Targeted therapy in Gastrointestinal (GI) tumors.

Essay
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KEY WORDS AND ABSTRACT

Key Words :

Molecular, targeted therapy, growth factors, Ras signaling, Matrix metalloproteinase, Cox- inhibitors.

Abstract:

Molecular targeted therapies seem to be a revolutionary approach to cancer treatment and the knowledge of tumor biology needs to be improved to facilitate the identification of potential new targets. A targeted therapy should attack a biologically important process preferably one central to a hallmark of cancer. These agents represent a new approach to gastrointestinal malignancies as for many other types of tumors.

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LIST OF ABBREVIATION

ACOSOG	American College of Surgeons Oncology Group.
ACTION	Adjuvant celecoxib therapy in oncology.
ASC	American Society of Clinical Oncology.
ATP	Adenosine triphosphate.
BSC	Best supportive care.
BTCs	Biliary tract cancers.
CA 19-9	Cancer antigen 19-9.
CALGB	Cancer and Leukemia Group B.
CDK	Cyclin-dependant kinases.
COX-2	Cyclooxygenase-2 inhibitors.
CRC	Colorectal cancer.
EC	Esophageal cancer.
ECM	Extracellular matrix.
ECOG	Eastern Cooperative Oncology Group.
EGF(R)	Epidermal growth factor (Receptor).
EMEA	European Medicines Evaluation Agency.
EVEREST	Evaluation of Various Erbitux® Regimens by Means of Skin Tumor Biopsies.
FAP	Familial adenomatous polyposis.
FDA	Food and Drug Administration.
FDG-PET	Fluoro-2-deoxy-D-glucose positron emission tomography.
FGFR	Fibroblast growth factor (Receptor).
FOLFOX	Xaliplatin, folinic acid and 5FU.
FTI	Farnesyl transferase inhibitors.
GC	Gastric cancer.
GDP	Guanosine 5 –diphosphate.
GEJC	Gastro-esophageal junction cancer.
GEMOX	Gemcitabine and oxaliplatin.
GISTs	Gastrointestinal stromal tumors.
GTP	Guanosine 5 –triphosphate.
HCC	Hepatocellular carcinoma.
IFL	Irinotecan/5-FU/Leucovorin.
IHC	Immunohistochemistry.
mAb	Monoclonal antibody.
MAPK	Mitogen-activated protein kinase.

mCRC	Metastatic colorectal cancer.
MDR	Multi drug resistance.
MMP	Matrix metalloproteinase inhibitors.
mOS	Median overall survival.
mPFS	Median progression-free survival.
MSKCC	Memorial Sloan-Kettering Cancer Center study.
mTOR	Mammalian target of rapamycin.
mTTP	Median time to progression.
NCCN	National comprehensive cancer network.
NF-kB	Nuclear factor kappa B.
NSABP	National Surgical Adjuvant Breast and Bowel Project.
NSCLC	Non small cell lung cancer.
pCR	Pathologic complete response.
PDGFR	Platelet-derived growth factor receptor.
PFL	Cisplatin, fluorouracil, leucovorin.
PFS	Progression-free survival.
PR	Partial response.
RECIST	Reassessment of the Response Evaluation Criteria in Solid Tumors.
SCC	Squamous-cell carcinoma.
SCF	Stem cell factor.
SD	Stable disease.
SHARP	Sorafenib HCC Assessment Randomized Protocol.
SWOG	Southwest Oncology Group.
TACE	Transcatheter arterial chemoembolization.
TGF-a	Transforming growth factor-a.
TKI	Tyrosine kinase inhibitors.
VEGF(R)	Vascular endothelial growth factor (receptor).
VICTOR	VIOXX in colorectal cancer therapy: definition of optimal regimen.
VMTN	Volumetric measurement of percent tumor necrosis.
XELOX	Capecitabine and oxaliplatin.

