



Review Article

The advent of precision therapy in gastrointestinal malignancies: Targeting the human epidermal growth factor receptor family in colorectal and esophagogastric cancer

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Abstract

Until recently, systemic therapy for gastrointestinal malignancies was restricted to relatively noncancer-specific cytotoxic chemotherapy. Over the last 15 years targeted therapies have become available, most notably bevacizumab in the case of advanced colorectal cancer. Unfortunately, there are no predictive biomarkers to guide the use of this agent. In this review article, we describe the advent of “Precision Medicine” (in part, the use of patient-specific molecular markers to inform treatment) in gastrointestinal cancers: The use of monoclonal antibodies targeting epidermal growth factor receptor in advanced colorectal cancer, and human epidermal growth factor receptor 2-neu in advanced esophagogastric cancer. In both instances, biomarkers help in selecting appropriate patients for such treatment.

Keywords: Colorectal cancer, esophagogastric cancer, precision therapy, targeted therapy

INTRODUCTION

Systemic cancer therapy emerged in the 1940s with an initial focus on cytotoxic agents that took advantage of the fact that cancer cells proliferate more rapidly than normal cells, and are less able to recover from damage to the proliferative mechanisms. Such treatments were rarely specific to any one cancer and were associated with potentially profound toxicities due to “collateral damage” to normal tissues.

Advances in our understanding of the biology of cancer have led to the promise of more targeted therapies—treatments that exert their effect on identified deranged pathways or over-expressed molecules associated with a specific cancer. The promise of this approach is already being realized in a variety of cancers. Monoclonal antibody (mAb) therapy clearly extends survival in patients with specific subtypes of lymphoma^[1] and breast cancer.^[2] Multi-targeted small molecule tyrosine kinase inhibitors have become first-line therapy in a host of advanced malignancies including clear cell renal cell carcinoma, hepatocellular carcinoma, gastrointestinal stromal tumors and chronic myelogenous leukemia.

Many of these new therapies target molecular events commonly implicated in the development of a specific type of cancer, and yet yield no measurable benefit for many of the patients with that type of cancer. This suggests the need for

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validated biomarkers, predictive of a response to the therapy, to guide patient selection.

As defined by the European Society for Medical Oncology, personalized or precision medicine describes “the use of an individual patient’s molecular information (including genomics and proteomics) to inform diagnosis, prognosis, treatment and prevention of cancer for that patient.”^[3]

Targeted therapy has been in common clinical use in colorectal cancer for over 10 years, following the demonstration that adding bevacizumab (a mAb targeting vascular endothelial growth factor [VEGF]) to multi-agent chemotherapy (irinotecan, 5-fluorouracil and leucovorin) led to a 5 months improvement in median survival in patients with metastatic disease.^[4] Unfortunately, addition of bevacizumab to more modern chemotherapy, in the adjuvant,^[5] first line metastatic^[6] and second line metastatic^[7] settings has yielded far less impressive benefit, likely reflecting the fact that this agent is used in unselected patients, since there is no proven predictive biomarker.

More recently “personalized” precision therapy has become a reality in gastrointestinal cancers. In this review we summarize the use of precision therapies for advanced colorectal and esophagogastric cancers.

THE HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY: MOLECULAR TARGETS IN GASTROINTESTINAL CANCERS

The human epidermal growth factor receptor (HER) family consists of four members belonging to the ErbB lineage of proteins. These include epidermal growth factor receptor (EGFR)/HER1/ErbB1, HER2/ErbB2, HER3/Erb3 and HER4/ErbB4.^[8] These receptors are each composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity. They function in the activation of intracellular signal transduction cascades regulating epithelial cell growth, proliferation, and differentiation.^[9]

The EGFR is a 170,000 kDa transmembrane receptor tyrosine kinase^[10] that is expressed in cells throughout the body. There are multiple ligands for EGFR, including epidermal growth factor and transforming growth factor alpha.^[8] Upon ligand binding, the EGFR undergoes significant conformational changes that allow dimerization with a second ligand bound EGFR molecule^[11] resulting in phosphorylation of the intracellular tyrosine kinase domain and initiation of downstream signaling. The signaling pathways involved

with EGFR activation are complex and include the Ras/Raf/mitogen-activated protein kinases (MAPK) pathway, phosphatidylinositol 3-kinase (PI3K), and the signal transducers and activators of transcription (STAT) pathway among others.^[12] These pathways are primarily involved in cell growth, proliferation, migration, and apoptosis.

