



Targeted Therapies For Treatment Of Solid Tumor

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ABSTRACT :

There are various targeted therapies that inhibit the growth of cancerous cells by targeting particular molecules. Chemotherapy is mainly used as a method that targets all proliferating cells. EGFR-Targeting treatment is particularly used for colorectal cancer, in this method Cetuximab binds with EGFR and inhibits the ligand binding and causes the reduction of EGFR expression. Angiogenesis Inhibitors are promising anti-cancer drugs with low side effects. Bevacizumab is an angiogenesis inhibitor used for colorectal, breast and lung cancer. Bevacizumab particularly binds with VEGF which interacts with cell surface receptors and reduces tumor blood vessel development. Sunitinib is used for renal cell carcinoma which inhibits several tyrosine kinases. Cell-cycle inhibitors prevent cell cycle progression by binding to and inhibiting cell-cycle kinases. Flavopiridol is used as an active cell cycle inhibitor which inhibits the activity of several cyclin-dependent kinases. Indisulam is a newly developed drug particularly used to treat solid tumors. Indisulam arrests the cell cycle in G1 phase and prevents the growth of cancerous cells.

Introduction :

The terms "molecular targets," "molecularly targeted drugs," and "molecularly targeted therapies" refer to drugs that inhibit cancer growth by targeting specific molecules. Molecules implicated in tumor development and progression. Traditional chemotherapies target all proliferating cells, whereas targeted therapies target specific molecular targets expressed by neoplastic cells, resulting in significant efficacy. The "ideal target" is a protein that is highly expressed on the membrane or within tumor cells, is genetically stable, is not shed or secreted, and plays a causal role in tumor development or progression. Current targets include cell-surface trans-membrane proteins such as tyrosine kinase receptors, intracellular proteins such as transcription factors that play a role in cytoplasmic or nuclear signaling, and growth factors. The treatment of gastrointestinal stromal tumors (GIST) is the most effective paradigm for targeting receptor tyrosine kinases. This rare gastrointestinal tract

neoplasia is caused by the production of a cell-surface transmembrane protein produced by the KIT proto-oncogene with tyrosine kinase activity. Constitutive activation of KIT signaling causes excessive cell proliferation and resistance to apoptosis. In 2002, George Demetri and researchers found that imatinib mesylate, a selective inhibitor of protein tyrosine kinases, including the KIT, a transmembrane receptor, causes a response in 98.5% of individuals with unresectable or metastatic GIST [1].

Now, many multitargeted treatments, such as imatinib mesylate, sunitinib malate, sorafenib tosylate, and dasatinib, are being used to treat many hematologic malignancies and solid tumors, including GIST and advanced renal cell cancer (RCC)[2]. Tamoxifen, a synthetic estrogen-blocker, was approved for the treatment of metastatic breast cancer (MBC) in the 1970s, marking the first instance of targeting intracellular nuclear receptors. This agent is targeting the estrogen receptor (ER) which is a steroid hormone nuclear receptor. When attached to oestrogen, it regulates the transcription of genes involved in breast cancer cell proliferation and survival. Since the pioneering observations Beatson reported a remission in premenopausal women who had a surgical oophorectomy for advanced breast cancer, hormone therapy is still a common treatment option. The concept of tailored therapeutic approaches in medical history[3]

Molecular profiling helps choose tailored therapy for individuals with lung, breast, and colon cancers. When utilized in molecularly identifiable patients with the mentioned tumor types, medicines targeting human HER2, EGFR, and v-raf murine receptors Sarcoma viral oncogene homolog B1 (BRAF), 3 and Hedgehog pathway 4 has been one of the most effective medicines introduced over the last 20 years. The low incidence of targeted molecular alterations in non-indicated tumors (typically 5%) has made it challenging to recruit patients for traditional drug development studies, despite anecdotal reports of activity. Basket studies investigate the effectiveness of targeted medicines in patient groups with unique characteristics. Molecular tumor abnormalities, rather than by histology of the main location or tumor.[4] studies such as Vemurafenib is being studied in BRAF V600 mutation-positive non-melanoma tumors.[5].

