Does tumor profile in gastric and gastroesophageal (GE) junction cancer justify off-label use of targeted therapy?—a narrative review

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Abstract: Despite significant therapeutic progress, gastric cancer remains among the most deadly forms of cancer encountered in clinical practice, and this remains true even in the context of declining incidence. Outcomes in advanced disease remain poor and therapy is rarely curative in this setting. As our understanding of tumor profile gains sophistication, a growing interest in targeted therapies and moreover the use of tumor profile to inform these therapies has developed in the hopes of altering nearly uniformly poor outcomes. A wide and growing array of molecular targets have been identified in the recent past. Targets of potential clinical interest include human epidermal growth factor receptor-2 (HER2), epidermal growth factor receptor (EGFR), poly(ADP-ribose) polymerase (PARP), mammalian target of rapamycin (mTOR), c-MET, and fibroblast growth factor receptor (FGFR). This advanced molecular understanding has been increasingly used to justify the off-label usage of targeted therapies, though the efficacy of this approach warrants careful consideration. While targeted agents have demonstrated efficacy across a wide range of malignancies, even with molecular profiling data, efficacy is not assured. It will also be demonstrated that even within the same malignancy, what holds true in the metastatic setting does not necessarily apply to the adjuvant or neoadjuvant setting. This review will assess the current evidence for the use of targeted therapies utilizing these biomarkers in the context of gastric and gastroesophageal (GE) junction cancers.

Keywords: Gastric cancer (GC); targeted therapy; tyrosine kinase inhibitor; human epidermal growth factor receptor-2 (HER2); vascular endothelial growth factor (VEGF); epidermal growth factor receptor (EGFR); poly(ADP-ribose) polymerase (PARP)

Introduction

Despite a decreasing incidence, gastric cancer (GC) remains an important cause of cancer-related death and morbidity. This year in the US alone, approximately 27,600 patients will be diagnosed and 11,010 will die from the disease (1). Importantly, GC is typically diagnosed in incurable stages, which contributes to its rank as the third leading cause of

cancer death (2). While incomplete, our understanding of the molecular pathogenesis of GC has evolved rapidly and contributed to a growing array of targeted therapeutic options in late stage disease. Notwithstanding these advances, the story of targeted therapy in GC is marked by repeated failures, and additional treatments are sorely needed. This fact has driven the off-label prescription of

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targeted therapies with or without reference to molecular tumor profile. This article will review the pathobiology of GC, evaluate the evidence for the use of targeted therapies, especially treatment based on biomarkers, and describe the rationale behind off-label use in this deadly disease. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3510).

Methods

An English language literature search utilizing the PubMed database for years 2010–2010 was undertaken. Data collection was confined to published research only. Keywords included advanced gastric cancer and molecular/targeted therapy. Prospective and retrospective analyses were included.

Discussion

Basic pathobiology

It is crucial to recognize the inherent heterogeneity of GC and to note that no classification system can adequately capture the histological and clinical variety encountered in daily practice. The molecular pathways involved in carcinogenesis can vary widely even within the same histologic type. This may in part explain the failure of many targeted therapies. Nevertheless, an understanding of the basic classification and pathobiology of GC is important toward interpreting or even predicting treatment efficacy. Despite some question as to the prognostic value of such categorization, there is evidence that histologic subtype can indicate molecular tumor profile (3).

Close to 95% of GCs are adenocarcinomas and within this classification, tumors can be broken down into intestinal or diffuse forms based on a histologic schema first proposed by Lauren in 1965 (4). The molecular mechanisms of this system have since been elucidated and to some extent explain the divergent phenotypes seen in clinical practice. The intestinal type of GC is a well-differentiated tumor with gland structure that resembles normal colon. These cancers have a lesser predilection for local invasion and metastasis and this is thought to be because of preserved expression of E-cadherin, an important mediator of cell-cell adhesion (5). The diffuse type carries a worse prognosis in general and is associated with loss of E-cadherin with a corresponding increased risk of early invasion and metastasis (6). A third category of histologic and genomic classification

is the mixed type, which indicates intermediate pathologic findings on the intestinal-diffuse disease spectrum. There is a growing recognition that expression profiling (GEP) shows an incomplete concordance between histologic classification and GEP-based classification, and this may in turn drive future efforts at classification (7).

