Review Article

State of the art management of metastatic gastroesophageal cancer

Adrian G. Murphy[1], David Lynch[2], Ronan J. Kelly[1]

[1]Upper Aerodigestive Malignancies Division, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA; [2]Faculty of Education & Health Services, University of Limerick, Limerick, Ireland

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Correspondence to: Ronan J. Kelly, MD, MBA. Director of The Gastro-esophageal Cancer Therapeutics Program, The Bunting Blaustein Cancer Research Building, The Sidney Kimmel Comprehensive Cancer Center Johns Hopkins, 1650 Orleans Street, Room G93, Baltimore, MD 21231, USA. Email: rkelly25@jhmi.edu.

Abstract: The anatomical locations of upper gastrointestinal (GI) tumors have changed remarkably in the western world and reflect the increasing impact of obesity and gastroesophageal (GE) reflux rather than infectious etiologies. Incidence rates of GE tumors are rising rapidly and survival rates for patients with metastatic disease remain poor. Traditionally, cytotoxic chemotherapy has had some survival advantages but increasingly complex combination regimens are limited by toxicities. The advent of molecularly targeted therapy has provided additional options for patients with advanced disease including trastuzumab and ramucirumab. There has also been detailed molecular characterization of upper GI tumors which hopefully will result in improved tailoring of clinical trial design accounting for the heterogeneity inherent in GE tumors. While numerous targeted therapies are currently being studied in clinical trials, there is much excitement regarding the role of immunotherapy in GE cancers. Although further investigation is warranted, it represents a promising avenue for patients with advanced GE tumors.

Keywords: Gastric cancer; esophageal cancer; chemotherapy; immunotherapy; targeted therapy

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Introduction

In the United States it is anticipated that 24,590 and 16,980 patients will be newly diagnosed with gastric cancer and esophageal cancer respectively in 2015 while 26,310 men and women will die as a result of an upper gastrointestinal (GI) tumors (1). Gastroesophageal (GE) cancer has an estimated new cancer incidence of 1,471,000 or 11.6% of the global cancer burden and a death rate annually of 1,144,000 people or 15.1% of cancer-related deaths worldwide. When combined, esophageal cancer and gastric cancer are second only to lung cancer in incidence and in mortality (2).

The anatomical location of GE tumors in western countries has changed dramatically in recent years. Gastric cancer was previously predominated by distally located tumors but the relative incidence of tumors of the gastric cardia and gastroesophageal junction has increased dramatically. Distal esophageal adenocarcinomas only represented 0.8-3.7% of esophageal cancers as recently as the 1970's yet are now the most common locations (3). Over the past three decades, there has been a sevenfold increase in the incidence of esophageal adenocarcinoma among US white males, now accounting for more than half of the cases of esophageal cancer. For the past three decades, the increases in the rates of these tumors have been on the order of 5-10% per year, a faster pace than for virtually any other cancer in the United States (3). This has been attributed to declining chronic infection rates by *Helicobacter pylori* and an increased incidence of gastroesophageal reflux disease and obesity (4-6).

There are considerable variations in the histology and

locations of upper GI tumors between developing and developed countries. Despite GE cancer being endemic in some parts of the world, there have been relatively few substantial breakthroughs in these tumor types which have resulted in significant survival benefits. Over 50% of patients present with metastatic disease and systemic chemotherapy is the principal modality used in this setting with radiation therapy or surgery reserved for purely palliative purposes. The advent of targeted therapies has provided incremental improvements in survival in this patient group. However, most of these have been studied in a non-specific manner. More detailed information is now available regarding the molecular characterization of GE cancers and it is hoped that this will lead to improved clinical trial design of personalized therapies which may positively impact the current poor survival rates in patients with these tumors. Immunotherapeutics, most notably utilizing checkpoint inhibitors, are now being evaluated in upper GI tumors and preliminary results have demonstrated that there is a sub-population of patients that may derive significant benefits.

