Chapter 7

Molecular Prognostic Factors in Gastric Cancer

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Additional information is available at the end of the chapter

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Abstract

Gastric cancer represents a major health problem worldwide. Literature data have demonstrated that gastric tumors present a high molecular heterogeneity, responsible for the process of carcinogenesis and dissemination. By revealing the molecular subtype of the tumor, it is possible to assess its behavior, the outcome of the patient, and the treatment approach, according to its genetic and epigenetic profile. This chapter aims to highlight some of the many different genetic mutations, epigenetic alterations, as well as aberrant signaling pathways involved in the pathogenesis of stomach cancers, each of these molecular abnormalities acting in a specific stage of the disease. Moreover, the manuscript describes the novel therapeutic agents that target some of these aberrant molecular signaling pathways. Unfortunately, only a few agents are currently part of the standard treatment of gastric cancer, while most of the others remain to prove their therapeutic efficacy in the setting of clinical trials. By discovering the different molecular subtypes of gastric cancer, as well as numerous classes of targeted molecular agents, in the future, we would be able to perform an individualized treatment, associated with maximum efficiency and less costs.

Keywords: gastric cancer, molecular classification, gene expressions-based prognostic scoring system, molecular biomarkers, molecular targeted treatment

1. Introduction

Despite a decline in the incidence in past decades, gastric cancer remains a major health problem globally [1, 2], being the fifth most common type of cancer worldwide, with almost one million new cases estimated to have occurred in 2012, according to Globocan [3]. Furthermore, stomach cancer represents the third leading cause of cancer death in both sexes worldwide (723,000 deaths) [3].

According to the World Health Organization classification, the vast majority of gastric cancers are adenocarcinomas, divided into papillary, tubular, mucinous (colloid), and poorly cohesive carcinomas (including signet-ring cell carcinoma and other variants) [4]. Although it was proposed a long time ago (1965), the Lauren classification is still widely used in clinical practice and subdivides gastric carcinomas into intestinal and diffuse types, associated with different pathogenesis, ways of spreading, and outcome [5]. Unfortunately, these two classification systems have little clinical impact, making the development of classifiers that can define prognosis and guide patient's treatment as an urgent need.

Literature data have demonstrated that the development of gastric cancer is associated in the majority of cases with infectious agents such as the Gram-negative spiral bacterium *Helicobacter pylori* (most often) [6] and Epstein-Barr virus (EBV) (about 9% of all cases of gastric cancer) [7]. Only a small percentage of gastric cancer patients (hereditary cases) are associated with germline mutation in E-cadherin (CDH1) [8] or mismatch repair genes (Lynch syndrome) [9]. In contrast to the familial clustering of gastric cancer, sporadic mismatch repair-deficient gastric tumors present epigenetic silencing of hMLH1 and p16 in the context of a CpG island methylator phenotype (CIMP) [10].

Due to a lack of early specific clinical features, most patients with gastric cancer are diagnosed in advanced stages, resulting in poor 5-year survival rates [11], with a median survival of less than 1 year in case of metastatic stage IV patients [12–14]. Nowadays, survival has gained only minor improvement despite the advances in diagnostic techniques, the multidisciplinary therapeutic management, and the development of novel molecular targeted treatment agents.

Unfortunately, despite modern treatments, less than a quarter of gastric cancer patients survive longer than 5 years after surgery. Gastric cancer represents a complex disease, showing major differences in their tumor cell behavior and responses to chemotherapy.

Recent data have demonstrated that gastric tumors present a high molecular heterogeneity involved both in the process of carcinogenesis and cancer spread. By identifying the specific molecular patterns of the tumor, it is possible to assess its behavior, the prognosis of the patient, and also to decide the most appropriate treatment, a much more personalized one. It is well known that in the pathogenesis of stomach cancers many different genetic mutations, epigenetic alterations, as well as dysregulated signaling pathways are involved, each of these molecular abnormalities acting in a different stage of the disease.

Currently, novel therapeutic agents that target some of these aberrant molecular signaling pathways are already part of the standard treatment of gastric cancer, while others remain to prove their therapeutic efficacy in the setting of clinical trials [15].

2. Oncogenic pathway combinations predict outcome of gastric cancer patients

Gastric cancers are molecularly heterogeneous tumors, showing different dysregulated oncogenic pathways such as E2F, K-RAS, p53, and Wnt/β-catenin signaling that occur with varying

frequencies in these types of tumors [16, 17]. In contrast to the previous studies that have focused on single pathways [18–20], experimental evidence indicates that, in most cases, carcinogenesis is dictated by complex interactions between multiple pro- and anti-oncogenic signaling pathways [21].

Unlike previous gastric tumor microarray researches relating different gene expression patterns to specific histological features or anatomical location [22], Ooi et al. [23] have succeeded in subdividing gastric cancers into molecularly homogenous subgroups that enable personalizing patient treatments and improving prognosis. It was for the first time when, by using multiple patterns of oncogenic pathway activation, a novel cancer classification approach has been developed, namely a genomic taxonomy of gastric cancer. They developed an in silico technique to define activation levels of different oncogenic pathways implemented in context of complex tumor profiles and validated this classification approach using proof-of-concept examples from breast cancer. Afterward, they have applied this method to gastric tumors and evaluated 11 oncogenic pathways previously known to be involved in gastric tumorigenesis [16–20, 24–27]. They have assessed over 300 primary stomach cancers coming from three independent patient cohorts. The researchers have discovered three oncogenic pathways, nuclear factor-kB (NF-κB), Wnt/β-catenin, and proliferation/stem cell, which were dysregulated in over 70% of gastric cancers and validated the patient stratification in vitro using gastric cancer cell lines. Patient classification by oncogenic pathway combinations revealed significant survival differences, suggesting a major role for pathway combinations in determining gastric cancer behavior. Therefore, gastric cancer can be taxonomized into biologically, molecularly, and clinically significant subtypes.

