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REVIEW

New advances in targeted gastric cancer treatment

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Abstract

Despite a decrease in incidence over past decades, gastric cancer remains a major global health problem. In the more recent period, survival has shown only minor improvement, despite significant advances in diagnostic techniques, surgical and chemotherapeutic approaches, the development of novel therapeutic agents and treatment by multidisciplinary teams. Because multiple genetic mutations, epigenetic alterations, and aberrant molecular signalling pathways are involved in the development of gastric cancers, recent research has attempted to determine the molecular heterogeneity responsible for the processes of carcinogenesis, spread and metastasis. Currently, some novel agents targeting a part of these dysfunctional molecular signalling pathways have already been integrated into the standard treatment of gastric cancer, whereas others remain in phases of investigation within clinical trials. It is essential to identify the unique molecular patterns of tumours and specific biomarkers to develop treatments targeted to the individual tumour behaviour. This review analyses the global impact of gastric cancer, as well as the role of *Helicobacter pylori* infection and the efficacy of bacterial eradication in preventing gastric cancer development. Furthermore, the paper discusses the currently available targeted treatments and future directions of research using promising novel classes of molecular agents for advanced tumours.

Key words: Gastric cancer; *Helicobacter pylori* infection; Chemotherapy; Targeted therapy; Clinical trials; New treatment advances

Core tip: Recent research attempts to determine the molecular heterogeneity of gastric tumours. Currently, some novel agents targeting aberrant molecular signalling pathways are already part of the standard treatments for gastric cancer, whereas others remain in phases of clinical trials. By identifying the unique molecular patterns of tumours, new horizons in gastric cancer treatment towards personalized medicine will emerge. This review analyses the role of *Helicobacter*

pylori infection and the efficacy of bacterial eradication in gastric cancer prevention, as well as the currently available targeted treatments and future directions of research using promising novel classes of molecular agents.

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INTRODUCTION

Gastric cancer represents a major health problem worldwide[1,2]. Despite a decrease in incidence in past decades, stomach cancer remains the fifth most common type of cancer and the third leading cause of cancer-related mortality worldwide[3]. There is broad variation in the geographic distribution of gastric carcinoma, with this neoplasia being the most common malignancy in some regions, such as Japan.

In developed countries, the incidence of cardia tumours has paralleled the trend in oesophageal cancer, while distal cancers have tended to decrease in incidence[4,5]. In contrast, the incidence of non-cardia neoplasias remains high in Japan and other parts of the world[6].

There are differences in environmental factors, such as dietary patterns and salt intake, the prevalence of *Helicobacter pylori* (*H. pylori*) infection and the virulence of strains, as well as host factors, which determine the regional variations in the incidence of stomach cancer.

Data from the literature, based on epidemiological data and observational and therapeutic trials, as well as *in vitro* and *in vivo* models, have revealed that *H. pylori* infection is the most important proven risk factor for human non-cardia gastric neoplasia. The risk of developing stomach cancer proved to be 20-fold higher or more in the presence of *H. pylori* infection[7-10].

H. pylori prevalence has demonstrated great variability determined by factors such as geographic location, age, ethnicity and socioeconomic conditions. For these reasons, its prevalence is usually high in developing regions, where *H. pylori* infection represents a public-health issue, and lower in developed countries. Its prevalence can show variability within regions of different countries and between more crowded urban populations and rural populations, mostly due to socioeconomic differences between populations.

H. pylori eradication is an effective method for preventing gastric cancer if it is performed before the development of premalignant lesions. There have been numerous studies suggesting that *H. pylori* eradication is the most effective approach to gastric cancer prevention, but we should bear in mind that this intervention is more effective in patients who do not have atrophic gastritis or IM at the same time[11-13]. In a pooled analysis of six studies including 6695 patients (most of them from Asia) followed up for 4-10 years, Fuccio and collaborators showed that the relative risk for gastric cancer after *H. pylori* eradication was 0.65 (95%CI: 0.43-0.98)[14].

De Vries *et al*[15] found out that the incidence of premalignant gastric lesions was declining, and they concluded that a further decrease of at least 24% in the incidence of gastric cancer in the coming decade could be anticipated in Western countries.

The study by Lee showed that mass eradication of *H. pylori* infection led to an important reduction in the incidence of gastric atrophy shortly after implementation, supporting the use of this strategy to prevent gastric cancer in populations in whom *H. pylori* is endemic and the incidence of gastric cancer is high[16].

Usually, the diagnosis of gastric cancer is delayed by a lack of early specific symptoms, and most patients are diagnosed in advanced stages, resulting in poor 5-year survival rates[17], with median survival of less than 1 year for metastatic disease[18-20].

Based on the evidence that exists regarding prognostic factors and the management of specific types of gastric cancer, there is an imperative need to improve the tumour node metastasis (TNM) staging system. The 7th edition of the TNM staging system emphasizes the importance of both depth of invasion and the number of locoregional lymph nodes involved as major prognostic factors, as a consensus approach of Eastern and Western countries[21,22]. Currently, gastro-oesophageal (GE) junction cancers are now classified as oesophageal cancers because of the similarity. However, we should bear in mind that it is sometimes difficult to interpret data from the literature and to implement them because many gastric cancer clinical trials include a significant proportion of GE junction tumours, while many trials designed for oesophageal cancer have also included some proximal gastric tumours.

Surgical resection is the mainstay of stomach cancer treatment, with adjuvant chemotherapy or chemoradiation[23,24]. In recent years, the survival rate has shown only minor improvement despite significant progress in diagnostic techniques, surgical and chemotherapy approaches, the discovery of novel therapeutic agents and treatment of gastric cancer patients by multidisciplinary teams. In patients with locally advanced or metastatic cancers, treatment relies mainly on chemotherapy, although the results are often limited by the high grade toxicity of aggressive regimens associating three agents or by the poor performance status of patients[25]. In such cases, palliatives and BSC are unfortunately the only appropriate treatments.

Because the pathogenesis of gastric cancers involves many different genetic mutations, as well

as epigenetic alterations, and the dysfunction of molecular signalling pathways, many efforts have been undertaken in recent years to emphasize the molecular heterogeneity responsible not only for the process of carcinogenesis but also for cancer spread and metastasis. Each of these molecular alterations is involved in a different stage of cancerous disease. Currently, some of these aberrant molecular signalling pathways are used as targets of interventions with novel therapeutic agents, some of which are already approved for the treatment of gastric cancer, while others remain in the phase of clinical trials[26]. It is essential to identify the unique molecular patterns of tumour carcinogenesis and progression in to develop specific treatments targeted to the individual tumour biology and behaviour.

METHODS

A literature search modality was applied for all English language literature published in the last 16 years, before March 2016, by assessing the PubMed electronic database. The keywords used for our research purposes were "gastric cancer", "stomach neoplasm", "treatment", "targeted treatment", and "molecular treatment". The specific search was also performed to identify clinical studies involving novel agents for gastric cancer treatment using the ClinicalTrials.gov database. Furthermore, the search was also performed on different cancer-related Web sites.

TARGETED THERAPIES

Numerous targeted therapies belonging to different classes of drugs have been investigated as therapeutics in gastric cancer, starting with preclinical studies and continuing into clinical trials, such as human epidermal growth factor receptor type 2 (HER2), vascular endothelial growth factor (VEGF) receptor, epidermal growth factor receptor (EGFR), the insulin-like growth factor receptor, phosphatidylinositol 3-kinase (PI3k)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, c-MET, fibroblast growth factor receptor (FGFR), poly [adenosine diphosphate (ADP)]-ribose polymerase (PARP) inhibitors, and immunotherapies[26] (Table 1).

Anti-HER2 therapies

The HER2 receptor belongs to the EGFR/HER family and is involved in signal transduction, cell growth and differentiation. The *HER2* proto-oncogene encodes for a 185 kDa transmembrane glycoprotein receptor with intracellular tyrosine kinase activity[27]. Data from the literature have revealed *HER2* over-expression and amplification in 7%-34% of patients with gastro-oesophageal adenocarcinomas. HER2 immunoreaction is considered to be negative if the immunohistochemistry (IHC) is 0 or 1+ and positive if the IHC 3+. IHC of 2+ requires confirmatory testing with fluorescence *in situ* hybridization (FISH)[28].

Anti-HER2 therapies have demonstrated efficiency for both *in vitro* and *in vivo* gastric cancer models[29]. Therapies evaluated in clinical trials of patients with gastric cancer have included inhibition by monoclonal antibodies (trastuzumab and pertuzumab) and tyrosine kinase inhibitors (TKIs) (lapatinib).

