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A Comprehensive Review on Novel Approaches In Cancer Treatment

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ABSTRACT

Cancer drug development is leading the way in exploiting molecular biological and genetic information to develop 'personalized' medicine. The therapies such as immunotherapy, gene targeted nucleic acid therapy, targeting angiogensis for treatment, chemotherapy are introduced for the treatment of cancer. In chemotherapy the drug new drug are introduced nivolumab, bevacizumab, belinostat, bilinatumomab.

Keywords: cancer treatment, immunotherapy, chemotherapy, targeting angiogensis, nucleic acid therapy.

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INTRODUCTION

At the current stage of modern medicine, one of the most important projects is to increase the effectiveness of cancer treatment by searching for and developing new therapies and improving traditional therapeutic approaches. A combination of surgery, radio- and chemotherapy is still the golden standard for cancer treatment, and these approaches have led to an 8-fold increase in patient survival over the last 30 years. The negative features of surgery-only treatment are recurrent tumors, the spread of metastases, and the formation of unresepctable malignant malformations. This forces doctors to use radio- and chemotherapy. Alas, even this combination of powerful cancer therapies often doesn´t bring positive results. Therefore, despite the undeniable achievements of modern oncology, increasing the effectiveness of cancer treatment is of utmost importance. [1]

During the last several decades, complex chemotherapy has become the main approach for treating cancer patients. Its use however is limited, despite the fact that it increases survival rates by 30% to 90%, depending on the type of malformation. The main hindrances are systemic toxicity, nonselective action (the effect is not specifically targeted towards tumor tissue), and the emergence of drug-resistant tumor cell clones. Recent discoveries have provided scientists with detailed knowledge of the molecular processes underlying carcinogenesis, tumor invasiveness, angiogenesis, and metastasis, as well as other processes, such as tumor suppression, growth control, apoptosis, and immune response. These data have led to the development of a new generation of chemotherapeutic drugs, such as Gleevec (aka Glivec or Imatinib mesylate), Mabthera (aka Rituximab), etc., which have a highly not20 years of research, and improving its selectiveness increases its cost manifold. [2]

RECENT TREATMENT IN CANCER

Immuontherapy

Immunotherapy in cancer is a type of treatment discovered in the 1970s, with the onset of bladder cancer therapy with BCG and IFN therapy in malignant melanoma. Various immune therapies such as IL 2 cytokine used in solid tumors like melanoma were discovered. A period of decline of these therapies followed, with powerful side effects and minor results. Along with studying the mechanisms of the immune response, there are cells involved in the immune response, mediators that cause stimulation or inhibition of the immune response, developing new therapies. Cancer immunotherapy involves the use of therapeutic modalities that lead to a manipulation of the immune system by using immune agents such as cytokines, vaccines, cell

therapies, and transfection agents. Immunotherapy of cancer: stimulates the host's anti-tumor response by increasing the effector cell number (like DC based vaccines) and production of soluble mediators (like increased tumor cell immunogenicity) and decreases the host's suppressor mechanisms by inducing tumor killing environment and by modulating immune checkpoints. Immunotherapy seems to work better in more immunogenic tumors. The article presents some new immunologic treatments in different types of cancers less presented in the latest conferences, cancers. Immunotherapies, also known as cancer vaccines, stimulate a patient's immune system to destroy cancer cells. In 2010, the FDA approved the first such vaccine –sipuleucel-T (Provenge) to treat advanced hormone-refractory prostate cancer. Because vaccines trigger an immune response, they may protect patients against metastasis and relapse. As with mAbs, their side-effects profile is generally mild, primarily limited to injection-site inflammation.[3]