Advances in the molecular classification of gastric cancer

Molecular profiling studies have been performed in gastric cancer using gene expression/ DNA sequencing and have helped to identify distinctive molecular signatures which may predict responsiveness to systemic therapies. Microarray-based gene expression profiling has identified characteristic expression patterns to distinguish premalignant from malignant tissues (7) and subsequent studies have explored their potential to predict sensitivity to chemotherapy (8). Genomic subtypes (intestinal and diffuse) identified from *in vitro* studies in gastric cancer and subsequently validated in primary tumors were found to be prognostic of survival and had the ability to predict sensitivity to 5-FU and/or platinum agents (using immunohistochemical analysis of *LGALS4* and *CDH17* expression). These studies may ultimately identify predictive biomarkers allowing physicians to personalize chemotherapy selection in gastric cancer.

Gene expression patterns were analyzed with advanced bioinformatics tools to identify molecular signature subtypes which predicted response to inhibitors of the PI3K/Akt/mTOR pathway (9).

The Cancer Genome Atlas Research Network (TCGA) performed a comprehensive molecular characterization of gastric tumors from 295 previously untreated patients (10). Detailed genetic analysis resulted in four distinct subtypes—(I) tumors positive for Epstein-Barr virus (EBV); (II) microsatellite unstable tumors; (III) genomically stable tumors and (IV) tumors with chromosomal instability.

This study has added to our knowledge of the underlying biology of gastric cancer and it is hoped molecular classification systems that have moved beyond the somewhat outdated Lauren histological system will allow improved patient selection for future clinical trials.

Molecular classification of esophageal cancer

Esophageal cancer contains characteristic molecular features although these have not been characterized as thoroughly as gastric cancer to date. Chromosomal aberrations leading to gene dysregulation have been reported including amplifications on 8q and 17q mapped to the *C-MYC* and *ERBB2* oncogenes (11,12).

Goh *et al.* performed an integrative analysis of array-comparative genomic hybridization and matched gene expression profiling to reveal novel genes with prognostic significance in esophageal adenocarcinomas (13). Seventeen common regions (>5%) of gain and 11 common regions of losses were identified in 56 resected specimens along with long-term clinical follow-up data. Genes with high copy number and expression correlations included two deletions (*p16/CDKN2*, *MBNL1)* and four gains (*EGFR*, *WT1*, *NEIL2*, *MTMR9*). These genes individually (P<0.06) and collectively had prognostic significance (P=0.008).

High-density genomic profiling arrays in 296 esophageal and gastric cancers noted amplified genes in 37% of gastric/ esophageal tumors, including *ERBB2*, *FGFR1*, *FGFR2*, *EGFR* and *MET*, suggesting some of these may be viable targets in esophageal cancer (14).

Systemic chemotherapy

Chemotherapy, as monotherapy, was originally reported to have modest response rates (≈20%) in metastatic GE cancer and combination regimens were largely developed based on the histological subtypes that were common at the time. Platinum/fluoropyrimidine combinations were originally the subject of clinical trials in esophageal cancer based on their success in head and neck SCC cancers due to the predominance of the esophageal SCC histological subtype in the 1970-1980's (15-18). These combinations in locally advanced/metastatic esophageal cancer are associated with

response rates ranging from 35-40%.

Cisplatin with or without 5FU given by continuous infusion over 5 days was administered to 88 patients with locally advanced/metastatic esophageal SCC (19). Combination 5-FU/cisplatin resulted in improved overall survival (OS) compared to cisplatin alone (33 *vs.* 28 weeks) and improved survival at 1 year (34% *vs.* 27%). There was also a higher response rate in the combination arm (35% *vs.* 19%) although this arm was more toxic than monotherapy with higher rates of grade 3/4 neutropenia and thrombocytopenia (14% *vs.* 0%).

The combination of fluoropyrimidine and anthracycline drugs held promise in early clinical studies but did not demonstrate improved outcomes in randomized trials. Efforts to improve combination therapy in advanced GE cancer lead to the combination of platinum, fluoropyrimidine and anthracycline drugs. The ECF regimen (epirubicin, cisplatin, 5-FU) was reported to have response rates of 71% in patients with advanced GE cancers (20). ECF was originally compared to older methotrexate-containing regimens which are no longer commonly used. Compared to FAMTX (5-FU, doxorubicin, methotrexate), ECF improved the response rate (45% *vs.* 21%, P=0.0002) and median OS (8.9 *vs.* 5.7 months, P=0.0009) (21).