EGFR-Targeting Treatment :

The epidermal growth factor receptor (EGFR), also known as HER-1 or ErbB1, is a member of a family of tyrosine kinase type receptors anchored in the cell membrane of the cytoplasm that also includes the proteins HER-2/ErbB2, HER-3/ErbB3, and HER-4/ErbB4[1]. Anti-Epidermal Growth Factor

Receptor (EGFR) treatments have recently been developed to treat a variety of cancer types. This therapy is highly focused on colorectal cancer. Colorectal cancer (CRC) is one of the most frequent cancers globally. About 40-50% of newly diagnosed patients have metastatic illness. [7] Targeting the epidermal growth factor receptor (EGFR) in the therapy of several tumor types is a recent advancement in oncology. Cetuximab (CTX) (Erbiximab®, Merck KGaA, Darmstadt, Germany) is a chimeric immunoglobulin G1 monoclonal antibody that binds the EGFR with high affinity while competitively inhibiting ligand binding. [8] Binding of the antibody to the EGFR stops endogenous ligands from stimulating the receptor, resulting in reduction of cell proliferation, increased apoptosis, and decreased angiogenesis, invasiveness, and metastasis. Cetuximab binding to the receptor also causes internalization of the antibody-receptor complex, resulting in an overall reduction in EGFR expression levels. The EGFR is a promising target for novel cancer treatments, and other drugs in development include tiny molecular tyrosine kinase inhibitors and antisense therapies. [9].

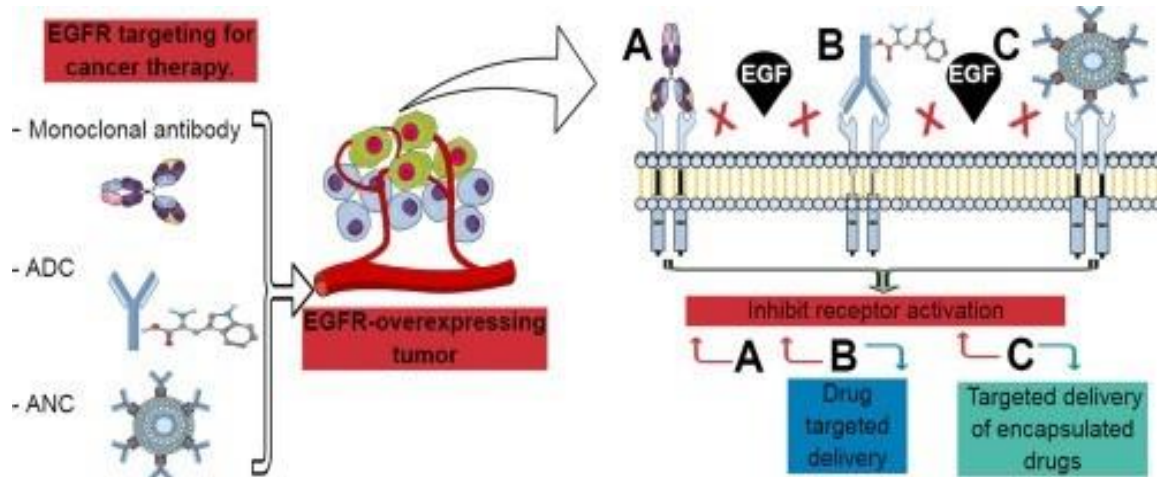


Fig:1.0 EGFR targeted therapy

Myeloid Cell-Targeted Therapies For Solid Tumours :

