Biological therapy in gastrointestinal cancers

Essay

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Abstract

There is also increase in the importance of the role of predictive tumour markers in managing a patient's response to treatment leading to choosing the right drug for right patient such as Her-2 gene overexpression in gastric cancers and mutational status of Kras gene in cancer colon and CD117 (KIT) overexpression in gastrointestinal stromal tumors. In gastric cancers, overexpression of the HER2 protein seems to possess the best predictive value for treatment with trastuzumab.

Key word

Bevacuzimab –MMPs- anti-VEGF- anti-EGFR- gastrointestinal

بسم الله الرحمن الرحيم

(قَالُوا سبحانك لا علم لَنَا إِلا مَا علمتنا إِنك أَنت العليم الحكيم)

صدق الله العظيم

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List of Abbreviations

AC : Ampullary cancer
AFP : Alpha fetoprotein
AJCC : American Joint Committee on Cancer
AMD : Age-related macular degeneration
Apaf-1 : Apoptotic Protease Activating Factor-1
APC : Adenomatous polyposis coli
APR : Abdominal perineal resection
ASCO : American Society of Clinical Oncology
ATP : Adenosine triphosphate
BE : Barrett's epithelium
Bev : Bevacizumab
BH : Bcl-2 homology
CALGB : Cancer and Leukemia Group B
CAPOX : Capecitabine ; Oxaliplatin
CARD : Caspase-recruitment domain
CD : Cluster of differentiation
CDDP : Cis -diamminedichloroplatinum
CDKs : Cyclin-dependent kinases
CEA : Carcinoembryonic antigen
CI : Confidence interval
CIMP : CpG island methylator phenotype
CISH : Chromogenic in situ hybridization
COX-2 : Cyclo-oxygenase-2
CPT-11 : Camptothecin (Irinotecan)
CR : Complete response
CRC : Colorectal cancer
CRT : Chemoradiotherapy
CT : Computed tomography
Cys : cysteine
DACH : Diaminocyclohexane
DCC : Deleted in Colorectal Cancer
DD : Death Domain
DED : Death-effector domain
DFS : Disease-free survival

DG : Dystroglycan
DKK1 : Dickkopf-1
DNA : Deoxyribose Nucleic Acid
DPD : Dihydropyrimidine dehydrogenase
DR : Diabetic retinopathy
EBRT : External beam radiotherapy
EBV : Epstein-Barr virus
EC : Endothelial Cell
ECF : Epirubicin-Cisplatin- 5-FU
ECM : Extracellular matrix
ECOG : Eastern Cooperative Oncology Group
ECX : Epirubicin-Cisplatin-Capecitabine
EDAR : Ectodysplasin A receptor
EGF : Epidermal growth factor
EGFR : Epidermal growth factor receptor
EMEA : European Medical Agency
EOF : Epirubicin-Oxaliplatin-Fluorouracil
EOX : Epirubicin-Oxaliplatin-Capecitabine
ER : Estrogen receptor
ERCC : Excision repair cross-complementing
ERCP : Endoscopic Retrograde Cholangiopancreatography
EUS : Endoscopic ultrasound
5-FU : 5-Fluorouracil
FA : Folinic acid
FAP : Familial adenomatous polyposis
FDA : Food and Drug administration (US)
FDG-PET : Fluorodeoxyglucose positron emission tomography
FGFR : Fibroblast growth factor receptor
FGF : Fibroblast growth factor
FISH : Fluorescence in situ hybridization
FNA : Fine Needle Aspiration
FUDR : Floxuridine
GEJ : Gastroesophageal junction
GERD : Gastroesophageal reflux disease
GF : Growth factors
GFR : Growth factor receptors
GI : Gastrointestinal

GIST : Gastrointestinal Stromal Tumor
GSTP : Glutathione S-transferase
Gy : Gray
H. pylori : Helicobacter pyloi
HAMAs : Human antimonoclonal antibodies
HBV : Hepatitis B virus
HCC : Hepatocellular carcinoma
HDGC : Hereditary diffuse gastric cancer
HLA : Human leukocyte antigen
HNPCC : Hereditary Non-polyposis Colorectal Cancer
HPF : High-power field
HR : Hazard ratios
HSP90 : Heat shock protein 90
HSPG : Heparan sulphate proteoglycans
HtrA : High-temperature-requirement
IAP : Inhibitor of apoptosis protein
IBD : Inflammatory bowel disease
IgG_2 : Immunoglobulin G_2
IHC : Immunohistochemistry
INR : International normalized ratio
INT : Intergroup
IRS-1 : Insulin receptor substrate-1
Lap : Laparoscopy
LARC : Locally advanced rectal cancer
LASSO : Least absolute shrinkage and selection operator
LOH : Loss of heterozygosity
LV : Leucovorin
mAb : Monoclonal antibodies
MALT : Mucosa-Associated Lymphoid Tumors
MDR1 : Multidrug-resistant gene
MiRs : MicroRNAs
MMP : Matrix metalloproteinases
MMPIs : MMP inhibitors
MOMP : Mitochondrial outer membrane potential
MRCP : Magnetic resonance cholangiopancreatography
MRI : Magnetic resonance imaging
MSI : Microsatellite instability