CONTENTS

I – INTRODUCTION AND AIM OF WORK

Gastrointestinal (GI) cancer continues to be a common health problem. Approximately 253,500 new cases of GI malignancy were estimated to occur in the United States in 2005 **(Jemal et al, 2005)**.

These cases will account for 18.5% of all new cancers and 23.9% of cancer deaths **(Arthur et al, 2006)**.

Although colorectal tumors account for more than 50% of the cases in the United States, cancers of the esophagus, stomach, liver, and pancreas continue to occur with regularity and high mortality, and the incidence of hepatoma is increasing rapidly. Gastric and hepatic cancers are two of the most common causes of cancer incidence and death worldwide. Hereditary factors play a role in the etiology of GI cancer, and environmental toxins are causative agents in certain diseases. A significant problem with many GI cancers relates to a delay in clinical presentation. Signs that give early warning of other types of cancer (e.g. pain or palpation of a mass) do not occur early in patients with GI cancers. For example, the severe back pain that can occur with pancreatic cancer is usually a manifestation of unresectability due to posterior tumor extension. In general the early warning signs include vague abdominal discomfort, unexplained weight loss, change in bowel habits, or new onset of anemia **(Joel and Leonard, 2007)**.

5-fluorouracil, synthetized in 1957, has been the main agent in gastrointestinal tumors (alone or in association with other drugs as mytomicin C and doxorubicin) for many years. Recently, several new antineoplastic agents (irinotecan, taxanes, raltitrexed, oxaliplatin,

gemcitabine) have been introduced in clinical practice. In the last few years, our knowledge of molecular oncology about the growth control mechanisms of tumor cells has recognized the main signaling pathways that lead to cancer. The major models of action of chemotherapy is by activation of apoptosis, but the treatment of gastrointestinal carcinomas (such as other solid tumors) remains problematic because of intrinsic or acquired drugs resistance. The challenge of cancer treatment by targeted therapies is to maximize efficacy and minimize toxicity by agents that act on transcription factors, growth factors receptors, apoptosis- related proteins, and DNA-repair factors (**Nicolella et al, 2003)**.

Molecular targeted therapies have been added to cytotoxic and antiendocrine drugs in the treatment of cancer, with the aim to target the molecular pathways that underlie the carcinogenic process and maintain the cancer phenotype **(Green et al, 2004)**.

It is popular to make a distinction between "targeted" anticancer drugs and "traditional" or "cytotoxic" anticancer drugs. The biggest difference between the new "targeted" therapies and most cytotoxic drugs is that, most of the cytotoxic drugs were discovered by screening compounds for antineoplastic activity against established cell lines, rather than by looking for drugs to hit a particular molecular target. In general, the older cytotoxic agents are though to be more toxic than the newer "targeted" treatment such as monoclonal antibodies, tyrosine kinase inhibitors and protease inhibitors **(Armitage, 2006)**.

Targeted therapies need two main requisites: (A) a target being abundant, specific, stable and readily available for ligand molecules coming from the blood stream; (B) a ligand molecule being easily diffusible to the tumor with

high affinity for the target. Five areas of research seem promising in gastrointestinal tumors, with drugs in early clinical development stages:

1) Epidermal growth factor receptor (EGFR) pathway targeting.

2) RAS signaling pathways [farnesyl transferase inhibitors (FTI)].

3) VEGF and other angiogenesis pathways (antiangiogenic agents).

4) Matrix metalloproteinase (MMP) inhibitors.

5) Cyclooxygenase-2 (COX-2) inhibitors **(Nicolella et al, 2003)**.

AIM OF WORK

In this research we will discuss the role of targeted therapy in GI cancer, the various pathways of action, the reported responses and survival benefits as well as the side effects related to targeted therapy. Future look is also included.