Cancer stem cells

Cancer stem cells are cancer cells that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. It is often considered to be associated with chemo-resistance and radio-resistance that lead to the failure of traditional therapy [4]. There appear to be several sources from which cancer stem cells may arise. They may arise from normal ASCs (adipose-derived stromal cells), from more restricted progenitor cells or even from differentiated cells [5]. Normal stem cells are more likely to be the targets of mutants and leading to the formation of CSCs for they already posses active self-renewal pathways. It is also possible for progenitors and other differentiated cells to give rise to CSCs, though they would have to acquire more genetic mutations, especially in self-renewal genes. However, it has been hypotheses that CSCs arising from normal stem cells are more aggressive than those from progenitor cells, though this remains to be proven [6]. In cancer research experiments, tumor cells are sometimes injected into an experimental tens of thousands of cells to be introduced, however, only a small fraction of the injected.

Target signal pathways

Based on the research of the regulation mechanism of the cancer stem cell, cancer stem cells relied highly on the signal path ways' stability if they want to maintain the ability to self-renewal and differentiate. Some researchers have suggested that signal path ways' disorder or excessive activation may lead to the tumorigenicity. Understanding the mechanisms that underlie the self-renewal behavior of CSCs is of greatest importance for discovery and development of anticancer drugs targeting CSCs. During those pathways, Wnt, Notch and Hedgehog signaling pathways may play an important role in the recurrence and maintenance of cancer stem cell.

Though experimental evidence for CSC dependence on these pathways is limited, it will be important to develop CSC-selective therapies that avoid potential significant side effects caused by inhibition of normal stem cell function.

