Overview on Gastric Cancer

Chapter 3

Targeted Therapies in Gastric Cancer

Filipa Macedo[1]; Nuno Bonito[1]; Adhemar Longatto-Filho[2,3,4,5]; Sandra F Martins[2,3,6] *

[1]Portuguese Oncology Institute – Coimbra; Portugal

[2]Life and Health Science Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

[3]ICVS/3B's-PT Government Associate Laboratory, Braga/Guimarães, Braga, Portugal

[4]Molecular Oncology Research Center, Barretos, São Paulo, Brazil

[5]Laboratory of Medical Investigation (LIM) 14, Faculty of Medicine, University of Sao Paulo, Brazil

[6]Surgery Department, Coloproctology Unit, Braga Hospital, Braga Portugal

***Correspondence to: Sandra F Martins, MD., PhD,** Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*

Phone: + 351 933361345; Fax: +351 253604847; Email: sandramartins@med.uminho.pt

1. Introduction

The incidence of gastric cancer varies widely worldwide, but it is considered the second most prevalent tumour. There are places of higher incidence like Japan and China with >20 cases per 100.000 habitants, and places with lower incidence like Northern Europe and Northern America with <10 cases per 100.000 habitants [1].

The most frequent type of gastric cancer (> 90%) is adenocarcinoma. According to the Lauren classification, gastric cancer can be divided as intestinal and diffuse type. [2] The intestinal type is related to *Helicobacter pylori* infection, which leads to chronic gastritis, metaplasia and finally adenocarcinoma. [3] This type of cancer is localized to the corpus and antrum and its incidence in Western countries is decreasing, maybe due to a higher concern about eradicating the infection when it is diagnosed. On the other hand, proximal tumours are increasing in prevalence. [4] The diffuse type of gastric adenocarcinoma is related with the loss of an intracellular adhesion molecule called E-cadherin, encoded by cadherin 1 gene (CDH1). [5] In 2010, the World Health Organization (WHO) issued a classification that is more detailed and included not only adenocarcinoma of the stomach but also all other types of gastric tumours of lower frequency. [6] [**Table 1**].

Table 1: Lauren and WHO classification of gastric cancer

Lauren Classification (1965)	World Health Organization Classification (2010)
Intestinal Type	Tubular adenocarcinoma Mucinous Adenocarcinoma Papillary Adenocarcinoma
Diffuse Type	Signet-ring cell carcinoma (and other poorly cohesive carcinoma)
Indeterminate Type	Mixed carcinoma Adenosquamous carcinoma Squamous cell carcinoma Hepatoid adenocarcinoma Carcinoma with lymphoid stroma Choriocarcinoma Carcinosarcoma Parietal cell carcinoma Malignant rhabdoid tumor Mucoepidermoid carcinoma Paneth cell carcinoma Undifferentiated carcinoma Mixed adeno-neuroendocrine carcinoma Endodermal sinus tumor Embryonal carcinoma Pure gastric yolk sac tumor Oncocytic adenocarcinoma

At diagnosis, only 26% of the gastric cancer is localized. The 5-year overall survival rate is 28.3%, which has not changed significantly over the past 30 to 40 years [1]

2. Classical Treatment

Surgery is the only curative modality for localized gastric cancer. For reliable pathological TNM staging, a minimum of 15 lymph nodes must be recovered and analyzed. [4] The standard surgical approach comprises a D2 dissection. [**Table 2**]

Table 2: N1 and N2 lymph nodes (correspondence with **figure 1**)

N1 Lymph nodes (perigastric)	N2 Lymph nodes (coeliac axis)
1 - Right cardiac nodes	7 - Nodes along the left gastric artery
2 - Left cardiac nodes	8 - Nodes along the common hepatic artery
3 - Nodes along the lesser curvature	9 - Nodes around the coeliac axis
4 - Nodes along the greater curvature	10 - Nodes at the splenic hilus
5 - Suprapyloric nodes	11 - Nodes along the splenic artery
6 - Infrapyloric nodes	

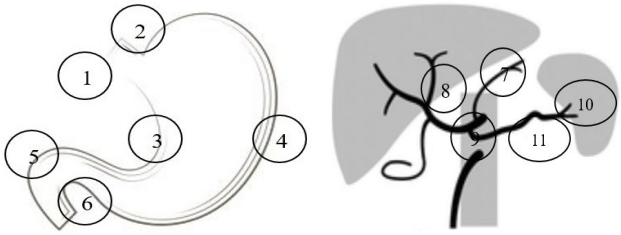

Figure 1: N1 and N2 lymph nodes (correspondence with **table 2**)

