



Original Article

Individualized targeted therapy in oncology is highly needed in modern era of Radiation oncology practices!

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Abstract

Individualized or Personalized therapy is a way of medicine will evolve through the use of specific treatments best suited to an individual genotype. This focuses on the role of personalized medicines in cancer and explores its use in current clinical practice in oncology and the challenges to be overcome to achieve this goal. Therefore cancer therapy presents a unique example of personalized therapy in which an individual's genotype not only determines therapeutics and toxic response to a drug, but also the nature of a specific tumor

Keywords: Targeted therapy, personalized therapy.

Discussion

Personalized medicines models how medicine will evolve through the use of specific treatments and therapies tailored to each individual genotype. It's driven by patients demand for safer and more effective medicines and therapies. Its capitalizes essential molecular process in the body, Such as cell cycle control, angiogenesis, cell signaling , factors expressed through each person's specific genetic burden influence his or her response to specific drugs .

Pharmacogenomics is defined as study of how an individual genetic makeup affects the body response to specific drugs.

The term Individualized medicine is mainly used in context of pharmacogenomics that includes such as disease susceptibility and molecular traits.

Why Individualized medicine having crucial role in oncology practice?

Personalized therapy and medicines is more important for cancer patients than those with other

disease for several reasons first cancer is a highly heterogeneous disease with significant molecular differences in the expression and distributions of tumor cell markers that to among the patients with same type and grade of tumor, Second is Cellular mutations tend to accumulate as cancer progress that further adds to tumor heterogeneity. Third reason is currently use cancer chemotherapies at dose given are often toxic to normal cells.

Cancer patients often have a limited amount of time to try one kind of therapy and if it does not work then try other kind of therapy until unless optimal therapeutic regimen is being found, Therefore cancer therapy presents a unique example of Personalized therapy in which an individual's genotype not only determines therapeutics and toxic response to a drug, but also the nature of a specific tumor

Up to What Level We Achieved Personalization of Cancer Medicines

In past two decades a plethora of information collected detailing basic biological process in cancer, Now we know the key elements of growth factors binding, signal transduction, gene transcription control, cell cycle check points, apoptosis, angiogenesis, and metastasis till now more than 350 mutated genes have been detected in cancer development.

The new paradigm for cancer therapy is to develop agents that targets the precise molecular pathology driving the progression of individual cancers, genomics, genetics and cytogenetic studies has already resulted in large numbers of rationally designed anticancer drugs with many drugs currently under clinical trails.

High profile drugs such as Imatinib, Trastuzumab, Elrotinib, Bevacizumab specifically target underlying molecular deregulations and are in widespread clinical use. we are able to identify patients with precise molecular lesions that respond to these agents and so by provide important evidence for benefits of targeted therapy in cancer therapy.

Using target therapy against defined molecular lesion is a move towards target based rather than disease based approach for example Imatinib was developed to target the Bcr-Abl receptor tyrosin kinase which is formed from reciprocal chromosomal translocation between long arm of chromosomes 9 and 22, this process fuses the body of Abelson tyrosin kinase gene (Abl) on chromosome 9 with the breakpoint cluster region (bcr) gene on chromosome 22 to generate an Oncogene that encodes the chimeric Bcr-Abl protein this protein or oncogene transforms primary myeloid cells to leukemic myeloid cells via ABL receptor tyrosin kinase activity, Imatinib selectively inhibits Bcr-Abl by occupying the ABL adenosine triphosphate binding site thereby inhibiting its tyrosin kinase activity, Subsequently it has also revealed that activity against tyrosin kinase associated with c-Kit protein and platelet derived growth factor receptor

(PDGFR), activation of c-Kit has been shown to be critical in the pathogenesis of Gastrointestinal stromal tumor (GIST), henceforth Imatinib found effective in GIST tumors as well.