Dysregulation of EGFR signaling has been linked with malignant transformation in cell lines and animal models, and overexpression of EGFR has been demonstrated in many human malignancies including head and neck, esophageal, colon, pancreas, breast, kidney and gliomas.^[13] There is also evidence to suggest that autocrine stimulation of EGFR may be a driving force in tumor growth.^[14] EGFR is, therefore, a logical target for the development of novel anticancer therapies.

Human epidermal growth factor receptor 2 was first identified in the 1980s,^[15] and became clinically relevant when HER2-overexpressing breast cancers were associated with aggressive tumor biology and poor prognosis.^[16] Since this discovery, the development of rationally designed HER2-targeted therapies has dramatically improved outcomes among women with HER2-positive disease. While the extracellular domains of HER1/EGFR, HER3, and HER4 interact with a defined set of ligands, HER2 is considered an orphan receptor with no known natural ligand.^[17] Instead, HER2 serves as a dimer partner for ligand-bound HER1/EGFR, HER3, and HER4, and these HER2-containing heterodimers have particularly high signaling capacity.^[18]

While most widely studied in breast cancer, HER2 is overexpressed in various other tumor types including esophagogastric adenocarcinomas, where it has recently emerged as an important therapeutic target.^[9]

MONOCLONAL ANTIBODIES TARGETING EPIDERMAL GROWTH FACTOR RECEPTOR IN COLORECTAL CANCER

Early phase trials

Monoclonal antibodies directed at EGFR (e.g. C225, now known as cetuximab) were developed in the early 1980s.^[19] They were demonstrated to inhibit cell proliferation, promote apoptosis and potentiate the effects of chemotherapy and radiotherapy in a number of human tumor cell lines including colon cancer.^[20] Phase I trials performed in patients with a variety of tumor types to establish safety, dosage and scheduling in humans, identified disease stability in a number of patients with advanced colorectal cancer.^[21]

Based on the above findings, a Phase II study was performed using cetuximab in patients with proven metastatic colorectal

cancer who had failed previous chemotherapy with irinotecan as a single agent or in combination.^[22] Patients were required to have EGFR expression identified on pathological samples of their tumor tissue via immunohistochemistry (IHC). A partial response was seen in 9% patients, with another 37% demonstrating disease stability. Interestingly, and importantly as it turned out, the response did not correlate with the degree of EGFR expression.

Given the preclinical data indicating that the cetuximab may heighten the effect of chemotherapy, a randomized trial was performed using cetuximab alone versus the cetuximab with irinotecan in patients with metastatic colorectal cancer, which had progressed after irinotecan-based therapy.^[23] A greater response rate was seen with combination therapy (22.9% vs. 10.8% $P = 0.007$). However there was no difference in survival.

Antiepidermal growth factor receptor therapy after development of chemotherapy resistance

The first Phase III trials of mAbs against EGFR logically targeted patients with progressive metastatic disease despite treatment with all available chemotherapy (fluoropyrimidine, irinotecan, and oxaliplatin). Cetuximab and panitumumab were both compared with best supportive care (BSC) in patients with EGFR-expressing tumors.^[24,25] When compared with BSC, an improvement in progression-free survival (PFS) was seen with both cetuximab (hazard ratio [HR] = 0.68, $P < 0.001$) and panitumumab (HR = 0.54, $P < 0.0001$). In addition, the cetuximab arm demonstrated a significantly improved overall survival (OS) of 6.1 months versus 4.6 months with BSC. No significant improvement in survival was seen with panitumumab, although this may have been related to crossover from BSC to the study drug at progression.