The REAL trial reported in 2008 was the first large randomized trial to compare multiple chemotherapy regimens in patients with advanced gastric cancer. It compared ECF, ECX (epirubicin, cisplatin, capecitabine), EOF (epirubicin, oxaliplatin, 5-FU) and EOX (epirubicin, oxaliplatin, capecitabine) in 1,002 patients and was designed to demonstrate non-inferiority in OS for the triplet therapies containing 5-FU *vs.* capecitabine and for oxaliplatin *vs.* cisplatin (22). This trial concluded that regimens containing 5-FU compared to capecitabine were non-inferior (95% CI, 0.8-0.99) and equally, that regimens containing oxaliplatin compared to cisplatin were non-inferior (95% CI, 0.92-1.10). Median survival groups in the ECF, ECX, EOF and EOX groups were 9.9, 9.9, 9.3 and 11.2 months, respectively. Despite being underpowered to accurately make this conclusion, these data lead to an increase in popularity for the use of EOX as a standard first-line therapy. In addition, capecitabine has the advantage of not requiring central venous access unlike infusional 5-FU.

Taxanes have been studied in advanced GE cancers although there have been concerns regarding its tolerability, in particular concerning neuropathy. Paclitaxel has been combined with 5-FU and cisplatin in a phase II trial in 102 patients with advanced esophageal cancer and reported a response rate of 15% (95% CI, 6-24%) in those who had previously been untreated and median survival of 9.1 months (range, 0.7-39.2 months) (23). However, the combination produced neurological toxicity in 44% of patients and neutropenia in 31% of patients.

Docetaxel has been combined with cisplatin and 5-FU (DCF regimen) and compared to 5-FU/cisplatin in a phase II/III study involving 457 patients with advanced gastric cancer in the first-line setting (24). The addition of docetaxel was associated with improved time-to-progression (5.6 *vs.* 3.7 months; HR =1.47; 95% CI, 1.19-1.82; P<0.001) and OS (9.2 *vs.* 8.6 months; HR =1.29; 95% CI, 1.0-1.6; P=0.02). Although neutropenia and diarrhea were more common in those treated with DCF, rates of grades 3/4 toxicity were equivalent in both groups. Due to concerns regarding tolerability, a modified DCF regimen (mDCF) has been devised incorporating a shortened 5-FU schedule and reduced cisplatin/docetaxel doses (25). This study of 44 patients treated with mDCF and bevacizumab had median progression-free survival (PFS) of 12 months (95% CI, 8.8-18.2 months) and OS of 16.8 months (95% CI, 12.1-26.1 months). This regimen had fewer rates of febrile neutropenia, nausea/vomiting, mucositis and diarrhea than the original DCF regimen although these regimens were not directly compared to each other.

DCF and ECF were directly compared to each other in a randomized phase II trial in 81 patients with unresectable and/or metastatic gastric cancer (26). This study was powered to assess whether DCF was non-inferior to ECF in terms of objective response rate (ORR) and DCF was shown to have higher ORR than ECF (36.6% *vs.* 25%).

Although oxaliplatin has more commonly been studied in combination with anthracycline (REAL trial), it has also been studied in combination with infusional 5-FU/leucovorin. The FOLFOX regimen (infusional and bolus 5-FU, leucovorin, oxaliplatin) is more commonly associated with colorectal cancer but a phase II study in advanced gastric cancer patients showed a response rate of 44.9% and median OS of 8.6 months (27).

Until recently, options for patients who progress after first-line therapy were limited however there is no consensus regarding the optimal regimen. Patients who are still eligible and willing for additional therapy should be considered for clinical trials where possible. For patients who have progressed on regimens containing a platinum and fluoropyrimidine agent, the anti-angiogenic agent ramucirumab should be considered (discussed below). In

terms of alternative cytotoxic agents, irinotecan has been studied in the 2nd line setting compared to best supportive care (BSC) in patients with gastric cancer (28). Although there were no objective responses, irinotecan therapy modestly prolonged median survival (4.0 *vs.* 2.4 months, P=0.012) and there was some improvement in tumor-related symptom control. Paclitaxel has also been studied in the 2nd line setting and has been found to be non-inferior to irinotecan (29).