The authors defined concomitant activation of different oncogenic pathways, such as of E2F, MYC, p21 (repression), and the "proliferation/stem cell" pathway, most likely due to increased cellular proliferation in tumor cells [28], and in stem cells (embryonic stem cells (ESCs)) [29]. Co-activation of different pathways demonstrates the ability of the cancer cell to dictate the activity of multiple pathways.

The study showed that NF-κB signaling may be elevated in a significant proportion of gastric cancers probably due to *H. pylori* infection [30]; therefore, targeted NF-κB inhibitors may represent an appropriate treatment for gastric tumors. Pathway-based taxonomies may be useful in developing potential pathway inhibitors and novel targeted therapies that would be studied on prestratifying patients using molecular or pathologic criteria.

3. Molecular classification of gastric cancers by "The Cancer Genome Atlas (TCGA)" project

The goals of "The Cancer Genome Atlas (TCGA)" project were to develop a molecular classification of gastric cancer with clinical impact and to detect the major dysregulated pathways of distinct subtypes of gastric cancer [31].

The researchers have analyzed fresh frozen gastric adenocarcinoma primary tumor tissue from 295 patients with no prior chemo- or radiotherapy, using six genomic and molecular platforms

including genome/exome/methylome DNA sequencing, RNA sequencing, and protein arrays. Germline DNA from blood/nonmalignant gastric mucosa was used as a control for detecting somatic alterations. Nonmalignant gastric samples were also collected for DNA methylation (n = 527) and expression (n = 529) assessment.

Tumors were first subgrouped by EBV-positivity (9%), then by MSI-high status (named MSI; 22%), and the remaining tumors were classified by degree of aneuploidy into genomically stable cancers (20%) or those exhibiting chromosomal instability (CIN; 50%).

This project revealed that the vast majority of the diffuse histological subtype belongs to the genomically stable group. CIN tumors were mostly located in the gastroesophageal junction/cardia, whereas most of the EBV-positive tumors were located in the gastric fundus or body. Genomically, stable tumors were diagnosed at an earlier age compared to MSI tumors; most EBV-positive cases were male (81%), in concordance with previous results [32].

As previously reported [33], all EBV-positive tumors exhibited extreme CIMP, distinct from that in the MSI subtype [10] (CDKN2A promoter hypermethylation versus MLH1 hypermethylation) [34]. Furthermore, in concordance with prior data [35, 36], the study revealed a strong predilection for PIK3CA mutation in EBV positive tumors, with nonsilent PIK3CA mutations found in 80% of this subgroup ($P < 0.001$), that could be targeted using PI(3)-kinase inhibition.

By assessing 63 hypermutated tumors, there were identified 37 significantly mutated genes including TP53, KRAS, ARID1A, PIK3CA, ERBB3, PTEN, and HLA-B. The analysis of genes mutated within MSI subgroup of gastric cancers revealed alterations in major histocompatibility complex class I genes, a beneficial event for hypermutated tumors by dysregulating antigen presentation to the immune system.

Through the analysis of the 215 nonhypermutated cancers, there were identified 25 significantly mutated genes, including TP53, ARID1A, KRAS, PIK3CA, and RNF43, genes involved in the β-catenin pathway, the TGF-b pathway, RASA1, and ERBB2 (therapeutic target).

In addition to PIK3CA mutations, EBV-positive tumors had frequent ARID1A and BCOR (encoding an anti-apoptotic protein) gene mutations. TP53 mutations were detected in 71% of CIN tumors. The genomically stable subtype presented a high frequency of CDH1somatic mutations and inactivating ARID1A mutations. RHOA mutations were detected almost exclusively in genomically stable tumors. In its activated form, RHOA controls cellular motility [37, 38] and activates STAT3 to initiate tumorigenesis [39, 40]. It seems that the activation of RHOA-driven pathways contribute to the invasive phenotype of diffuse gastric cancer.

Oncogenic signaling pathways, including candidate therapeutic targets such as receptor tyrosine kinases (RTKs), RAS, and PI(3)-kinase signaling were characterized. EBV-positive tumors contained PIK3CA mutations and recurrent JAK2 and ERBB2 amplifications. MSI cases presented some mutations in PIK3CA, ERBB3, ERBB2, and EGFR [41]. The genomically stable subtype expressed recurrent RHOA and CLDN 18 events. CIN tumors showed genomic amplifications of RTKs that may be therapeutically blocked. Recurrent amplification of the gene encoding ligand VEGFA and frequent amplifications of cell cycle mediators highlight the role of the VEGFR2 targeting antibody (the already approved agent ramucirumab) [42] and suggest the possible efficacy of cyclin-dependent kinases.

