World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i26.5896

World J Gastroenterol 2016 July 14; 22(26): 5896-5908
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Gastric Cancer: Global view

Exploring the role of molecular biomarkers as a potential weapon against gastric cancer: A review of the literature

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Conflict-of-interest statement: The authors declare that they have no competing interests.

Manuscript source: Invited manuscript

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Received: March 15, 2016
Peer-review started: March 18, 2016
First decision: May 12, 2016
Revised: May 25, 2016
Accepted: June 13, 2016
Article in press: June 13, 2016
Published online: July 14, 2016

Abstract

Gastric cancer (GC) is a global health problem and a major cause of cancer-related death with high recurrence rates ranging from 25% to 40% for GC patients staging Ⅱ-Ⅳ. Unfortunately, while the majority of GC patients usually present with advanced tumor stage; there is still limited evidence-based therapeutic options. Current approach to GC management consists mainly of; endoscopy followed by, gastrectomy and chemotherapy or chemo-radiotherapy. Recent studies in GC have confirmed that it is a heterogeneous disease. Many molecular characterization studies have been performed in GC. Recent discoveries of the molecular pathways underlying the disease have opened the door to more personalized treatment and better predictable outcome. The identification of molecular markers is a useful tool for clinical managementin GC patients, assisting in diagnosis, evaluation of response to treatment and development of novel therapeutic modalities. While chemotherapeutic agents have certain physiological effects on the tumor cells, the prediction of the response is different from one type of tumor to the other. The specificity of molecular biomarkers is a principal feature driving their application in anticancer therapies. Here we are trying to focus on the role of molecular pathways of GC and well-established molecular markers that can guide the therapeutic management.

Key words: Gastric cancer; Molecular therapy; Targeted therapy; Biomarkers; Bioinformatics

Core tip: We tried to highlight the role of molecular biomarkers as a predictor to chemotherapeutic response to existing regimens, aiming for better personalized therapy. Also we provided a summary of molecular markers that may aid in the development of rational therapeutic options for gastric cancer (GC) patients, aiming for improving their outcomes. However, among the plethora of agents targeting VEGF, EGFR, HER-2, IGF and mTOR pathways, trastuzumab and ramucirumab have been the only approved therapeutic options for use in advanced GC. Despite having many promising studies in their early stages, a lot have failed to prove their effectiveness in GC on the long run.

Matboli M, El-Nakeep S, Hossam N, Habieb A, Azazy AEM, Ebrahim AE, Nagy Z, Abdel-Rahman O. Exploring the role of molecular biomarkers as a potential weapon against gastric cancer: A review of the literature. *World J Gastroenterol* 2016; 22(26): 5896-5908 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i26/5896.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i26.5896

INTRODUCTION

Gastric cancer (GC) is the second cause of cancer mortality[1] and the fifth most common malignancy in the world, fifty percent of the cases are from Eastern Asia[2], where China has the highest incidence[3]. These statistics are considered to be an improvement compared to the very first estimates in 1975 where GC was the most common neoplasm[4]. In spite of the apparent global decline in incidence and mortality estimates of GC in age-standardized figures, the absolute number of GC cases remains stable or even increasing[5].

The five year survival rates remain disappointing despite improvements in the diagnosis and treatment of GC cases because they are usually diagnosed at an advanced stage which is rarely curable, this is in addition to the quite high rate of recurrence[6]. Surgery has been the cornerstone in GC treatment[7], however a high rate of intra-abdominal metastasis (80%), loco-regional (40%-80%) as well as distant (20%-40%) recurrences has been reported and luckily a survival benefit has been observed from the addition of chemotherapy or radiotherapy to surgery[8-12].

The treatment of GC is dependent on the type of cancer tissue, the TNM staging and the general condition of the patient[1]. Metastatic GC gives us fewer options in dealing with the disease, aiming for palliative rather than curative goal[3].

The standard treatment options for GC include mainly: adjuvant chemotherapy or adjuvant chemo-radiation with perioperative chemotherapy. On the other hand, several recent studies evaluated the use of neoadjuvant chemotherapy solely in GC[13], which plays a role in down-staging the disease, in addition to the eradication of any possible micrometastasis[14-16].