As noted above, activation of EGFR leads to the initiation of intracellular signaling pathways including the Ras/Raf/MAPK pathway, the phosphoinositide 3-kinase/Akt pathway and the STAT pathway.^[12] There are three human Ras genes, including NRAS, HRAS and KRAS, which encode intracellular G proteins that function as binary molecular switches.^[26] The RAS proteins are turned on when bound to GTP, and turned off when bound to GDP. Missense mutations in the Ras genes, which are found in 30% of all human cancers, confer resistance to GTPase-activating proteins resulting in a constitutively active protein.^[27] These mutations are found in 40–50% of colorectal adenocarcinomas, with most of the mutations occurring on the KRAS, codons 12 and 13 of exon 2.^[28] These mutations have been associated with the promotion of cellular proliferation, transformation, invasion and metastasis.^[29]

Mounting evidence indicated that a lack of response to treatment with an anti-EGFR mAb was associated with KRAS mutations, leading to downstream activation of the intracellular signaling pathway.^[30] Based on this knowledge, a correlative analysis was performed using the Phase III data from the previously mentioned NCIC CTG CO.17 trial^[24] to determine if the presence of KRAS gene mutations modified the effect of cetuximab on OS and PFS.^[31] Among patients with mutated KRAS, there was no difference in OS or PFS in patients receiving cetuximab or BSC. In patients with wild-type KRAS, however, there was a clear improvement in OS in those receiving cetuximab (HR = 0.55, $P < 0.001$). A similar analysis was performed using the phase 3 data from the previously mentioned panitumumab trial.^[32] As with cetuximab, only patients with wild-type KRAS had improved outcomes compared with patients treated with BSC.

Whereas tumor expression of EGFR had proven to be of no clinical relevance in selecting patients for treatment with anti-EGFR mAb therapy, the mutational status of KRAS was pivotal in determining which patients had little to no likelihood of benefit from such treatment. Further studies have indicated that mutations in BRAF, NRAS and PI3K are also correlated with poor response to treatment, although these mutations occur less commonly.^[33,34]

Antiepidermal growth factor receptor therapy in conjunction with chemotherapy

The demonstrated survival benefit in chemotherapy-refractory patients and the ability to select for patients with a higher likelihood of response, led to considerable optimism that much greater benefit would be seen in patients at an earlier stage in the treatment of their colorectal cancer. Additional trials have evaluated the role of anti-EGFR mAb in combination with various regimens of chemotherapy and during different lines of treatment. Despite the early data, the findings from these trials have been less than game-changing. Many of these trials were conceived and initiated prior to the recognition of the pivotal role of KRAS mutations, and required protocol changes and *post-hoc* analysis of relevant subgroups, limiting the conclusions that could be reached.

Studies in the setting of first-line therapy for metastatic disease have yielded mixed results. The Crystal trial was a Phase III randomized trial that compared FOLFIRI with cetuximab versus FOLFIRI (fluorouracil, leucovorin and irinotecan) alone in patients with previously untreated EGFR positive metastatic colorectal cancer.^[35] A significant improvement in PFS was demonstrated (HR = 0.85, $P = 0.048$), but not in OS (HR = 0.93, $P = 0.31$). In patients with KRAS wild-type tumors, PFS remained significantly improved while there was again no difference in survival. A subsequent

analysis was performed after an increase in ascertainment of KRAS mutational status from 45% of patients to 89%.^[36] This analysis did demonstrate a significant improvement in OS with the addition of cetuximab in KRAS wild-type patients (23.5 vs. 20.0 months $P = 0.0093$), suggesting a role for combination therapy in the first-line setting.

Two Phase III trials have evaluated the addition of cetuximab to an oxaliplatin-based chemotherapy backbone. The MRC Coin trial demonstrated no difference in OS between KRAS wild-type patients treated with a fluoropyrimidine plus oxaliplatin compared with those treated with the same chemotherapy plus cetuximab (17.9 months vs. 17.0 months, $P = 0.67$).^[37] In the NORDIC VII trial, patients were randomized to FLOX (fluorouracil, leucovorin, and oxaliplatin) chemotherapy, FLOX plus cetuximab, or intermittent FLOX plus cetuximab.^[38] No significant difference in OS with the addition of cetuximab in patients with wild-type KRAS was found.