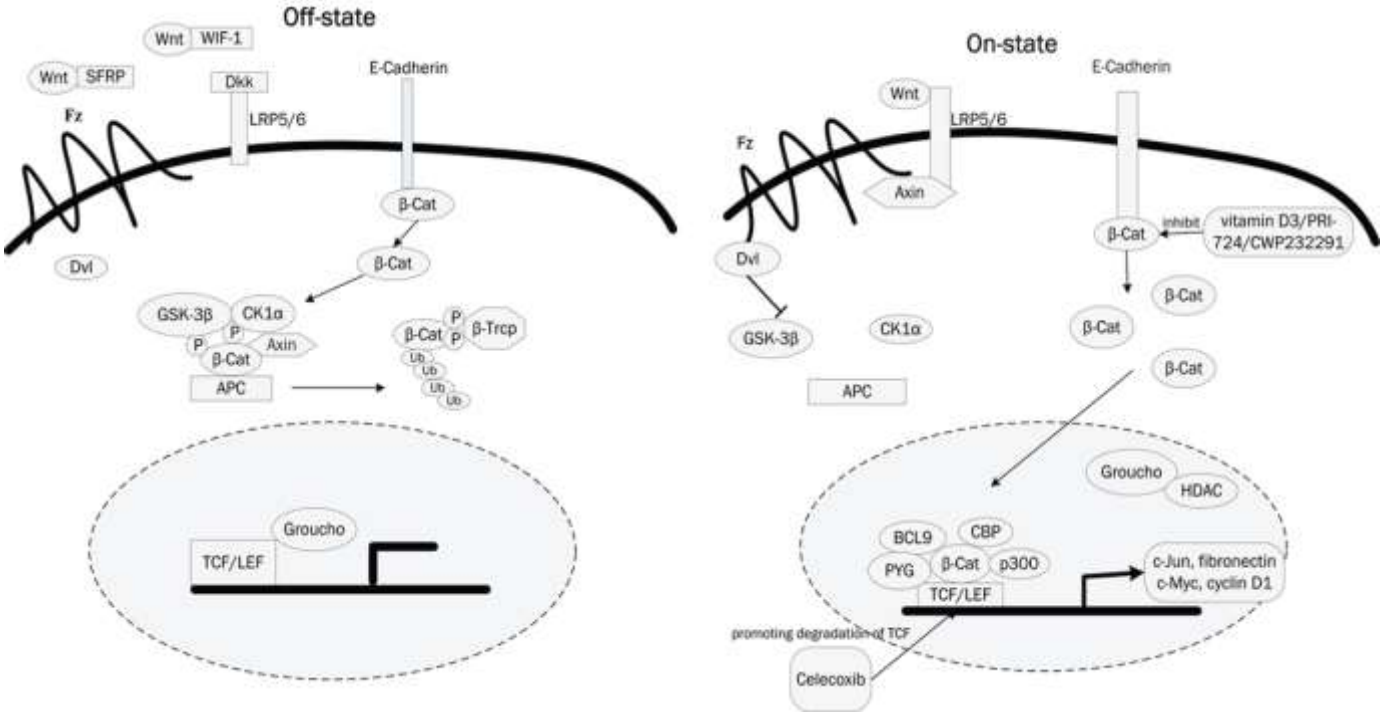


Figure 1: The Wnt/β-Catenin signaling pathway and their inhibitors.

A: In the off-state, Wnt ligands usually bind with soluble frizzled-related proteins (SFRP) and Wnt inhibitory factor-1 (WIF-1) which prevent them from interact with frizzled (Fz) receptors. Dickkopf (Dkk) interacts with low density lipoprotein receptor-related protein 5/6 (LRP5/6) to inhibit binding of Wnt ligands. β-Catenin that is not bound with cadherin is phosphorylated by a complex formed by casein kinase 1α (CK1α), glycogen synthase kinase-3β (GSK3β), adenomatous polyposis coli (APC), and Axin, then it is identified by β-TrCP and lead to the ubiquitin-proteasome pathway. B: In the on state, Wnts bind to and activate FZD (Frizzled) and LRP (LDL-related receptor protein) receptors on target cells. Phosphorylation of β-Catenin is suppressed and β-Catenin escapes from the degradation. Free cytoplasmic β-Catenin translocates to the nucleus, forms a complex with TCF/LEF, and activates the transcription of target genes, such as cyclin D1, c-myc, c-Jun, and fibronectin. The compounds vitamiD3, PRI-724, CWP232291 inhibit the β-Catenin that lead to the inhibition of Wnt/β-Catenin signaling pathway, and Celecoxi worked through promoting degradation of TCF.[7]

Gene-Targeted nucleic acid therapy

Antitumor drugs based on nucleic acids are highly specific tools which allow the gene expression to be regulated, and they have been attracting the attention of scientists as possible regulators of carcinogenesis at the molecular level. The suppression of several genes whose anomalously high expression is associated with neoplastic transformation can be achieved by nucleic acid-based drugs, such as antisense oligonucleotides (asON), small interfering RN As (siRN A), ribozymes, and DNA enzymes. Generally speaking, the mechanism of gene suppression by these drugs is the complementary binding of oligonucleotides to their mRN A target, which causes the target mRN A molecule to be destroyed or blocks its translation. AsON are synthetic single-strand DNA, 15–20 nucleotides long, and they can form a complementary complex with the target mRN A sequence 8. Protein synthesis is suppressed by asON due to the fact that the mRN A target is degraded by the intracellular RN ase H, which identifies the hybrid DNA/RN A complex, or due to a block of translation, since the formation of a hybrid complex hampers the ribosome's movement on the mRN A strand[9] Recently discovered asON can block the transfer of spliced mRN A from the nucleus to the cytoplasm; other asON can block a splicing site in pre-mRNA and thus cause the expression of an alternate protein product.

Mitomycin is used in cancer of bladder, breast, cervix, stomach, head, neck, lung and pancrease.

