

New Paradigm in Treating Cancer: Right on Target

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ABSTRAK

Prevalensi kanker meningkat setiap tahun dan sekarang kanker merupakan penyebab kematian ketiga tertinggi di negara-negara berkembang. Terapi antikanker yang efektif dapat memperpanjang hidup dan memperbaiki kualitas hidup pasien. Terapi target adalah suatu modalitas terapeutik baru yang tertuju pada molekul-molekul spesifik dalam sel-sel kanker dan memutus jalur-jalur pensinyalan abnormal yang terlibat dalam karsinogenesis. Oleh karena terapi target tidak menyerang sel-sel normal, efek sampingnya dianggap lebih rendah dibandingkan kemoterapi. Lebih dari 15 jenis obat telah disetujui penggunaannya pada berbagai kanker manusia. Obat-obatan tersebut secara garis besar dapat digolongkan menjadi inhibitor tirosin kinase dan antibodi monoklonal. Tinjauan pustaka ini akan difokuskan pada obat-obatan yang paling sering digunakan dari kedua kelompok tersebut.

Kata kunci: *antibodi monoklonal, inhibitor tirosin kinase, terapi antikanker, terapi target.*

ABSTRACT

Cancer prevalence is increasing every year and now cancer is the third highest cause of death in developing countries. Effective anticancer treatment can prolong life and improve the patient's quality of life. Targeted therapy is a new therapeutic modality which targets specific molecules in the cancer cell and disrupts dysregulated signaling pathways involved in carcinogenesis. Since targeted therapy does not attack normal cells, its side effects are considered low compared to chemotherapy. More than 15 drugs have been approved for treatment in various human cancers. These drugs can largely be grouped into tyrosine kinase inhibitors and monoclonal antibodies. This review will focus on the most common agents within both groups.

Keywords: *anticancer therapy, monoclonal antibodies, targeted therapy, tyrosine kinase inhibitors.*

INTRODUCTION

Cancer treatment remains challenging today because conventional treatments such as chemotherapy, radiation and surgery do not always results in complete disease control or prolonged survival. Cancer kills one in two people in high-income countries and one in three people in low-to-middle-income countries.¹ Therefore, researchers are still looking for agents

that can effectively kill cancer cells without affecting normal cells.

One of the widely studied therapeutic modalities is targeted therapy, a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells.² There are two broad categories of targeted therapy: small molecules (molecular weight \pm 500 Dalton) and monoclonal

antibodies (molecular weight ± 150.000 Dalton). Small molecules are protein kinase inhibitors, usually tyrosine kinase inhibitors, (i.e. those names ending with -nib) that can penetrate membrane cell and interact with targeted protein enzyme and modulate enzymatic activities. Monoclonal antibodies (i.e. those names ending with mab) are large molecules that bind specific antigens on the cell surface, such as growth factor receptors.

The mechanism of targeted therapy is by interfering signaling cascades that control cell proliferation, survival, invasion and apoptosis. In contrast to chemotherapy that also kills normal cells; targeted therapy attacks cancer cells indirectly by identifying potential targets that play a role in cancer.

Since targeted therapy only affects cancer cells, its side effects are considered less than chemotherapy. It can be tailored to individual needs, depends on the presence or absence of the specific target molecules; thus, it may require specific test before starting the treatment. Currently, there are many kinds of targeted therapy for use in various cancers. This review will focus only on some agents that are frequently used in common cancers.

SMALL MOLECULES

Protein kinases are enzymes that are involved in phosphorylation and transfer of a phosphate group from adenosine 3 phosphates (ATP) to tyrosine, serine or threonine residues. There are two broad categories of protein kinase, i.e.:

- Receptor tyrosine kinase (RTK): EGFR, PDGFR, FGFR, IR
- Non-receptor tyrosine kinase (NRTK): SRC, ABL, FAK, JAK

RTK have many domains for extracellular ligand. After binding to a specific ligand, a signal will pass the cell membrane and the tyrosine kinase will be activated. Agents that block the activation of RTK are called tyrosine kinase inhibitors (TKIs). The NRTK acts in a similar fashion, but beside of the tyrosine kinase domain, it has additional domains such as serine/threonine kinase domain. This review will focus in tyrosine kinase inhibitors only.

