Targeted Therapy
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ABSTRACT
This is a review on targeted therapy that blocks the growth and spread of cancer by interfering with specific molecules involved in tumour growth and progression in comparison to chemotherapy, which targets the rapidly dividing cells. There are targeted therapies for breast cancer, multiple myeloma, lymphoma, prostate cancer, and other cancers. The drug targeted therapies interfere with a specific biochemical pathway responsible for growth, development, and spread of that particular cancer.

KeyWords
Targeted therapy, small molecule inhibitors, and monoclonal antibodies.

ABBREVIATION
EGFR, epidermal growth factor receptors or HR1, TK, tyrosine kinase, HER2/neu, Fab, fragment antigen binding, and Fc, fragment crystallizable, VEGF, vascular endothelial growth factor
INTRODUCTION

The basis of targeted therapies involves blocking the growth and spread of cancer by interfering with specific molecules known as “molecular targets” appropriately named for specific drugs as “molecularly targeted drugs” and for therapies as “molecularly targeted therapies.” Molecular therapy may vary individual-to-individual. Molecular targets are known for some type of cancers but as some molecular targets are still being identified for other types of cancers and some types of cancers can have different molecular targets, identifying the molecular targets in any particular cancer has to be carefully analyzed in cancer pathology.

U.S. Food and Drug Administration (FDA) has approved many targeted cancer therapies for the treatment of specific types of cancer while some therapies are undergoing clinical trials, and some still are in preclinical testing stage. Diseases treated with targeted therapies are brain cancer, breast cancer, gastrointestinal (GI) cancer, head and neck cancer, kidney cancer, leukemia, lung cancer, melanoma, mesothelioma, myeloma, prostate cancer, and thyroid cancer.

A comparative approach to targeted therapies

In traditional intravenous cytotoxic chemotherapy which has been a novel approach for treatment of cancer, there is inhibition of cell division but chemotherapy also affects other rapidly dividing cells like hair, bone marrow, and gastric epithelium hence many patients experience classic toxicities of alopecia, gastrointestinal symptoms, and myelosuppression. Targeted therapies work by blocking proliferation of cancer cells interfering with specific molecules required for tumor development and growth of cancer. These molecules are present in normal tissue as well but mutated in cancer cells.

The first targeted therapy involves antibodies directed against cell surface markers cluster of differentiation 20 (CD20), CD33, and CD52, present on lymphoma and leukemia cells. Targeting CD20 affects overall immune function as it is present on normal lymphoid cells too. This led to development of anti-CD20 monoclonal antibody rituximab (Rituxan) for the treatment of autoimmune diseases such as rheumatoid arthritis and non-Hodgkin's lymphoma.

SMALL MOLECULE INHIBITORS AND MONOCLONAL ANTIBODIES

Monoclonal antibodies and small molecule inhibitors have played a vital role in the treatment of cancer for more than a decade and have become an important part of cancer therapy for malignancies, including breast, colorectal, lung, and pancreatic cancers, lymphoma, leukemia, and multiple myeloma. Targeted therapies are better tolerated than traditional chemotherapy but mechanisms of action and toxicities of targeted therapies differ from those of traditional cytotoxic chemotherapy. Targeted therapies have several adverse effects, such
as acneiform rash, cardiac dysfunction, thrombosis, hypertension, and proteinuria. Small molecule inhibitors are metabolized by cytochrome P450 enzymes and are subject to multiple drug interactions.

Comparative approach

Small molecular inhibitors and monoclonal antibodies differ in many aspects,

Route of administration: Small molecule inhibitors are administered orally and chemically manufactured in a much less expensive way compared to bioengineering required for manufacturing of monoclonal antibodies.

Target specificity: Small molecule inhibitors achieve less specific targeting than monoclonal antibodies. Multi targeting nature (small molecule inhibitors) of the kinase inhibitors imatinib (Gleevec), dasatinib (Sprycel), sorafenib (Nexavar), and sunitinib (Sutent).

Drug interactions: Small molecule inhibitors are metabolized by cytochrome P450 enzymes, which may result in drug interactions with medications as macrolide antibiotics,azole antifungals, certain anticonvulsants, protease inhibitors, warfarin, and St. John's wort.