While the chemotherapeutic agents that have proven effectiveness in the treatment of GC are more than a few, we cannot ignore the fact that the targeted therapy for GC is still very limited, mainly to vascular endothelial growth factor (VEGF) pathway - and HER2 - targeted agents. Recent achievements in the field of epigenetics and genetic background of the disease may enhance our chances of targeted therapeutic options in GC[17].

On the other hand, multiple molecular biomarkers had shown their potential efficacy as diagnostic and prognostic tools in GC but they still need further validation to be used in the day-to-day clinical practice. Up till the time being, the only used markers for GC in clinical practice are carcino-embryonic antigens; CA 19-9, CA-50[18] and CA-72[19], which lack the high sensitivity and specificity that is needed in assessing diagnosis and prognosis of GC, making their efficacy questionable.

But as the link between the new era of the molecular markers and the treatment options is increasing; where some predict response to chemotherapy while others predict the post treatment survival or recurrence; the current review focuses on the role of molecular aberrations in affecting the therapeutic guidelines, either used for predicting the outcome of specific therapeutic agents or exploited as a therapeutic target in the tumor cells.

MOLECULAR BIOMARKERS PREDICTING THE TREATMENT RESPONSE

Prediction of chemo-resistance is an important goal in personalized medicine, where each patient is treated according to his epigenetic and genetic background. Pharmacogenomics is a rapidly growing field with hope of decreasing the burden on both the patient; by adjusting the dose, type and combination of drugs used; and the burden of cost on the healthcare system[20,21].

Multiple genetic and epigenetic markers have been shown to have a predictive value in GC therapy, although their use is limited in the routine management of the disease, where treatment decision depends mainly on the clinical staging of the patient[20] (Table 1).

Genetic markers

Lin *et al*[22] compared the already published gene expression profiling signatures in GC as well as the more integrated genomic features of GC from gene

Table 1 Showing the molecular markers used in gastric cancer pharmacogenomics

Marker type	Name	Drug predicted	Predicted drug effect
Genetic markers	13 gene signature[48]	5-FU	Sensitivity or resistance to 5-FU
Genetic markers	MRP4[49]	Cisplatin	DDP resistance
Genetic markers	Metallothionein-IG and HBEGF[25]	Cisplatin	DDP resistance
Genetic markers	Dihydropyrimidine Dehydrogenase and HB-EGF-like growth factor genes[25]	5-FU	5-FU resistance
Genetic markers	Panel of genes[26]	Doxorubicin	Predicts response to chemotherapy
Genetic markers	Dihydropyrimidine Dehydrogenase and HB-EGF-like growth factor genes[25]	5-FU	5-FU resistance
Genetic markers	TP53 codon 72 polymorphism[50]	Paclitaxel and cisplatin	Certain genotypes predict response to combination therapy
lncRNA	lncRNA MRUL[36]	Multiple chemotherapeutic drugs	Multidrug resistance
Epigenetic Markers	Methylation BMP4[38]	Cisplatin	High expression predicts resistance to the drug
Epigenetic Markers	Promoter methylation of RPRM[39]	CDDP and 5-FU	Prediction of response to treatment
Epigenetic markers	Methylation of BNIP3 and DAPK[37]	Fluoropyrimidine-based chemotherapy	Methylation predicts lower response to chemotherapy
miRNA	miRNA27a[34]	Fluoropyrimidine combined with oxaliplatin or paclitaxil	Prediction of response to treatment
MicroRNA	58 signature mi-RNA; among them: let-7g, miR-342, miR-16, miR-181, miR-1, and miR-34[33]	Cisplatin and 5-FU	Chemotherapeutic response
Protein markers	Thymidylate synthetase (TS) and Dihydropyrimidine dehydrogenase (DPD)[27,40]	5-FU	Correlation with tumor sensitivity to 5-FU
Serum protein	AMBP[41]	paclitaxel–capecitabine	Predicts response to chemotherapy
Tissue protein Transcription factor	FOXM1[43]	Docetaxel	Resistance to Docetaxel
Protein markers	Ribosomal proteins S13 and L23[47]	vincristine, adriamycin, and 5-FU	Multidrug resistance by inhibition of chemotherapy related cell death and detoxification system
Serum protein (ELISA)	REG4[42]	5-FU	Resistance to 5-FU containing regimens
Protein markers	Class Ⅲ β tubulin serum level[45,46]	Paclitaxel plus capecitabine	Prediction of response to treatment