MitomycinM –

(i) Mitomycin C as a single agent was continually found to be active both first line and second line in therapy of advanced breast cancer including patients who had undergone prior chemotherapy;

(ii) The activity of MMC was modestly enhanced in combination with other agents, particularly anthracycline-type agents and vinca alkaloids;

(iii) Because of its cumulative myelosuppression, the use of MMC first line and for adjuvant use was not recommended;

(iv) There was the impression that when MMC was given with care to certain patients the side-effect profile was milder than other therapies and the quality of life was superior even if responses were short-lived.[10]

Targeting angiogenesis for treatment

Angiogenesis is the phenomenon of formation of new blood capillaries from existing small blood vessels. It usually accounts for normal physiological and pathological changes involved in normal functioning of body, like development of endometrium during menstrual cycle or during wound healing. A tumor consists of a group of cancerous cell, which are bodies own cells but have lost their ability to divide in controlled fashion. For their growth they require oxygen and nutrients, this

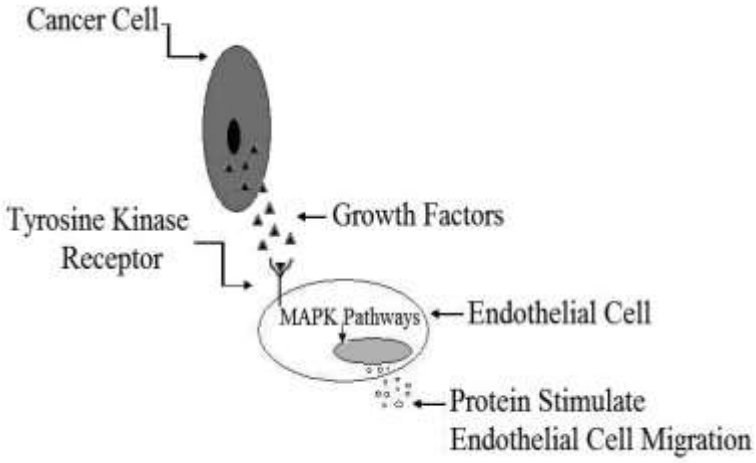
demand can be fulfilled by the angiogenesis. Hence, it was hypothesised that angiogenesis is a factor enabling malignant tumor growth in cancer[11]. These growth factors penetrate into surrounding tissue and stimulate the endothelial cells of the parent blood vessels to release proteases. This enzyme responsible for digestion of basement membrane presents on the same cells and allows movement of these endothelial cells from their original place and allows the cells to migrate in the direction of secretion of growth factor to form a sprout. This sprout then forms a loop followed by formation of full-fledged vessel after maturation. The migrations of endothelial cells are stimulated by tumor, hence the phenomenon is also known as tumour driven angiogenesis. In this way a nonvascular tumor gets converted in to highly vascularised tumour. Some important growth factors responsible for tumor-driven angiogenesis include acidic fibroblast growth factor (aFGF), basic FGF (bFGF), angiogenin, placental growth factor, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor-α, tissue necrosis factor-α and vascular endothelial growth factor (VEGF).[12]

Effects of growth factors:

As shown in fig. 1, growth factors like VEGF or bFGF are first trascripted inside the tumour cell by the hypoxia inducible factor-α, followed by their translation and secretion. When they encounter endothelial cells, they bind with specific receptors know as receptor tyrosine kinase (RTK) present on the endothelial cells. This binding causes the receptor to undergo autophosphorylation, which stimulates Mitogen-activated protein kinases (MAPK) pathway.

This pathway causes the secretion of proteases, like matrix metalloproteinases (MMPs). This group of enzymes is responsible for the degradation of the basement membrane present on the endothelial cells of blood vessel and making them to migrate towards the stimulus[13].

Figure



ANTIANGIOGENIC AGENTS

The fact that tumour stimulates the formation of blood vessels, development of antiangiogenic agents will have potential anticancer activity. Antiangiogenic agents induce their effect by inhibiting the enzymes responsible for proliferation, or sequestering the growth factor or inhibiting the receptor responsible for binding with growth factors. Most of the available literature points out that newly formed blood vessels are highly selective towards low dose of antiangiogenic agents. These agents include humanized monoclonal antibodies (HMABs) against growth factors, matrix metalloproteinases inhibitors (MMPIs), and small molecule inhibitor of tyrosine kinase.