Tyrosine kinase proteins are enzymes that catalyze the transfer of phosphate polypeptide of ATP to a target protein. The active form of the enzyme causes an increase in growth and cell proliferation, induces anti-apoptotic effects, induce angiogenesis and metastasis, and resistance to other therapies.³ Active autophosphorylation of the tyrosine kinase domain occurs in the cytoplasm and activate the downstream cascade like the Ras-Raf pathway, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase pathway (PI3K), signal transducers and activators of transcription (STAT) pathway, and protein kinase C.⁴ Initiation of PI3K signaling would then inhibit the phosphatase and tensin homolog (PTEN) tumor suppressor gene signaling pathway.⁵

Cancer cells have several mechanisms that may cause dysregulation of tyrosine kinase. Mutations can occur and may increase the expression of tyrosine kinase receptor or ligand such as breast cancer with positive HER2 receptor.³ Tyrosine kinase inhibitors are metabolized by cytochrome P450 enzymes and work on targets inside the cell, so that the components can fit easily into the cells.^{6,7} This therapy usually blocks the action of the enzyme on the target protein.⁸ Several agents in this group are the epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and bcr-abl tyrosine kinase inhibitors.

Ligand binding to the extracellular domain of the tyrosine kinase receptor causes dimerization that consequence in autophosphorylation and activation of the intracellular kinase domain. It leads to the recruitment of enzymes (phosphoinositide 3-kinase (PI3K)), phospholipase C γ 1 (PLC γ 1), SRC and signal transducer, activator of transcription 3 (STAT3) and adaptor molecules, and activation of downstream signaling pathways. The signaling pathways regulate a various array of processes including transcription, translation, metabolism, cell proliferation, survival, differentiation and motility. Gene mutations or overexpression can trigger unregulated activation of receptor tyrosine kinases, leading to deregulation of downstream signaling pathways that can ultimately cause malignant proliferative disorders.⁹

Epidermal Growth Factor Receptors (EGFR) Signaling

EGFR family of receptors called HER tyrosine kinase family consists of 1-4 erbB oncogene encoded ERB. Small molecules that inhibit EGFR are gefitinib, erlotinib, and lapatinib. They act by blocking the phosphorylation of EGFR dimerization, thereby inhibiting protein signaling. Gefitinib and erlotinib are reversible EGFR inhibitors that compete with ATP for binding to catalysis pouch. Gefitinib inhibits the activity of cyclin-dependent kinases, inhibits tumor angiogenesis, and arrest the cell cycle. Mutation of EGFR in exon 19-21 needs to be confirmed before starting treatment.¹⁰

Lapatinib irreversibly inhibits EGFR, HER2, and Akt pathways. This therapy has a broader spectrum and a smaller resistance than other types of anti-EGFR.¹¹ Drug similar to lapatinib is neratinib. Neratinib inhibit dimerisation EGFR- HER4 or EGFR- HER2.¹²

Afatinib also irreversibly inhibits human HER2 and EGFR kinases. Afatinib does not active only against EGFR mutations as first line, like erlotinib or gefitinib, but also against those not sensitive to these standard therapies.¹³

Canertinib is an anti-EGFR that is irreversible and has anti-tumor activity with a broad spectrum effects. However, not all mutations in EGFR are sensitive to anti-EGFR therapy.¹⁴ In addition, EGFR is also present in normal epithelial cells (skin and mucosa); therefore, inhibition of the EGFR may trigger side effects in the skin and gastrointestinal system.^{7,15}

Vascular Endothelial Growth Factor (VEGF) and VEGF Receptor (VEGFR) Signaling

The VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placenta growth factor (PlGF) and three receptors, namely VEGF receptor (VEGFR) 1, 2 and 3.¹⁶ VEGF-A and VEGFR-2 are expressed in all malignant tumors.¹⁷ VEGFs work on vascular endothelial cells by inducing vascular permeability, resulting in deposition of fibrin in the extracellular matrix that triggers cell proliferation and migration. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis.¹⁵