All the subtypes (to a lesser degree the genomically stable tumors) showed increased expression of components involved in the mitotic process, such as AURKA/B and E2F, DNA damage response pathways, targets of MYC activation, and FOXM1 and PLK1 signaling pathways. In addition, the genomically stable subtype exhibited elevated expression of cell adhesion pathways, the B1/B3 integrins, syndecan-1 mediated signaling, and angiogenesis-related pathways, suggesting more potential therapeutic targets, including the aurora kinases (AURKA/B) and polo-like (PLK) family members. The elevated IL-12-mediated signaling expression, along with evidence of PD-L1/2 overexpression in EBV-positive tumors, suggests the importance of immune checkpoint inhibitors evaluation in this subtype of gastric cancer [31].

Therefore, the four major genomic subtypes defined by "The Cancer Genome Atlas (TCGA)" may provide a guide to molecular targeted agents that should be assessed in clinical trials for distinct populations of gastric cancer patients.

4. Gene-expression signatures as markers for cancer grades and stages

Cui et al. [43] developed for the first time a computational study aimed to identify a set of genes whose expression patterns can distinguish among gastric cancers of different grades, with the aim of developing a gene expression-based grading system for gastric cancer.

A total of 452 genes were found to be differentially expressed in the 54 gastric cancer specimens studied. It was revealed that genes whose expression changes correlated with the degree of differentiation are highly enriched among secreted/membrane proteins, involved in signaling pathways (ErbB, FAS, NOD-like receptor, PPAR and Wnt signaling), as well as cell adhesion molecules (CAMs) and tight junctions.

The researchers identified a 19-gene group that can distinguish between well versus poorly differentiated tumors (overall agreement at 79.2%), based on the expression fold change in cancer versus control tissues. The protein products of these 19 genes mentioned above are involved in cell growth, differentiation (IL17RB, SMYD1, SHCBP1), and motility (ACTG2), angiogenesis (ADIPOQ), tumorigenesis (ECRG4), matrix protein synthesis (COL3A1, COL6A3), and extracellular communication.

Moreover, there is a 198-gene group which can distinguish among the four different cancer grades (well-, moderate-, poorly-, and un-differentiated) and the control group according to their gene expression (74.2% accuracy). In addition, the functions of the 198-gene group involve cell division, immune response control, signal transduction, and transcription.

There were also analyzed grade-specific gene signatures. LAPTM4B gene has demonstrated a high classification accuracy for tumor and control samples in the well-differentiated group (AUC = 0.97), a gene known to be essential for cell growth and survival; its up-regulation has been previously found to be correlated with the degree of differentiation of hepatocellular carcinoma [15]. Similarly, they have also identified single gene discriminators for each grade group.

Cui et al. have identified two multigene signatures that can distinguish early stage (stages I and II) and advanced stage gastric cancer (stages III and IV), namely a 10-gene group (CPS

1+DEFA5+DES+DMN+GFRA3+MUC17+OR9G1+REEP3+TMED6+TTN) and a 9-gene group (DPT+EIF1AX+FAM26D+IFITM2+ LOC401498+OR2AE1+PRRG1+REEP3+RTKN2). The overall classification accuracy obtained on the three groups, early, advanced stomach cancer, and control, was 71.4%. Among the early-stage signature genes, there are signaling and immune-related genes that may represent the early changes of tissue cells during carcinogenesis. A few genes were found to be in both the cancer grading and staging signatures (e.g., CPS1, DES, GFRA3, TMED6, and DPT), indicating some functional connection between cancer differentiation and progression. LANCL3, MFAP2, and PPA1 were genes highly correlated with different pathological stages, showing consistent upregulation or downregulation along with tumor progression.

There were found 62 genes with consistent differential expression in gastric cancer versus control tissues, related to extracellular processes such as CAMs, tight junction, cytokine-cytokine receptor interaction, and ECM receptor interaction, the plasminogen activation cascade, as well as signaling pathways (Wnt and Integrin signaling) related to the control of cell growth and proliferation.

The study revealed that the differential expression patterns of 15 genes are highly specific to gastric cancer (e.g., GKN2, CLDN7, THY1, GIF, and PGA4), while most others are general to numerous cancer types, including a few members of the collagen gene family, the carcinoembryonic antigen-related cell adhesion molecule, matrix metalloproteinases, topoisomerase, and secreted phosphoprotein. Only three genes, CLDN7, CLDN1, and DPT, were significantly differentiated in all grades and stages of gastric neoplasia; the consistent expression of dysregulation across all the cancer subgroups may indicate their involvement in major biological pathways leading to cancer development and progression. Dermatopontin (DPT) represents an extracellular matrix protein that creates a link between the dermal fibroblast cell surface and its extracellular matrix, previously found to be downregulated in both uterine leiomyomas and keloids [44].

5. Gene expression-based prognostic scoring systems

Data from literature revealed the important role of the molecular biological characteristics of gastric cancer in the prognosis of the patients and determination of a most suitable clinical therapy for these patients. There are some dysregulated gene expressions found to be associated with the prognosis, such as the overexpressions of HER2 [45] and p53 genes [46]. Also, the hypoxia inducible factor-1 alpha (HIF-1α) seems to be related to the early development of gastric tumor [47].