MSP : Methylation-specific polymerase chain reaction
MT : Metallothionein
MVD : Microvessel density
NADP : Nicotinamide Adenine Dinucleotide Phosphate
NF-KB : Nuclear factor-kappa B
OIS : Oncogene-induced senescence
OPN : Osteopontin
OS : Overall survival
OX : Oxaliplatin
PCR : Polymerase chain reaction
PDA : Pancreatic ductal adenocarcinoma
PDGFR-β : Platelet-derived growth factor receptor
PET : Positron-emission tomography
PENK : Proenkephalin A gene
PFS : Progression-free survival
PPP : Pentose phosphate pathway
PR : Partial response
PSCA : Prostate stem cell antigen
PTC : percutaneous transhepatic cholangiography
PVTT : Portal vein tumor thrombus
QPCR : Quantitative PCR
RCT : Randomized controlled trial
RFA : Radiofrequency ablation
RFS : Relapse free survival
RPTPs : Receptor protein tyrosine phosphatases
RR : Response rate
RTOG : Radiation Therapy Oncology Group
ROS : Reactive oxygen species
RT-PCR : Reverse transcriptase PCR
SD : Stationary Disease
TACE : Transarterial Chemoembolization
Tcf/LEF : T-cell factor/lymphocyte enhancer factor
TF : Tissue factor
TGF : Transforming growth factor
TKTL1 : Transketolase like gene 1
TNF : Tumour Necrosis Factor
TNM : Tumor size-lymph Nodes-Metastases

Topo I	:	Topoisomerase I
TP	:	Thymidine phosphorylase
TRADD	:	TNF-receptor associated death domain
TRAIL	:	TNF-related apoptosis-inducing ligand
TS	:	Thymidylate synthase
Tsp-1	:	Thrombospondin-1
TTP	:	Time-to-progression
UCAN	:	Ulcerative colitis associated neoplasia
UGT1A1	:	Uridine diphosphate glucoronosyltransferase
UK	:	United Kingdom
U.S.	:	United States
VEGF	:	Vascular endothelial grown factor
vs	:	Versus
Waf1	:	wildtype p53-activated fragment 1
WHO	:	World Health Organization
WT	:	Wild type
XRCC1	:	X-ray cross complementing factor 1
Y^{90}	:	$Yttrium^{90}$

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Introduction

Cancer is a major human health problem worldwide and is the second leading cause of death in the United States. Over the past 30 years, significant progress has been achieved in understanding the molecular basis of cancer. The accumulation of this basic knowledge has established that cancer is a variety of distinct diseases and that defective genes cause these diseases **(Luo et al., 2005).**

Cancer, among other diseases, is caused by the deregulation of gene expression. Some genes are overexpressed, producing abundant supplies of their gene products, whereas other crucial genes are suppressed or even deleted such as p53 and Rb genes. The expression levels of genes associated with cancer influence processes such as cell proliferation, apoptosis, and invasion. Genes involved in growth, for example, are often overexpressed in tumor tissues compared with normal adjacent tissue from the same organ such as Her-2 gene, VEGF gene, Ras and Myc genes. It is imperative to elucidate which genes are overexpressed or down-regulated in tumors because these genes could represent critical therapeutic targets **(Weir et al., 2007).**

Scientists are able to study the expression levels of numerous genes simultaneously. The ability to analyze global profiles of gene expression in normal tissue compared with tumor tissue can help to reveal how gene expression affects the overall process of carcinogenesis **(Offit et al ., 2008).**

Gastrointestinal cancers account for 21 % of all cancers incidences and 25 % of the cancer mortality in the United States **(Schottenfeld et al., 2007).**

New genomic technologies have led to important therapeutic advances in oncology. The discovery of molecular prognostic markers events and the discovery of predictive marker to classify response to specific treatment options could be used to guide the selection of treatment and identify targets for the development of new molecular-targeted therapies. Prognostic markers can be used to determine the need for further treatment. Patients at very low risk of disease events can safely avoid treatment if risks of side effects outweigh the estimated benefits. Alternatively, high-risk patients may benefit from a more aggressive treatment regimen. Predictive markers could be used to select the most appropriate treatment by identifying patients most likely to respond and avoiding treatment for patients unlikely to respond or those at unacceptably high risk of adverse events such as Her-2 gene overexpression in gastric cancers and mutational status of Kras gene in cancer colon. ToGA (Trastuzumab for GAstric Cancer) trial demonstrated that Her-2 is a predictive biomarker for treatment with trastuzumab in gastric cancer. CRYSTAL trial demonstrated that wt-KRAS is a predictive biomarker for treatment with cetuximab in metastatic colorectal cancer. Randomised control trials are essential to assess the effectiveness and optimal use of prognostic and predictive markers and biomarker-guided therapies **(Simon, 2010).**

Aim of the work

In the present essay, our aim is to review the biological, genetic and molecular features in gastrointestinal cancers and evaluate their predictive and prognostic value that could affect the choice of therapy according to expected response and outcome.

OVERVIEW OF GASTRO-INTESTINAL CANCERS