Monoclonal antibodies targeting HER-2

Trastuzumab (trade names Herclon, Herceptin) is a humanized monoclonal antibody that targets the extracellular binding domain of the HER2 receptor; the first therapeutic indication for this agent was for breast cancer (FDA approval since 1998). The efficacy of trastuzumab for gastric cancer was assessed in an international, open-label, phase Ⅲ trial (ToGA) that randomized naïve patients with metastatic or locally advanced unresectable gastric or gastro-oesophageal junction adenocarcinoma with over-expressed *HER2* to chemotherapy associated with trastuzumab *vs* chemotherapy alone[30]. Because this study demonstrated an improvement in median overall survival (OS) (2.7 mo), as well as significantly better response rates, time to progression of disease, and duration of response for patients who received trastuzumab, the FDA approved this drug as a targeted therapy for gastric and gastro-oesophageal junction adenocarcinoma in 2010. The results of this study demonstrated that adding trastuzumab to classic chemotherapy could increase the OS of patients with advanced gastric cancer to more than 1 year, thus proving the essential role of trastuzumab in the treatment of patients with this advanced stage of disease. Currently, trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction; it is approved for use only in patients with *HER2* overexpression, which is defined as an IHC 3 positive result or an IHC 2 and FISH double-positive result.

There are several other ongoing studies of trastuzumab, such as the HELOISE trial (trastuzumab plus chemotherapy in patients with HER2-positive metastatic gastric or gastro-oesophageal junction cancer)[31], the phase Ⅱ study NCT01130337 in non-metastatic gastric cancer using trastuzumab and chemotherapy in perioperative setting[32], the TOXAG study (a combination of chemotherapeutic agents plus trastuzumab and chemoradiotherapy in an adjuvant setting in operated patients with HER2+ gastric or gastro-oesophageal junction cancer)[33], the HER-FLOT study (chemotherapy plus trastuzumab as a perioperative treatment for patients with HER2-positive locally advanced oesophago-gastric adenocarcinoma)[34] and the phase Ⅲ trial RTOG 1010 for locally advanced oesophageal or gastro-oesophageal junction adeno-

Table 1 Targeted agents that have been studied for the treatment of gastric neoplasia

Class (target)	Type	Agent	Current status in GC treatment	Indications	Treatment benefits
HER2 inhibitors	mAb	Trastuzumab	FDA approval 2010	HER2+ metastatic GC	↑ OS, ORR, PFS[30]
	mAb second generation	Pertuzumab	Phase Ⅲ clinical trials ongoing	HER2+ metastatic/locally advanced unresectable GC	Under investigation[38]
	Antibody-drug conjugate	Trastuzumab etansine	Phase Ⅱ/Ⅲ clinical trials ongoing	HER2+ advanced GC	Under investigation[39]
	TKI	Lapatinib	Phase Ⅲ clinical trials	First-line and second-line HER2+ advanced/metastatic GC	Benefits in some subgroups of patients; ↑ RR in second-line setting[42,43]
			Phase Ⅲ clinical trials ongoing	Resectable GC	Under investigation[44]
EGFR inhibitors	mAb	Cetuximab	Phase Ⅱ/Ⅲ clinical trials	Advanced/metastatic GC	No benefits in first-line setting; modest benefit, reduced toxicity in second-line setting[52,57-59]
	Humanized mAb	Panitumumab	Phase Ⅲ clinical trials	Advanced GC	No benefits[60]
		Nimotuzumab	Phase Ⅱ clinical trials	Advanced GC	Promising results in EGFR2+/3+ subgroups of patients[69]
	TKI	Gefitinib	Phase Ⅰ/Ⅱ/Ⅲ clinical trials ongoing	Resectable/advanced and metastatic GC	No benefits[72-74]
		Erlotinib	Phase Ⅱ	Advanced/metastatic GC	No benefits so far; phase Ⅱ trials pending results[75]
VEGF/VEGFR inhibitors	Anti-VEGF humanized mAb	Bevacizumab	Phase Ⅲ clinical trials	Advanced GC, first-line treatment	↑ PFS, ORR, benefits in specific subgroups of patients[106-108]
			Phase Ⅲ clinical trials	Perioperative chemotherapy in resectable GC	Under investigation[44,110]
	Anti-VEGF humanized mAb	Ramucirumab	FDA approval 2014	Advanced GC, second-line treatment	↑ OS, PFS[119-122]
	TKI	Apatinib	CFDA approval 2014	Metastatic GC, third-line treatment	↑ OS, PFS[127,129,131]
VEGFR, PDGFR, c-KIT, FMS, FLT inhibitor	TKI	Sunitinib	Phase Ⅰ/Ⅱ clinical trials	Advanced GC	↑ OS, ORR (second-line); promising results[133-136]
RAF, VEGFR, PDGFR inhibitor	TKI	Sorafenib	Phase Ⅰ/Ⅱ clinical trials	Advanced GC	↑ PFS, OS (second-line)[143]; conflicting data[144,145]
VEGFR, PDGFR, c-KIT inhibitor	TKI	Pazopanib	Phase Ⅰ/Ⅱ clinical trials	Advanced GC	Under investigation[150-152]
VEGFR, RAF inhibitor	TKI	Regorafenib	Phase Ⅰ/Ⅱ ongoing clinical trials	Refractory advanced GC	↑ PFS, OS, drawback: drug-related toxicity[156]; under investigation[157-159]
IGF-1 inhibitor	Humanized mAb	Figitumumab	Phase Ⅰ ongoing clinical trials	Advanced GC	Under investigation[167,168]
FGF- inhibitors	TKI	AZD2171	Phase Ⅱ clinical trials	Advanced GC, second-line treatment	Promising results[172]
		JNJ-42756493	Phase Ⅰ ongoing clinical trials	Advanced GC	Promising results[173]
		Dovitinib Brivanib INCB054828	Phase Ⅰ/Ⅱ ongoing clinical trials	Advanced GC	Under investigation[183-185]
HGF/c-MET inhibitors	Humanized mAb	Rilotumumab	Phase Ⅱ clinical trials Phase Ⅲ clinical trials	Advanced/metastatic GC	↑ OS in MET (+) subset of patients[188,189] Increased toxicity, ↓ OS, PFS
		Onartuzumab	Phase Ⅲ clinical trials	MET(+), HER2(-) GC	Negative results
	TKI	Foretonib	Phase Ⅱ clinical trials	Metastatic GC	Minimal efficacy[194]
PI3 kinase/mTOR inhibitors	Inhibitor	Everolimus	Phase Ⅲ clinical trials	Advanced GC, second/third-line treatment	Negative results[207,208]
		Sirolimus	Phase Ⅰ ongoing clinical trials	Advanced GC	Under investigation[209]
PARP inhibitors	Inhibitor	Olaparib	Phase Ⅱ clinical trials	Metastatic/recurrent GC, second-line treatment	↑ OS in specific subgroup of patients; under investigation[211-213]
		Veliparib	Phase Ⅰ ongoing clinical trials	Advanced GC	Under investigation[216]

Immuno-therapy/Immuno-checkpoint blockade	CTLA-4 inhibitor	Ipilimumab	Phase Ⅱ clinical trials	Advanced/metastatic GC	Negative results[224]
	CTLA-4 inhibitor	Tremalimu-mab	Phase Ⅰ/Ⅱ ongoing clinical trials	Advanced GC	Synergistic effects for Tremelimumab and Durvalumab combination; under investigation[240,241]
	Binding of PD-1 with PD-L1 blockade	Nivolumab	Phase Ⅰ/Ⅱ ongoing clinical trials	Advanced/metastatic GC	Promising results[228]
		Pembrolizu-mab	Phase Ⅰ-Ⅲ ongoing clinical trials	Advanced/metastatic GC, naive patients and progression under treatment	Promising results[230]; under investigation[231-238,243,244]
	PD-L1 inhibitor	Durvalumab	Phase Ⅰ clinical trials	Advanced GC	Promising results[239]
GCC inhibitor	Humanized mAb	MLN0264	Phase Ⅰ/Ⅱ ongoing clinical trials	Advanced/metastatic GC, GCC (+)	Promising results[247,248]
Tumour cell cycle inhibitor	CKI	Flavopiridol	Phase Ⅱ clinical trials	Advanced GC	Negative results[251,252]
Tumour cell apoptosis	Proteasome inhibitor	Bortezomib	Phase Ⅱ clinical trials	Advanced/metastatic GC	Negative results[262]
MMP inhibitors	Inhibitor	Marimastat	Randomized, double-blind, placebo-controlled study	Non-resectable GC, maintenance treatment	Survival benefit[265]

GC: Gastric cancer; mAb: Monoclonal antibody; OS: Overall survival; ORR: Overall response rate; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; HER2: Human epidermal growth factor receptor type 2; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; c-KIT: Stem cell factor receptor (CD117); FLT: Fms-related tyrosine kinase; RAF (protein): rapidly accelerated fibrosarcoma or rat fibrosarcoma; IGF-1: Insulin growth factor 1; FGF: Fibroblast growth factor; HGF: Hepatocyte growth factor; mTOR: Mammalian target of rapamycin; PARP: Poly (ADP-ribose) polymerase; CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4; PD-1: Programmed cell death-1; PD-L1: Programmed cell death-ligand 1; GCC: Guanylyl cyclase C; CKI: Cyclin-dependent kinase inhibitor; MMP: Matrix metalloproteinase; FDA: Food and Drug Administration; CFDA: Chinese Food and Drug Administration.

carcinoma (chemoradiation ± trastuzumab prior to surgery)[35]. Patients with cancer have shown good drug tolerance.