MRP4: Multi drug resistance protein 4; HBEGF: Heparin-binding epidermal growth factor-like growth factor; DDP: Dihydropyrimidine; MRUL: MDR-related and upregulated lncRNA; CDDP: Cisplatin; DAPK: Death-associated protein kinase; AMBP: Alpha-1-microglobulin/bikunin precursor; foxm1: Forkhead box protein M1; REG4: Regenerating family member 4; 5-FU: 5-fluorouracil.

expression, chromosomal instability, somatic mutation, and DNA methylation. Moreover, they identified the consensus patterns across these signatures, the biological functions and the underlying molecular pathways[22,23]. Tanaka *et al*[23] identified the precise prediction models of *in vitro* activity for 8 anticancer drugs (5-FU, TXL, CDDP, DOX, CPT-11, MMC, SN-38, and TXT), along with individual clinical responses to 5-FU using cDNA microarray analysis[24].

Suganuma *et al*[25] reported that metallothionein-IG and heparin-binding epidermal growth factor-like growth factor (HB-EGF), glutathione-S-transferase and cyclooxygenase-2 genes were potential candidate cisplatin-resistance-related genes by oligonucleotide microarrays. For 5-FU resistance, dihydropyrimidine dehydrogenase (DPD) and HB-EGF-like growth factor genes were also suggested to be resistance-related genes[25]. Doxorubicin response has also been linked to panel of genes including; ADAM22, CYR61, FN1, SPHK1 and GNAI1 by real-time RT-PCR in one study[26], but the main concern of most of these genetic signature studies is that the number of GC samples used for validation were always small in number, which means that there is a long way to go till the actual incorporation of these markers into the clinical practice.

A link was discovered between the response to cisplatin therapy and Multi-drug resistance-associated protein (MRP): when the phenotype of DDP resistance was reversed by lowering the MRP4 expression with small interfering RNA technique in GC cell line[27].

Moreover, genetic polymorphism was linked to the response of 5-FU and cisplatin in two studies, where rs715572 and rs5754312 were linked to survival of patients treated with 5-FU + cisplatin[28]. Also paclitaxel and cisplatin treatment response was predicted with TP53 codon 72 SNP[29].

A group of researchers used gene expression data to describe four molecular subtypes of GC linked to disease progression and prognosis. The mesenchymal-

like type with highest recurrence frequency (63%) of the four subtypes; microsatellite-unstable tumors are hyper-mutated displaying the best overall prognosis and the lowest frequency of recurrence (22%) of the four subtypes; tumor protein 53 (TP53)-active and TP53-inactive types include patients with intermediate prognosis and recurrence rates (with respect to the other two subtypes)[30].

Scientists proposed a molecular classification dividing GC into four subtypes: Epstein-Barr virus positive tumors with recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, CD274 and PDCD1LG2; microsatellite unstable tumors with elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins; genomically stable tumors, with mutations of RHO-family GTPase-activating proteins; and tumors with chromosomal instability with marked aneuploidy and amplification of receptor tyrosine kinases. Identification of these molecular subtypes provides an efficient roadmap for patient stratification and targeted therapies[31].

Epigenetic markers

MicroRNA: MicroRNA was linked to the resistance to trastuzumab in one study, where it was shown that miR-21/PTEN pathway may have a regulatory effect on the treatment response[32]. MicroRNA let-7i might predict the pathologic response to neoadjuvant chemotherapy[29]. Also 58 signature mi-RNAs were found to predict the chemotherapeutic response of cisplatin/fluorouracil; among the apoptosis inducers are let-7g, miR-342, miR-16, miR-181, miR-1, and miR-34[33]. miRNA-27a higher expression predicts resistance to treatment with fluoropyrimidine-containing therapy[34].