Stage 0 and stage IA only need surgical resection, with negative margins. Positive margins, even if microscopic, confer a worse prognosis. [D]

For stages between IB and III, radical gastrectomy should be performed. However, since most patients still relapse following total gastrectomy, a combined therapy is the standard of care for theses stages. Perioperative chemotherapy (pre and postoperative) with a combination of platinum and fluoropyrimidine is the recommendation for patients with resectable disease. Several trials are currently studying the role of radiation as adjuvant or neoadjuvant concomitantly with chemotherapy. Patients diagnosed with metastatic disease should be considered for palliative chemotherapy (doublet or triplet platinum and fluoropyrimidine, if the patient is fit; taxane or irinotecan in monotherapy if the patient is unfit for combination agents).

3. Molecular Classification

The Cancer Genome Atlas Research Network proposed a molecular classification dividing GC into four subtypes. [7] [**Table 3**]

Table 3: Molecular classification of gastric cancer

EBV (10% of the gastric cancers)	MSI (20% of the gastric cancers)	CIN (50% of the gastric cancers)	GS (20% of the gastric cancers)
• Tumors containing Epstein Barr Virus (EBV) – the etiologic agent of infectious mononucleosis;	• Tumors containing microsatellite instability	• Tumors containing chromosomic instability.	• Tumors genomically stable
• Localized in the fundus or body of the stomach;	• Hypermutation rate	• Localized in the cardia and gastroesophagic junction;	• Lack aneuploidy
• Mutation in the PIK3CA gene pathway – 80% of this type of gastric cancer;	• Hypermethylation of the MLH1 promoter	• High aneuploidy	• Mutations of the RHO GTPase activating proteins and CDH1
• Extreme DNA hypermethylation;	• MSI-High phenotype has been associated with intestinal-type carcinomas, and is associated with a better prognosis than MSI-Low or MSS tumors	• Amplification of receptor tyrosine kinase	• High metastatic potential

• Amplification of Janus kinase 2 (JAK2);	• Older age at diagnosis	• Alterations in the RAS signaling pathway	• Diffuse subtype
• Extra copies of programmed death ligand 1 (PD-L1) and PD-L2 genes.		• TP53, PIK3CA, ERBB2, and APC mutations • Intestinal subtype	• Younger age at diagnosis

4. Targeted Therapy

Several new biomarkers are being studied in gastric cancer and they are being evaluated in the setting of possible target to systemic therapy [**Figure 2**].

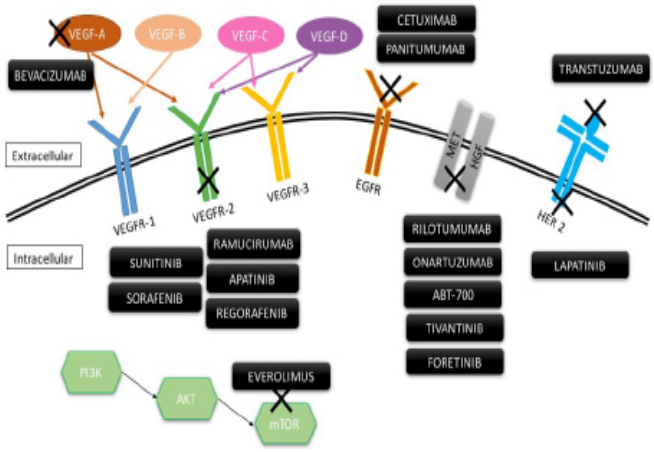

Figure 2: Targets to systemic therapy.

4.1. Anti-VEGF

The vascular endothelial growth factor (VEGF) and its receptor (VEGFR) have major roles in regulation of the angiogenesis, vascular permeability and lymphangiogenesis. [8] VEGF positive gastric cancers are larger, more invasive, more advanced stage and the patients have lower survival rates [9].