Humanised monoclonal antibodies:

HMABs act by either directly blocking the receptor or exfoliating growth factors[14]. Both the mechanisms prevent the activation of the receptor, thereby blocking the signalling cascade responsible for secretion of MMPs[15]. These agents are specific for particular protein, e.g. bevacizumab is humanized monoclonal antibody against VEGF, cetuximab and panitumumab against endothelial growth factor receptor (EGFR) (Table 1).

Table 1: Different humanized monoclonal antibodies with their currents status

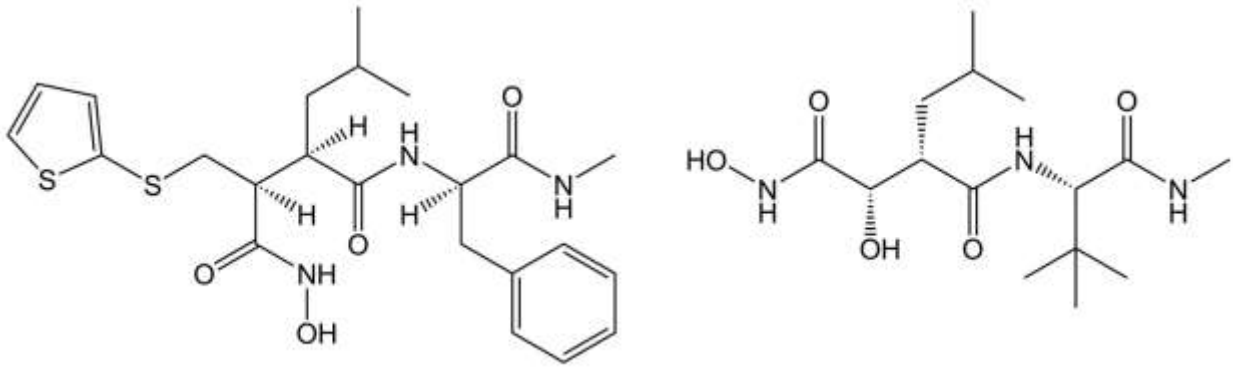
Generic name	Mechanism of action	Brand name	Status
Bevacizumab	Inhibition of VEGF	Avastin	Approved by US FDA for the treatment of metastatic colorectal cancer in combination with 5 Fluorouracil[16] and for non-small lung carcinoma combination with carboplatin and paclitaxel.[17]
Cetuximab	Inhibition of EGFR	Erbitux	Approved by US FDA for the treatment of EGFR positive metastaic colorectal cancer as a single agent in patients who does not tolerate Irenotecan based therapy.
Panitumumab	Inhibition of EGFR	Vectibix	Approved by US FDA for the treatment of EGFR positive refractory metastatic colorectal cancer.

VEGF- Vascular endothelial growth factor, EGFR-Endothelial growth factor receptor

Matrix metalloproteinases inhibitors:

MMPs are a group of enzymes, which are destructive in nature and require zinc ion (Zn+2) for their activity. They play an important role in normal turnover and remodelling of extracellular matrix. It has been reported that, MMPs are over expressed in a variety of malignant tumour types and this is associated with tumour growth and metastasis potential. MMPs degrade the basement membrane and extracellular matrix present on parent blood vessel, making endothelial cells to migrate from their original place and play a pivotal role in angiogenesis. Inhibition of MMPs prevents metastasis and progression of angiogenesis, therefore, can actively peruse as anantiangiogenic agent. The gives the current status of the MMPIs as antiangiogenic agents.

Inhibitors of MMPIs are categorised as peptidomimetic inhibitors, nonpeptidomimetic inhibitors, modified tetracycline derivatives. Compounds of peptidomimetic inhibitors (first generation MMPIs) class are hydroxamic acid derivatives designed to mimic the structure of collagen at the site where the MMPs are thought to bind for the cleavage. Compounds like marimastat and batimastat (figure 2) bind reversibly at the active site of the enzyme in stereospecific manner and chelate the zinc ion present on the enzyme active site[18].