The results of two phase Ⅱ clinical trials assessing the efficacy and safety of trastuzumab plus XELOX (capecitabine/oxaliplatin)[36] and SP (S-1/cisplatin)[37], respectively, for advanced gastric cancer therapy confirmed that trastuzumab associated with these chemotherapy regimens was efficient in treating gastric cancer.

The second generation of anti-HER2 agents was developed because of emerging resistance to anti-HER2 therapy. Pertuzumab (trade name Perjeta), which binds to a distinct site on the HER2 (and potentially HER3) receptor and has demonstrated efficacy in preclinical studies of oesophago-gastric adenocarcinoma, as well as in combination with trastuzumab in breast cancer, is currently being investigated in the phase Ⅲ JACOB study (first-line treatment with trastuzumab and chemotherapy ± pertuzumab) in patients with HER2-positive metastatic or locally advanced unresectable gastro-oesophageal junction or gastric cancer[38]. Trastuzumab emtansine is an antibody-drug conjugate that utilizes *HER2* overexpression to deliver a cytotoxic agent directly into neoplastic cells, and it is currently being evaluated in a second-line phase Ⅱ/Ⅲ trial in advanced gastric cancer[39].

TKIs of HER2: Lapatinib (Tykerb/Tyverb) is an oral small molecule dual TKI of EGFR and HER2 that has been approved for the treatment of HER2-positive advanced breast cancer progressing under trastuzumab and in association with hormonal therapy for triple positive metastatic breast cancer[40,41]. Lapatinib was studied in combination with standard chemotherapy in patients with HER2-positive advanced gastric and gastro-oesophageal junction adenocarcinomas in the phase Ⅲ LOGIC study[42] without demonstrating an improvement in OS, although certain subgroups were shown to have a benefit, nor did the phase Ⅲ Asian TyTAN trial demonstrate an OS or progression free survival (PFS) benefit for the lapatinib group as a second-line treatment, although there was a statistically significantly increased response rate[43].

The MAGIC-B trial is evaluating the addition of the HER2 TKI lapatinib to perioperative epirubicin, cisplatin, capecitabine (ECX) chemotherapy in a subgroup of patients whose tumours demonstrate *HER2* overexpression[44].

EGFR inhibition

EGFR is a transmembrane glycoprotein[45] overexpressed in several gastrointestinal malignancies. Ligand binding to the extracellular domain determines EGFR activation and phosphorylation of the intracellular tyrosine kinase, leading to activation of Ras/Raf/mitogen-activated protein kinase or the Akt/mTOR pathway[46]. EGFR overexpression is found in 30%-50% of gastro-oesophageal malignancies, associated with a more aggressive histology and advanced stage[47]. In gastric cancer, EGFR is expressed at a relatively high level, whereas the mutation rate of *KRAS* is much lower than that in colorectal cancer (4.2%)[48].

Inhibition of EGFR can be undertaken using monoclonal antibodies (*i.e.*, cetuximab and panitumumab) or TKIs (*i.e.*, gefitinib, erlotinib).

Anti-EGFR monoclonal antibodies: Cetuximab (trade name Erbitux) is a chimeric monoclonal antibody that binds to the extracellular domain of human EGFR and inhibits ligand-induced EGFR tyrosine kinase activation[49]; it is currently approved for the treatment of advanced *KRAS* wild-type colorectal cancer, as well as squamous cell head and neck cancers[50,51]. Unfortunately, the phase Ⅲ EXPAND trial (chemotherapy associated with cetuximab in advanced gastro-oesophageal cancers) did not show a PFS or OS benefit for cetuximab in the treatment of gastric cancer[52]. Other clinical trials evaluating cetuximab in gastric cancer settings have shown no benefits in PFS and OS, or they included insufficient numbers of patients[53-55], whereas others are pending results[56].

Based on numerous studies, there is no benefit of adding cetuximab to a first-line chemotherapy regimen for advanced gastric cancer, compared to a single-agent chemotherapeutic regimen; the former treatment represents an alternative choice for first-line treatment because of its lower toxicity. As a second-line treatment, combination regimens including cetuximab are advantageous; however, it is debatable whether these regimens will be used as standard treatment because of economic constraints[57-59].

Panitumumab (trade name Vectibix) is a fully human monoclonal anti-EGFR antibody. The REAL-3 study, a trial of the efficacy of chemotherapy with or without panitumumab in naïve patients with advanced oesophago-gastric cancer, did not show any benefit[60]. Other trials of panitumumab associated with different chemotherapy schemes were stopped early due to poor tolerability[61] or preliminary results from other trials[62]. There are still other trials ongoing using panitumumab[63,64].

The failure of the EXPAND and REAL3 trials could be explained by EGFR perhaps not being the major oncogenic pathway in advanced gastric cancer, and neither study evaluated patients for EGFR expression by IHC/FISH to select the treatment group. Therefore, it is essential to identify predictive markers to determine the population group that would most likely benefit from anti-EGFR therapy[65].

Nimotuzumab (h-R3) is a recombinant humanized monoclonal antibody with high binding specificity to human extracellular EGFR, with strong destructive effects on EGFR(+) cancer cells and showing some advantages compared to cetuximab, such as a longer half-life, higher dose-effect rate, and less severe dermatological toxicity[66]. *In vitro*, nimotuzumab showed effects of antiproliferation, antiangiogenesis and apoptosis on EGFR-overexpressed tumour cells[67,68]. A double-blind phase Ⅱ trial[69] evaluated irinotecan-naïve patients with advanced gastric cancer who received nimotuzumab plus irinotecan *vs* irinotecan alone, and it showed no difference in PFS or OS between these two groups. However, it should be noted that a significant benefit was detected in EGFR2+/3+ subgroups. The phase Ⅲ clinical trial NCT01813253 of nimotuzumab and irinotecan as a second line treatment for advanced or recurrent gastric or gastro-oesophageal cancer is currently recruiting patients[70] to determine the efficacy of nimotuzumab in these conditions. The efficacy of nimotuzumab seems to be proportional to the tumour surface EGFR density in patients, and the treatment is associated with a low adverse events rate.

A recent randomized phase Ⅱ trial performed to test the effect of adding nimotuzumab to cisplatin and S-1 in untreated advanced gastric carcinoma showed no additional benefit over nimotuzumab, raising the hypothesis that a negative interaction could exist between nimotuzumab and S-1 chemotherapy[71].

TKIs of EGFR: Gefitinib (trade name Iressa) is an oral EGFR TKI with promising results against several types of malignancies in early phase trials. An open, single centre, phase Ⅰ/Ⅱ study of gefitinib in combination with chemoradiation in subjects with resectable gastric cancer (NCT00237900) is awaiting results[72]. Also, a multicentre phase Ⅱ study was designed to evaluate tumour response rates in patients with surgically unresectable and/or metastatic oesophageal or gastric carcinomas treated with induction chemotherapy followed by gefitinib[73], and a phase Ⅲ trial (NCT01243398) randomized patients with advanced oesophageal or gastro-oesophageal junction cancers to gefitinib *vs* placebo after progression on chemotherapy[74]. The pending results of these studies could help to define the role of gefitinib in gastric cancer.

Erlotinib (trade name Tarceva) is an oral EGFR TKI, which has been approved for the treatment of lung and pancreatic cancers. A phase Ⅱ trial revealed that erlotinib was active in patients with gastro-oesophageal cancer (response rate of 9%), but it showed no responses in gastric cancer[75].

In conclusion, data from numerous current studies, using either small molecule TKI or monoclonal anti-EGFR antibodies, have revealed no significant curative effects of these agents as treatments for metastatic gastric cancer.