Takeno et al. [48] elaborated a gastric cancer regulatory network with CDKNIA as the node and examined the expression levels of seven genes in different stages of gastric cancer (iMMP7, SPARC, SOD2, INHBA, IGFBP7, NEK6, and LUM). Their results showed that these seven genes were activated as the disease progressed, suggesting the association of these genes with cancer development.

Wang et al. [49] proposed the hypothesis that molecular features are determining the tumor behavior and can be used to establish prognostic scoring system. Based on the Cancer Genome Atlas (TCGA) data and using different multivariate clustering techniques to identify the key

genes for prognostic classification of these analyses, they created a 53-gene expression prognostic scoring system and successfully implemented it to predict overall survival (OS) in the TCGA and the GSE15459 data (Gastric Cancer Project 2008).

These prognostic scores are able to distinguish between patients with good prognosis and bad prognosis, respectively. These genes include TNFAIP2 [50], FGFR4 [51, 52], CXCL10 [53], CEP55 [54], CXCL1 [55], LIMK1 [56], LAMC2 [57], APOE [58], INHBA [59], OSMR [60], APOC1 [61], KLF4 [62], MMP14 [63], ADH1C [64], COL6A3 [65], CCT2 [66], NOL8 [67], EPHB4 [68], and MCM2 [69]. The high expression of FGFR4 protein was previously reported to be associated with a poor prognosis in patients with advanced gastric tumors [51], while the FGFR4 Gly388Arg polymorphism proved to be a useful prognostic marker for early gastric cancer patients [52]. CEP55 functions in cell cycle regulation; knockdown of CEP55 led to diminished proliferation in gastric cancer cell lines acting on the PI3K/AKT signaling pathway and the expression of cyclin-related proteins, suggesting a potential role of CEP55 as a target used in gastric cancer treatment [54]. Some studies show that MCM2 expression levels are a useful tool for the diagnosis and prognosis of gastric tumors [69] and that SNPs in miRNA-binding sites may represent susceptibility markers for gastric cancer [50]. Chemokine (C-X-C motif) ligand (CXCL1) seems to play a major role in tumor metastasis; it has been previously reported that its expression is associated with hepatocellular carcinoma survival [55]. The study of Wang showed that CXCL1 is also involved in gastric cancer overall survival. ATP-binding cassette E1 (ABCE1) known to play a crucial role in the metastasis of lung cancers, and therefore, a potential therapeutic target in this setting [70], was also elevated in gastric tumors and predicted the prognosis of patients.

6. The role of molecular biomarkers in the treatment of gastric cancer

Besides the few standard chemotherapeutic agents having efficiency in the treatment of gastric cancer, molecular targeted therapy for gastric cancer is limited, including mainly agents acting on the HER2 and vascular endothelial growth factor (VEGF) pathways [71].

On the other hand, until present, the only used markers for gastric cancer in clinical practice are carcinoembryonic antigens, CA 19-9 [72] and CA-72 [73], with questionable efficacy. Nowadays, there are multiple molecular biomarkers that had shown their accuracy as diagnostic or prognostic tools but still need further validation for implementing in the routine clinical practice, predicting the response to chemotherapy, posttreatment survival, or disease recurrence.

6.1. Molecular biomarkers predicting the treatment response

The future of cancer treatment aims for a personalized medicine, treating the patient according to his genetic and epigenetic profile, and identifying the occurrence of chemoresistance using specific markers in order to obtain maximum treatment efficiency with lower costs [74]. Heretofore, the vast majority of data regarding predictive biomarkers derive from small retrospective studies; therefore, these biomarkers cannot be used for the moment in clinical practice, outside the setting of clinical trials.

6.1.1. Genetic markers

Lin et al. [75] described the link between integrated genomic signatures, the biological functions, and the background molecular pathways [76]. There were developed prediction models of activity for eight anticancer drugs [76], along with clinical responses to 5-FU (cDNA microarray analysis) [77] and resistance-related genes such as dihydropyrimidine dehydrogenase (DPD) and HB-EGF-like growth factor genes [78]. Also, it was reported that metallothionein-IG and heparin-binding epidermal growth factor-like growth factor (HB-EGF), glutathione-S-transferase, and cyclooxygenase-2 genes were cisplatin-resistance-related and genes such as ADAM22, CYR61, FN1, SPHK1, and GNAI1 were linked to doxorubicin response [79]. Furthermore, in some studies, the genetic polymorphism was linked to the response of 5-FU, cisplatin [80], and paclitaxel [81].

Cristescu et al. described four molecular subtypes of gastric tumors related to disease progression and prognosis: the mesenchymal-like type with highest recurrence frequency, microsatellite-unstable tumors that are hyper-mutated and are associated with the best overall prognosis, tumor protein 53 (TP53)-active and TP53-inactive types that have intermediate prognosis and recurrence [82].

As already mentioned, researchers from "The Cancer Genome Atlas (TCGA)" project proposed a molecular classification dividing gastric tumors into four subtypes, useful for stratifying patients and choosing the appropriate targeted treatment: (1) Epstein-Barr virus positive tumors: PIK3CA mutations, DNA hypermethylation, and amplification of JAK2, CD274, and PDCD1LG2; (2) microsatellite unstable tumors: increased mutation rates, including genes encoding targetable proteins involved in oncogenic signaling pathways; (3) genomically stable tumors: mutations of RHO-family GTPase-activating proteins; (4) tumors with chromosomal instability: marked aneuploidy and amplification of receptor tyrosine kinases [41].