Long non coding RNAs: Long non coding RNAs (lncRNAs) are potential biomarkers for GC especially those in blood and gastric secretions which offer a minimally invasive route[35]. But the tissue samples are still the main site of research; where lncRNA MRUL (MDR-related and up regulated lncRNA) was associated with multi-drug chemotherapeutic resistance[36].

Methylation related biomarkers: Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 and death associated protein kinase DAPK methylation predicts lower response to fluoropyrimidine-based chemotherapy[37].

Decreased methylation of the Bone morphogenic protein 4 (BMP4) genes will lead to increased expression of the secreted protein, which is correlated with cisplatin resistance. BMP4 is highly expressed in cisplatin-resistant tissues and cisplatin sensitization was markedly increased with genetically targeting of BMP4 resulting in its inhibition[38].

A study showed that increased promoter methylation will cause increased expression of Reprimo (a highly glycosylated cellular protein) which was associated with a lower response to cisplatin and 5-FU chemotherapy, in addition the Reprimo Knockdown is associated with tumor suppression effect[39].

Protein markers

Cellular enzymatic activity: Cellular enzymatic activity was linked to the chemotherapeutic resistance where thymidylate synthetase (TS) and DPD were associated with 5-FU tumor sensitivity[27,40].

Cellular proteins: (1) AMBP (Alpha-1-Microglobulin/Bikunin Precursor) protein in serum was shown to predict the chemotherapeutic response to paclitaxel-capecitabine[41]; (2) Regenerating gene family, member 4 (Reg Ⅳ or REG4) predicted resistance to 5-FU containing regimens[42]; (3) As for tissue proteins; Forkhead Box M1 Transcription Factor (FOXM1) was shown to predict resistance to docetaxel[43]; (4) Increased expression of β-tubulin Ⅲ protein (TUBB3) in serum has been linked to taxane resistance in non small cell lung cancer[24] and ovarian carcinoma[44]; moreover, in a study on Chinese patients with advanced GC it was shown to predict lower response of GC to paclitaxel plus capecitabine[45] which was confirmed later in another study[46]; and (5) Ribosomal proteins: It was found that genetically unregulated ribosomal proteins S13 and L23 enhances vincristine, adriamycin, and 5-FU resistance by inhibition of cell death and detoxification systems induced by chemotherapy[47].

Thus, a number of predictive biomarkers have been extensively evaluated in the setting of GC systemic therapy. However, the vast majority of these markers were derived from small scale retrospective studies; and thus, we cannot recommend incorporating any of these markers into routine practice except after careful assessment within the setting of prospective controlled clinical trials.

MOLECULAR ABERRATIONS AS POTENTIAL THERAPEUTIC TARGETS

Tumor angiogenesis inhibition

Anti-VEGFR mAbs (Ramucirumab): VEGF has long been recognized as a key regulatory pathway of angiogenesis and thus several therapeutic agents were developed to target VEGF including neutralizing antibodies to VEGF or its receptor in GC[48-52] (Table 1). Several studies reported that the expression of VEGF and SSTR was associated with progression of GC[53,54]. A research group used a mouse model in which VEGF-A was expressed *via* adenovirus, enabling a stromal response marked by immune infiltration and angiogenesis, and identified specific stromal gene expression signatures to discover predictive biomarkers of therapeutic response, especially to immunotherapy

and antiangiogenic agents[55]. Ramucirumab is a fully humanized IgG1 monoclonal antibody targeting VEGFR2 thus antagonizing VEGF-A, VEGF-C and VEGF-D leading to a decrease of endothelial cell proliferation, migration and tumor vascularity, also decreasing lymphatic penetration, growth and metastasis to regional lymph node[56,57]. Its efficacy as a second line treatment of advanced GC has been proven following the recent publication of two phase Ⅲ studies (either alone or in combination with paclitaxel), and in both studies it had shown a clear overall survival benefit *vs* the control regimen (placebo in one study and paclitaxel monotherapy in another study)[58,59]. Several trials are still ongoing to validate its effect in earlier stages of GC[60].