The addition of panitumumab to first-line chemotherapy has also been explored. The PRIME trial compared the use of FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) alone with FOLFOX4 plus panitumumab in patients with untreated metastatic colorectal cancer.^[39] While the initial analysis did not demonstrate a significant difference in OS between the treatment arms in patients with wild-type KRAS, an updated exploratory analysis for OS with more events did demonstrate a significant improvement with the addition of panitumumab (HR = 0.83, $P = 0.03$).^[40] Of note, PFS in those with a mutant KRAS was significantly reduced with the addition of panitumumab, indicating a potential harm in patients with the incorrect biomarker profile.

Overall, the addition of cetuximab to chemotherapy in the first-line setting for metastatic disease has yielded mixed and disappointing results. Despite the early evidence, anti-EGFR therapy does not conclusively prolong the lives of patients with metastatic colorectal cancer when used as initial therapy, even when KRAS mutational status is taken into account.

In the second line setting, there is a suggestion of benefit, particularly when an anti-EGFR mAb is added to an irinotecan backbone.^[23,41,42] While this approach has yielded improvements in PFS, no increase in OS has been demonstrated. As such, the optimal choice between combination and sequential use of anti-EGFR therapy after first progression remains unclear.

The evidence of potential treatment response in the metastatic setting has led to the study of anti-EGFR therapy in the adjuvant setting. Unfortunately, this approach has yielded no

evidence of benefit. In a large Phase III study, patients with resected Stage 3 KRAS wild-type colon cancer were treated with either 12 cycles of adjuvant mFOLFOX6 (a variant of FOLFOX4), or the same chemotherapy with the addition of cetuximab.^[43] There was no difference in PFS in those receiving cetuximab.

The addition of cetuximab to chemotherapy in the setting of potentially resectable liver metastasis has also been evaluated. In the New EPOC trial, patients with colorectal cancer with potentially resectable liver metastases and wild-type KRAS were randomized to either oxaliplatin with a fluoropyrimidine or the same chemotherapy backbone plus cetuximab.^[44] Treatment was given both before and after resection of the liver lesions. Unexpectedly, PFS was significantly shorter in patients receiving cetuximab and standard chemotherapy compared with chemotherapy alone (HR = 1.48, $P = 0.030$).

Thus, despite increasing knowledge about the EGFR pathway and the role of mutations, anti-EGFR therapy has yielded disappointed results. At present, the use of cetuximab and panitumumab is limited to patients with metastatic disease with wild-type KRAS status. This is in essence a negative selection: We are able to determine with some accuracy those patients who have little to no chance of benefit.

MONOCLONAL ANTIBODIES TARGETING HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 IN ESOPHAGOGASTRIC CANCER

Approximately, 15–25% of esophagogastric adenocarcinomas overexpress HER2, though this number varies substantially across series.^[45,46] HER2 positivity is most frequently seen in intestinal-type gastric cancers and is less common in diffuse-type cancers, with a high rate of concordance demonstrated between primary tumors and metastatic sites.^[47-49] In contrast to HER2-positive breast cancer, the prognostic value of HER2 overexpression in gastric cancer remains unclear, with studies yielding conflicting results.^[50-55]

Standard methodologies used to establish HER2 status include IHC to detect overexpression of the HER2 protein, and fluorescence *in situ* hybridization (FISH) to detect gene amplification.^[56] Protein expression on IHC is categorized by the intensity of staining and the percentage of cancer cells stained, into one of four levels ranging from 0 to 3+. Gastric cancers differ from breast cancers in terms of increased frequency of tumor heterogeneity, as well as a basolateral rather than circumferential membrane staining pattern.^[57] As such, the American Society of Clinical Oncology/College of American Pathologists HER2 IHC scoring criteria have been

modified specifically for gastric and gastroesophageal (GE) junction tumors.^[56,58]

Trastuzumab is a humanized mAb against HER2, which inhibits tumor cell growth through a variety of incompletely understood mechanisms, including HER2 receptor down regulation, direct inhibition of downstream signaling, suppression of VEGF, antibody-dependent immune recognition, and induction of apoptosis.^[59,60] It was originally developed for the treatment of metastatic breast cancer, and firstly approved for this indication in 1998.^[61] It was subsequently proven to reduce recurrence rates and mortality in early HER2-positive breast cancer.^[62-64]