6.1.2. Epigenetic markers

MicroRNA was linked by some studies to the resistance to trastuzumab [83], the pathologic response to neoadjuvant chemotherapy [81], and the chemotherapeutic response of cisplatin/fluorouracil [84].

Long noncoding RNAs (lncRNAs) are potential biomarkers for gastric cancer especially using minimally invasive routes (blood, gastric secretions) [85]. The lncRNA MRUL (Multidrug resistence (MDR)-related and upregulated lncRNA) originated from tissue samples was associated with multidrug chemotherapeutic resistance [86].

Methylation-related biomarkers: methylation of Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 and death-associated protein kinase (DAPK) correlate with poor response to fluoropyrimidine-based chemotherapy [87]; decreased methylation of the bone morphogenetic protein 4 (BMP4) correlates with cisplatin resistance, and the regain of treatment response may be achieved using targeted inhibition of BMP4 [88]. Also, the increased expression of Reprimo (a highly glycosylated cellular protein) due to methylation was associated with a lower response to cisplatin/5-FU chemotherapy [89].

6.1.3. Protein markers

Cellular enzymatic activity: Cellular enzymatic activity was correlated with the chemotherapeutic resistance, thymidylate synthetase (TS) and DPD being associated with tumor sensitivity to 5-FU-based regimens [90].

Cellular proteins: Serum level of alpha-1-microglobulin/bikunin precursor (AMBP) protein, as well as increased expression of β-tubulin III protein, was demonstrated to predict lower chemotherapeutic response to paclitaxel-capecitabine schemes [91, 92]; regenerating gene family member 4 (Reg IV or REG4) predicted resistance to 5-FU-based regimens [93]; forkhead box M1 (FOXM1) transcription factor seems to predict resistance to docetaxel [94]; and dysregulated ribosomal proteins were found to enhance vincristine, adriamycin, and 5-FU resistance [95].

6.2. Molecular aberrations as potential therapeutic targets

Although a great number of targeted therapies belonging to different classes of drugs have been investigated in both preclinical and clinical trials for the treatment of gastric cancer, their use in clinical practice is still limited for the moment.

6.2.1. Anti-HER2 therapies

The HER2 receptor belongs to the EGFR/HER family, having an important role in signal transduction, cell growth, and differentiation [96]. Recent data have revealed HER2 overexpression in 7-34% of patients with gastroesophageal adenocarcinomas and an efficiency of anti-HER2 therapies for both in vitro and in vivo gastric cancer models [97].

6.2.1.1. Monoclonal antibodies targeting HER-2

Trastuzumab (Herceptin) is a humanized anti-HER2 monoclonal antibody; its efficacy for gastric cancer being demonstrated in a phase III trial (ToGA) that randomized naive patients with metastatic or locally advanced unresectable gastric adenocarcinoma with overexpressed HER2 to chemotherapy associated with trastuzumab versus classic chemotherapy [98]. The results of this study demonstrated that adding trastuzumab to standard chemotherapy could increase the OS of these patients to more than 1 year. Currently, the combination of trastuzumab with capecitabine/5-fluorouracil and cisplatin is recommended for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach, defined as an immunohistochemical (IHC) 3 positive result or an IHC 2 and fluorescence in situ hybridization (FISH) double positive result.

There are several other ongoing studies of trastuzumab treatment in advanced gastric cancer, such as the HELOISE trial, the phase II study NCT01130337, the TOXAG study, the HERFLOT study, and the phase III trial RTOG 1010. Two phase II clinical trials confirmed the efficacy of trastuzumab combined with XELOX (capecitabine/oxaliplatin) or SP (S-1/cisplatin), respectively, for advanced gastric cancer treatment [99, 100].

The second generation of anti-HER2 agents includes Pertuzumab, which binds to a distinct site on the HER2 receptor. This drug is currently being investigated in the phase III JACOB study in patients with HER2-positive metastatic or locally advanced gastric cancer. [101]. Trastuzumab emtansine (TDM-1) is another second-generation agent currently assessed in a second-line phase II/III trial in advanced gastric cancer [102].

6.2.1.2. Tyrosine kinase inhibitors (TKIs) of HER2

Lapatinib is an oral TKI of EGFR and HER2, which was studied in combination with standard chemotherapy in patients with HER2-positive advanced gastric adenocarcinomas in the phase III LOGIC study [45] and in the phase III Asian TyTAN trial without demonstrating an improvement in OS. Currently, the MAGIC-B study is evaluating the addition of lapatinib to perioperative epirubicin, cisplatin, and capecitabine (ECX) chemotherapy in patients with HER2 (+) gastric cancers [103].

6.2.2. EGFR inhibition

EGFR overexpression is found in 30-50% of gastroesophageal tumors, associated with a more aggressive behavior [104].

6.2.2.1. Anti-EGFR monoclonal antibodies

Cetuximab (Erbitux) is a chimeric monoclonal anti-EGFR antibody. Unfortunately, clinical trials, including the phase III EXPAND trial did not demonstrate a PFS or OS benefit for cetuximab as first-line chemotherapy in the treatment of gastric cancer [105, 106].