Importantly, intestinal type histology appears to be associated with *H. pylori*. This ubiquitous organism causes chronic inflammation in a small percentage of individuals, and in an even smaller cohort can initiate the genetic alterations leading to carcinoma. The latter sequence is felt to offer a prototypical model of multistep carcinomatosis. Additional factors at play in inducing the chronic inflammation that can lead to carcinoma include high salt or nitrate consumption and cigarette smoking. Cag$^+$ expression on the *H. Pylori* organism itself is now felt to be a highly important factor in driving carcinomatosis. Unfortunately, the pathogenesis of the diffuse subtype is less well-characterized though is known to involve loss of E-cadherin expression (8).

While more modern classification systems, some based on TP53 expression and microsatellite stability, have evolved, a more important development has been the stratification of patients based on tumor molecular characterization. As discussed further below, though the results of biomarker-based treatment have been mixed, the hope is that this will allow for a more rational approach to treatment.

Human epidermal growth factor receptor-2 (HER2)

Despite our growing understanding of the mechanisms of disease in GC, with the exception of immunotherapy, there are only two FDA approved targeted therapies for advanced GC: trastuzumab and ramucirumab (see *Figure 1*, *Table 1*). The former targets HER2 and is approved for first-line treatment in advanced HER2-positive GCs (26).

HER2 is an oncogene found on chromosome 17 that that when amplified leads to receptor overexpression. Despite obvious success in targeting HER2 in gastric and breast cancer, the receptor itself is incompletely understood. While it is known to function partly as a ligand independent receptor with kinase activity, the particular ligand that causes direct activation is unknown. The downstream effects of receptor activation are better characterized and include anti-apoptotic, pro-migratory, and proliferation effects (27). The incidence of overexpression varies widely in clinical trials though the best available evidence is from the Trastuzumab for Gastric Cancer (ToGA) trial which found
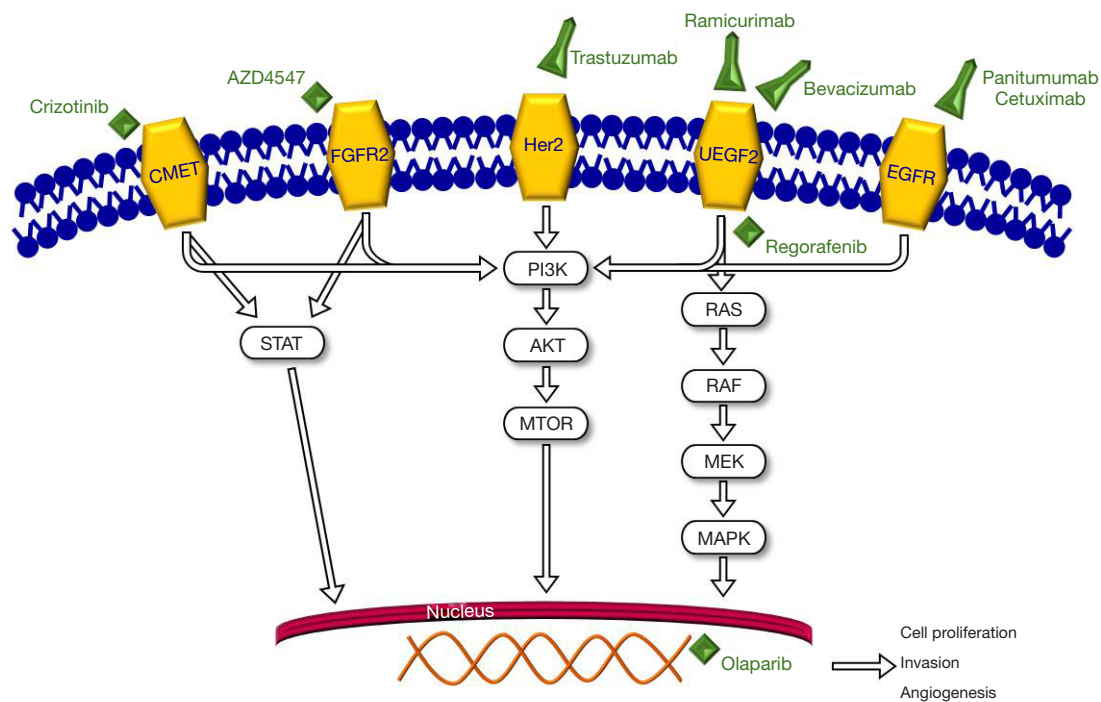
Figure 1 Summary of clinical targets.