Myeloid cells are the most prevalent immunological components in the tumor microenvironment, and they perform a variety of actions ranging from immunosuppressive to immunostimulatory. The myeloid cell sector contains a variety of cell types, including monocytes, macrophages, dendritic cells, and granulocytes, which are highly flexible and can develop into various phenotypes in response to cues from their microenvironment. [10] The release of tumor-derived substances alters physiological haematopoiesis, resulting in the formation of novel cells with immunosuppressive and tolerogenic activities, such as myeloid-derived suppressor cells. These pro-tumour myeloid cell populations not only support immune escape directly, but also aid tumor invasion through non-immunological actions. [11] Myeloid cells rapidly penetrate early neoplastic lesions and may influence tumor fate by encouraging T cell-mediated death by serving as specialized tumour antigen-presenting cells or by suppressing both adaptive and innate immunity. Tumor-associated macrophages (TAMs), MDSCs, tumour-associated neutrophils (TANs), and dendritic cells (DCs) are important tumor-infiltrating myeloid cells (TIMs). [11] TAMs interfere with the majority of anti-tumor therapy used in clinical practice, including typical chemotherapy, anti-angiogenic therapy, radiation, and new antibody-based immunotherapies targeting the molecules PD-1/PD-1L and CTLA-4: immune checkpoint blockade (ICB). [12]

Angiogenesis Inhibitors :

Since angiogenesis is a critical mechanism in tumor growth but a limited mechanism in healthy persons, finding angiogenesis inhibitors is a promising anticancer target with low side effects. Resistance to antiangiogenesis medications is also uncommon, or at least far lower than that seen with classic cytotoxic chemotherapeutics, especially if genetically stable endothelial cells (ECs) are targeted. The resistance to antiangiogenesis medications is also unlikely, or at least at a much lower rate than that reported with classic cytotoxic chemotherapeutics, especially if the genetically stable endothelial cells (ECs) are targeted. Resistance to antiangiogenesis medications is also unlikely, or at least at a much lower rate than that reported with classic cytotoxic chemotherapeutics, especially if the genetically stable endothelial cells (ECs) are targeted. [13]. The process of transforming a normal cell into a cancer cell requires a number of complex genetic and epigenetic modifications. [13]

Bevacizumab for colorectal , breast and lung cancer:

The US Food and Drug Administration (FDA) approved bevacizumab, a recombinant humanized monoclonal antibody, in February 2004 for use in combination therapy with fluorouracil-based regimens for metastatic colorectal cancer. Bevacizumab has a linear pharmacokinetic profile in the dose range of 0.3 to 10 mg/kg q2-3wk and reaches steady state in around 100 days. The expected half-life of bevacizumab is 20 days. After adjusting for body weight, clearance and V(d) are reported to be 26% and 22% higher in men than in women. Combining bevacizumab with chemotherapy or other innovative targeted medicines looks to be a reasonable approach that could improve efficacy while limiting typical nonselective effects. [14] Bevacizumab works by specifically binding circulating VEGF, which inhibits its interaction to cell surface receptors. This inhibition reduces the microvascular development of tumor blood vessels, limiting blood flow to tumour tissues. These effects also reduce tissue interstitial pressure, increase vascular permeability, potentially improve chemotherapeutic agent delivery, and promote tumor endothelial cell death [20]. Bevacizumab works by

specifically binding circulating VEGF(vascular endothelial growth factor), which inhibits its interaction to cell surface receptors. This inhibition reduces the microvascular development of tumor blood vessels, limiting blood flow to tumour tissues. These actions reduce interstitial pressure, increase vascular permeability, improve

chemotherapeutic delivery, and promote tumor endothelial apoptosis.[15]