Peptidomimetic matrix metalloproteinases inhibitors.(a) Batimastat, (b) marimastat

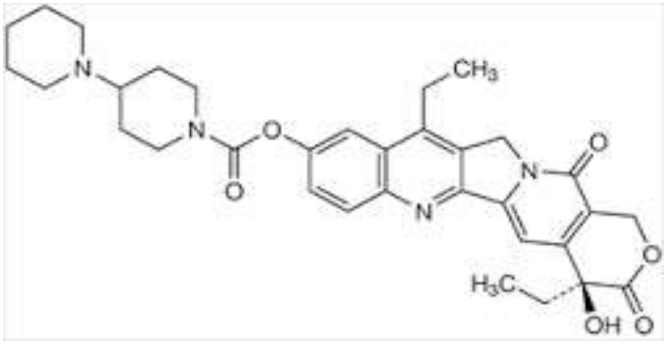
Small molecule tyrosine kinase inhibitors:

Tyrosine kinase inhibitors (TKIs) are the synthetic agents that target enzyme tyrosine kinase linked to the receptor of growth factors like VEGF, EGF and PDGF. Depending upon the type of enzyme targeted by the agents they are divided into following categories: endothelial growth factor RTK inhibitors (EGFR TKI), vascular endothelial growth factor receptor (VEGFR) TKIs, multiple TKIs.[19]

Chemotherapy drugs

A) Monoclonal antibiotics

1)Bevacizumab:

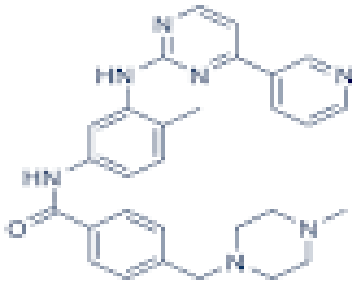


Bevacizumab targets the VEGF (vascular endothelial growth factor) protein, which is normally made by tumor cells to attract new blood vessels to feed their growth.[20]

Bevacizumab attaches to VEGF and blocks it from signaling for new blood vessels formation. It was approved by FDA in 2004 and is used to treat metastatic colorectal cancer, with intravenous 5-florouracil–based chemotherapy for first- or second-line treatment, non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unrespectable, locally advanced, recurrent or metastatic disease, metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer, glioblastoma, as a single agent for adult patients with progressive disease following prior therapy and, metastatic renal cell carcinoma with interferon alfa.[21]

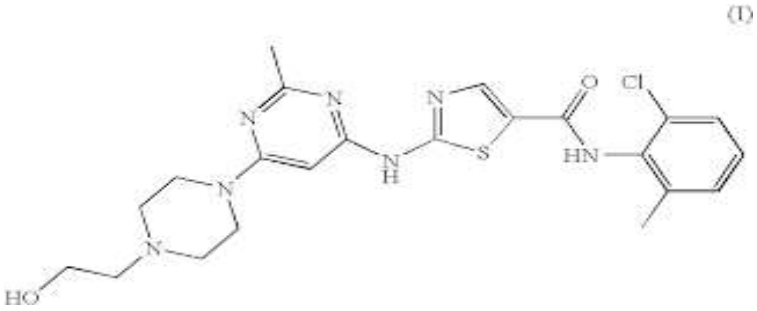
B) Other antibiotics

a) Imatinib(Gleeve)