overall HER2 expression in 22% of GCs. Histologic type is related to degree of expression: 32% of intestinal type tumors have been found to have expression of HER2 vs. 6% of diffuse-type (3). Overexpression, a key determinant of response to trastuzumab, is comparatively lower (6–30%) and seems to be dependent on location of the tumor, with esophagogastric junction (EGJ) cancers more highly expressing HER2 than gastric body cancers (3).

The ToGA trial established front-line trastuzumab as the standard of care in the metastatic setting, showing a median 2.7-month overall survival (OS) advantage for trastuzumab plus chemotherapy vs. chemotherapy alone (9). Following approval of trastuzumab, many clinical trials were undertaken to assess response in adjuvant, neoadjuvant and second line metastatic settings. Prior to maturation of this data, off label use in these settings was not uncommon, extrapolated from established benefit in breast cancer. Unfortunately, these trials failed repeatedly to demonstrate any response to other HER2-directed agents. In addition, the role for high-dose trastuzumab was not established after evaluation of this strategy in the IIIb HELOISE trial. Based on the *post hoc* observation in the ToGA trial that patients with lower trastuzumab serum trough concentrations had shorter OS, the latter compared high (10 mg/kg) vs. low

(6 mg/kg) maintenance doses of trastuzumab. There were no significant intergroup differences (10). Because the addition of pertuzumab to trastuzumab improves OS in breast cancer, the authors of the phase III JACOB trial hypothesized that a similar benefit might be seen in HER2-positive metastatic gastric or GEJ cancers. Unfortunately, this combination did not improve OS compared with placebo (11).

Despite overall promising data in the metastatic setting, it remains unclear whether the benefit of trastuzumab also applies to adjuvant therapy. Use in this setting would be considered off-label, notwithstanding the recent TOXAG trial. This phase II trial was a single-arm, open label study of adjuvant oxaliplatin, capecitabine and trastuzumab plus radiation. Results were reported in abstract form in February 2018 and were notable only for demonstrating the safety and tolerability of this regimen. Median OS, a secondary outcome, has not been reached after 25 months of follow-up (12). It should be noted that this was a small trial, enrolling only 34 patients, and it would seem premature to adopt this as a strategy for the routine care of curatively resected patients. As these data mature, the standard of care may likewise evolve to include trastuzumab or its derivatives for HER2 overexpressors in

Table 1 Summary of clinical trials of targeted therapies in gastric and gastroesophageal cancer