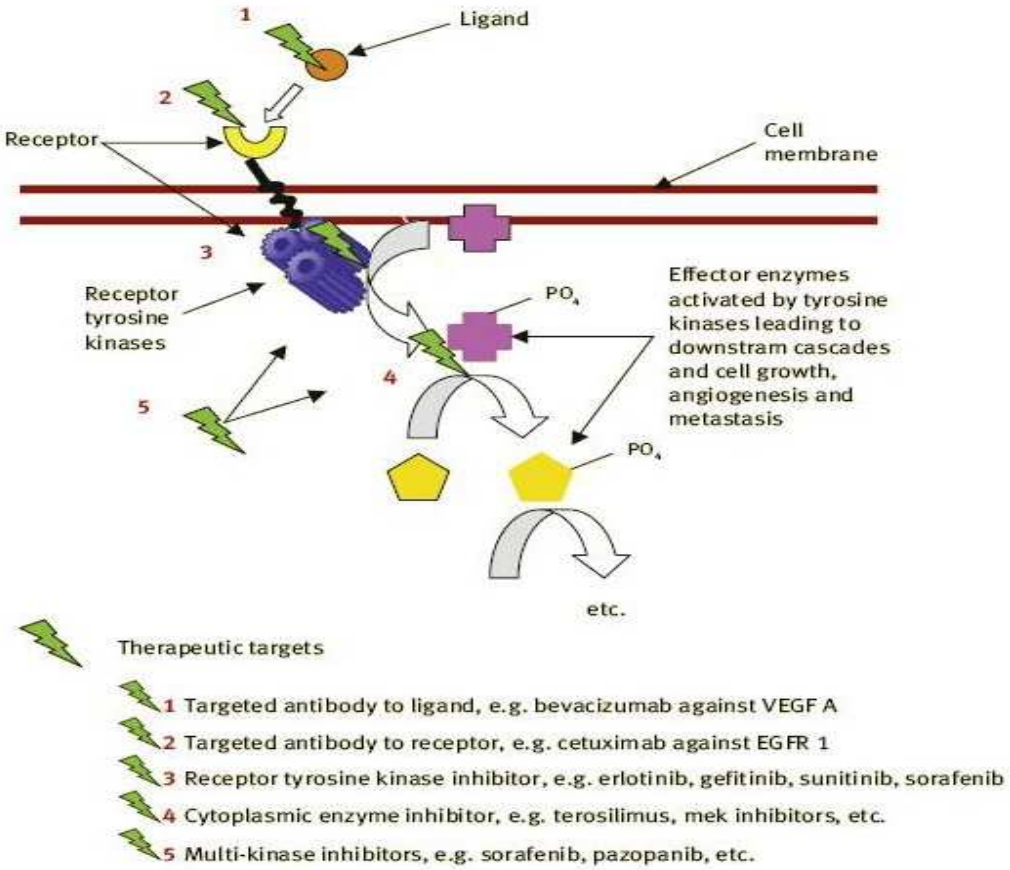
II – RATIONALE OF TARGETED THERAPY

Cancer cell biology:

Cells are subject to a milieu of biochemical signals, some of which prompt division, angiogenesis and metastasis, and some of which inhibit these functions. Unregulated responses to signals, or responses which are uncoupled from their signals and function independently of them, can lead to invasive cancers. A pathway typically involves a growth factor/ligand, the

Figure 1.

Ligand- receptors- enzymatic cascade with targets and examples of targeted therapies indicated.



(Hendrik-Tobias et al, 2007).

extracellular component of a growth factor receptor, the intracellular tyrosine kinase that signals by phosphorylating tyrosine amino acids on effector proteins, and the resulting cascade of pro-growth enzymatic reactions (Figure 1) **(Hendrik-Tobias et al, 2007)**.

Cancer growth and metastases are modulated by the tumor cell itself, the tumor stroma and by systemic influences (Fig. 2). As a result of the interaction of growth factors and growth factors receptors on the cell surface a cascade of enzymatic reactions is initiated aimed at transducing dual signal that stimulates the reproduction and inhibit the apoptosis (programmed cell death) of the tumor cell **(Faivre et al, 2006 a)**.

