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TARGETED CANCER THERAPY

Yadav Yuvraj Suryadev*, Vishwakarma Amar Kumar, Yadav Rajesh Kumar, Yadav Vimal, Yadav Piyush and Mittal Anuj

1. Department of Pharmacy, Prasad Institute of technology, Jaunpur.

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Corresponding author:
Yuraj Survadv Yadav, Department of Pharmacy, Department of Management Studies, Prasad Institute of technology, Jaunpur.

ABSTRACT

Cancer is a disease characterized by uncontrolled or abnormal cell proliferation. The cells divide and invade surrounding tissues and often trigger angiogenesis. Cancer treatment can be done by surgery, chemotherapy and radiation therapy or combination of this therapy is also use depending upon the severity of cancer. As chemotherapy targets rapidly dividing cell unfortunately hair follicle cells, red bone marrow cells, and cells lining the gastrointestinal tract also are rapidly dividing. Hence, the side effects of chemotherapy include hair loss due to death of hair follicle cells, vomiting and nausea due to death of cells lining the stomach and intestines, and susceptibility to infection due to slowed production of white blood cells in red bone marrow. Targeted therapy drugs do not work in the same ways as standard chemotherapy drugs. They are often able to attack cancer cells while doing less damage to normal cells by going after the cancer cells' inner workings i.e. the programming that sets them apart from normal, healthy cells. In this review article we have discussed about targeted therapy for cancer treatment.

INTRODUCTION

Targeted therapy or molecularly targeted therapy is one of the major modalities of medical treatmentfor cancer. As a form of molecular medicine, targeted therapy blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesisand tumor growth,[1] rather than by simply interfering with all rapidly dividing cells as in the case of traditional chemotherapy. Targeted cancer therapies are expected to be more effective than older forms of treatments and less harmful to normal cells.The deregulation of signaling pathways in tumors can lead to enhanced cancer cell growth, proliferation, survival, invasion, and metastasis or reduced apoptosis.[2, 3]Such

pathways became the focus of the development of targeted cancer therapies during the last decades. [4-6]Targeted therapy drugs do not work in the same ways as standard chemotherapy drugs. They are often able to attack cancer cells while doing less damage to normal cells by going after the cancer cells' inner workings i.e. theprogramming that sets them apart from normal, healthy cells.The drugs target certain parts of the cell and the signals that are needed for a cancer to develop and keep growing. These drugs are often grouped by how they work or what part of the cell they target.

Enzyme inhibitors:

Some enzymes serve as signals for cancer cells to grow. Some targeted therapies inhibit enzymes that are signals for cancer cells to grow. These drugs are called enzyme inhibitors. Blocking these cell signals can inhibit the cancer from getting bigger and spreading. [7]

Apoptosis-inducing drugs:

Some targeted therapies change proteins within the cancer cells and cause the cells to die. These are called apoptosis-inducing drugs.They are aimed right at the parts of the cell that control whether cells live or die.The serine/threonine kinase, PKB/Akt, promotes cell survival, and inhibitors of this protein are in preclinical development. [8]

Angiogenesis inhibitors:

Angiogenesis is the process of making new blood vessels. In cancer this same process creates new blood vessels that give atumor its own blood supply. This blood brings nutrients that allow the cancer to grow and spread. Angiogenesis inhibitors target and inhibit this process. They stop the tumors from making new blood vessels. This helps cut off the tumors' blood supply, and without blood, tumors can't grow.Another strategy to arrest tumor growth involves curtailing blood supplyto the tumor by inhibiting angiogenic factors such as vascular endothelialgrowth factor (VEGF) or its receptors. An antibody against VEGF, Avastin(bevacizumab), extends survival of patients with advanced colorectal carcinoma by several months on average, and has been approved by the FDA for thetreatment of such patients, in combination with 5-fluorouracilbasedchemotherapy.[9]

Fig. No. 1 Targeted Therapy

TYPES OF TARGETED THERAPY:

Today many different types of targeted therapies are used to treat cancer. Looking at examples helps a person understand how these drugs work.There are 2 main types of targeted therapy drugs:

1) Monoclonal Antibodies
2) Small Molecule Inhibitors

Monoclonal antibodies:

Antibody drugsare man-made versions of immune system proteins that have been designed to attack certain targets on cancer cells. Monoclonal antibodies are administered intravenously as their protein structure is denatured in gastrointestinal tract.Monoclonal antibodies contain an increased proportion of human components and a decreased proportion of murine components i.e. chimeric antibodies are65 percent human, humanized antibodies are 95 percent human and human antibodiesare100 percent human. [10]

Monoclonal antibodies exert their anticancer effect through a variety of mechanisms.