Anti-VEGF mABs (Bevacizumab): Bevacizumab has been evaluated for advanced GC in multiple phase Ⅱ and Ⅲ studies (3 phase Ⅱ and 2 phase Ⅲ); but unfortunately, the results were disappointingly negative in all these studies[61-65].

Direct multi-Tyrosine kinase inhibitors (sorafenib, regorafenib, suntinib, axitinib, dovitinib, apatinib, erlotinib, gefitinib, dacomitinib, afatinib)

Tyrosine kinase (TK) inhibition can be conducted by various drugs and most of the angiogenic factors and epidermal growth factors share a common end-pathway incorporating the TK in their receptors[20]. Several research groups found that tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (TIE-1) and mitogen-activated protein kinase kinase 4, might serve as promising molecular biomarkers for GC prognosis. On the other hand, overexpression of TIE-1 kinase in GC patients was associated with reduced survival rates[66-68].

Here, we give an overview on the multi-kinase TKIs which are mostly oral drugs (Table 2). Overall, they have weak to moderate activity and none of them has been approved yet in GC[69,70].

The only successful exception of this group of agents has been Apatinib, which is a selective tyrosine kinase inhibitor against VEGF-2. A phase Ⅱ trial of monotherapy in GC showed a favorable response[71]. Later in the phase Ⅲ trial, the drug showed a good safety profile and beneficial effect with improved overall survival and progression-free survival in advanced GC that was refractory to other lines of therapy[72].

Regorafenib which is a multi-kinase inhibitor used in advanced cancers, was tested on xenograft model of patients with GC, it gave positive results regarding effectiveness for further research[73].

Suntinib and sorafenib are multi-kinase inhibitors (VEGF, PDGF, KIT) that have proven to be effective in a number of solid tumors, but when tested as a monotherapy or in combination in advanced GC showed a limited - if any - efficacy[71].

Epidermal growth factor receptor inhibition based agents

EGFR is a cell surface receptor that is activated by EGF and transforming growth factor alpha. Upon activation it initiates a downstream signaling through intracellular tyrosine kinase domain resulting in DNA synthesis and cell proliferation. Among the family of EGFRs; EGFR-1 and HER-2 which are currently targets for development of drugs for GC treatment[60]. Recent studies reported that serum HER2 levels are highly specific and demonstrated moderate diagnostic performance for HER2 tissue status in GC[74-76].

Anti-EGFR mAbs (cetuximab/panitumumab): EGFR is commonly over expressed in gastrointestinal malignancies. Its over expression is associated with a more aggressive phenotype and poorer survival, which suggests that EGFR may be a rational therapeutic target[77]. Cetuximab is a humanized monoclonal antibody against EGFR and it is the most investigated in GC[78]. Several randomized studies comparing the addition of cetuximab to conventional chemotherapies concluded that there was no clinically significant benefit associated with adding cetuximab to the conventional chemotherapies[78].

Anti-HER-2 mAbs (Trastuzumab): HER-2, also called ERB-2; is a tyrosine kinase receptor that when mutated exerts an oncogenic effect on cell proliferation, differentiation, programmed death and mobility; while mostly connected to breast cancer, it has proven to be the culprit in other tumors as well[79]. HER-2 is related to increased invasiveness and metastatic potential of the tumor[17].

HER-2 over expression has been reported in 10%-38% of GC patients[80]. Trastuzumab is a fully humanized anti-HER-2 monoclonal antibody that is already widely accepted as a standard agent for HER-2-positive breast cancer[81]. It is the first biological treatment to show improved survival in case of GC, immunohistochemistry score of more than +3 should receive the treatment, while > +2 should repeat the test using *in situ* hybridization[17].

Lapatinib is another HER-2 antagonist that is used in breast cancer resistant to trastuzumab therapy, its use in GC is not supported by evidence as it did not show any activity in GC patients in many studies[17].

