**Name of journal:** ***World Journal of Gastroenterology***

**ESPS Manuscript NO: 25573**

**Manuscripttype: 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**

Matboli M *et al*. Molecular markers and gastric cancer

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

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**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:**

**Published online:**

**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 gastric cancer 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; Biomarkers; molecular therapy; targeted therapy; bioinformatics

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**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 gastric cancer. 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; In press

**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 gastric cancer was the most common neoplasm[4]. In spite of the apparent global decline in incidence and mortality estimates of gastric cancer in age-standardized figures, the absolute number of gastric cancer cases remains stable or even increasing[5].

The five year survival rates remain disappointing despite improvements in the diagnosis and treatment of gastric cancer 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 gastric cancer 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 gastric cancer 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 gastric cancer[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 (table 1)**

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].

***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 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 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 gastric cancer 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 gastric cancer 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 5FU + 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 gastric cancer 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 gastric cancer 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 (BNIP3) 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 dihydropyrimidine dehydrogenase (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-fluorouracil 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 gastric cancer 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 (table 1)**

***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 gastric cancer[48-52]. 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 gastric cancer 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 versus 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 gastric cancer[60].

**Anti-VEGF mABs (Bevacizumab):** Bevacizumab has been evaluated for advanced gastric cancer 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 (MKK4), might serve as promising molecular biomarkers for gastric cancer prognosis. On the other hand, overexpression of TIE-1 kinase in gastric cancer 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 gastric cancer 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 gastric cancer 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 gastric cancer, 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 gastric cancer 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 gastric cancer[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 gastric cancer 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 gastric cancer, 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 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 HIF-1α(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 gastric cancer 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 gastric cancer 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:** t 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 gastric cancer; however, randomized evidence is not yet mature to support its use.

***Targeting immune checkpoints***

cytotoxic T-lymphocyte antigen 4 (CTLA-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 gastric cancer, a phase IB study has assessed the safety, and antitumor activity of pembrolizumab (PD-1 inhibitor) in advanced gastric cancer.Overall response rate(ORR )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 (IGF1)***

*IGF1* 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 insulin growth factor-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 gastric cancer, 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 Gastrokine1 (GKN1) role in normal cells is to maintain integrity and mediate repair of gastric epithelium[105]. Rippa et al demonstrated that GKN1 mRNA present in normal gastric cells more than adenocarcinoma cells[106]. More recent study by Xing et al discovered role of GKN1 gene in gastric cancer progression, GKN1 could prevent epithelial to mesenchymal transition, decrease level of reactive oxygen species (ROS), re-expression of E-cadherin and decrease phosphatidylinositol 3-kinase (PI3K)/AKt pathway protein and so decrease metastasis in gastric cancer cell line[107].

***HDAC inhibitors***

Another epigenetic mechanism that plays a role in gastric cancer 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].

***Long non coding RNAs***

Long non coding RNAs (LNCRNAs) play a significant role in gastric cancer 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 gastric cancer 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 gastric cancer[116-124]. Tumor suppressor LNCRNAs which were less expressed in gastric cancer cell lines include FENDRR, GAS5 and MEG3[125-127]. LNCRNAs in gastric cancer may act as competing endogenous RNA (ceRNA) 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 gastric cancer[115]. In an interesting study by Kim *et al*[33], they demonstrated a specific miRNA signature which was also related to gastric cancer 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 gastric cancer is still unclear thus further studies are required to confirm their role in gastric cancer 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 gastric cancer patients. The use of molecular markers to predict response to gastric cancer 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 gastric cancer 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 gastric cancer. 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 gastric cancer cases; and thus, this has to be endorsed by all scientific entities involved in gastric cancer research.

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**P-Reviewer:** Ribas G, Terashima M **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

 **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-fluorouracil (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 | dihydropyrimidinedehydrogenase 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 | dihydropyrimidinedehydrogenase 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] | ﬂuoropyrimidinecombined 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 proteinTranscription factor | FOXM1[43] | Docetaxel | Resistance to Docetaxel |
| Protein markers | Ribosomal proteins S13 and L23[47] | vincristine, adriamycin, and 5-fludrouracil. | Multidrug resistance by inhitbiton 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.

**Table 2 molecularly-targeted drugs evaluated in clinical trials for gastric cance**r

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 | EffectiveFirst 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-HER2 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 | Effectiveapproved |
| 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 humanizedmonoclonal 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 cnacer | 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.