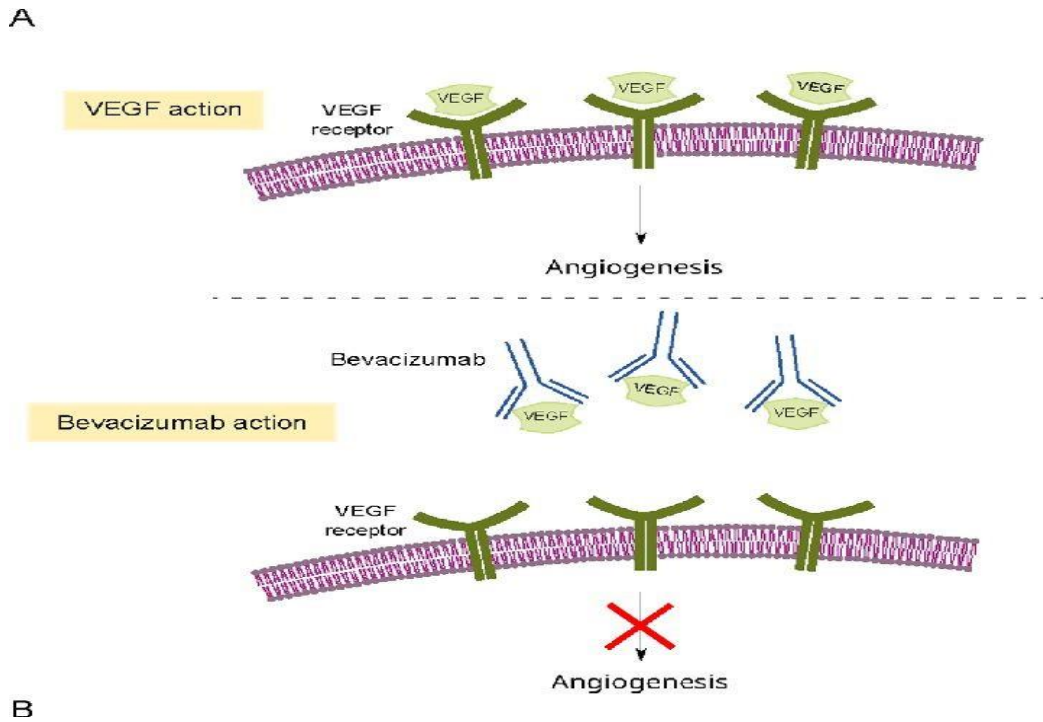


Fig 2.0 mechanism of action of bevacizumab

Sunitinib (Sutent) for renal cell carcinoma:

Sunitinib is an inhibitor of several tyrosine kinases, including PDGFR, KIT, RET, FLT3, and VEGFR1-3. This inhibits various signaling pathways, including RAS/MAPK, PI3K/AKT, and protein kinase C. As a result, sunitinib fights cancer by inhibiting tumor growth and angiogenesis while increasing vascular disruption. This figure is based from Faivre et al. (2007) [96] and Aparicio-Gallego et al. (2011) [91]. Source publication Sunitinib is an inhibitor of several tyrosine kinases, including PDGFR, KIT, RET, FLT3, and VEGFR1-3. This inhibits various signaling pathways, including RAS/MAPK, PI3K/AKT, and protein kinase C. As a result, sunitinib fights cancer by inhibiting tumor growth and angiogenesis while increasing vascular disruption.[16]