Anti-angiogenic therapy

Angiogenesis is important in tumorigenesis and preliminary clinical studies suggested a clinical benefit when bevacizumab, a monoclonal antibody against VEGF-A, was combined with chemotherapy in gastric cancer (30,31). Bevacizumab failed to improve OS in the phase III AVAGAST trial although it did appear from a subset analysis that a Western population may derive some benefit (32,33). Subset analyses in the AVAGAST trial showed that those with type 3 (distal non-diffuse) gastric cancer and those from European/American populations, derived more benefit from bevacizumab than other gastric cancer subtypes or patients from Asian/Pacific populations. The VEGFR-2 (vascular endothelial growth factor receptor-2) antagonist ramucirumab, as reported in the REGARD trial, demonstrated modest activity in patients with advanced gastric or gastroesophageal junction adenocarcinoma who had disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy (34). Median OS was 5·2 months (IQR, 2.3-9.9) in patients in the ramucirumab group and 3.8 months (IQR 1.7-7.1) in those in the placebo group (HR =0.776; 95% CI, 0.603-0.998; P=0.047). The subsequently reported RAINBOW trial investigated paclitaxel ± ramucirumab in patients with metastatic GEJ or gastric adenocarcinoma who had disease progression on or within 4 months after first-line platinum- and fluoropyrimidine-based combination therapy (35). Median OS was 9.63 months for ramucirumab and paclitaxel compared to 7.36 months for paclitaxel alone (HR =0.807; 95% CI, 0.678-0.962; P=0.017). Based on these results the combination of ramucirumab+paclitaxel has now become a standard of care treatment regimen in the second- line setting for metastatic upper GI tumors. When ramucirumab was combined with FOLFOX in the first-line setting, it did not improve median PFS (6.4 *vs.* 6.7 months; HR =0.98; 95% CI, 0.69-1.37; P=0.89) or OS (11.7 *vs.* 11.5 months; HR =1.08; 95% CI, 0.73-1.58) in patients with advanced gastric/GE junction tumors (36). Clinical trials investigating alternative combinations of chemotherapy with ramucirumab in the first-line setting are ongoing.

HER-2 targeting therapies

HER2 is a proto-oncogene which belongs to the HER family of membrane-bound receptor tyrosine kinases and is responsible for the initiation of cell signaling pathways via phosphoinositide 3-kinase, phospholipase C and mitogen-activated protein kinase (37). Although originally known for its effects in breast cancer, HER2 overexpression has been shown to result in worse prognosis in gastric cancer (38,39) although there are conflicting studies which suggest that it has no effect or is even beneficial in terms of prognosis (40,41).

The TOGA trial was a phase III prospective trial which demonstrated the benefits of adding trastuzumab, a humanized monoclonal antibody targeting HER2, to a platinum-based doublet in the presence of HER2 IHC 2+ or FISH amplified metastatic gastroesophageal or gastric cancer (42). In this trial, 594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy *vs.* chemotherapy alone). Median OS was 13.8 months (95% CI, 12-16 months) in those assigned to trastuzumab/chemotherapy compared to 11.1 months in the chemotherapy alone arm (HR =0.74; 95% CI, 0.60-0.91; P=0.0046). Only 15-20% of GE tumors are HER2 positive (41) and is almost exclusively observed in intestinal-type disease and tumors at the GE junction and proximal stomach have higher expression (42). The benefit of trastuzumab was confined to those with IHC 2+/3+ and FISH positivity.