Trials	Results	Drugs	Notes
HER2 (9-15)			
ToGA	Improved OS	Trastuzumab + chemo *vs.* chemo	Approved first-line therapy
HELOISE	No efficacy of high dose trastuzumab	Trastuzumab + chemo *vs.* high-dose trastuzumab + chemo	First-line metastatic
JACOB	No improvement in OS	Pertuzumab + trastuzumab + chemo *vs.* trastuzumab + chemo	First-line for metastatic disease
TOXAG	Safe and tolerable, but no efficacy in median OS	Trastuzumab + oxaliplatin + capecitabine + radiation	Adjuvant
TyTAN	No improvement in overall OS or PFS	Paclitaxel + lapatinib *vs.* paclitaxel	Second-line advanced disease
LoGIC	No improvement in overall OS or PFS	Lapatinib + capecitabine	First-line study
HER-FLOT	Safe and promising preliminary pCR	Trastuzumab + docetaxel + oxaliplatin + leucovorin + 5-FU	Perioperative setting
EGFR (16-18)			
REAL3	No improvement in PFS or OS	EOC + panitumumab *vs.* EOC	No selection for EGFR overexpression
EXPAND	No improvement in overall PFS or OS; improvement in subgroup with EGFR overexpression	Capecitabine + cisplatin +/− cetuximab	No selection for EGFR overexpression
ENRICH	Prematurely terminated	Nimotuzumab + chemo *vs.* chemo	Selected for EGFR expression
VEGF (19-24)			
AVAGAST	No improvement in OS or PFS	Bevacizumab + chemo *vs.* chemo	Improved OS in patients with high VEGF-A levels
AVATAR	No improvement in OS or PFS	Bevacizumab + chemo *vs.* chemo	
REGARD	Improvement in OS and PFS	Ramucirumab + supportive care *vs.* supportive care	No biomarker association; limited statistical power
Kim *et al.*	Safe and modest improvement in OS, PFS	Pazopanib +/− capecitabine + oxaliplatin	FGFR2 expression predicted PFS, though limited statistical power
INTEGRATE	Effective in prolonging PFS	Regorafenib *vs.* placebo	Second- and third-line therapy; INTEGRATE II (phase III) is ongoing
PARP (24)			
GOLD	No improvement in OS	Olaparib + paclitaxel *vs.* paclitaxel	
FGFR (25)			
SHINE trial	No difference in PFS	AZD4547 *vs.* paclitaxel	Significant intratumor heterogeneity for FGFR2 biomarker

OS, overall survival; PFS, progression-free survival; pCR, pathologic complete response; FGFR, fibroblast growth factor receptor; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

the adjuvant setting.

The phase III TyTAN trial evaluated the combination of paclitaxel with or without lapatinib, a dual HER2 and epidermal growth factor receptor (EGFR) inhibitor, the second line setting (13). There was no statistically significant benefit in OS or progression-free survival (PFS) overall, though a subgroup analysis did demonstrate increased PFS in IHC3+ patients (HR 5.6 *vs.* 4.2 months, P=0.01). This did not translate to an increase in OS however and is of doubtful clinical benefit.

The phase III LoGIC trial was a first-line evaluation of lapatinib combined with capecitabine and oxaliplatin in advanced GC. Despite an improvement in OS by 1.7 months, statistical significance was not reached, and the improvement in response rate (53% *vs.* 39% in the placebo arm, P=0.0031) came at a cost of increased toxicity, with diarrhea a prominent side effect (14). Even more disappointing for any justifiable off-label usage of lapatinib was the lack of a relationship between HER2 status by IHC and OS. EGFR expression status was not evaluated.

Encouragingly, there are several ongoing and/or recently completed clinical trials that seek to answer this question. These include the HER-FLOT trial, RTOG 1010, as well as NCTO01130337 (15). The latter in particular will look at trastuzumab maintenance for 1 year (28). This is likewise a phase II design but will address disease-free survival (DFS) as a primary outcome and may prove to be practice changing. RTOG 1010 compared RT, paclitaxel and carboplatin with or without trastuzumab in patients with GEJ or esophageal adenocarcinoma, stages T1N1–2 or T2–3N0–2. Unfortunately, this trial failed to demonstrate improved DFS when trastuzumab was added to trimodality therapy (29).

One exciting development presented at the American Society of Clinical Oncology (ASCO) 2020 was the presentation of the DESTINY-GASTRIC01 data. This was an open-label, randomized phase II trial of trastuzumab deruxtecan (DS-8201), a conjugate of anti-HER2 antibody and a topoisomerase inhibitor, in advanced GC patients who had received at least two prior therapies. An objective response was noted in 51% of the trastuzumab deruxtecan group compared to 14% of the physicians choice group. This translated to a significant OS benefit of 12.5 *vs.* 8.4 months. These results represent a meaningful advancement in the evolution of targeted therapy. Interestingly, the benefit was highest in patients with high HER2 expression, though the results of an exploratory analysis with lower HER2 expressors is as yet unpublished (30).