Sorafenib is a small molecule that inhibits several targets, i.e. VEGFR 1-3, PDGF-h receptor serine threonine kinase and Raf-1. The drug works through the Raf-MAPK signaling pathway, which plays a role in arresting cell proliferation and tumorigenesis. A proven efficacy has been shown in hepatocellular and renal cell carcinomas.¹⁸

Sunitinib is also small molecule with multiple targets. It is the oral form of the receptor protein against several VEGFRr 1-3, PDGF-h receptor, and others.

BCR-ABL Tyrosine Kinase Inhibitors

Imatinib mesylate is a targeted therapy for BCR-ABL protein. Mutations on bcr-abl gene may cause dysregulation of intracellular signaling, leading to increased cell proliferation and anti-apoptosis of hematopoietic cells.¹⁹ Imatinib also inhibits c-KIT mutation in mast cell of chronic myelogenous leukemia (CML) and acute myeloid leukemia (AML) patients and also inhibit platelet-derived growth factor receptor (PDGFR) tyrosine kinases that play a role in gastrointestinal stromal tumors (GIST).³

MONOCLONAL ANTIBODIES

Monoclonal antibodies are used on the target cell surface, such as excessive antigen expressed on tumor cells. Antibodies do not kill cells directly, but through other mechanism in the body's immune system or by initiating signaling pathways in target cells.⁸

Monoclonal antibodies recognize antigens on the surface of cancer cells, called the target. It works in four ways: 1) Monoclonal antibody bound to antigen activates complement components, leading to opsonization of cancer cells by phagocytic cells expressing complement receptors, direct lysis of tumor cells and inflammation with recruitment of inflammatory cells. 2) Monoclonal antibody binds to activating Fc receptors on the effector cells, leading to antibody-dependent cellular cytotoxicity (ADCC) or release of cytokines. 3) Monoclonal antibody binds to inhibitory Fc receptors (or to both activation and inhibitory Fc receptors), inhibiting effector cell activation. 4) Monoclonal antibody binds directly to growth factor receptors

or other signaling molecules on the cancer cell, leading to cell death.²⁰

EGFR Antibody

Cetuximab is a monoclonal EGFR antibody that plays a role in blocking the proliferation, invasion, and migration especially in solid tumors, such as colon cancer and head and neck cancer. Increased EGFR expression showed poor prognosis.²¹ Cetuximab inhibits the binding of ligands EGF and transforming growth factor- α (TGF α) with EGFR and inhibits the activation of receptor tyrosine kinase-induced ligand.²² In addition, cetuximab inhibits homodimerization, heterodimerization between EGFR and HER2, EGFR downstream signaling through the MAPK pathway and Akt. Cetuximab induces apoptosis and inhibits neovascularization. Before treating metastatic colon cancer with cetuximab, it should be confirmed that there is no mutation of K-Ras gene.²³

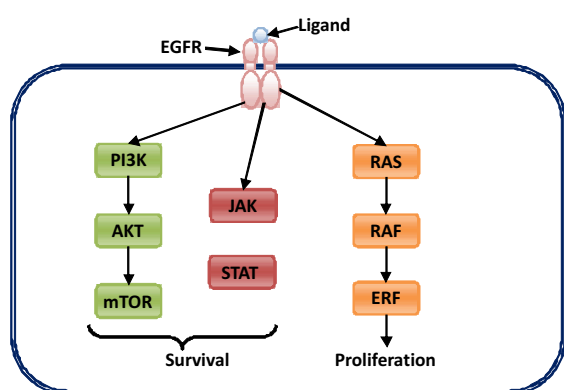


Figure 2. EGFR signaling pathway

HER2/neu Antibody

HER2 is a transmembrane receptor with tyrosine kinase activity. The first monoclonal antibody that blocks HER2 is trastuzumab.¹² It acts by binding to HER2 thereby preventing growth signaling pathways to occur. In addition, trastuzumab inhibits intracellular signaling pathways through MAPK and PI3K.¹² MAPK pathways play a role in tumor cell proliferation, whereas PI3K inhibits apoptosis by triggering and activating Akt phosphorylation. Trastuzumab inhibits the PI3K pathway and