Panitumumab is a fully human monoclonal anti-EGFR antibody without a demonstrated efficacy in naive patients with advanced esophagogastric cancer according to the results of clinical trials including the REAL-3 study [107, 108].

Nimotuzumab is a recombinant humanized monoclonal antibody that was evaluated in a double-blind phase II trial [109] including patients with advanced gastric cancer who received nimotuzumab plus irinotecan versus irinotecan alone, showing no difference in PFS or OS between these two groups. Nevertheless, the EGFR2+/3+ subgroups presented a significant benefit when treated with nimotuzumab.

6.2.2.2. TKIs of EGFR

Gefitinib is an oral EGFR TKI currently assessed in a phase I/II study, in combination with chemoradiation, in subjects with resectable gastric cancer [110], in a phase II study in patients with unresectable and/or metastatic gastric carcinomas, and also in a phase III trial in patients with advanced gastro-esophageal junction cancers after progression on chemotherapy [111]. The results of these studies could define the role of this agent in gastric cancer treatment.

Erlotinib (Tarceva) is an oral EGFR TKI, shown to be active in a phase II trial only in patients with gastro-esophageal cancer, but not in those with gastric cancer [112].

6.2.3. VEGF/VEGF receptor inhibition

Angiogenesis is an essential event in tumor growth and spread. VEGF has demonstrated a major role in tumor angiogenesis, growth, and metastasis in numerous tumors, including gastric cancer [113], therefore, being considered an essential therapeutic target. Data revealed that VEGF expression correlates with the clinical stage and prognosis of gastric cancer [114].

6.2.3.1. Anti-VEGF monoclonal antibodies

Bevacizumab (Avastin) efficacy as a first-line treatment in combination with cisplatin-based chemotherapy for advanced gastric cancer was evaluated in the phase III AVAGAST trial (Avastin in gastric cancer) [115], which demonstrated a median PFS and overall response rate significantly improved in the bevacizumab group, but without a significant benefit in OS. Another phase III study, AVATAR, also found that bevacizumab combined with capecitabine/cisplatin chemotherapy did not significantly improve OS in patients with advanced gastric cancer [116]. Possibly, the negative results of these studies might have resulted from not having selected the most molecularly suitable gastric cancer patients.

The MAGIC-B study is currently assessing the role of bevacizumab for perioperative chemotherapy in resectable adenocarcinoma of the stomach, [117]. 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 [118].

Currently, the safety and efficacy of adding bevacizumab to taxane-based chemotherapeutic regimens irinotecan [119] or anti-Her2-targeted treatment in advanced/metastatic gastric cancer is being evaluated in several clinical trials with pending results [120].

6.2.3.2. Anti-VEGF receptor monoclonal antibodies

Ramucirumab is a human monoclonal antibody that inhibits VEGFR-2. It was approved by the FDA as a single agent in gastric cancer after progression on a platinum- or fluoropyrimidine-containing regimen, based on the phase III REGARD study (second-line ramucirumab monotherapy for advanced gastric adenocarcinoma), which found significantly longer OS for ramucirumab versus best supportive care (BSC) [42]. Furthermore, the results of a phase III clinical trial of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the second-line treatment of metastatic gastric adenocarcinoma (RAINBOW trial) revealed 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. Therefore, ramucirumab is for the moment, the only antiangiogenic agent that has been approved for the treatment of gastric carcinoma [122].

Endostar is a novel recombinant human endostatin, which was investigated [123] combined with SOX (S-1/oxaliplatin) for the first-line treatment of patients with advanced gastric cancer; the results showed significantly better PFS for the group including Endostar. More studies for the efficacy of Endostatin in stomach cancer settings are needed.

6.2.3.3. TKIs of VEGF

Apatinib is an anti-VEGF-2 small molecule TKI evaluated in China [124]. Phase II and III studies have shown that apatinib was the first discovered anti-VEGF-2 molecule TKI with benefits for Asian patients with advanced gastric cancer [125], representing a significant progress for third-line treatment, although it prolonged OS by less than 2 months. Further studies are needed to assess the efficacy and safety of this agent in Caucasians. Based on these positive results, apatinib was approved by the Chinese Food and Drug Administration (CFDA) for metastatic adenocarcinoma of the stomach after second-line chemotherapy progression [126].

Sunitinib represents an oral multitargeted TKI of VEGFR, PDGFR, c-KIT (stem cell factor receptor), rearranged during transfection, and FMS-like tyrosine kinase-3 receptor; when administrated in a phase III trial as second-line monotherapy in patients with advanced gastric cancer, it showed a median OS of 6.8 months [127]. The efficacy of sunitinib in advanced gastric cancer was also confirmed by other studies [128].

Sorafenib (Nexavar) is a multitargeted TKI. A phase II study using sorafenib combined with docetaxel and cisplatin as a second-line treatment for gastric cancer patients obtained very long median PFS and median OS [129], although other clinical trials have been terminated early because of low response rates [130].

Pazopanib is an oral agent that inhibits angiogenesis through multiple pathways (VEGFR, PDGFR, and c-KIT), which is currently under investigation in two phase II trials in patients with advanced gastric tumors: the PaFLO trial (FLO ± pazopanib as first-line treatment) [131] and another trial associating pazopanib with capecitabine and oxaliplatin [132].