VEGF/VEGF receptor inhibition

Angiogenesis is a key element in tumour growth and spread. The importance of angiogenesis in tumour growth and dissemination was first discovered in 1971, when Folkman[76] proposed for the first time the hypothesis according to which "the solid tumours' growth and the development of metastases are dependent of the formation of new blood vessels"[77,78].

Cancer development is vascular-dependent, and beyond a tumour volume of 2 mm^3, tumour cells start to secrete a broad range of proangiogenic factors due to hypoxia to allow for growth and invasion. This fact provides the rationale for targeted antiangiogenic agents becoming a principal strategy in cancer therapy. Therefore, solid tumour growth depends on the development of new blood vessels[79]. To maintain

unlimited tumour growth, the tumour tissue depends on the sustained formation of new blood vessels, which is essential for tumours' growth beyond microscopic size, thus ensuring oxygenation and nutrient perfusion, as well as the elimination of the products of metabolism. Different from normal tissues, in which angiogenesis is strictly controlled, in neoplastic tissue, angiogenesis proved to be uncontrolled and immature[80].

Dvorak showed for the first time an association between tumour angiogenesis and microvascular permeability growth, which led to the identification of vascular permeability factor[81], which in turn was subsequently proved by Ferrara to be a specific angiogenesis inductor, known as VEGF[82].

VEGF is a mitogen and a stimulator of the endothelial cells with angiogenic effects *in vivo*[83,84], and its expression is correlated with the growth of blood vessels during angiogenesis[85,86], including angiogenesis in the female genital tract and with the development of the tumours. VEGF is a homo-dimeric protein of 40-45 kDa, secreted by a large variety of cells and by most tumour cells, existing in 5 different isomorphic forms (VEGF-A, B, C, D and E) and presenting two specific receptors in endothelial cells[87-90]. VEGF-A is an essential mediator of physiologic and pathologic angiogenesis[91]. VEGF-C is linked to Flt-4, preferably expressed by the lymphatic endothelium[92,93]. VEGF represents one of the most important tumour proangiogenic cytokines. VEGF expression is stimulated by the presence of hypoxia, and it is frequently higher in the proximity of necrosed areas[94,95]. Other effects of VEGF include inducing fenestrations in the endothelium of the small venules and capillaries, even in tissues in which microvascularization does not present normal fenestrations, which partially explains the enhanced permeability of tumour vessels[96,97].

VEGF has demonstrated a pivotal role in tumour angiogenesis, growth, and metastasis in numerous neoplasias, including gastric cancer[98], and for this reason, it is considered an essential therapeutic target for many tumours. Studies have shown that VEGF expression is related to the invasiveness, clinical stage and prognosis of gastric cancer[99].

Multiple anti-VEGF agents have been developed, including monoclonal antibodies (such as bevacizumab) and TKIs (such as apatinib) to inhibit the proangiogenic effects of VEGF or monoclonal antibodies directed against VEGF receptor (such as ramucirumab) to inhibit its function. Another antiangiogenic drug is recombinant human endostatin[68].

Anti-VEGF monoclonal antibodies: Bevacizumab (trade name Avastin) is the first FDA-approved anti-VEGF monoclonal recombinant humanized antibody for cancer treatment. This monoclonal antibody has been acknowledged for clinical use to treat numerous tumours, such as colorectal, breast, lung (non-small cell lung cancer, NSCLC), renal, and ovarian cancers and glioblastoma[100-105]. Bevacizumab treatment is associated with side effects such as thromboembolic events, gastrointestinal perforation, hypertension and proteinuria. The phase Ⅲ multinational AVAGAST trial (Avastin in gastric cancer)[106], designed to evaluate the efficacy of adding bevacizumab to cisplatin-based chemotherapy as a first-line treatment for advanced gastric cancer, demonstrated that both median PFS and overall response rate were significantly improved in the bevacizumab group, without a significant benefit in OS.

This study evaluated a panel of tumour angiogenic factors, including neuropilin, to find the most appropriate group of patients who might benefit from antiangiogenic treatment[107,108]. Neuropilin, as well as baseline plasma VEGF-A, seemed to be a promising prognostic biomarker, and with the potentially predictive properties for bevacizumab, its role is still under research.

There was another phase Ⅲ study, AVATAR, performed in China, which also found that bevacizumab added to capecitabine/cisplatin chemotherapy did not significantly improve OS in patients with advanced gastric cancer[109].

Unfortunately, the negative results of the AVAGAST and AVATAR studies might have derived from not having selected the most suitable gastric cancer patients for bevacizumab treatment; therefore, biomarkers and more fundamental research on the molecular typing of gastric tumours are needed for this purpose.

The MAGIC-B study (medical research council adjuvant gastric infusional chemotherapy) from United Kingdom is currently assessing the role of bevacizumab for peri-operative chemotherapy in resectable adenocarcinoma of the stomach and gastro-oesophageal junction, randomizing patients to receive the perioperative regimen administered in the original MAGIC trial[110], namely ECX with or without bevacizumab[44]. Hopefully, this trial will allow for the detection of predictive biomarkers that could identify the subset of patients with the greatest potential benefit from the use of perioperative VEGF-A inhibitory monoclonal antibody[111].

Currently, the safety and efficacy of adding bevacizumab to taxane-based chemotherapeutic regimens or irinotecan in advanced/metastatic gastric cancer is being evaluated in several clinical trials with pending results[112-114]. Also, studies are investigating the associated administration of bevacizumab plus anti-Her2-targeted treatment (trastuzumab) in the Her2(+) subset of gastric cancer patients[115,116]. Furthermore, several trials are assessing the benefit of administrating bevacizumab in neoadjuvant settings[117,118].

Anti-VEGF receptor monoclonal antibodies: Ramucirumab (trade name Cyramza) is a fully human monoclonal antibody that potently inhibits VEGFR-2. Based on the phase Ⅲ REGARD study (ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma),

which found significantly longer OS for ramucirumab used as a second line chemotherapy in gastric or gastro-oesophageal junction adenocarcinoma patients *vs* best supportive care (BSC)[119], the FDA approved this antibody for use as a single agent in gastric and gastro-oesophageal junction cancer after progression on a platinum- or fluoropyrimidine-containing regimen (2014)[120].

A phase Ⅲ clinical trial of ramucirumab plus paclitaxel *vs* placebo plus paclitaxel in the treatment of metastatic gastro-oesophageal junction and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination (RAINBOW trial) demonstrated significantly longer PFS and OS for the ramucirumab group[121], also leading to approval by the FDA of ramucirumab in combination with paclitaxel as a second-line therapy. Ramucirumab is currently the only antiangiogenic agent that has been approved for the treatment of advanced gastric cancer[122]. However, ramucirumab treatment has been associated with significant adverse reactions, such as neutropenia, leukopenia, hypertension and decreased strength, which must be considered. Unfortunately, a phase Ⅱ study of ramucirumab combined with the FOLFOX regimen did not show an improvement of early cure as the primary endpoint of PFS in advanced gastric cancer, once again emphasizing the urgent need for molecular biomarkers to select the most suitable patients for antiangiogenic treatment[123].

Endostar (YH-16, recombinant human endostatin) is a novel recombinant human endostatin, found to inhibit significantly VEGF-induced tumour cell proliferation and migration and to suppress VEGFR-2 expression[124]. This agent was approved for the treatment of non-small-cell lung cancer by China's Food and Drug Administration (CFDA) (2005). Xu *et al*[125] investigated the efficacy and safety of Endostar combined with SOX (S-1/oxaliplatin) for the first-line treatment of patients with advanced gastric cancer; although the curative effect was not significantly different, their results showed significantly better PFS for the group including Endostar, without the addition of severe toxicity. More trials of the efficacy and safety of Endostatin in gastric cancer settings are needed.

TKIs of VEGF: Apatinib (YN968D1) is an anti-VEGF-2 small molecule TKI developed in China[126]. Li *et al*[127] reported a phase Ⅱ, randomized, placebo-controlled study that treated patients with metastatic adenocarcinoma gastric cancer with apatinib mono-therapy who did not respond at least two chemotherapeutic regimens. There were statistically significant differences between the Apatinib and placebo groups for both OS and PFS, with adverse effects, such as handfoot syndrome, proteinuria and hypertension, which were clinically managed. The results of a phase Ⅲ, randomized, double-blind, placebo-controlled clinical study treating advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction with apatinib[128], which included patients from 32 centres in China with advanced gastric cancer who did not respond to second-line chemotherapy treatment, showed that median OS was significantly longer (by 55 d), and PFS was also significantly prolonged in the Apatinib group *vs* placebo. The disease control rate was approximately 50% in this group, although the efficiency of treatment was not as high.