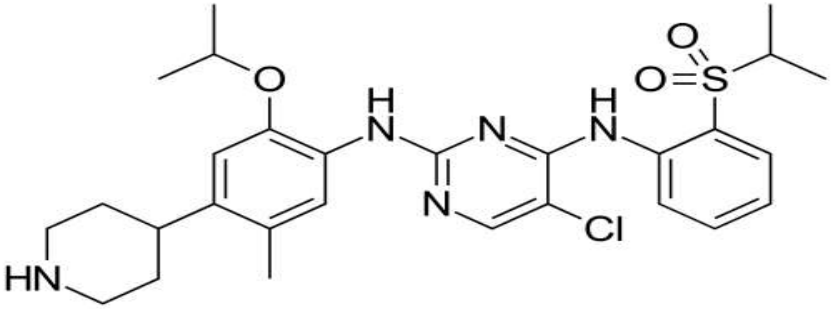
Molecularly targeted therapy is a novel approach in cancer treatment. Imatinib, a specific tyrosine kinase inhibitor, since its inception in 1990s, has become the first-line drug in management of chronic myelogenous leukemia (CML) chronic phase. It has also shown promising results in treatment of gastro-intestinal stromal tumors, clonal eosinophilic disorders and Philadelphia chromosome positive acute lymphatic leukemia.[22]

b)Blinatumomab(Blincyto)



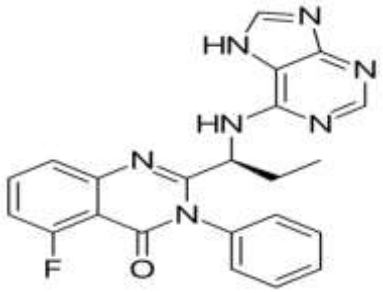
Bilnatumomab enables a patient's T cell to recognize malignant B cells. A molecule of billnatumomab combines two binding sites aCD3 site for T cell and a CD19 site for the target cells.CD3 is part to the T cell receptor. The drug works by linking these two cell types and activating the T-cell.[23] To treat relapsed or refractory pheripheral T-cell lymphoma.[24]

c)Ceritnib(Zykadia)



Certinib is an oral ATP-competitive ALK tyrosine kinase inhibitor. Its is used for lung cancer treatment. It is an anaplastic lymphoma kinase.[24,25] Ceritinib inhibits Anaplastic lymphoma kinase (ALK) also known as ALK tyrosine kinase receptor or CD246 (cluster of differentiation 246), which is an enzyme that in humans is encoded by the ALK gene. About 4-5% of NSCLCs have a chromosomal rearrangement that generates a fusion gene between EML4 (echinoderm microtubule-associated protein-like 4) and ALK (anaplastic lymphoma kinase), which results in constitutive kinase activity that contributes to carcinogenesis and seems to drive the malignant phenotype. Ceritinib exerts its therapeutic effect by inhibiting autophosphorylation of ALK, ALK-mediated phosphorylation of the downstream signaling protein STAT3, and proliferation of ALK-dependent cancer cells. Ceritinib has been shown to inhibit in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice and rats.[25]

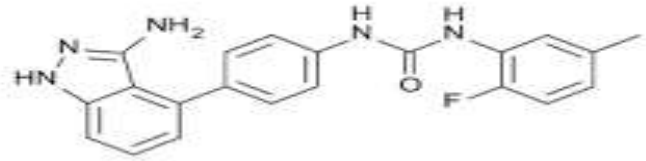
d)Idelaisib (Zydelig)



Idelaisib is a drug used for certain heamotologic malignacines.[26,27] Idelalisib specifically inhibits P110δ, the delta isoform of the enzyme phosphatidylinositol-4,5-bisphosphate 3-kinase, also known as PI-3K. The PI-3Ks are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. In contrast to the other class IA PI3Ks p110α and p110β, p110δ is principally expressed in leukocytes (white blood cells) and is important for the function of T cells, B cell, mast cells and neutrophils. By inhibiting this enzyme, idelalisib induces apoptosis of malignant cells and inhibits several cell signaling pathways, including B-cell receptor (BCR)