PI3K/AKT/mTOR (mammalian target of rapamycin) pathway inhibitors

mTOR is active in 60% of GC cases while PI3K/Akt is active in 30% of GC cases[82]. Intriguingly, most of the key mentioned growth factor receptors affected in GC share this pathway for signal transduction[73], so it is expected to examine the effect of its inhibition in treatment of GC. Unfortunately, most of the inhibitors have shown low to moderate efficacy if any, despite being theoretically eligible targets, and further research

Table 2 Molecularly-targeted drugs evaluated in clinical trials for gastric cancer

Drug name	Type	Molecular effect	Primary cancer which it is used	Effect on gastric cancer in studies
Trastuzumab[17]	Fully humanized monoclonal antibody	Anti-HER-2 receptor protein	Breast cancer	Effective First approved molecular therapy
Sunitinib[17]	Oral multi-tyrosine kinase inhibitor	Anti-VEGF, PDGF and KIT receptors	Gastrintestinal stromal tumors, renal cell carcinoma and pancreatic neuroendocrine tumors	Limited therapeutic effect
Bevacizumab[131,132]	Fully humanized monoclonal antibody	Anti-VEGF	Colorectal cancer, non small cell lung cancer and breast cancer	Gives better survival in peritoneal metastatic disease or combined with anti-HER-2 therapy
Lapatinib[17]	Oral dual tyrosine kinase inhibitor	Anti-EGFR and HER-2	HER-2 positive advanced breast cancer	Not effective
Everolimus[17]	Oral mTOR inhibitor	Anti-intracellular receptor FKBP12	Renal cancer	Effective in advanced gastric cancer
Ramucirumab[17]	Fully humanized IgG1 monoclonal antibody	Anti-VEGFR-2	Gastric and lung cancer	Effective approved
Cetuximab[17]	Monoclonal IgG antibody	Anti-EGFR	Colorectal cancer	Not effective
Panitumumab[17]	Fully humanized IgG2 monoclonal antibody	Anti-EGFR	Advanced colorectal cancer	Not effective
Gefitinib[133]	Tyrosine kinase inhibitor	Anti- EGFR	EGFR mutation positive lung cancer	Not effective
Matuzumab[134]	Fully humanized monoclonal antibody	Anti-EGFR	Not yet approved in any other indication	Moderately effective
Tivantinib[94]	Tyrosine kinase inhibitor	Selective c-Met inhibitor	Not yet approved in any other indication	moderately effective
Onartuzumab[135]	Fully humanized monoclonal antibody	Anti- extracellulardomain of the tyrosine kinase receptor MET	Not yet approved in any other indication	Not effective
Regorafenib[73]	Tyrosine kinase inhibitor	Anti-angiogenic factor	Gastrointestinal stromal tumors	Found effective when tested on xenograft model with GC
Pembrolizumab[100]	Monoclonal antibody	PD-1 inhibitor	Advanced melanoma, advanced lung cancer	Promising phase IB results. Phase Ⅲ results are awaited
Apatinib[72]	Tyrosine kinase inhibitor	Multikinase inhibitor	Not yet approved in any other indication	Shown to be effective in a phase Ⅲ Chinese study

VEGF: Vascular endothelial growth factor; PDGF: Platelet-drived growth factor; EGFR: Epidermal growth factor receptor; mTOR: Mammalian target of rapamycin; VEGFR: VEGF receptor; MET: Mesenchymal epithelial transition; PD-1: Programmed cell death protein-1.

is needed to determine the best drug to be used.

mTOR inhibitors including Rapamycin and its derivative everolimus have shown their effectiveness in various preclinical and early clinical trials, while their phase Ⅲ trials showed disappointing outcomes[83].

Everolimus: First introduced to GC in 2008, upon the suggestion that cisplatin-induced hypoxia will activate hypoxia inducible factor 1 alpha, and VEGF; the addition of everolimus has proven its efficacy *in vivo* in inhibiting these alternative pathways[84].