Studies have demonstrated that apatinib was the first discovered anti-VEGF-2 small molecule TKI with benefits for Asian patients with advanced gastric cancer, representing remarkable progress for third-line treatment in this setting, although it prolonged OS by less than 2 mo. Further data are needed to assess the efficacy and safety of this molecule in other ethnic groups (*e.g*., Caucasians).

This phase Ⅲ study of apatinib reassured scholars regarding the existence of a favourable safety profile of the agent compared to other antiangiogenic molecules, especially with regard to cardiovascular toxicity, making it a promising option for recurrent gastric cancer[129]. Data have proved that biomarkers could identify the subset of patients most likely to benefit from the antiangiogenic agents. The AVAGAST trial demonstrated a positive correlation of bevacizumab response with the levels of VEGF-A in serum and neuropilin-1 in tumour tissue in non-Asian patients[108], providing evidence to support further biomarker investigation for antiangiogenic treatment. A biomarker study of apatinib in patients with breast cancer revealed that both hypertension and high expression of phosphorylated VEGFR-2 could serve as potential markers for assessing treatment response[130].

Based on the positive results from the phase Ⅲ study in stomach cancer patients, apatinib was approved in October 2014 by the CFDA for metastatic gastric or gastro-oesophageal junction adenocarcinoma after second-line chemotherapy progression[131].

Sunitinib (trade name Sutent, previously known as SU11248) represents an oral multi-targeted TKI of VEGFR, platelet-derived growth factor receptor (PDGFR), c-KIT (stem cell factor receptor), rearranged during transfection, and FMS-like tyrosine kinase-3 receptor, exerting antitumor effects. It is currently indicated for the treatment of advanced renal cell carcinoma, gastrointestinal stromal tumours showing imatinib resistance/intolerance and progressive unresectable/metastatic neuroendocrine pancreatic tumours[132].

A phase Ⅱ trial of single agent sunitinib as a second line monotherapy in patients with advanced gastric and gastroesophageal cancer, showed a median OS of 6.8 mo[133]. Sunitinib was also evaluated in combination with chemotherapy (Docetaxel) in patients with metastatic gastric cancer, showing a similar time to progression but an increased response rate of 41.4% *vs* 14.3%[134].

Recent phase Ⅰ and Ⅱ clinical trials have confirmed the efficacy and tolerability of sunitinib combined with standard chemotherapies. Its clinical benefit in advanced gastric cancer treatment requires further studies[135,136].

Sorafenib (trade name Nexavar) is a multitargeted TKI. It is an inhibitor of the RAF tyrosine kinase and several other receptor tyrosine kinases (VEGFR-2, VEGFR-3, and PDGFR-β), and it is approved for the treatment of advanced hepatocellular carcinoma (HCC) and clear-cell renal-cell carcinoma[137,138]. In animal models of gastric cancer, sorafenib proved to inhibit tumour growth and angiogenesis[139]. Phase Ⅰ and Ⅱ trials are evaluating the efficacy of sorafenib for the treatment of advanced gastro-oesophageal junction carcinoma in combination with chemotherapy (FOLFOX4, S1 + cisplatin)/as a single agent[140-142]. A phase Ⅱ study including gastric cancer patients treated with sorafenib combined with docetaxel and cisplatin (second line) showed very long median PFS and median OS (5.8 and 13.6 mo, respectively)[143], although other studies have been terminated early because of low response rates[144,145].

A phase Ⅰ-Ⅱ study of sorafenib + capecitabine and cisplatin, including 21 patients with advanced gastric cancer, obtained a median PFS of 10 mo, a response rate of 63% and a median OS of 14.7 mo[146].

Pazopanib (trade name Votrient) is an oral agent that inhibits angiogenesis through multiple pathways (VEGFR, PDGFR, c-KIT), and it is approved by the FDA for use in the treatment of both metastatic renal cell carcinoma and soft tissue sarcoma[147,148]. A phase Ⅰ study of pazopanib in combination with cisplatin in patients with advanced solid tumours found that, despite activity observed in some patients, the potential to combine pazopanib and cisplatin appeared limited due to the safety profile and the pharmacokinetic interactions within the combination[149]. Another phase Ⅰ study evaluating the administration of pazopanib and a MET inhibitor in advanced solid tumours[150] is pending results.

There are two ongoing phase Ⅱ trials investigating pazopanib in advanced gastric tumours: the PaFLO trial (FLO ± pazopanib as first-line treatment)[151] and another trial adding pazopanib to capecitabine and oxaliplatin[152]. We are hoping that the results of these studies will determine whether there is a role for pazopanib in the treatment of advanced gastric cancer.

Regorafenib (BAY 73-4506) is an oral multikinase inhibitor that activates protein kinases, such as VEGFR and RAF[153], demonstrating efficacy in numerous tumours in different clinical trials. It has received approval for the treatment of advanced colorectal cancer (2012) and also for advanced gastrointestinal stromal tumours (2013)[154]. The antiangiogenic effect of regorafenib might occur *via* the principal antitumor pathway in gastric tumours; trials using xenograft models of gastric cancer have demonstrated a decreased level of VEGFR-2 proteins secondary to regorafenib[155].

A phase Ⅱ, double-blind, placebo-controlled trial investigating the efficacy of regorafenib in the treatment of refractory advanced esophagogastric cancer noted a significantly longer median PFS for the regorafenib group *vs* the placebo group (11 wk *vs* 3.9 wk) and a superior median OS (25 wk *vs* 19.4 wk)[156].

Although current data from the literature show a benefit of regorafenib in the second-line treatment of advanced gastric cancer, drug-related toxicity represents a serious problem for patients. The ongoing phase Ⅰ and Ⅱ trials assessing the role of regorafenib as single agent or in combination with other chemotherapeutics, such as FOLFOX or paclitaxel[157-159], mainly in a second-line setting, will better delineate the role of regorafenib in advanced gastric cancer.

IGF-1 inhibition

IGF-1 receptor (IGF-1R) is a transmembrane tyrosine kinase receptor that is activated after binding to IGF-1 and IGF-2, promoting tumour angiogenesis, growth, progression, anti-apoptosis and metastasis in several tumours, including gastro-oesophageal cancers[160]. Matsubara *et al*[161] found that IGF-1R expression in resected gastric tumours was correlated with poorer clinical outcomes. It was shown that patients with gastric cancers expressing low levels of both IGF-1R and EGFR had significantly longer OS. IGF-1R signalling has been associated with resistance to cytotoxic therapy, and inhibition of IGF-1R enhanced tumour cell apoptosis in numerous models[162]. The IGF-1R pathway can be targeted through monoclonal antibodies, IGF-1R antisense/small interfering ribonucleic acid (siRNA), and receptor tyrosine kinases.

Figitumumab (CP-751871) represents a completely humanized IgG2 monoclonal antibody against IGF-1R. A phase Ⅰ clinical study with figitumumab in combination with docetaxel demonstrated positive results[163], and phase Ⅰ and Ⅱ trials have also confirmed roles for this agent in Ewing's sarcoma and NSCLC; however, a phase Ⅲ trial investigating NSCLC was terminated early due to not reaching the endpoint[164-166]. Some phase Ⅰ clinical studies have evaluated the overall safety, tolerability and pharmacokinetic profile of figitumumab administrated in different chemotherapeutic combinations in patients with advanced solid tumours[167,168].

The role of figitumumab in gastric cancer treatment requires further research.

Fibroblast growth factor TKIs

Fibroblast growth factor (FGF) and its signalling receptors are involved in cell proliferation, differentiation, and transformation[169]. FGFR2 amplification occurs in approximately 5%-10% and polysomy in > 20% of gastric cancers, mostly in poorly differentiated gastric cancer (scirrhous cancer)[170].

In animal models of gastric cancer, AZD2171 (AZD),

a potent oral VEGF, FGFR1, PDGFRB, and VEGFR-2 TKI, led to tumour inhibition, with the most potent activity seen in tumours over-expressing FGFR2, suggesting a possible clinical benefit of AZD2171 in patients with FGFR2(+) gastric tumours[171]. At the 2015 ASCO meeting, Bang *et al*[172] presented the results of a phase Ⅱ study of AZD2171 *vs* paclitaxel in previously treated patients with advanced gastric cancer. They revealed that AZD was well-tolerated, but there was no statistically significant difference in PFS in favour of the AZD group in *FGFR2* amplified or polysomy patients selected by FISH. Marked intra-tumour heterogeneity of *FGFR2* amplification and low concordance with elevated FGFR2 expression were reported. The study provided evidence that AZD at this dose and with this schedule caused pharmacologic target inhibition.