- By recruiting host immune functions to attack the target cell.
- By binding to ligands or receptors thereby interrupting essential cancer cell processes.
- By carrying a lethal payload such as radioisotope or toxin to the target cell.[11]

Cancer immunotherapy involves the use of gemtuzumab, a CD-33 specific monoclonal antibody conjugated to a calicheamicin used for the treatment of acute myeloid leukemia.[12] On a similar note, radioisotope conjugated targeting antibodies have been developed for immune scintigraphy and radio immunotherapy strategies. ^{90}Y metal isotope based anti-CD20 ibritumomabtiuxetan has been developed for use in clinical therapy.[13, 14]

Moreover, apart from being used as therapeutic agent antibodies also serve as targeting agents. They are used in targeted therapy for the delivery of active therapeutics[15], prodrug activation enzymes[16,17] and chemotherapy toxins.[18,19,20]

Table 1. Monoclonal Antibodies for Cancer Treatment

Drug	Target	Cancer
Alemtuzumab(Campath)	CD52	Chronic lymphocytic leukemia
Bevacizumab (Avastin)	VEGF	Colorectal cancer
Cetuximab (Erbitux)	EGFR	Head and neck cancers
Trastuzumab (Herceptin)	HER2/ neu	Breast cancer
Gemtuzumab ozogamicin (Mylotarg)	CD33	Acute myeloid leukemia
Panitumumab(Vectibix)	EGFR	Colorectal cancer
Rituximab (Rituxan)	CD20	Non-Hodgkin's lymphoma

Small Molecule Inhibitors:

Small drugs constitute a pill that a patient takes orally. As they are smaller chemical components than monoclonal antibodies, the body absorbs them better. Small molecule inhibitors typically interrupt cellular processes by interfering with the intracellular signaling of tyrosine kinases. Tyrosine kinase signaling initiates a molecular cascade that can lead to cell growth, proliferation, migration, and

angiogenesis in normal and malignant tissues. EGFR, HER2/neu and VEGF receptors are tyrosine kinase.

Small moleculesinhibitors differ from monoclonal antibodies in severalways.They are usually administered orally rather than intravenously. They are chemicallymanufactured, a process that is often much less expensive than the bioengineering required for monoclonal antibodies.[21]They achieve less specific targeting than do monoclonal antibodies.[22]Whereas monoclonal antibodies have half-lives ranging from days to weeks, most small molecule inhibitors have half-lives of only hours and require daily dosing.

The small molecule inhibitors of cancer targets include, e.g. the gefitinib - inhibitor of epidermal growth factor receptor (EGFR) kinase and erlotinib- the inhibitor of EGFR in non-small cell lung cancer (NSCLC) patients; the lapatinib- inhibitor of EGFR/ERBB2 for ERBB2-positive breast cancer; and the sorafenib- inhibitor of vascular epidermal growth factor receptor (VEGFR) kinase, in renal cancer.[23]

Table 2. Small Molecule Inhibitors for Cancer Treatment

Drug	Target	Cancer
Erlotinib (Tarceva)	EGFR	Pancreatic cancer
Gefitinib (Iressa)	EGFR	Lung cancer
Lapatinib (Tykerb)	HER2/neu	Breast cancer
Sorafenib (Nexavar)	VEGFR	Renal cancer
Sunitinib (Sutent)	VEGFR	Renal cancer
Dasatinib(Sprycel)	BCR-ABL	Chronic myeloid leukemia

MECHANISM OF ACTION OF TARGETED THERAPY:

