tissues. The mechanism of action is that these drugs inhibit the growth of micro-vessels in cancerous tissues and prevent the development of the primary tumor and its metastases. Sutent and Nexavar target tyrosine kinase enzymes and are involved in intracellular signaling cascades. The mechanism of action of both drugs is similar but not identical since the spectra of inhibited kinases do not entirely match. Thus, sunitinib which inhibits VEGF, PDGF, c-KIT, and other tyrosine kinase domains, has an anti-angiogenic effect that prevents the formation of vessels in the tumor tissue. In addition to specific tyrosine kinases, sorafenib targets include serine-threonine Raf kinase; thus, Sorafenib is not only an inhibitor of angiogenesis but also an inhibitor of tumor cell proliferation. Over the past 15 years, about twenty specific molecular inhibitors have been introduced into clinical practice. In addition, more than a hundred targeted drugs are currently undergoing various stages of clinical trials.

Conclusion: Targeted therapy is one of the components of drug therapy. There is an alternative meaning to "biological therapy" in the medical literature. It means that the drugs used are biopharmaceuticals. This fact shows a significant difference between chemotherapy and targeted therapy. Cytostatics inhibit the reproduction of all rapidly dividing cells.

Moreover, targeted drugs act at the molecular level. Their purpose is to select tumor cells and prevent the growth of the tumor vasculature. These drugs are combined into one targeted drug for certain types of cancer: antibody-based drugs contain both a biological and a cytostatic component. Targeted therapy involves immune mechanisms classified as immunomodulators - drugs that stimulate the body's immune resources.

This method gives a positive result when using cytostatics and radiation (radiation therapy), with surgical intervention - before or after execution. There is a minimum number of side effects when using targeted therapy. Its appointment is possible in cases that are contraindicated in cancer patients with severe somatic pathology and other therapeutic measures. The essence of the method is to recognize atypical cells at the molecular level. Active ingredients of drugs used in targeted therapies bind to specialized proteins. The molecular targets of these cells are already being used to develop a new type of targeted therapy. One of the problems hindering the effective use of targeted therapy is the comprehensive connection of signaling pathways that allows part of the tumor cells to use other proliferative signals and mutations that occur in the receptors that can lead to loss of sensitivity of the tumor cell to the signaling inhibitor. In this regard, a more in-depth research is required to study molecular biology, the mechanisms of its multifaceted, multilateral effects, and signaling pathways that determine the pathogenesis of the most common cancers.

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ТҰЖЫРЫМ

ОНКОЛОГИЯЛЫҚ ТӘЖІРИБЕДЕГІ МАҚСАТТЫ ТЕРАПИЯНЫҢ АРТЫҚШЫЛЫҚТАРЫ МЕН ҮМІТТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Қазіргі уақытта қатерлі ісік әлемдегі өлімнің екінші жетекші себебі болып табылады және 2022 жылы шамамен 19,3 миллион жаңа ауруға және 10 миллион өлімге жауап береді деп күтілуде. Адамның қатерлі ісігінің дамуы мен дамуын басқаратын молекулалық жолдарды түсіну арқылы жаңа емдеу тәсілін мақсатты терапия қатерлі ісікке қарсы медицина саласындағы жаңа жетістіктерге айналды. Адамның қатерлі ісігінің дамуын және прогрессиясын қозғаушы молекулалық жолдарды түсіну арқылы жаңа мақсатты терапия онкологиялық медицинадағы таңғажайып жаңа жетістіке айналды. Бұл мақсатты емдеу, сонымен қатар биологиялық емдеу деп те аталады, қатерлі ісік жасушаларының өсуін тежейтін, жасушалардың өсуіне және туморигенезге қажетті молекулаларға бағытталған медициналық емдеудің негізгі әдісі болды. Өзінің ерекшелігінің арқасында бұл жаңа емдеу басқа емдеу әдістерімен, соның ішінде гормондық терапиямен және химиятерапиямен салыстырғанда шектеулі жанама әсерлері және тиімділігі жоғары терапия болады деп күтілуде.*

Берілген зерттеудің мақсаты: *Онкологиялық тәжірибеде мақсатты терапияның артықшылықтары мен үміттері туралы шолумен қамтамасыз ету.*

Әдістері: *Іздеу 2016-2021 жылдарға арналған Scopus, Medline, Cochrane, PubMed және ScienceDirect дерекқорларында жүргізілді. Дереккөздерді іздеу келесі кілт сөздер бойынша жүргізілді: клиникалық сынақтар, иммунотерапия, моноклоналды антиденелер, төмен молекулалы ингибиторлар, мақсатты терапия.*