The pan-FGFR TKI JNJ-42756493 is an FGFR 1, 2, 3, and 4 inhibitor with nanomolar affinity; orally bioavailable, it has demonstrated broad spectrum antitumor activity in cell line, xenograft and patient-derived explant models with abnormality in the FGFR signalling pathway, such as *FGFR* gene amplification, mutation and translocation. A multipart, phase Ⅰ, first in humans study of JNJ-42756493 was initiated in advanced solid tumour patients (including gastric cancer) (NCT01962532); promising interim data showed that this agent had excellent pharmaceutical properties and appeared safe with manageable side effects at dose levels that elicited anti-tumour activity[173].

Ki23057 is an oral broad-range TKI of FGFR2, FGFR1 and VEGF2 that inhibits the proliferation of gastric scirrhous cancer cells presenting *FGFR2* gene amplification. Nakamura and collaborators revealed that Ki23057 inhibited the growth and peritoneal dissemination of gastric cancer cells, mainly through FGFR2-RAS/extracellular-regulated kinase (ERK) inhibition[174]. The study of Qiu *et al*[175] found that the FGFR2 inhibitor Ki23057 might be therapeutically promising for treating drug-resistant gastric cancer cells, especially when used in combination with other chemotherapeutic drugs. The synergistic effects of these combinations might be driven by the apoptosis process and the involvement of the *ERCC1* and *p53* genes[175].

Dovitinib (TKI 258) strongly inhibits the phosphorylation of FGFR3, leading to the inhibition of tumour cell proliferation and the induction of tumour cell death. Furthermore, this agent might inhibit other members of the RTK superfamily, including VEGFR, FGFR1, PDGFR type 3, FMS-like tyrosine kinase 3, stem cell factor receptor (c-KIT), and colony-stimulating factor receptor 1, resulting in an additional reduction in cellular proliferation and angiogenesis and the induction of tumour cell apoptosis. The activation of FGFR3 has been demonstrated to be associated with cell proliferation and survival in certain cancer cell types[176,177].

Brivanib is the alanine ester of the VEGFR-2 inhibitor BMS-540215, which is a dual TKI that has shown potent and selective inhibition of VEGFR and FGFR tyrosine kinases[178,179]. Furthermore, BMS-540215 has been shown to inhibit selectively the proliferation of endothelial cells stimulated by VEGF and FGF *in vitro*. It has also shown broad-spectrum *in vivo* antitumor activity, with a suggested role in the treatment of HCC[180-182].

The FGFR inhibitor INCB054828 is an orally bioavailable inhibitor of FGFR types 1, 2, and 3 (FGFR1/2/3), with potential antineoplastic activity by inhibiting proliferation in FGFR1/2/3-overexpressing tumour cells.

Phase Ⅰ and Ⅱ clinical trials using dovitinib, brivanib and INCB054828 in patients with advanced gastric cancer are ongoing; we expect this research to add new data regarding the role of FGF inhibitors in this type of tumour[183-185].

Hepatocyte growth factor/c-MET (mesenchymal-epithelial transition factor receptor) inhibitors

C-MET represents a receptor tyrosine kinase that is expressed in both epithelium and endothelial cells; its overexpression and activating mutations have been demonstrated in many tumour types, including gastric cancer, and it has been correlated with poor prognosis[186]. Its ligand is represented by hepatocyte growth factor (HGF), which is expressed by cells of mesenchymal origin. c-MET and its signal pathway activation induced gastric cancer cell proliferation, survival, and migration[187]. There are various types of HGF/MET inhibitors, such as monoclonal antibodies (rilotumumab and onartuzumab) and small molecule tyrosine kinase (foretinib).

Anti-HGF/c-MET monoclonal antibodies: Rilotumumab (AMG102) is a human monoclonal antibody directed against HGF, and it was demonstrated by a phase Ⅱ study to show efficacy in a subset of locally advanced/metastatic gastric or oesophago-gastric junction cancer patients with MET overexpression by IHC. Data have shown that adding rilotumumab to standard chemotherapy regimens provided some survival benefit[188,189]. The results of the phase Ⅲ RILOMET-1 trial, an international, phase Ⅲ, multicentre, randomized, double-blind, placebo-controlled trial of rilotumumab plus ECX as a first-line therapy in patients with advanced MET-positive gastric or gastro-oesophageal junction adenocarcinoma, were presented at the ASCO 2015 annual meeting, revealing that both OS and PFS were statistically worse in the rilotumumab group, independent of MET expression[190]. Due to the increased toxicity of the drug and treatment-related deaths in the combination group in the RILOMET-1 trial, all of the clinical trials investigating the role of rilotumumab in gastric cancer, including the phase Ⅲ RILOMET-1 (with ECX) and RILOMET-2 (with cisplatin

and capecitabine) trials, were terminated early.

A multicentre, open-label, randomized, phase Ⅱ trial is ongoing in 30 centres in France, investigating the efficacy of FOLFOX alone or in combination with rilotumumab (AMG 102) or panitumumab as a first-line treatment for patients with advanced gastroesophageal adenocarcinoma[64].

Onartuzumab is a humanized monovalent antibody directed against MET that is also being evaluated in a first line, randomized, phase Ⅲ trial in MET-positive, HER2-negative GE patients in combination with mFOLFOX6. Data regarding this study were presented at the 2015 ASCO annual meeting, revealing unfortunately that the combination treatment could not prolong OS, not even in the group with MET highly expressed (MET 2+/3+). Severe adverse reactions, such as the reduction of neutrophils, thrombocytopenia, oedema, and pulmonary embolism, were not significantly increased in the combined group[191].

The possible explanations for obtaining negative results with these monoclonal antibodies might be that the *MET* gene is not the driver gene of gastric cancer; currently, there is not an accurate assessment of MET protein expression or a demonstration that gastric tumours present c-MET heterogeneity.

Anti-HGF/c-MET tyrosine kinase: Foretonib (GSK1363089) is an oral small molecule inhibitor of c-MET and VEGFR-2A. Kwak[192] reported good efficacy and tolerability of this agent in a phase Ⅰ clinical study, leading to FDA approval of the drug to enter directly into phase Ⅲ trials for the treatment of NSCLC.

Foretonib was demonstrated in preclinical studies to inhibit effectively the growth of gastric cancer cells[193]. It was also investigated in a phase Ⅱ study as a single agent in patients with metastatic gastric adenocarcinoma (c-MET unselected subjects), showing good tolerability but only minimal antitumor efficacy[194]; these results indicated that few gastric carcinomas are driven solely by MET and VEGFR2, emphasizing the diverse molecular oncogenesis of this disease[195].

PI3 kinase/mammalian target of the rapamycin pathway inhibition

Studies have shown that PI3K enzymes play a role in the phosphorylation of membrane inositol lipids[196,197]. Upregulation of the PI3k/Akt/mTOR pathway was correlated with poor prognosis and could contribute to the chemoresistance of gastric tumours[198]. Data showed that the mTOR signalling pathway was frequently used in gastric tumoural cells. Studies *in vitro* and animal models reported that blockage of the mTOR signalling pathway could inhibit the proliferation and metastasis of gastric cancer cells[199].

Everolimus (RAD-001, Afinitor) is an oral mTOR inhibitor that prevents the phosphorylation of p70S6K and 4E-BP1 mediated by mTOR, resulting in G0/G1 arrest[200]. The FDA approved everolimus for the treatment of non-responding advanced renal cell carcinomas (2009)[201], treatment of progressive neuroendocrine tumours of pancreatic origin (2011)[202], paediatric and adult patients with subependymal giant cell astrocytoma[203] and hormone receptor-positive and HER2-negative advanced postmenopausal breast cancer patients (2012)[204]. Anticancer activity has been shown in both phase Ⅰ and phase Ⅱ studies, which concluded that everolimus monotherapy as a second-line treatment had a good disease control rate for advanced gastric cancer patients[205,206].

Unfortunately, the phase Ⅲ GRANITE-1 trial investigating the safety and efficacy of everolimus monotherapy as a second or third line in patients with advanced gastric cancer did not show a survival benefit. Furthermore, grade 3-4 adverse reactions, including anaemia, loss of appetite, and fatigue, were observed in these patients[207,208]. The use of everolimus in the treatment of advanced gastric cancer must be further investigated.

Sirolimus (also known as rapamycin) has potent immunosuppressive and antiproliferative properties due to its ability to inhibit mTOR. A phase Ⅰ trial is ongoing of mTOR inhibition with rapamycin (sirolimus) for enhancing intranodal dendritic cell vaccine-induced anti-tumour immunity in patients with cancer-testis antigen (NY-ESO-1)-expressing solid tumours, including gastric cancer. Biological therapies, such as sirolimus, might stimulate the immune system and stop tumour cells from growing. Vaccines made from a person's white blood cells mixed with tumour proteins might help the patient to build an effective immune response to kill tumour cells that express NY-ESO-1[209].