EGFR

Also part of the ErB family of tyrosine kinase inhibitors is the EGFR. Estimates of EGFR gene amplification and protein overexpression in GC are 5% and 27.4% respectively (16,31). Unfortunately, attempts at targeting EGFR in GC have failed to demonstrate meaningful clinical benefit. There have been two major negative trials including the REAL3 and EXPAND trials (17,18). The

former evaluated cetuximab with or without chemotherapy in the first-line advanced GC setting and demonstrate a statistically nonsignificant difference in OS of 10.7 *vs.* 9.4 months. The latter added panitumumab, a monoclonal antibody against EGFR, to a chemotherapy backbone and again found no difference in OS or PFS.

Importantly, these trials did not in any way select for EGFR overexpression. It is at least worth mentioning that subgroup analysis of EXPAND did show improvement in PFS and OS in patients with high EGFR overexpression. Given the relatively low expression seen in GC, it was felt with proper patient selection a benefit could exist. Unfortunately, the phase III ENRICH trial, itself based on a phase II trial that did find benefit in subgroup analysis of high EGFR expressors with EGFR inhibition, was terminated due to negative results in a mid-term follow-up (19). Off-label use of anti-EGFR therapies cannot be justified on the basis on available data.

Vascular endothelial growth factor (VEGF)

The vascular endothelial growth factor receptor family (VEGFR) and its ligands in the VEGF class are known stimulators of angiogenesis, a process crucial for tumor growth across a broad array of malignancies. There is a known association in GC with both tumor and peripheral VEGF expression and survival (20). Observation of this association has not translated in a meaningful way to clinical benefit.

Bevacizumab targets only VEGF-A and this may in part explain the failure of this agent to improve outcomes in multiple GC trials. The phase III AVAGAST trial added bevacizumab to capecitabine/cisplatin without OS benefit. This study did, in a prospective manner, assess for VEGF-A plasma levels at baseline. While the authors report a trend toward improved OS in patients with high baseline VEGF-A levels *vs.* low, this was not statistically significant (21). Three years later, the AVATAR study demonstrated similar findings, and there was no biomarker assessment made (22). These data taken together do not offer a clinical rationale for off-label bevacizumab in the first-line setting.

Ramucirumab is an IgG1 monoclonal antibody that functions as a receptor antagonist to VEGFR-2. This is in direct contrast to bevacizumab, which targets only the ligand of VEGFR-2. Ramucirumab is a highly specific and therefore potent inhibitor of VEGFR-2. This compelling mechanism of action has translated to significant clinical benefit in the advanced setting, leading to FDA approval for second line advanced GC. The REGARD trial showed

a statistically significant improved OS of 1.4 months when ramucirumab was added to best supportive care *vs.* placebo in patients with refractory advanced GC. The extrapolation of this data to off-label usage is limited by the relatively low number of patients selected for biomarker analysis: in this case, 43% of patients underwent biomarker testing including VEGFR-2 and HER2 tumor analysis and serum VEGF. Certainly, it is telling that there was no biomarker association with OS/PFS, but statistical power per the authors admission was quite limited (32). Further studies with ramucirumab are underway that may add to this dilemma.

Pazopanib is a tyrosine kinase inhibitor with a wide spectrum of activity that blocks VEGF1–3, fibroblast growth factor receptor (FGFR) 1 and 3, PDGFR and c-kit among others (23). It is commercially available for sarcoma and advanced renal cell carcinoma and has been evaluated for first-line and refractory treatment in combination with chemotherapy. Kim and colleagues performed a phase II trial of pazopanib plus CapeOX for first-line patients with metastatic or advanced GC. Clinical benefit was modest: OS was reported at 10.5 months while PFS was 6.5 months. The regimen was well tolerated (33). Intriguingly, a biomarker analysis was subsequently performed in 81% (n=54) of patients. FGFR2 expression predicted PFS: among expressors, PFS was 8.5 *vs.* 5.6 months among non-expressors (34). Given the limited statistical power, these data need to be validated with larger trials before they are put into clinical practice.