The trastuzumab for gastric cancer (ToGA) trial was an open-label, international, Phase III, randomized controlled trial in which patients with advanced HER2-positive gastric or GE junction cancers were randomly assigned to receive chemotherapy (cisplatin plus either infusion 5-FU or capecitabine) alone or in combination with trastuzumab.^[45] Prior to this, only case reports and three very preliminary phase II clinical studies had looked at the use of trastuzumab in gastric cancer, with only one clinical study being published in full.^[65-67] The results of the ToGA trial demonstrated significantly longer survival in the trastuzumab arm, with an increase of 2.7 months in median OS (13.8 vs. 11.1 months; HR = 0.74; 95% CI: 0.60–0.91; $P = 0.0046$). The addition of trastuzumab to chemotherapy was well tolerated, with only a small increased incidence of asymptomatic decreases in left ventricular ejection fraction (5% vs. 1%) and grade 3 or 4 diarrhea (9% vs. 4%). A substudy of the ToGA trial has since shown that extending survival through the addition of trastuzumab did not compromise quality of life.^[68]

In the ToGA trial, all tumors were screened for HER2 status by both IHC and FISH.^[45] Patients were eligible if their tumor samples were scored as 3+ on IHC or if they were FISH positive (HER2:CEP17 ratio of 2 or greater). Among enrolled patients, >90% of tumors were FISH positive, whereas protein expression by IHC varied with nearly one-quarter of tumors being negative (IHC 0 or 1+). A preplanned exploratory analysis according to HER2 protein expression suggested that trastuzumab was most effective in the subgroup of patients whose tumors had high HER2 expression (IHC 3+), and ineffective in those patients with HER2 gene-amplified but nonprotein-expressing (i.e. FISH positive and IHC 0 or 1+) tumors.

In October 2010, the Food and Drug Administration granted approval for the use of trastuzumab in patients with metastatic gastric or GE junction adenocarcinomas with a HER2 status meeting the eligibility criteria of the ToGA trial (i.e. FISH positive or IHC 3+), who have not received prior treatment

for metastatic disease.^[69] The European Medicines Agency approved trastuzumab with minor modifications of the ToGA trial criteria, notably including the recommendation that IHC be used as the first test, with eligible patients being those whose tumors are IHC 3+, or IHC 2+ with confirmatory FISH-positive results.^[70] As such, trastuzumab now represents an important treatment option in this molecularly-selected group of patients.

Going forward, there are multiple other HER2-targeted agents currently under investigation in the treatment of esophagogastric cancers.^[71,72] Many of these are already approved in the treatment of HER2-positive metastatic breast cancer, and include the oral tyrosine-kinase inhibitor lapatinib, the antibody-drug conjugate T-DM1, as well as the humanized mAb pertuzumab, which in combination with trastuzumab provides better HER2 signaling blockade than either agent alone.^[73] Whether these targeted therapies will improve outcomes in HER2-positive gastric cancer patients remains to be seen.

CONCLUSION

Although it can be fairly stated that personalized/precision medicine has reached the clinic in the management of colorectal and esophagogastric cancers, the full promise of this approach has yet to be realized.

Monoclonal antibody therapy against EGFR clearly extends survival in KRAS wild-type patients with metastatic colorectal cancer who have progressed on all available chemotherapy. If anti-EGFR mAb therapy provides a benefit in conjunction with chemotherapy, it is modest at best. Disappointingly, even with molecular knowledge guiding enrichment of patient cohorts for those who should benefit, the anti-EGFR mAbs have made no impact in the adjuvant therapy of resected Stage 3 colon cancers.

Monoclonal antibody therapy against HER2-overexpressing esophagogastric cancers similarly teases us with an incompletely realized potential. Unlike colorectal cancer where knowledge of KRAS status acts as a negative predictor, HER2 status of esophagogastric cancers positively predicts for treatment-related benefit, but the benefit is limited to a few short months, and to a minority of patients.

Clearly, we still have much to discover as we focus on molecularly-driven treatment of gastrointestinal cancers.

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