PARP inhibitors

The DNA damage response is the coordinated activation of sensors and effectors, inducing cell cycle arrest, activation of DNA repair, and, if necessary, subsequent induction of apoptosis.

PARP inhibitors prevent the cancer cell's single stranded break repair mechanism, allowing tumour cell death to occur[210]. These inhibitors have shown some efficacy in BRCA1- and BRCA2-deficient breast and ovarian cancers.

A phase Ⅱ trial in metastatic/recurrent gastro-oesophageal cancer studied the benefit of administrating the PARP inhibitor olaparib (AZD-2281, trade name Lynparza). Patients received as a second-line treatment paclitaxel with or without olaparib[211]; the results demonstrated improved OS in the olaparib group, although PFS was not significantly different. In accordance with preclinical data showing greater olaparib sensitivity in patients with low ataxia telangiectasia-mutated (ATM) protein[212,213], this study found that low ATM patients had improved OS with olaparib. A phase Ⅲ study of second line treatment using paclitaxel with or without olaparib in advanced gastric cancer patients is currently ongoing[214].

Olaparib is also being investigated in a trial evaluating the role of some novel antitumoural agents. This is a phase Ⅰ, open-label, multicentre study of AZD6738 administered orally in combination with cytotoxic chemotherapy regimens (carboplatin) and/or novel anti-cancer agents (olaparib, durvalumab) to patients with advanced malignancies, including gastric cancer. It is currently recruiting patients[215]. *AZD6738* is an ataxia, telangiectasia and Rad3-related (ATR) serine/threonine protein kinase inhibitor. ATR is a member of the PI3K-like kinase family, activated by replication-associated DNA damage. AZD6738 induces S-phase cell cycle delay consistent with replication stress and increased sub-G1 "cell death" populations *in vitro*. Durvalumab is an Fc-optimized monoclonal antibody directed against programmed cell death-1 ligand 1 (PD-L1; B7 homolog 1; B7H1), with potential immune checkpoint inhibitory and antineoplastic activities.

Veliparib (ABT-888) is another PARP inhibitor developed to help prevent DNA repair in cancer cells and to increase the effectiveness of common DNA-damaging therapies, such as chemotherapy or radiation. Veliparib is currently being studied in many cancers and tumour types, including phase Ⅲ studies of breast cancer and NSCLC. A study of the efficacy of veliparib combined with the FOLFIRI regimen in gastric cancer is awaiting results[216].

The influence on DNA repair mechanisms in tumours opens a new dimension of research in the targeted therapy of gastric cancer[217].

Immunotherapy/Immuno-checkpoint blockade

Because tumours evade host immune recognition through a multitude of mechanisms[218], immunotherapy has developed as a novel field of anticancer treatment, which acts by increasing immune activity and using the blockage mechanism of the inhibitory immune regulatory pathways. Recent data have shown that programmed cell death-1 (PD-1) represents an immunoinhibitory receptor belonging to the CD28 family that plays a crucial role in the phenomenon of immune escape of tumours[219]; one of the most important mechanisms consists of activating immune checkpoints that block host T-cell activation. The presence of PD-L1 is needed for tumour cells to escape the cytotoxic effects of T cells. Promising new agents targeting immune checkpoints (PD-1 and PD-L1) have been recently developed.

Ipilimumab (trade name Yervoy, formerly known as MDX-010 and MDX-101) releases a negative immune regulatory pathway by blocking the inhibitory receptor called cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). The FDA approved ipilimumab for unresectable/metastatic melanoma patients who received at least one prior systemic treatment for melanoma (2011)[220]. It is undergoing clinical trials for the treatment of NSCLC, small cell lung cancer (SCLC)[221], bladder cancer[222] and metastatic hormone-refractory prostate cancer[223]. As a new maintenance concept, sequential administration of immunotherapy might prolong the clinical benefit of first-line chemotherapy before disease progression. Unfortunately, a phase Ⅱ trial comparing the efficacy of ipilimumab and BSC after first-line chemotherapy in unresectable locally advanced or metastatic gastric/gastro-oesophageal cancer patients revealed detrimental PFS with ipilimumab *vs* the BSC group (2.7 mo *vs* 4.8 mo, $P = 0.03$), as well as no statistically significant improvement in OS (16.7 mo *vs* 12 mo, $P = 0.64$)[224].

Nivolumab (Opdivo, anti-PD-1, BMS-936558, ONO-4538) acts by blocking the binding of receptor inhibitor PD-1, which is expressed on T-cells, to PDL-1 which prevents T cell death. Blockade of interactions between PD-1 and PD-L1 stimulated immune function *in vitro* and mediated antitumor activity in preclinical models. A phase I trial of nivolumab in advanced solid tumours also included patients with gastric adenocarcinoma. Antibody-mediated blockade of PD-L1 induced durable tumour regression and prolonged the stabilization of disease in patients with advanced cancers. Unfortunately, gastric cancer patients were not included in the efficacy analysis[225,226].

A phase Ⅰ/Ⅱ study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumours, including gastric cancer, is still recruiting patients[227]. Available data for the group using the single agent nivolumab revealed that nivolumab monotherapy was well tolerated, and it demonstrated encouraging antitumor activity in heavily pretreated gastric cancer patients. Objective responses occurred in patients with both PD-L1-positive and -negative tumours[228].

Also, a phase Ⅲ trial is currently investigating the safety and efficacy of nivolumab in patients with unresectable advanced or recurrent gastric cancer refractory to or intolerant of standard therapy[229].

Pembrolizumab (MK-3475) is an agent that blocks the binding of PD-1 to PDL-1 (as well as PDL-2). A phase 1 study of pembrolizumab in recurrent and metastatic gastric and gastro-oesophageal junction adenocarcinoma patients with PD-L1 tumour positivity demonstrated good tolerability, as well as anti-tumour activity[230]. Other phase Ⅰ-Ⅲ trials of pembrolizumab are investigating this agent in advanced gastric cancer, administered as monotherapy or associated with chemotherapy in naïve patients/after progression under treatment[231,232], with the aim of integrating the molecular subtypes of gastric cancer through integrative genomic analysis[233]. Other phase Ⅰ/Ⅱ studies are evaluating the efficacy of pembrolizumab in combination with other classes of agents, such as anti-HER2 monoclonal antibodies[234,235], anti-VEGFR monoclonal antibodies[236] or multitargeted TKIs (PLX 3397)[237]. An innovative approach in gastric cancer

treatment, included in a phase Ⅰ study, consists of administering of pembrolizumab in combination with PEPGH20, a new molecular entity for tumours rich in hyaluronan (HA) that form a coating over the surface of the tumour cell; this agent removes the HA coating[238].

Durvalumab (MEDI4736), an antiPDL-1 agent, has shown some efficacy in gastric cancer[239].

Based on previous data showing a synergistic effect of the combination of CTLA-4 and PDL-1 blocking agents, the combination of durvalumab and tremelimumab (anti-CTLA-4) plus first-line chemotherapy is being investigated in advanced solid tumours, including gastric neoplasms[240,241]. A phase Ⅰ/Ⅱ study is currently assessing the safety, tolerability, pharmacokinetics, immunogenicity and preliminary efficacy of INCB024360 in combination with MEDI4736 in subjects with selected advanced solid tumours, including gastric cancer[242]. Epacadostat (INCB 024360) is a potent and novel indoleamine-2,3 dioxygenase (IDO) inhibitor. IDO is an immunomodulatory enzyme produced by some alternatively activated immunoregulatory cells, and it is used as an immune subversion strategy by many tumours. The molecule exhibits potent *in vitro* and *in vivo* immunomodulating and antineoplastic activities.

Other ongoing trials are evaluating pembrolizumab in association with other classes of targeted therapies in advanced gastric tumours, such as anti-HER2 molecules as maintenance treatment[243], anti-VEGFR antibodies[244], and ATR serine/threonine protein kinase inhibitors[215].

Guanylyl cyclase C inhibitors

Guanylyl cyclase C (GCC) is a trans-membrane cell surface receptor, expressed not only on normal intestinal tissue but also on the tumour cells of patients with gastrointestinal neoplasias, precisely in approximately 95% of cases of metastatic colorectal cancer, and subsets of gastric and pancreatic tumours. Because the epithelial tight junctions are altered in tumour tissue, systemically delivered GCC-targeting agents would have access only to GCC receptors expressed by the tumour tissue. Tumour GCC expression seems be a good prognostic marker.