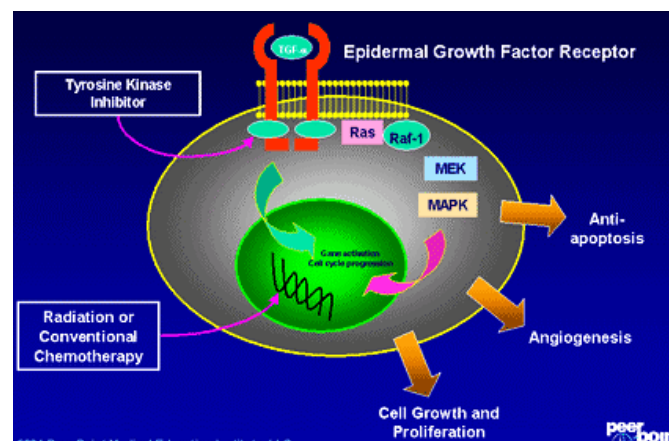


Fig 1- Tyrosine kinase inhibition

The advantages of using biomarkers to identify patients who are likely to be benefited from particular treatment further describe by the success of the humanized murine monoclonal antibody trastuzumab in breast cancer, Trastuzumab targets human epidermal growth factors receptor -2 (HER-2), which belongs to the family of four transmembrane receptor tyrosin kinase that mediates cell growth, differentiation, survival of cells. Over expression of HER-2 protein, amplification of HER-2 gene or both occurs in 15 to 30% of breast cancers these events are associated with increase proliferation, decrease cell death and increase metastasis, henceforth trastuzumab therapy significantly improves outcome and response rate alone or in combination with chemotherapy in women with HER-2 positive breast cancers.

Molecular Mediators of Tumor Angiogenesis

Several Angiogenic growth factors found which modulates tumor angiogenesis

A-Directly acting factors

B-Indirectly acting growth factors.

Directly acting growth factors include

- 1-VEGF family include Tyrosine kinases.
- 2- Angiopoietine.

3-Notch signaling receptor specially notch, all factors have high degree of specificity for endothelial cells associated Neovascularization,

Indirectly Acting

Angiogenic factors those who amplify Angiogenic process are

TNF α & TNF β ,

1-Transforming growth factors,

2-Inflammatory cytokines such as IL6 and IL8,

3-Granulocyte stimulating factor,

4-PDGF platelet derived growth factor,

4- Estrogen and Androgen hormone as well.

VEGF was discovered in 1989 and replaced to be highly specific and potent mutagen for vascular endothelial cells.

There are four role of VEGF by which it promotes tumor angiogenesis

1-stimulate endothelial cells division

2-induce endothelial cells migrations

3-enhanced endothelial cells survival

4-mobilizes endothelial progenitors cells from bone marrow to the site of tumorigenesis.

Elevated expression of VEGF commonly associated with tumor hypoxia so hypoxia in tumor cells leads to over expression of VEGF thus leads to Neovascularization of tumor cell mass. In addition to antibody/protein therapy a large number of small molecule and receptor Tyrosin kinase inhibitors have been developed to block VEGF receptor phosphorylation. Such drugs are SUNITINIB and SORAFENIB these drugs action is not only inhibition of Angiogenesis but also they directly act by inhibition of tumor cell.

Biomarkers are,elevated levels of VEGF are associated with poor prognosis, thus if high levels of VEGF bevacizumab treatment would be more helpful, VEGF receptors diagnosis and test, Require tissue specimen for Immunohistochemistry study but the tissue specimen must be from primary tumor site not from tumor metastasis site.

Benefits of Anti-Vegf Therapy

A- Inhibit the new vessels growth in tumor tissue.

B- Blockade OF development of endothelial progenitor cells.

C-Normalization of vasculature thus decrease permeability of and increase chemotherapy drug delivery to tumor tissue.

D- Direct effect on tumor as antitumor effect.

E-Inhibition of damage of endothelial cells by chemotherapy drugs.

F-Immunomodulatory effect.

For the tumors other than renal cell carcinoma anti VEGF therapy only provide benefits when it given in combination with chemotherapy drugs, Tyrosin kinase inhibitors in metastatic colorectal cancer enhanced its effect when given with chemotherapy drugs like metastatic breast cancer bevacizumab augments the effects of paclitaxil based chemotherapy ,

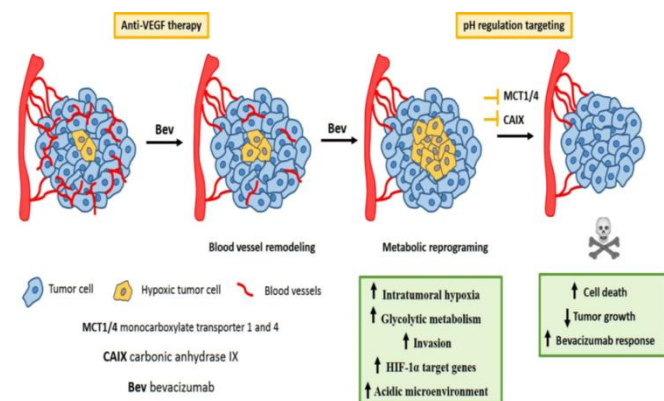


Fig2-Benefits of Bevacizumab Therapy

Toxicity of Anti VEGF Therapy

A-Hypertension

B-Proteinuria

C-Bowel perforation.

C-Anti thrombotic events

D-Hypertensions do occur due to anti VEGF causes inhibition of endothelial cells derived nitric oxide which is known vasodilator.

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