Growth factors may be generated in the tumor cell itself (autocrine production), in the stromal cells (paracrine production) or they may be secreted by distant organs (e.g., insulin-like growth factor 1 or erythropoietin may act as tumor growth stimulating factors) **(Henke et al, 2006)**.

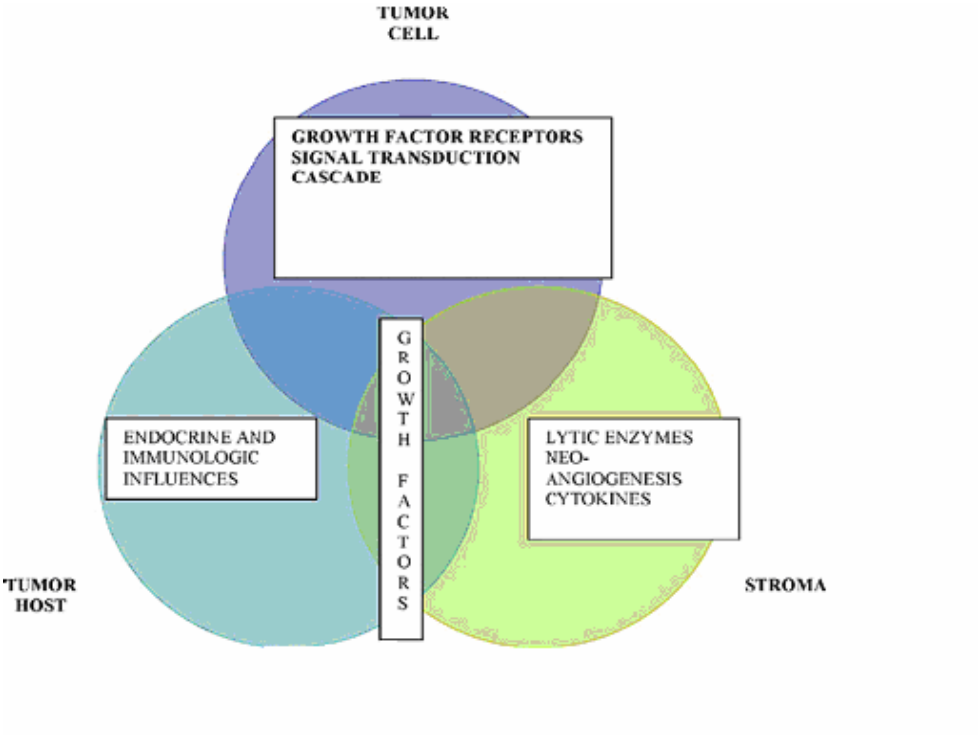
In addition to stimulating the replication of tumor cells, a number of growth factors produced by both the neoplastic cells and the stroma are responsible for stimulating the growth of endothelial cells needed for the formation of new blood vessels (neo-angiogenesis) **(Wilson, 2006)**.

Neo-angiogenesis is essential to the growth of the tumor, by providing essential nutrients, and to its metastatic spread. Neo-angiogenesis may also play an important role in protecting the tumor from antineoplastic treatment. The increased permeability of new tumor vessels causes accumulation of fluid in the tumor interstitium. Increased interstitial pressure prevents the diffusion of chemotherapy to the tumor cells. Clinical evidence supports this hypothesis, as the combination of anti-angiogenic agents appear synergistic

with cytotoxic chemotherapy in cancer of the large bowel, the breast, and the lung **(O'Dweir, 2006)**.

Figure 2.

Interactions of tumor cells. Tumor host and tumor stroma in modulating tumor growth.



(Balducci, 2007).

The tumor stroma has at least two additional roles in cancer development. It provides lytic enzymes, such as the metalloproteinases, that favor the tumor invasion of adjacent organs and of the lymphatic system. It also produces a number of inflammatory cytokines that may affect in different ways the viability of the tumor cells. Some of these cytokines, such as tumor necrosis factor may lead to necrosis of the neoplastic tissue and to neoplastic transformation of normal tissues **(Baglole et al, 2006)**.