Degradation: Monoclonal antibodies have half-lives ranging from days to weeks hence the frequency of administration is once every one to four weeks whereas small molecule inhibitors have half-lives of only hours and require daily dosing.

MECHANISM

Traditional cytotoxic chemotherapy.

Alkylating agents like nitrogen mustards, nitrosoureas, and alkyl sulfonates interfere with DNA base pairing, leading to strand breaks and arresting DNA replication. Topoisomerase inhibitors prevent DNA uncoiling. Taxanes and vinca alkaloids interfere with micro-tubule function required for cell mitosis. Antimetabolites block the formation and use of nucleic acids essential for DNA replication. The molecular pathways most often targeted in the treatment of solid tumors e.g., breast, lung, and colorectal cancers.
Targeted therapy

The EGFR Axis

Inhibition Strategies:
- EGFR-TK inhibitors
- Anti-EGFR mAb inhibitors
SMALL MOLECULE INHIBITORS

Small molecule inhibitors typically interrupt cellular processes by interfering with the intracellular signaling of tyrosine kinases (i.e., enzymes that transfer phosphate groups from adenosine triphosphate to tyrosine amino acid residues in proteins). Tyrosine kinase signaling initiates a molecular cascade that can lead to cell growth, proliferation, migration, and angiogenesis in normal and malignant tissues. EGFR/HER1, HER2/neu, and VEGF receptors are tyrosine kinases.

Angiogenesis. The growth of new blood vessels from preexisting vasculature. Epidermal growth factor receptor (EGFR/HER1). A tyrosine kinase binds to specific ligands for activation that triggers intracellular signaling leading to cell proliferation, invasion, and migration. It is a target of treatment with monoclonal antibodies cetuximab [Erbitux] and panitumumab [Vectibix], and the small molecule...
inhibitors erlotinib [Tarceva], gefitinib [Iressa], and lapatinib [Tykerb]) in multiple tumor types. HER2/neu, a tyrosine kinase related to epidermal growth factor receptor. It is a target of treatment with the monoclonal antibody trastuzumab [Herceptin] and the small molecule inhibitor lapatinib [Tykerb]) mainly in pathogenesis of breast cancer in which HER2/neu is overexpressed. Overexpression of HER2/neu results in relapse and bad prognosis. HER2 is named so because of its resemblance with structure of human epidermal growth factor receptor (HER1 and neu as it was derived from a neuroglioblastoma cell line. Vascular endothelial growth factor (VEGF). A signaling protein involved in angiogenesis; it binds to tyrosine kinases (VEGF receptors) to initiate and promote angiogenesis. It is a target of treatment with the monoclonal antibody bevacizumab (Avastin).

Some drugs (e.g., sorafenib [Nexavar], sunitinib [Sutent], imatinib [Gleevec], dasatinib [Sprycel]) have multiple targets (CD = cluster of differentiation; BCR-ABL = breakpoint cluster region-Abelson; EGFR = epithelial growth factor receptor; VEGFR = vascular endothelial growth factor receptor; VEGF = vascular endothelial growth factor.)

EGFR is present in multiple tumor types responsible for cancer cell proliferation, invasion, and migration but as EGFR is also present in normal epithelial tissue i.e. skin and mucosa, EGFR inhibition leads dermatologic and gastrointestinal toxicities and therefore development of a rash is considered a sign of positive response to treatment. Severe dermatologic toxicities may need topical, systemic antibiotic, or steroids use and much more complications may need discontinuation of EGFR inhibitor. Patients under EGFR inhibitors treatment may develop diarrhea which can be relieved by symptomatic options like loperamide (Imodium) but severe diarrheal cases may need parenteral fluids administration due to volume loss from body.