Recently, the results of the Granite study evaluating everolimus for previously treated advanced GC have been reported and it was disappointingly negative; however, this same study showed that PIK3CA mutation and pS6 increased expression could be clues to everolimus effective salvage therapy but further prospective assessment for this point is needed[82,85].

Rapamycin: mTOR increased expression raises the risk of recurrence by three folds, but its definite role in activation and progression of GC is not fully comprehended[86].

Rapamycin-first known for its antifungal activity- has also anticancer activity and antiangiogenic properties. It was highly effective in preclinical trials and animal models against GC; in addition it has been shown to increase the effectiveness of chemotherapeutic drugs against GC[83,87]. However, clear level Ⅰ evidence supporting its use in GC is lacking.

Mesenchymal epithelial transition factor inhibitors

Many studies have suggested that mesenchymal epithelial transition (MET) protein was over expressed in GC patients[88-90]. Aberrant gastric MET activation can lead to increased mesenchymal characteristics and less epithelial features, and promote cancer cell stemness, invasion, metastasis, and chemo-resistance with repressed E-cadherin; which allows tumor cells to disseminate and spread throughout the body. Stress, and hypoxia could aggravate GC *via* MET, which was significantly correlated with disease prognosis[91].

Rilotumumab: It is a monoclonal antibody against hepatocyte growth factor receptor, thus inhibiting the MET pathway responsible for cell invasion and

proliferation[71], it affects mainly MET-positive GC patients with good safety profile in phase Ⅱ studies[92]. Phase Ⅲ studies are currently ongoing to better delineate its position in the treatment armamentarium of GC[93].

Tivantinib and foretinib: A phase Ⅱ trial to test the efficacy of tivantinib (a selective c-MET inhibitor) as a monotherapy in GC in Asian population concluded that the drug has a modest effect as a second or third choice in metastatic cases[94]. Foretinib on the other hand; which is an oral multi-kinase inhibitor showed no benefit as a monotherapy in metastatic GC[71].

Onartuzumab: Onartuzumab is a monoclonal antibody inhibiting the MET pathway, used mainly in advanced solid tumors either as a single agent or in addition to bevacizumab[95], it could also be of benefit in GC; however, randomized evidence is not yet mature to support its use.

Targeting immune checkpoints

Cytotoxic T-lymphocyte antigen 4 and programmed cell death protein 1 (PD-1) are both inhibitory receptors expressed by T cells. These molecules usually appear on the surface of T cells after their activation and send an inhibitory signal[96]. In GC, PD-1 expression on CD8+ lymphocytes is significantly higher than that of normal gastric mucosa and peripheral blood[97]. PD-L1 overexpression, may also serve as a predictive biomarker in GC[98].

Immunotherapy in general and immune checkpoint inhibitors - in particular - has achieved major breakthroughs in the management of a number of difficult to treat cancers like melanoma and non small cell lung cancer[99]. For GC, a phase IB study has assessed the safety, and antitumor activity of pembrolizumab (PD-1 inhibitor) in advanced GC. Overall response rate was 32% in Asian pacific patients and 30% in rest of the world[100]. This has lead to the launch of a number of randomized studies to further evaluate the role of this new group of agents in the management of this disease[101].

Other pathways like insulin like growth factor-1

Insulin like growth factor (IGF)-1 gene expression may be associated with GC susceptibility and a research group showed that serum IGF-I and IGFBP-3 levels in GC patients were significantly decreased compared to the controls[102]. But unfortunately Figitumumab; a monoclonal antibody against IGF-1; was withdrawn from phase Ⅲ clinical trial of treating lung cancer due to excessive deaths, and showed no benefit in breast cancer treatment[103]. In GC, we did not have randomized evidence supporting the use of this agent or any other agents targeting the IGF-1 pathway till now and their use should be restricted to controlled clinical studies[104].