cell proliferation through an increase in PTEN activity. Trastuzumab can stop cell proliferation by arresting at G1 phase. Trastuzumab increases the body's immune response through the working of natural killer (NK) cells, which induces cell lysis. Trastuzumab decreases angiogenesis and it is widely used for breast cancer with Her-2 positive 3 (strongly positive).¹²

VEGF and VEGFR

Monoclonal antibodies therapy includes neutralizing antibodies to VEGF (e.g. bevacizumab) or its receptor, VEGFR (e.g. ramucirumab). Antibody to VEGF neutralized VEGF after it is secreted from the tumor cells. Bevacizumab is an example of humanized monoclonal antibody that inhibits new vessel growth, regresses a newly formed tumor vasculature, alters vascular function and tumor blood flow, and acts on tumor cells directly. It is used in combination with standard chemotherapy for metastatic colon cancer. It has been approved for use in certain lung cancers, renal cancers, ovarian cancers, and glioblastoma multiforme of the brain.²⁴

Cluster of Differentiation (CD)

Antibodies that attack the cell surface markers CD20, CD33, and CD52 on lymphoma and leukemia are the first discovered targeted therapy. Chimeric anti-CD20 monoclonal antibody (rituximab) works by inducing ADCC and CDC that inhibits cell proliferation and stimulates apoptosis. ADCC stimulate NK cells to produce interferon- γ (IFN γ) which have anti-tumor effects and can activate immune cells.²⁵ Positive CD20 is a prerequisite for the administration of rituximab. Common treatment side effects include infection (31%), headache (19%), nausea (23%), vomiting (10%), and others. Rituximab can induce fever, thrombocytopenia, bronchospasm, hypoxemia, and others.

Alemtuzumab is a specific targeted therapy against CD52. Alemtuzumab induce apoptosis and through CDC directly. Side effects include infection, anemia, thrombocytopenia and myocardial infarction.²⁶ Brentuximab vedotin is used in the treatment of non-Hodgkin's lymphoma with CD30 positive.²⁶

OTHER TARGETS

Mechanistic of Rapamycin (mTOR) Inhibitor

The mechanistic (formerly mammalian) target of rapamycin (mTOR) is a serine-threonine kinase that is a member of the phosphatidylinositol kinase-related kinase (Pik) family of kinases (9).²⁷ It presents in two multi-protein complexes (mTORC1 and mTORC2). It has broad antitumor effects such as arresting cell cycle, angiogenesis, and apoptosis. mTOR is a protein complex composed of two mTORC1 and mTORC2. PI3K activation would trigger catalyzing phosphoinositide-3,4,5-tri-phosphate (PIP3), then activate Akt that becomes active mTORC1. The mTORC2 is directly activated by PIP3. These mutations will lead to growth, anti-apoptosis, and cell proliferation.²⁸

Key molecular factors activate the PI3K/AKT/mTOR pathway in either endothelial or cancer cells. In addition to effects reported in cancer cells, mTOR inhibitors might also act as anti-angiogenic agents by intercepting the VEGF and PDGF signaling cascades.²⁹

CONCLUSION

Cancer is a disease of intracellular signaling dysregulation leading to uncontrolled cell proliferation. Targeted therapy is a new treatment modality which can directly disrupt the growth signaling pathway, either by inhibiting enzymatic activity (such as tyrosine kinase inhibitor) or by blocking cell surface receptors with monoclonal antibodies. Targeted therapy has an important role in cancer therapy because it has minimal side effects and higher efficacy compared to chemotherapy. However, resistance against targeted therapy can occur and the high cost may also be a problem.

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