Bevacizumab was the first humanized monoclonal antibody targeting VEGF, approved for treating several types of cancer, like metastatic colorectal cancer, metastatic breast cancer, non-small cells lung cancer and ovarian cancer. The studies performed on gastric cancer were not so profitable. In AVAGAST Trial in 2011, Bevacizumab + fluoropyrimidin/cisplatin was compared to placebo + fluoropyrimidin/cisplatin in first line in metastatic gastric cancer and unresectable disease. Bevacizumab arm got more 1.3 months (p=0,1) in overall survival (OS) and 1.4 months (p=0,0037) more in progression free survival (PFS). [10] In AVATAR Trial in 2015, Bevacizumab + capecitabine/cisplatin was compared to placebo + capecitabine/ cisplatin in first line in metastatic gastric cancer and unresectable disease. Bevacizumab arm got 0.9 months less (p=0,56) in overall survival (OS) and 0.3 months (p=0,47) more in progression free survival (PFS). [11] At last, the ST03 Trial in 2017, Bevacizumab + epirubicine/capecitabine/cisplatin was compared to placebo + epirubicine/capecitabine/ cisplatin in the periopera-

tive setting in resectable gastric cancer. The 3-year OS was higher for the placebo arm (48.1 vs 50.3%, p=0,36). [12]

Ramucirumab is a humanized IgG1 monoclonal antibody that targets the VEGF receptor 2, so it blocks the effect of VEGF-A, VEGF-C, and VEGF-D. Ramucirumab is approved for metastatic non-small cells lung carcinoma as second line after platinum therapy, metastatic colorectal carcinoma as second line after oxaliplatin and fluoropyrimidin chemotherapy, and it is approved for advanced gastric cancer in combination with paclitaxel after progression with a platinum and fluoropyrimidin treatment. The REGARD Trial in 2014, ramucirumab was compared with placebo in second line in unresectable or metastatic gastric cancer. The ramucirumab got 1.4 months more (p=0,047) in OS and 0.8 months more (p=0,001) in PFS. [13] The RAINBOW Trial in 2013, ramucirumab + paclitaxel was compared to placebo + paclitaxel in second line in unresectable or metastatic gastric cancer. The ramucirumab arm got 2.2 months more (p=0,017) in OS and 1.5 months more (p<0,0001) for PFS. [14]

4.2. Anti-HER2 (ERB2)

The human epidermal growth factor receptor 2 (HER 2) is a member of the epidermal growth factor receptor family and it is considered a proto-oncogene. When this receptor is activated, or is constitutionally activated by a mutation, the tyrosine residues are auto-phosphorylated, leading to uncontrolled proliferation and evasion from apoptosis. HER 2 is associated with more invasive tumors and metastatic potential. [15] HER-2 is overexpressed in approximately 7-34% of patients with gastric cancer, [16] with amplification reported in 2-27% of the cases and mutations detected in 5% of the cases [17]. It is often found in intestinal-type (30%) rather than in diffuse-type (5%) gastric cancer.

Transtuzumab is a humanized IgG1 monoclonal antibody against HER 2 approved for metastatic breast cancer, early breast cancer and metastatic gastric cancer. In ToGA Trial in 2010, 5-fluoruracil (5FU) or capecitabine + cisplatin was compared to 5FU or capecitabine + cisplatin + transtuzumab in first line in HER2 positive advanced gastric cancer. The transtuzumab arm got a median OS of 13.8 months compared with 11.1 months of the control arm (p=0,0046). In addition, the transtuzumb arm got more 2.8 months of survival with response rate of 37% vs 51% (p=0,00017) [18].

Lapatinib is a tyrosine kinase inhibitor anti-HER2 that binds the ATP-protein kinase domain preventing the auto-phosphorylation and activation of the receptor. It is approved in advanced or metastatic breast cancer with HER 2 overexpression, in association with capecitabin or transtuzumab or an aromatase inhibitor. The LOGIC Trial in 2016, compared capecitabine + oxaliplatin with and without lapatinib in first line in advanced gastric carcinoma with HER 2 amplification. The lapatinib arm got a median OS of 12.2 months compared with 10.5 months of the control group, that was not statistically significant. The response rate was higher

in the experimental group (53% vs 39%, p=0,0031). [19] The TyTAN Trial in 2014, compared the treatment of advanced gastric cancer in second-line setting with paclitaxel, with or without lapatinib. The lapatinib arm got a median OS of 11.0 months compared with 8.9 months of paclitaxel in monotherapy (p=0,10), concluding that lapatinib did not significantly improve OS. The response rate was higher with monotherapy (27% vs 9%, p=0,001) [20].

4.3. ANTI-EGFR

The epidermal growth factor receptor (EGFR), also called HER 1, suffers dimerization when it contacts with its ligands and stimulates its tyrosine kinase activity. The phosphorylation leads to an activation of the downstream signaling which leads to cell proliferation and migration. Activation of EGFR occurs in 9-30% of the cases [17], and that can happen by EGFR amplification (2-8%) or mutation (5%) [21].