FUTURE CANDIDATE MOLECULARMARKERS TO BE EXPLOITED AS CANDIDATE THERAPEUTIC TARGETS

Gastrokine 1

Certain studies suggested that Gastrokine 1 (GKN1) role in normal cells is to maintain integrity and mediate repair of gastric epithelium[105]. Rippa *et al*[103] demonstrated that GKN1 mRNA present in normal gastric cells more than adenocarcinoma cells[106]. More recent study by Xing *et al*[104] discovered role of GKN1 gene in GC progression, GKN1 could prevent epithelial to mesenchymal transition, decrease level of reactive oxygen species, re-expression of E-cadherin and decrease phosphatidylinositol 3-kinase (PI3K)/AKt pathway protein and so decrease metastasis in GC cell line[107].

HDAC inhibitors

Another epigenetic mechanism that plays a role in GC is histone modifications in the form of histone post translationalmodifications[108]. Histone deacetylase is thus a major target for therapeutic epigenetic inhibition.

Cancer cells are characterized by over expression of histone deacetylases (HDACs) and dysregulation of histone methyltransferases/demethylases where HDAC inhibitors have a metal binding domain that block the Zn chelation at the HDAC active sites[109]. HDAC inhibitors represent a potential approach for cancer treatment where they act mainly through cell cycle arrest at G1 or G2-M phase together with induction of apoptosis and inhibiting angiogenesis[110]. HDAC inhibitors are classified according to their structure into four groups: short chain fatty acids (*e.g.*, phenylacetate and valproate), hydroxamic acids (*e.g.*, panobinostat and belinostat), cyclicpeptides (*e.g.*, romidepsin) and benzamide derivatives (*e.g.*, MS-275)[108]. HDAC inhibitors include also sodium butyrate[111].

lncRNAs

lncRNAs play a significant role in GC progression. As lncRNAs regulate genes at different levels; namely: transcriptional, posttranscriptional and epigenetic, some of lncRNAs may have an oncogenic while other may have a tumor suppressor action[112-115]. lncRNAs with oncogenic function show high expression in GC and its expression was correlated to TNM staging and overall survival, including HOTAIR, ANRIL, H19, GHET1, CCAT1, MALTA1, HULC and MRUL which were associated with multidrug resistance and failure of chemotherapy in GC[116-124]. Tumor suppressor lncRNAs which were less expressed in GC cell lines include FENDRR, GAS5 and MEG3[125-127]. lncRNAs in GC may act as competing endogenous RNA to antagonize

miRNA and relieve its repressing effect on target mRNA[128].

Like lncRNAs; miRNA regulates gene expression at different levels[129]. Several studies suggested that miRNA has a versatile role in GC[115]. In an interesting study by Kim *et al*[33], they demonstrated a specific miRNA signature which was also related to GC chemo resistance. Also miR-610 might have a role in preventing cancer metastasis through inhibiting actin binding protein[130].

The exact mechanism and role of lncRNAs and miRNA in GC is still unclear thus further studies are required to confirm their role in GC and consequently devising suitable therapeutic agents targeting them.

CONCLUSION

GC is a global health problem that necessitates exploiting all the available scientific advances to improve the outcome of GC patients. The use of molecular markers to predict response to GC systemic therapy has been experimented extensively. However, most of the available data were derived from small-scale retrospective analyses which do not translate to the routine use of any of these markers in day-to-day clinical practice till the time-being. On the other hand, the exploitation from our better understanding of the biology of GC has paved the way to evaluating novel agents targeting potentially carcinogenic pathways in this disease. Thus, among the plethora of agents targeting VEGF, EGFR, HER-2, IGF and mTOR pathways, only trastuzumab and ramucirumab have been approved for clinical use in advanced GC. So, while Apatinib showed impressive activity in a phase Ⅲ Chinese study and may progress further to approval and pembrolizumab showed very encouraging results in early phase clinical studies, with phase Ⅲ studies are ongoing, but we still have to wait to the final results because many drugs has lost the battle of approval before in GC.

We believe that properly conducted prospective randomized studies are the key to improve the outcomes of GC cases; and thus, this has to be endorsed by all scientific entities involved in GC research.

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P- Reviewer: Ribas G, Terashima M **S- Editor**: Gong ZM
L- Editor: A **E- Editor**: Ma S

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ISSN 1007-9327