MLN0264 consists of a fully human monoclonal antibody targeting GCC that has shown antitumor efficacy in xenograft models of GCC-expressing tumours. A phase Ⅰ trial evaluating the safety, maximum tolerated dose, and clinical pharmacokinetics of MLN0264 in patients with gastrointestinal malignancies expressing GCC showed promising results, demonstrating good tolerability of the molecule[245,246]. A phase Ⅱ study of MLN 0264 in previously treated patients with gastric and gastro-oesophageal junction cancers whose tumours express GCC by IHC is currently recruiting patients[247]. Another phase Ⅰ/Ⅱ study is evaluating the effects of MLN0264 in previously treated Asian patients with advanced gastrointestinal carcinoma or metastatic/recurrent gastric or gastro-oesophageal junction adenocarcinoma expressing GCC; we are waiting to confirm the benefit of this agent in the treatment of gastric malignancies[248].

Inhibitors of the tumour cell cycle

In the tumour setting, there is an alteration of cell cycle regulatory mechanisms accomplished by molecules such as cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors (CKIs). CDKs bind to cyclins, facilitating cell cycle progression, whereas the combination of CDKs with CKIs leads to inhibition of cell cycle progression/apoptosis[249].

Flavopiridol (Alvocidib, HMR-1275), a semi-synthetic flavonoid, CKI, was the first inhibitor of the cell cycle investigated in a clinical trial. This inhibitor is in development as a frontline combination therapy for acute myeloid leukaemia and relapsed/refractory chronic lymphocytic leukaemia and other haematological disorders. Flavopiridol suppresses messenger RNA translation, stopping cell proliferation-related protein expression[250]. Unfortunately, flavopiridol demonstrated low efficacy and serious adverse reactions in gastric cancer[251]. Because, as a single agent, it seems to have poor anti-tumour activity, it must be investigated in combination with other chemotherapeutic agents. Its efficacy was assessed in combination with irinotecan in advanced gastric tumours in a phase Ⅱ clinical trial, but there was only a small number of patients included[252].

Agents inducing tumour cell apoptosis

The induction of tumour cell apoptosis is a promising target in cancer treatment.

Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis in many tumours. Although gastric tumour cells often exhibit resistance to TRAIL, studies have demonstrated that some standard chemotherapeutics might enhance sensitivity to TRAIL[253]; therefore, the association of TRAIL with different chemotherapeutics for the treatment of gastric cancer is worth investigating.

NF-κB expression is positively correlated with the degree of malignancy and is negatively correlated with cancer prognosis. Bortezomib (PS-341, Velcade) is a highly selective and potent, reversible proteasome inhibitor that specifically inhibits the chymotrypsin activity of the 26S proteasome, subsequently inhibiting activation of the NF-κB signalling pathway. The agent has a broad spectrum of *in vitro* and *in vivo* activity[254,255]. It has FDA approval for multiple myeloma and mantle cell lymphoma[256,257]. Bortezomib demonstrates anti-cancer activity in gastric cancer cell lines, potentially mediated by the inhibition of the ERK1/2 and Akt signalling pathways. In gastric cancer, preclinical studies demonstrated synergistic growth inhibition of this agent in combination with conventional chemotherapy[258,259]. However, the combination of irinotecan and bortezomib was assessed in a multicentre phase Ⅱ study, which concluded that

bortezomib was not effective for the treatment of advanced adenocarcinoma of the stomach, whether used alone or in combination with irinotecan[260]. Also, another phase Ⅱ study of metastatic gastro-oesophageal neoplasias explored the response rate with a first-line, three-drug regimen that consisted of bortezomib in combination with paclitaxel and carboplatin; the scheme was considered inactive, prompting premature study closure[261]. Based on these data, a multi-institution phase Ⅱ study of single agent bortezomib in gastric adenocarcinoma was performed to determine anti-tumour efficacy[262]. Unfortunately, this trial showed no benefit of bortezomib monotherapy in locally advanced/metastatic gastric neoplasia.

Future studies of the class of proteasome inhibition in gastric setting are needed and should include combination regimens with targeted agents acting on different oncogenic pathways.

Matrix metalloproteinase inhibitors

The matrix metalloproteinase (MMPs) constitute a family of proteolytic enzymes that cause the breakdown of connective tissue proteins and that play major roles in the normal processes of growth, differentiation and repair. There are tissue inhibitors (TIMPs) that tightly regulate their activity. The aberrant synthesis of MMPs determines local tumour invasion by destroying the extracellular matrix and the basement membrane. Studies have associated the high expression of some MMPs with a poor prognosis of gastric cancer[263,264]; therefore, it could be feasible that specific MMP inhibitors might restore the normal balance of proteolytic activity, preventing tumour growth and metastasis.

Marimastat (BB-2516, TA-2516) is a broad-spectrum MMP inhibitor that proved to exert anti-tumour activity in gastric cancer. A randomized, double-blind, placebo-controlled study designed to evaluate the ability of marimastat to prolong survival in patients with non-resectable gastric and gastro-oesophageal adenocarcinoma provided the first indication of a survival benefit for an MMP inhibitor, supporting a possible role for this inhibitor as a maintenance treatment with response/stable disease following chemotherapy[265].

The correlation of proteolytic gene expression (MMP and TIMP) profiles with clinicopathological features of the tumour could aid in revealing tumour behaviour and could guide management strategies in gastric cancer[266].

CONCLUSION

Despite the decrease in incidence in past decades, gastric cancer remains a major global health problem; therefore, efficient treatments are needed to achieve increased OS and improved prognosis of patients.

Data from the literature have indicated that eradication of *H. pylori* could prevent gastric cancers. However, carcinogenesis is a multistep process, and it is unclear at which step *H. pylori* eradication would prevent gastric cancer onset. There may be a so-called "point of no return" in the histological cascade from chronic gastritis to intestinal-type adenocarcinoma after which *H. pylori* therapy is unlikely to prevent stomach cancer development. This "point of no return" may be represented by the appearance of gastric preneoplastic lesions. Thus, *H. pylori* eradication may have a decreased efficacy in preventing stomach neoplasia once these lesions appear.

For some decades, standard chemotherapeutic agents have been the mainstay of systemic treatment, unfortunately leading to reduced rates of response, poor clinical outcomes and compromised quality of life due to their significant associated toxicities.

Due to major advances in cancer research, numerous molecular alterations underlying gastric carcinogenesis and multiple signalling pathways involved in gastric cancer development and metastasis have been identified.

Along with these major discoveries, numerous drugs targeting genes and molecular signalling pathways have been investigated in clinical trials. The positive results obtained with some of these agents in gastric cancer treatment have led to improved outcomes, especially in advanced cancers, by incorporating them into the standard treatments for patients. The 2015 edition of the gastric cancer guideline from the United States National Comprehensive Cancer Network therefore recommends trastuzumab as the first line and ramucirumab as the second line for the treatment of advanced gastric tumours. Moreover, based on positive results from a phase Ⅲ study, apatinib was approved by the CFDA for metastatic gastric/gastro-oesophageal junction tumours as the third line treatment.

Because of the complexity of the molecular alterations and the simultaneous activation of multiple signalling pathways in gastric cancer, targeting a single molecular pathway using one of the novel agents as a monotherapy or even in combination with standard chemotherapeutic regimens might be insufficient to provide a significant benefit to patient survival. One potential option would be to combine targeted drugs that act on different molecular pathways with the goal of achieving a synergistic effect, but our knowledge about these schemes currently remains limited, although they are being investigated in clinical trials that that have the purpose of determining the efficacy, safety and possible increased toxicities of these associations. Perhaps a possible solution to improve efficacy would be the development of novel multi-targeted molecules. Another drawback is represented by the very high costs of these molecular agents, which must decrease to be used widely.

There are impressive emerging of new agents involved in different stages of clinical studies, waiting to demonstrate their roles in the treatment of gastric neoplasias. Future directions in gastric cancer

treatment include novel classes of targeted agents, such as c-MET and FGFR inhibitors, epithelial cell adhesion molecule, IGF-1R inhibitors, mTOR pathway and MMP inhibitors, blockade of the tumour cell cycle, proteasomes, histone deacetylases, chaperone proteins, and promising immunotherapy.

Due to the molecular heterogeneity of tumours and the existence of multiple aberrant molecular pathways involved in gastric cancer development, the discovery of the exact molecular profile of the tumour and the detection of specific biomarkers and genes will help to identify the specific subsets of patients who might benefit from certain molecular therapies. This approach will open new horizons in gastric cancer treatment, allowing for personalized therapy using drugs directly targeting the particularly altered molecular pathways of the tumour.

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