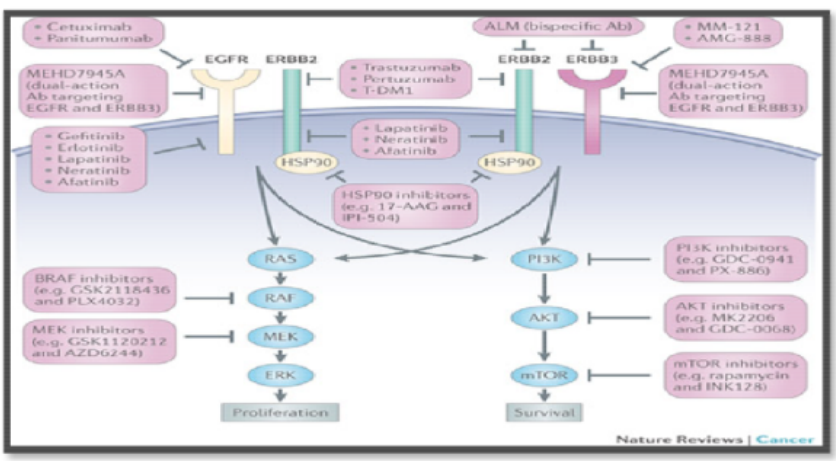

Fig. No. 2 MOA of Targeted Therapy

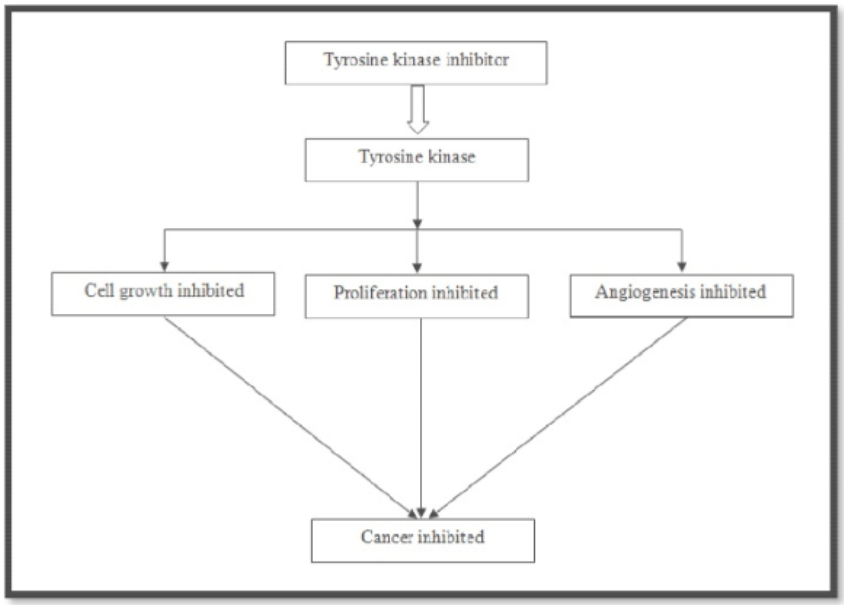

Fig. No. 3 Flowchart of Targeted Therapy

IMPLICATIONS OF TARGETED THERAPY:

The use of targeted therapy markedly changed outcomes for some diseases. Imatinib has had a dramatic effect on chronic myeloid leukemia, and rituximab, sunitinib and trastuzumab have revolutionized the treatment of renal cell carcinoma and breast cancer respectively.In patients with advanced pancreatic cancer, the addition of erlotinib to standard chemotherapy increases survival rate from 17 to 24 percent.[24]

CONCLUSIONS:

Molecularly targeted cancer therapies have a short but rich history, an exciting present and a promising future.[25] Despite the availability of improved drugs and new therapeutic strategies, including targeted cancer therapies, cancer is still one of the leading causes of death worldwide. However, due to novel technology and improved knowledge of the genetic and epigenetic make-up of a particular cancer, cancer treatment may change radically over the next few years. Moreover, the discovery and development of targeted cancer therapy is new hope in cancer treatment. Although more research is warranted, the results recently achieved by targeted cancer therapy efforts suggest that tailored therapy for most, if not all, cancer patients may become a realistic approach in the near future.

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