Regorafenib is an oral multikinase; a phase II trial investigating the efficacy of regorafenib in the treatment of refractory advanced esophagogastric cancer demonstrated a significantly longer median PFS (11 wk versus 3.9 wk) and OS (25 wk versus 19.4 wk) for the regorafenib group versus the placebo group [133] but with serious drug-related toxicity. The role of regorafenib in advanced gastric cancer will be better assessed by the ongoing phase I and II trials.

6.2.4. IGF-1 inhibition

IGF-1 receptor (IGF-1R) is a transmembrane tyrosine kinase receptor promoting tumor angiogenesis, growth, and metastasis in several cancers, including gastroesophageal tumors [134].

Figitumumab is a humanized IgG2 monoclonal antibody against IGF-1R. Some phase I clinical trials have assessed the overall safety and pharmacokinetic profile of figitumumab administrated in patients with advanced solid tumors [135]. Its role in gastric cancer treatment requires further studies.

6.2.5. Fibroblast growth factor TKIs

Fibroblast growth factor (FGF) and its signaling receptors have a major role in cell proliferation, differentiation, and transformation [136].

Although AZD2171 (AZD), a potent oral FGF TKIs, led to tumor inhibition in animal models of gastric cancer, unfortunately, the results of a phase II study [137] showed no statistically significant difference in PFS for FGFR2 amplified gastric cancer patients treated with AZD.

A phase I, first in-human study of JNJ-42756493 (a pan-FGFR TKI) was initiated in advanced solid tumor patients, including gastric cancer, showing that this agent had excellent pharmaceutical properties and safety profile [138].

Ki23057 is an oral TKI broad-range FGF TKI that inhibits the proliferation of gastric scirrhous cancer cells presenting FGFR2 gene amplification. The study of Qiu et al. 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. [139].

We expect the results of the ongoing phase I and II clinical trials using TKI such as dovitinib, brivanib, and INCB054828 (FGF inhibitors) in patients with advanced gastric cancer to add new informations regarding the role of FGF inhibitors in this type of tumor [140].

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

C-MET and its signal pathway activation determine gastric cancer cell proliferation, survival, and migration [141].

6.2.6.1. Anti-HGF/c-MET monoclonal antibodies

Rilotumumab is a human monoclonal antibody directed against HGF, demonstrated to show efficacy in locally advanced/metastatic gastric cancer patients with MET overexpression by immunohistochemistry (phase II study). Unfortunately, due to the increased toxicity of the agent and treatment-related deaths in the RILOMET-1 trial, all of the clinical trials investigating the role of rilotumumab in gastric tumors, including the phase III RILOMET-1 (with ECX) and RILOMET-2 (with cisplatin and capecitabine) studies, were interrupted.

Onartuzumab is a humanized antibody directed against MET that is also being investigated in a first-line, phase III trial in MET-positive, HER2-negative gastroesophageal patients in combination with mFOLFOX6. The results of this study revealed unfortunately that this treatment could not prolong OS [142].

6.2.6.2. Anti-HGF/c-MET tyrosine kinase

Foretonib is an oral molecule inhibitor of c-MET and VEGFR-2A, which was investigated in a phase II study as a single agent in patients with metastatic gastric cancer, demonstrating good tolerability but only minimal antitumor efficacy [143].

6.2.7. PI3 kinase/mammalian target of the rapamycin pathway inhibition

Upregulation of the PI3k/Akt/mTOR pathway was associated with poor prognosis and could be implicated in the chemoresistance of gastric cancer [144].

Everolimus is an oral mTOR inhibitor demonstrated to have efficiency in both phase I and phase II studies, which have shown that everolimus monotherapy had a good response rate for advanced gastric cancer patients in the second-line setting [145, 146]. Unfortunately, the phase III GRANITE-1 trial investigating the everolimus monotherapy as a second-/third-line in patients with advanced gastric cancer did not show OS benefit, only the association of severe adverse reactions [147]. Therefore, the use of this agent in the treatment of gastric cancer needs further investigations.

Rapamycin has shown efficiency in preclinical studies and animal models against gastric cancer, increasing also the effectiveness of chemotherapeutic drugs [148]; nevertheless, its use in gastric cancer does not have enough support yet.

6.2.8. PARP inhibitors

These agents were demonstrated to prevent the cancer cell's single stranded break repair mechanism, leading to tumor cell death [149].

A phase II trial in metastatic/recurrent gastroesophageal cancer studied the effectiveness of administrating the PARP inhibitor olaparib as a second-line treatment [150], demonstrating improved OS. There is also an ongoing phase III study of second-line treatment using paclitaxel with or without olaparib in advanced gastric cancer patients [151].

Veliparib was developed to increase the effectiveness of DNA-damaging therapies, such as chemo- or radiotherapy. A study of the efficacy of veliparib associated with the FOLFIRI regimen in gastric cancer is pending results [152].

6.2.9. Immunotherapy/immuno-checkpoint blockade

Because it was revealed that tumors evade host immune recognition [153], immunotherapy has emerged as a novel field of antitumor treatment, which acts by using the blockage mechanism of the inhibitory immune regulatory pathways. New agents targeting immune checkpoints, programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1), have been recently investigated.