Cetuximab is a quimeric IgG1 monoclonal antibody against EGFR approved for metastatic colorectal cancer RAS wild-type and head and neck tumors. The EXPAND Trial in 2013, compared capecitabine + cisplatine with chemotherapy with cetuximab in first-line in locally advanced and metastatic gastric cancer. The main goal was PFS, which was higher without the antibody (4.4 months vs 5.6 months) [22]. Cetuximab was also tested s monotherapy, but the results were disappointing, with a response rate of 3% [23].

Panitumumab is a humanized IgG2 monoclonal antibody against EGFR approved for metastatic colorectal cancer RAS wild-type. In the REAL3 Trial in 2013, chemotherapy with epirubicin + oxaliplatin + capecitabin was compared with the same drugs with panitumumab in untreated metastatic or locally advanced gastric cancer. The OS in chemotherapy alone was higher (11.3 months vs 8.8 months), so its addition cannot be recommended [24].

4.4. PI3K/AKT/mTOR inhibitors

The phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling are essential in some physiological as well as in pathological conditions. The PI3K/Akt pathway is a key regulator of survival during cellular stress. [25] The mTOR signaling is necessary for cell growth, cell cycle progression, and cell metabolism. They are so interconnected that they are usually regarded as a single pathway. When PI3K is activated, it phosphorylates and activates AKT, which activates mTOR and several transcription factors are ready to originate their substrates. mTOR is active in 60% of GC cases while PI3K/Akt is active in 30% of GC cases [26].

Everolimus is a mTOR inhibitor, derived from sirolimus, that has approval for advanced breast cancer with positive hormonal receptors, neuroendocrine tumors and renal cell carcinomas. It is also used as immunosuppressant to prevent rejection of organ transplants [27] and

for tumors derived from tuberous sclerosis [28]. In the GRANITE-1 Trial in 2013, placebo + best supportive care was compared with everolimus + best supportive care in advanced gastric cancer after one or two lines of treatment. The median OS was 5.4 months for everolimus arm and 4.3 months for placebo (p=0.12), and median PFS was 1.7 months and 1.4 months respectively, which did not show any significant benefit. [26] In the RADPAC Trial, paclitaxel + placebo was compared with paclitaxel + placebo in patients with gastric cancer that had progressed after chemotherapy with fluoropyrimidine/platinum-containing. There was no significant difference in median PFS (placebo 2.1 months, Everolimus 2.2 months, p= 0.3) and median OS (placebo 5.1months, everolimus 6.1 months, p= 0.48) [29].

4.5. MET inhibitors

The mesenchymal epithelial transition (MET) is a tyrosine kinase receptor which stimulates proliferation and invasion when is coupled with its ligand, hepatocyte growth factor (HGF). MET receptor is a proto-oncogene and could be aberrantly activated by amplification, mutation or protein overexpression. [30] In gastric cancer, it was showed an overexpression of MET in 26-82% of the cases, and an overexpression of HGF in 73-88% of the cases. These alterations are associated with poor prognosis [31].

Rilotumumab is a humanized monoclonal antibody IgG2 that binds and neutralizes HGF preventing its binding to MET receptor. Iveson T and colleagues have tested in a phase II study in 2014, the rilotumumab with epirubicin, cisplatin and capecitabine in first line in metastatic or advanced gastric cancer. An improvement in OS and PFS was observed for the patients that received rilotumumab + capecitabine (OS: 5.7 months vs 4.2 months). [32] However, the phase III study RILOMET Trial in 2017, was interrupted early after a higher number of deaths in the rilotumumab group [33].

Onartuzumab is a humanized monoclonal antibody which binds directly to the extracellular domain of MET receptor, impeding the binding of HGF. The METGastric Trial in 2015, combined onartuzumab with FOLFOX6 in metastatic HER2-negative and MET-positive gastric cancer. The combination therapy was ineffective. The only ones that can benefit were the non-Asian and patients without prior gastrectomy [34].

ABT-700 is an anti-c-Met antibody, only tested in a phase I trial. It was well tolerated and appeared to have substantial single-agent activity [35]. Additionally, ABT-700 induces tumor regression and tumor growth delay in preclinical tumor models of gastric cancer [36].

Tivantinib is an oral inhibitor of c-Met who underwent a phase II study combined with FOLFOX in metastatic gastric cancer untreated. The OS was 9.6 months and the PFS was 6.1 months, which the authors considered a good result [37].

Foretinib is an oral inhibitor of MET receptor and vascular endothelial growth factor receptor 2 (VEGFR2). A phase II trial in 2013 concluded that foretinib lacked efficacy in unselected patients with metastatic gastric cancer [38].