Зерттеу нәтижелері: *Бұл шолуда біз мақсатты қатерлі ісік терапиясының клиникалық дамуын, жетістіктері мен қиындықтарын, соның ішінде төмен молекулалар ингибиторларын және мақсатты антидене терапияларын зерттейміз. Мұнда біз эпидермальды өсу факторы рецепторларын, тамырлы эндотелий өсу факторына, адамның эпидермальды өсу факторы 2 рецепторларын, анапластикалық лимфома киназасын, BRAF және Т-жасушалық делдалдық иммундық реакция ингибиторларын, цитотоксикалық Т-лимфоцитарлық байланысқан ақуызды және бағдарламаланған жасуша өлімі ақуызын-1/лиганд PD-1 енгіземіз.*

Қорытынды: *Соңғы онжылдықта онкологиялық ауруларды емдеуде айтарлықтай өзгерістер болды, оның ішінде таргеттік терапия кеңінен қолданыла бастады. Алайда, монотерапияда мақсатты препараттар төмен белсенділікті көрсетеді. Сонымен қатар, мақсатты терапия үшін пациенттерді таңдау қиын міндет болып қала береді, өйткені көптеген мақсатты агенттердің әрекетін болжау үшін сенімді биомаркерлер жетіспейді. Осыған байланысты онкологиялық аурулардың патогенезін анықтайтын молекулярлық биология мен сигналдық жолдарды толығырақ зерттеу қажет.*

Түйінді сөздер: *Клиникалық сынақтар; Иммунотерапия; Моноклоналды антиденелер; Төмен молекулалы ингибиторлар; Мақсатты терапия.*

АННОТАЦИЯ

ПРЕИМУЩЕСТВА И ПЕРСПЕКТИВЫ ТАРГЕТНОЙ ТЕРАПИИ В ОНКОЛОГИЧЕСКОЙ ПРАКТИКЕ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак в настоящее время является второй ведущей причиной смерти в мире и, как ожидается, станет причиной примерно 19,3 млн. новых случаев заболевания и 10 млн. смертельных исходов за 2021 год. Благодаря беспрецедентному пониманию молекулярных путей, которые управляют развитием и прогрессированием рака человека, новые целевые методы лечения стали многообещающим новым достижением в области противораковой медицины. Эти таргетные (или биологические) методы лечения позволяют блокировать рост раковых клеток, специально нацеливаясь на молекулы, необходимые для роста клеток и генеза опухоли. Ожидается, что, благодаря своей специфичности, эти новые методы лечения обеспечат лучшую эффективность и меньшие побочные эффекты по сравнению с другими вариантами лечения, включая гормональную и цитотоксическую терапию.*

Цель исследования *– представить подробный обзор преимуществ и перспектив применения таргетной терапии в онкологической практике.*

Методы: *Поиск проводился в базах данных Scopus, Medline, Cochrane, PubMed, ScienceDirect за 2016-2021 гг. Поиск источников осуществлялся по следующим ключевым словам: клинические испытания, иммунотерапия, моноклональные антитела, низкомолекулярные ингибиторы, таргетная терапия.*

Результаты: *В этом обзоре авторы исследовали клиническое развитие, успехи и проблемы, стоящие перед таргетной противораковой терапией, включая как низкомолекулярные ингибиторы, так и таргетную терапию антителами. Представлены данные по таргетной терапии рецептора эпидермального фактора роста, сосудистого эндотелиального фактора роста, рецептора эпидермального фактора роста человека 2, киназы анапластической лимфомы, BRAF и ингибиторов Т-клеточного опосредованного иммунного ответа, цитотоксического Т-лимфоцитарного ассоциированного белка 4 и белка запрограммированной клеточной смерти-1/лиганда PD-1.*

Заключение: *За последнее десятилетие произошли серьезные изменения в лечении рака, в том числе более широко стала применяться таргетная терапия. Однако в монотерапии таргетные препараты показывают низкую активность. Кроме того, отбор пациентов для таргетной терапии остается сложной задачей, так как не хватает надежных биомаркеров для прогнозирования действия большинства таргетных агентов. В связи с этим необходимо более глубоко изучать молекулярную биологию, а именно сигнальные пути, определяющие патогенез онкологических заболеваний.*

Ключевые слова: *Клинические испытания; иммунотерапия; моноклональные антитела; низкомолекулярные ингибиторы; таргетная терапия.*

Transparency of the study: *Authors take full responsibility for the content of this article.*
Conflict of interests: *Authors declare no conflict of interest.*
Financing: *Authors declare no financing of the study.*
Authors' input: *contribution to the study concept – Uaisova A.R.; study design – Ergalieva A.M.; execution of the study – Uaisova A.R.; interpretation of the study – Murina A.I.; preparation of the manuscript – Murina A.I.*
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