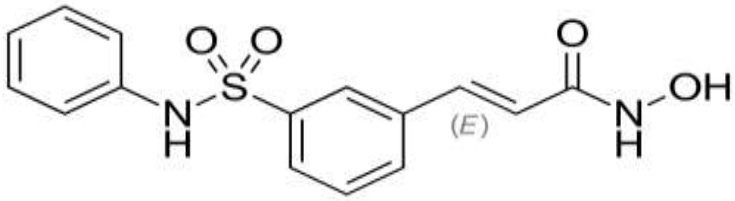
signaling and C-X-C chemokine receptors type 5 and type 4 signalling, which are involved in trafficking and homing of B-cells to the lymph nodes and bone marrow. Treatment of lymphoma cells with idelalisib has been shown to result in inhibition of chemotaxis and adhesion, and reduced cell viability.[26]

d)Nivolumab(Opdivo)



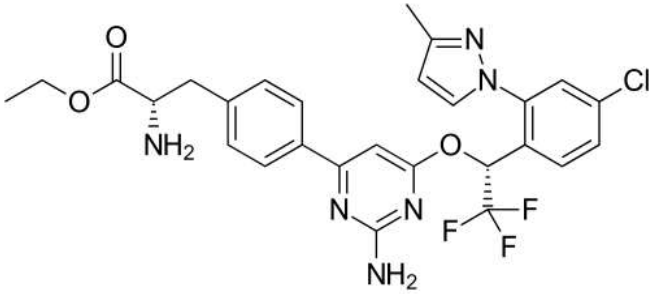
Nivolumab act by blocking as negative regulator of T-cell activation and response thus allowing the immune system to attack the tumor.[28] PD-1 is a protein on the surface of activated T cells. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death 1 (PD-1) receptor and selectively blocks interaction with its programmed death ligands PD-L1 and PD-L2. Upregulation of PD-1 ligands occurs in some tumors and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumour tissue. The inhibitory effect of PD-1 and its ligands occurs through the promotion of apoptosis in antigen specific T cells while simultaneously blocking apoptosis in suppressor T cells. Blocking PD-1 activity has been shown to lead to decreased tumour growth in mouse tumour models.[27]

e) Belinostat (Beleodaq)



Belinostat is a histone deacetylase inhibitor drug developed for treatment of hematological malignancies and solid tumors. It is used for treatment of pheripheral T-cell lymphoma.[29]. Beleodaq is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. In vitro, belinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Belinostat shows preferential cytotoxicity towards tumor cells compared to normal cells. Belinostat inhibited the enzymatic activity of histone deacetylases at nanomolar concentrations (<250 nM).[28]

f) Xermrlo(Telotristat)



Xermelo (telotristat ethyl) is a tryptophan hydroxylase inhibitor. Tryptophan hydroxylase mediates the rate limiting step in serotonin biosynthesis. The in vitro inhibitory potency of telotristat towards tryptophan hydroxylase is 29 times higher than that of telotristat ethyl. Serotonin plays a role in mediating secretion, motility, inflammation, and sensation of the gastrointestinal tract, and is over-produced in patients with carcinoid syndrome. Through inhibition of tryptophan hydroxylase, telotristat and telotristat ethyl reduce the production of peripheral serotonin, and the frequency of carcinoid syndrome diarrhea.[29]

CONCLUSION

The given therapy target immune-system to change its internal environment and tried to destroy new cells growth. In cancer stem cell therapy it give rise to cell type found in a particular cancer sample. In these adipose derived stromal cells differentiat from progenitor cells. In gene targeted nucleic acid therapy suppression genes anomalously leads to high expression associated with neoplastic transformation achieved by nucleic acid based drug. Targeting angiogensis for treatment in this as angiogensis play role of formation of new blood capillaries. Its agents inhibits the enzyme for proliferation or binding the growth factors. In chemotherapy the agents like idelaisib, nivolumab, belinostat, ceritinib, blinatumomb, in which they destroy infected cells or inhibit the binding of receptors.

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