The practice of maintenance trastuzumab and continuing trastuzumab until evidence of disease progression are commonplace in the management of breast cancer (43,44) but there is a lack of data indicating that this is a successful strategy in GE cancer although a Japanese trial is investigating this approach (45). The development of resistance to trastuzumab has prompted investigating alternative drugs which target HER2 such as lapatinib, an oral dual tyrosine kinase inhibitor targeting EGFR and HER2 domains (46). The phase III TYTAN study compared paclitaxel with or without lapatinib in HER2 positive gastric cancer in the second-line setting in Asian patients (47). Median OS was 11 months with paclitaxel/lapatinib compared to 8.9 months

with paclitaxel alone (P=0.1044). There was also no significant difference in PFS or TTP. Pertuzumab, a monoclonal antibody which binds to HER2 preventing its dimerization with other HER receptors (48), is currently the subject of a phase III trial (JACOB) comparing pertuzumab/trastuzumab + chemotherapy to pertuzumab + chemotherapy (49). Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate combining trastuzumab and DM1 which is a cytotoxic/microtubule polymerization agent (50). The ongoing GATSBY trial is currently investigating T-DM1 versus a taxane in patients with previously treated HER2-positive metastatic or locally advanced gastric cancer (51).

Targeting EGFR

The epidermal growth factor receptor (EGFR) is known to play an important role in the initiation of signaling transduction cascades via phosphorylation of numerous cellular proteins (52). EGFR expression has been shown to correlate with decreased survival in gastric cancer in a meta-analysis of 7 studies (53). Cetuximab is a monoclonal antibody directed against the EGFR receptor and was shown to improve outcomes in *kras* wild-type metastatic colorectal cancer (54). The EXPAND study was a phase III trial which compared capecitabine and cisplatin with or without cetuximab in previously untreated advanced gastric cancer (55). Median PFS for chemotherapy/cetuximab was 4.4 *vs.* 5.6 months for those who received capecitabine and cisplatin alone (HR =1.09; 95% CI, 0.92-1.29; P=0.32). Adding cetuximab to this chemotherapy combination also did not improve OS (9.4 months in both arms, HR =1.0; 95% CI, 0.87-1.17; P=0.95). The phase III REAL-3 trial compared EOX with or without panitumumab, a fully human antibody targeting the EGFR receptor (56). There was a reduction in median OS in the chemotherapy group and panitumumab group compared to patients who received chemotherapy alone (11.3 *vs.* 8.8 months, HR =1.37; 95% CI, 1.07-1.76; P=0.013). An additional EGFR-targeting drug matuzumab also gave disappointing results in advanced esophagogastric cancer (57). A combination of ECX chemotherapy/matuzumab failed to improve OS (9.4 months for matuzumab group compared with 12.2 months, HR =1.02; 95% CI, 0.61-1.70; P=0.945).

While these results may highlight the lack of importance of the EGFR pathway in esophagogastric cancer and anti-EGFR therapies cannot be recommended for use in patients with these tumors, it is important to note that many negative studies were conducted in unselected populations which may explain their negative results.

C-Met targeted therapy

C-Met has been proposed as a promising new target in advanced disease and a number of phase III trials are now in progress combining MET inhibitors with chemotherapy in the first-line setting for metastatic GE cancer. C-Met is a receptor tyrosine kinase which interacts with its ligand HGF (hepatocyte growth factor) (58). Its function is dysregulated in gastric cancers and is involved with tumor proliferation, invasion and angiogeniesis and has anti-apoptotic functions in cancer cells (59,60). High C-Met expression in tumors is correlated with poor survival rates (61). In a phase II study, the anti-HGF monoclonal antibody rilotumumab was combined with chemotherapy with PFS as the primary endpoint. PFS was 5.7 months in rilotumumab treatment arms *vs.* 4.2 months in the placebo group (HR =0.60; 80% CI, 0.45-0.79; P=0.016) (62). However there was no improvement in OS and due to safety concerns combination studies with rilotumumab have been discontinued (63). Although originally regarded as a c-MET inhibitor, tivantinib has been shown to function independently of the c-MET pathway. *In vitro* studies in lung cancer cell lines have shown that tivantinib does not inhibit cellular MET activity or downstream phosphorylation of Akt or ERK 1/2 in MET-dependent cell lines (64). Another pre-clinical study has shown that tivantinib inhibits microtubule polymerization independent of c-MET (65). However, tivantinib has shown promising efficacy as a single agent in a phase II study meriting further study in combination with chemotherapy in a phase III design (66).