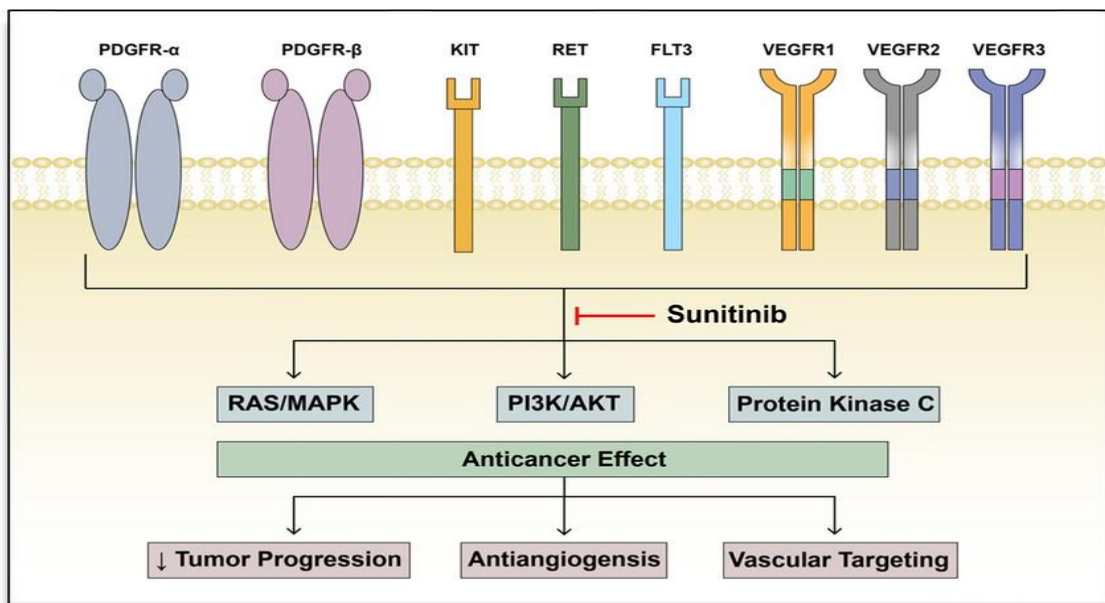


Fig : 3.0 mechanism of action of Sunitinib

Cell Cycle Inhibitor :

Cell- cycle impediments help cell cycle progression by binding to and inhibiting cell- cycle kinases. p21cip and p27kip can inhibit the CDK4- and CDK6- cyclin D complexes. In addition, the INK4 family members(p16INK4a, p15INK4b, p18INK4c, and p19INK4d) inhibit monomeric CDK4 and CDK6, precluding complex conformation with corresponding cyclins. p21cip and p27kip can inhibit the CDK4- and CDK6- cyclin D complexes. likewise, the INK4 family members(p16INK4a, p15INK4b, p18INK4c, p19INK4d) block monomeric CDK4 and CDK6, hence precluding complex conformation with corresponding cyclins.(17) The maturity of oncogenes and excrescence- suppressor genes are involved in pathways that regulate natural processes, similar as cell- cycle entry and exit. When cyclins are overexpressed or CDKs are inactivated, checkpoint integrity is constantly lost. bone cancer is linked to cyclin D1 overexpression. Targeting CDKs may thus drop growth or detector apoptosis while also restoring cell- cycle checkpoints.(18). By interacting to the corresponding free CDK4, the inhibitory-dependent protein of CyclinD- associated kinase prevents CDK4 from binding to the corresponding cyclinD to form a catalytic dimer complex.(19)

Flavopiridol A new semisynthetic flavone outgrowth of the alkaloid rohitukine is flavopiridol. It's well known that flavopiridol effectively inhibits the exertion of several cyclin-dependent kinases.Daily gelcap intravenous(IV) boluses of flavopiridol caused the thymus, spleen, and lymph bumps to shrink as a result of the picky death of their cells.(20) By fastening on distinct cyclin and CDK proteins of the G1 and G2 phases, flavopiridol regulates the progression of the cell cycle.Through ATP- competitive inhibitions, flavopiridol primarily inhibits CDK(i.e., CDK1, 2, 4, 6, and 7) and laterally reduces the situations of cyclins(i.e., cyclin D1 and cyclin D3) or CDK impediments(p21 and p27). In addition to lowering CDK enzymatic exertion, dropped situations of cyclin D(cyclin D1, cyclin A, and cyclin E) also affect phosphorylation of the pRb, p107, and p120 proteins.(21)

IndisulamA new sulfonamide anticancer medicine called Indisulam(N-(3- chloro-7-indoly1) - 1,4-benzenedisulfonamide, E7070) is being developed clinically to treat solid excrescences. Indisulam's multifaceted medium of action involves arresting the cell cycle in the G1 phase, significantly altering the situations of gene expression in at least 60 reiterations, and explosively inhibiting carbonic anhydrase, an essential enzyme involved in multitudinous physiological processes and whose link to cancer has lately come to light.Subsequent exploration demonstrated that indisulam targets colorful checkpoints during the G1 and G2 stages of the cell cycle, dismembering and downregulating cyclin A, cyclin B, CDK2, and CDC2 via p21/ p53 dependent mechanisms5. Indisulam's excrescence retrogression in HCT116 xenografts was superior to that of other anticancer agents similar as 5-FU and Irinotecan6, egging Phase I/ II clinical trials of indisulam as an anticancer treatment for multitudinous advanced solid excrescences. Despite respectable safety biographies, clinical responses have been minimum, and the efficacy of indisulam has noway been studied in neuroblastoma.

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