Ipilimumab blocks the inhibitory receptor called cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Unfortunately, a phase II trial assessing the efficacy of ipilimumab after first-line chemotherapy in unresectable locally advanced or metastatic gastric cancer patients revealed no statistically significant improvement in OS [154].

Nivolumab blocks the interactions between PD-1 and PD-L1 stimulated immune function in vitro, showing antitumor activity in preclinical models. A phase I/II study of nivolumab monotherapy versus nivolumab combined with ipilimumab in patients with advanced or metastatic solid tumors, including gastric cancer, is still ongoing [155]. Interim results revealed that nivolumab monotherapy demonstrated encouraging antitumor activity in heavily pretreated gastric cancer patients [156]. Furthermore, a phase III trial is currently assessing the tolerability and efficacy of nivolumab in patients with unresectable advanced or recurrent gastric cancer refractory to standard chemotherapy [157].

Pembrolizumab is an agent that blocks the binding of PD-1 to PDL-1, demonstrated to have good tolerability, as well as anti-tumor activity in a phase 1 study including recurrent and metastatic gastric adenocarcinoma patients with PD-L1 (+) tumors [158]. Other phase I-III trials are investigating this agent in advanced gastric cancer [159, 160], with the aim of investigating the molecular subtypes of gastric tumors through integrative genomic analysis [161]. Some phase I/II studies are assessing its efficacy in combination with other classes of agents (anti-HER2 or anti-VEGFR monoclonal antibodies, multitargeted TKIs) [162–165].

Durvalumab, an anti-PDL-1 drug, has shown some activity in gastric cancer treatment [166]. The combination of durvalumab and tremelimumab (anti-CTLA-4) plus first-line chemotherapy is currently being investigated in advanced solid tumors (including gastric cancers) [167, 168].

6.2.10. Guanylyl cyclase C inhibitors

Guanylyl cyclase C (GCC) is a transmembrane cell surface receptor, expressed both on normal intestinal tissue and on the tumor cells of gastrointestinal neoplasias. MLN0264 consists of a human monoclonal antibody targeting GCC, demonstrating good tolerability of the drug and promising results in a phase I trial in patients with gastrointestinal malignancies expressing GCC [169, 170]. Phase I-II studies of MLN 0264 in previously treated patients with metastatic/recurrent gastric GCC (+) cancers are currently recruiting patients [171, 172].

6.2.11. Inhibitors of the tumor cell cycle

In gastric tumors, there is an alteration of cell cycle regulatory mechanisms [173]. Flavopiridol is a cyclin-dependent kinase inhibitor, unfortunately demonstrated to have low efficacy and serious adverse effects in gastric cancer [174]. Because of its low activity as a single agent, it must be investigated in combination with other chemotherapeutics.

6.2.12. Agents inducing tumor cell apoptosis

The induction of tumor cell apoptosis seems to be a promising target in cancer treatment. NF-κB expression showed to be positively correlated with the degree of the tumor and is negatively correlated with cancer prognosis.

Bortezomib is a highly potent proteasome inhibitor that acts by inhibiting activation of the NF-κB signaling pathway. Preclinical studies have demonstrated an effect of growth inhibition of this agent in combination with standard chemotherapy for gastric cancer [175, 176]. However, phase II studies assessing the efficacy of bortezomib either alone or in combination with irinotecan or paclitaxel plus carboplatin showed no positive results [177–179].

6.2.13. Matrix metalloproteinase inhibitors

The aberrant synthesis of matrix metalloproteinase (MMPs) leads to local tumor invasion by destroying the extracellular matrix and the basement membrane. Literature data have previously associated the high expression of some MMPs with a poor prognosis of gastric cancer [180, 181].

Marimastat is a broad-spectrum MMP. There was a study in patients with nonresectable gastric adenocarcinoma that revealed the first indication of a survival benefit for an MMP

inhibitor, supporting a possible role for this agent as a maintenance treatment following chemotherapy [182].

7. Conclusion

Gastric cancer represents a major health problem worldwide, with most of the patients being diagnosed in advanced stages of the disease, associated with poor prognosis. Gastric tumors are molecularly heterogeneous; therefore, it is of major importance to identify the molecular subtype of the tumor and specific molecular biomarkers in order to assess the prognosis of the patient.

Furthermore, it is essential to identify molecular biomarkers that could predict treatment response according to the genetic and epigenetic profile of the patients and also to identify the occurrence of chemoresistance using specific markers, in order to obtain maximum response. The discovery of the molecular background of gastric cancer leads to the development of novel molecular targeted treatments. Heretofore, among the multitude of classes of agents targeting different signaling pathways, such as VEGF, EGFR, HER-2, IGF, immunotherapy, and mTOR pathways, only anti-HER2 monoclonal antibody trastuzumab and anti-VEGFR antibody ramucirumab have been approved for the treatment of advanced gastric cancer. Also, Apatinib, an anti-VEGFR2 TKI demonstrated efficiency in Chinese gastric cancer patients, receiving approval for treatment in this setting. Moreover, there are other classes of agents such as immunotherapy drugs (e.g., Pembrolizumab) that showed encouraging results in clinical trials, but we have still to wait for the final results until implementing them in clinical practice.

Therefore, further clinical studies are needed to demonstrate the effectiveness of molecular targeted treatments in order to have a personalized treatment approach and to improve the outcome of gastric cancer patients.

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