Regorafenib is another multi-kinase inhibitor with a broad spectrum of activity including VEGFR1–3, TIE-2, PDGFR-B, FGFR, as well as RAF, RET and KIT. The phase two INTEGRATE study of advanced esophagogastric cancer in the second- or third-line setting showed encouraging results in advanced GC patients (PFS *vs.* placebo 2.6 and 0.9 months) (24). The INTEGRATE II phase III study is ongoing. The latter will include prognostic and predictive biomarkers as part of secondary endpoint analysis but will not randomize patients according to biomarker status (35). While FDA approved for metastatic colorectal cancer in 2012 and gastrointestinal stromal tumor (GIST) in 2013, there is currently no rationale for off-label use of this in the metastatic or advanced GC setting.

Poly(ADP-ribose) polymerase (PARP) inhibition

PARP inhibitors prevent repair of single-strand DNA breaks leading to apoptosis (24). Olaparib is FDA approved in recurrent ovarian cancer, metastatic breast cancer, and *BRCA*-mutated metastatic pancreatic cancer. After multiple positive phase II trials, in 2017 the phase III GOLD trial evaluated olaparib plus paclitaxel *vs.* paclitaxel and placebo. OS did not significantly differ. Ataxia-telangiectasia mutated protein (ATM)-negative tumors were hypothesized to be more responsive however secondary analysis revealed no significant different when stratified based on ATM status (36).

Mammalian target of rapamycin (mTOR)

The mammalian target of rapamycin or mTOR is a PI3K related protein that is intimately involved in cellular proliferation, growth, and metabolism and is known to be deregulated in a wide array of human cancers (37). Everolimus is an mTOR inhibitor with approval across breast, neuroendocrine, and renal cell cancers. Multiple phase III studies have failed to demonstrate a benefit in advanced GC in the second or later line setting (38). Biomarkers have not been adequately assessed in these trials however.

c-MET

c-MET is a tyrosine kinase receptor that when activated by hepatocyte growth factor (HGF) leads to a variety of downstream effects including the promotion of metastasis, cell growth, and angiogenesis (39). Unfortunately, results of studies targeting this pathway in GC to date have returned negative (40). In the third-line setting, we are awaiting the results of a pilot study of crizotinib using c-MET as a biomarker in advanced GC (25).

FGFR

FGFR2 is another tyrosine kinase that is amplified in approximately 5–10% of GCs and is therefore an appealing target for molecular based therapy. The phase II SHINE trial evaluated the FGF2 inhibitor AZD4547 as monotherapy *vs.* paclitaxel in the advanced setting. Patients were randomized according to *FGFR* gene amplification or polysomy. PFS was not improved compared to paclitaxel. Interestingly, an exploratory biomarker analysis found a high degree of intratumor heterogeneity for expression of FGFR2 amplification/polysomy suggesting that this is a highly flawed biomarker (41). A recent phase I trial evaluated bemarituzumab, a humanized IGG1 monoclonal antibody against FGFR2B, for activity in advanced GC

and GEJ adenocarcinoma in the late-line setting. Seventy-nine patients were enrolled and were stratified according to FGFR2b expression level (high, medium, low, none). Seventeen point nine percent of patients with FGFR2B high level expression demonstrated a partial response (42). We eagerly await an upcoming phase III trial which will combine this agent with chemotherapy.

Conclusions

A wide array of anti-neoplastic agents targeting the various molecular pathways known to be at play in advanced GC have been assessed. Despite this enormous research effort, a minority have found efficacy. We are thus witnessing the sizable discordance between identified targets and meaningful efficacy. The use the HER2 targeted agent trastuzumab has demonstrated efficacy in the advanced setting, though it seems unlikely that this translates to benefit in the adjuvant or neoadjuvant setting. Whether this hold true for the antibody-drug conjugate trastuzumab deruxtecan is unknown. Targeting of the EGFR and VEGF pathways has resulted in generally disappointing outcomes, though there is hope that initial positive results with pazopanib will be borne out in larger trials. Trials targeting FGFR are ongoing after some encouraging early data, while the same cannot be said of c-MET, mTOR, or PARP directed therapies. While off-label use may appropriately evolve as the above data mature, at present there is little justification for such use.

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Footnote

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