Targeting of VEGF prevents angiogenesis thus not providing new blood vessels formation due to which tumors cannot grow more than few mm beyond the existing vasculature. However targeting VEGF may affect normal blood vessels, leading to bleeding, thrombosis, hypertension and alterations to glomerular capillaries leading to proteinuria. The anti-VEGF monoclonal antibody bevacizumab (Avastin) is approved for treatment of non-small cell lung cancer in patients with adenocarcinoma histology, but not in those with squamous cell tumors.
MONOCLONAL ANTIBODIES

Monoclonal antibodies weight of approximately 150,000 Da), target extracellular components of these pathways, such as ligands and receptor-binding domains. In contrast, small molecule inhibitors (typical molecular weight of approximately 500 Da) can enter cells, thereby blocking receptor signaling and interfering with downstream intracellular molecules.

In 1986, the FDA approved the first monoclonal antibody, muromonab-CD3 (Orthoclone OKT3), which prevents acute organ rejection after transplantation by blocking T-cell function. The fragment antigen binding (Fab) of a monoclonal antibody, is responsible for the highly specific targeting that is possible with such therapies.

Fragment antigen binding (Fab). This region of an antibody is responsible for recognizing and binding of antigen.

Fragment crystallizable (Fc). The region of an antibody responsible for interacting with immune system components such as natural killer cells and the complement cascade.

Ligand. A molecule that binds to a specific receptor.

MECHANISMS

Monoclonal antibodies use host immune functions like natural killer cells and the complement cascade to attack the target cell by binding to ligands or receptors and interrupting essential cancer cell processes or by carrying a lethal payload, such as a radioisotope or toxin, to the target cell (i.e., conjugated monoclonal antibodies). Monoclonal antibodies do not undergo hepatic metabolism as they are administered intravenously and hence are not subject to significant drug interactions.

Infusion reactions may occur with all monoclonal antibodies administered intravenously mostly in cases of murine and chimeric antibodies and are not listed as toxicities.

Murine (antibodies obtained by immunizing mice with target antigen) composed of mouse proteins, hence there was severe risk of hypersensitivity reaction during infusion and the patient developed anti-mouse protein antibodies thus neutralizing the effect therapeutic antibody,. To overcome the undesirable effects, nowadays monoclonal antibodies contain an increased proportion of human components and a decreased proportion of murine components; chimeric antibodies are 65 percent human, humanized antibodies are 95 percent human,
and human antibodies are 100 percent human. The type of antibody can be identified by the suffix of the drug name: -momab (murine), -ximab (chimeric), -zumab (humanized), or -mumab (human).

Small molecule inhibitors are administered orally and undergo metabolism by cytochrome P450 enzymes and are therefore subject to multiple potential interactions (e.g., with anticonvulsants, azole anti-fungals, dexamethasone, isoniazid [Nydrazid], macrolide antibiotics, protease inhibitors, rifampin [Rifadin], St. John's wort, verapamil [Calan], and warfarin [Coumadin]. Exception is, administered intravenously.

Imatinib, approved in 2002 as one of the first small molecule inhibitors is most effective in treatment of chronic myeloid leukemia. It inhibits a continuously active tyrosine kinase that results from the translocation of chromosomes 9 and 22 (the Philadelphia chromosome). Because this molecular abnormality occurs in essentially all patients with chronic myeloid leukemia, imatinib therapy results in a complete hematologic response in 98 percent of patients. More recently, small molecule inhibitors targeting the EGFR pathway have been used in the treatment of solid tumors, such as non-small cell lung cancer.

CONCLUSION

Targeted therapies are considered over novel cytotoxic chemotherapy because it is potentially less harmful to normal cells, fewer side effects, improved effectiveness in combination with chemotherapy, and improved quality of life. The use of targeted therapy has 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 non-Hodgkin's lymphoma, renal cell carcinoma, and breast cancer, respectively. In patients with advanced pancreatic cancer, the addition of erlotinib to standard chemotherapy increases the one-year survival rate from 17 to 24 percent, which correlates to an increase in median survival from 24 to 27 weeks.

In addition to prolonging survival in patients with certain cancers, targeted therapies provide treatment options for some patients who may not otherwise be candidates for anticancer therapy. For instance, non-small cell lung cancer and non-Hodgkin's lymphoma primarily affect elderly patients, many of whom have medical comorbidities that limit the use of standard chemotherapy. Targeted therapies such as erlotinib and rituximab are often less toxic and better tolerated than traditional chemotherapy, offering these patients additional treatment options.

REFERENCES


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