Future directions in targeted therapies in GE cancer

Several clinical trials are currently being conducted involving promising targets in GE cancer. PARP inhibitors (poly ADP-ribose polymerase) have been extensively studied in BRCA mutated breast cancer and function by preventing DNA repair and producing double-strand DNA breaks (67). In a phase II study, patients with advanced

gastric cancer which had progressed after first-line therapy, were randomized to receive paclitaxel 80 mg/m^2 days 1, 8 and 15 of a 28 day cycle, with or without olaparib, a PARP inhibitor, taken orally 100 mg twice daily or placebo (68). *In vitro* studies in gastric cancer cell lines have previously shown that the rate of BRCA mutations is low but that cells with low ataxia telangiectasia mutated levels (ATM_{low}) have increased responsiveness to olaparib. This study was enriched so that 50% of participants have ATM_{low} and the screening prevalence of ATM_{low} patients was 14%. There was no significant difference in PFS in patients with ATM_{low} or normal ATM levels. However, there was a significant difference in OS in the overall population in patients who received paclitaxel/olaparib *vs.* paclitaxel/placebo (13.1 *vs.* 8.3 months; HR =0.56; 80% CI, 0.41-0.85; P=0.005). Patients with ATM_{low} levels also had improved OS (not reached *vs.* 8.2 months, HR =0.35; 80% CI, 0.22-0.56; P=0.002). The combination of olaparib and paclitaxel was generally well tolerated and while this is potentially exciting, additional investigation is required.

Immune therapies

The role of inflammation in the pathogenesis of gastric (*Helicobacter pylori* infection) and esophageal (Barrett's esophagus) cancer is well known (69,70). Historically, immunotherapeutic strategies designed to target GE cancers have consisted of cancer vaccines and adoptive cell therapies. These clinical studies have involved relatively small numbers of patients and generally have had modest effects (71-73). The recognition of checkpoint pathways as potential targets in cancer have had unprecedented results in other tumor types, e.g., melanoma, lung cancer (74,75). Immune checkpoints are inhibitory pathways that are crucial for maintaining self-tolerance and help modulate the physiological immune response. Binding of PD-L1 to its receptor programmed death 1 (PD-1) suppresses T-cell mediated secretion of cytotoxic mediators resulting in decreased cell death. TCGA molecular profiling identified elevated PD-L1 expression in the EBV subtype of gastric cancer indicating the potential for PD-1 directed therapies in gastric cancer and studies have reported that 40-45% of gastric cancers express PD-L1 either as membranous or stromal staining (10,76,77). The KEYNOTE-012 trial (NCT01848834) involved the anti-PD-1 monoclonal antibody pembrolizumab in patients with previously treated GE cancers whose tumors were PD-L1 positive (78). Preliminary data show clinical activity with an ORR of 33% (95% CI, 19-50%), 6-month PFS rate of 24% and 6-month OS rate of 69%.

Given these preliminary data, current phase I/II clinical trials involving immunotherapy focus on administering PD-1 targeting agents alone or in combination with other checkpoint inhibitors, enrolling patients with previously treated advanced gastroesophageal cancer. A phase Ib/II study has recently opened comparing MEDI4736 (IgG antibody targeting PD-L1) *vs.* tremelimumab (IgG2 antibody targeting CTLA-4) *vs.* both drugs in combination in patients with previously treated metastatic/recurrent gastric or GE tumors (NCT02340975). It is expected that in time, checkpoint inhibitors will form part of a new treatment paradigm for advanced gastroesophageal cancer.

Conclusions

There have been considerable changes in the histologic profiling of GE cancers over the past 30 years and as a result, chemotherapy regimens have evolved to address this shift. Survival rates for metastatic GE tumors remain abysmally poor despite intensification of combination cytotoxic agent protocols. Further knowledge of the molecular biology of GE tumors from the TCGA has highlighted additional targets/pathways that may lead to improved outcomes for patients. Future clinical trials in GE tumors need to address the molecular heterogeneity that is inherent in these tumors and stratify patients based on individual molecular characteristics. While there is room for optimizing cytotoxic chemotherapy regimens, it is likely that the real progress in the future will come from immunotherapy. The prospect of durable remission, as seen in other tumor types, provides significant hope for patients with advanced GE cancer.

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Footnote

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