4.6. Tyrosine kinase inhibitors (TKI)

A tyrosine is an amino acid and a kinase is an enzyme with the ability of transfer a phosphate group from an adenosine triphosphate (ATP) to a protein. In the case of a tyrosine kinase, the phosphate group is attached to the tyrosine amino acid of a protein. The phosphorylation by kinases is an important mechanism of signaling in a cell. The mutation of a kinase leads to an uncontrolled growth of the cell. The tyrosine kinase inhibitors can exert their effect by several mechanisms: competition with ATP, competition with the agent that phosphorylate the substrate, competition with the substrate, and by conformational change when it binds outside de active site of the receptor [39].

Apatinib is a selective tyrosine kinase inhibitor against VEGF-2, approved in China for the treatment of advanced o metastatic gastric cancer. Li J et al, in a phase III clinical trial in 2015, compared oral apatinib with placebo in advanced gastric cancer in patients whom two or more lines of chemotherapy had failed. The OS was superior in apatinib group (6.5 months vs 4.7 months, p=0,0156) as PFS (2.6 months vs 1.8 months, p<0,001). [40] Qin S et al, in another phase III trial in 2014, compared oral apatinib with placebo in patients with advanced gastric cancer who had progressed with two-lines of chemotherapy. They concluded that OS was longer in the apatinib arm (195 days vs 140 days, p<0,016) as PFS (78 days vs 53 days, p<0,0001) [41].

Regorafenib is a multi-kinase inhibitor approved for treatment of metastatic colon cancer previously treated with chemotherapy or target therapy, and advanced gastrointestinal stromal tumors that has progression with imatinib or sorafenib. The INTEGRATE Trial in 2016, compared regorafenib with placebo in advanced gastric cancer patients. Regorafenib was effective in prolonging PFS (2.6 months vs 0.9 months, p<0,001) [42]. We are waiting the results from INTEGRATE II trial.

Sorafenib is a multi-kinase inhibitor of VEGF, platelet-derived growth factor (PDGF), KIT, BRAF and RAS pathway. It induces autophagy, suppressing tumor growth. Sorafenib is approved for the treatment of hepatocellular carcinoma, advanced renal cell carcinoma, and advanced thyroid carcinoma that do not respond to radioactive iodine. The GEMCAD study, a phase II trial, implemented sorafenib + oxaliplatin as second-line after chemotherapy with cisplatin and fluoropyrimidines. Their results did not support a phase III trial (median PFS was 3 months and median OS was 6.5 months) [43]. In the STARGATE Trial, a phase II study, the sorafenib was added to cisplatine + capecitabine in first-line in metastatic gastric cancer. The OS and PFS did not differ between the two arms [44].

Sunitinib is an oral multi-kinase inhibitor of VEGF, PDGF, KIT and rearranged during transfection (RET). It is approved for the treatment of advanced or metastatic renal cell carcinoma and for imatinib-resistant gastrointestinal stromal tumor (GIST). In 2011, Bang Y et al performed a phase II trial in advanced gastric cancer patients who had received prior chemotherapy, with insufficient clinical results (median OS was 6.8 months and median PFS was 2.3 months) [45]. In 2012, Yi J et al compared docetaxel alone and with sunitinib in metastatic gastric cancer after failure with platinum and fluoropyrimidines chemotherapy. The time to progression was similar (3.9 months in the combination group vs 2.6 months) but the objective response rate was higher in the combination group (41.1% vs 14.3%, p=0.002) [46]. Finally, in the AIO Trial in 2016, the addiction of sunitinib to FOLFIRI was evaluated as second or third line in advanced refractory gastric cancer. The median PFS was similar between the two arms (3.5 vs 3.3 months) and the OS was slightly higher in the combination group, although not statistically significant (10.4 vs 8.9 months, p=0,21) [47].

Lapatinib is a dual TKI inhibiting both HER-2 and EGFR, already specified above.

5. Conclusion

Some efforts have been made to improve the survival and the quality of life of patients with gastric cancer. The targeted therapy brought few benefits to these patients. Nowadays, in patients with HER2-overexpressing advanced gastric cancer could be offered chemotherapy plus transtuzumab, and the ramucirumab could be considered as second-line. There is still a lack of phase III clinical trials in gastric cancer patients who may benefit from TKI agents. Results from double targeting HER-2 with pertuzumab plus trastuzumab plus chemotherapy are expected. Targeted therapy must be individualized given the significant heterogeneity in gastric cancer patients.

6. References

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