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Genomic Alterations and Targeted Therapy in Gastric and Esophageal Adenocarcinoma

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ABSTRACT

Purpose: Gastric and esophageal adenocarcinomas are common and aggressive malignancies. Systemic therapy for these tumors is based primarily on cytotoxic chemotherapy, but outcomes remain poor. Precision medicine, where treatments are tailored to specific molecular abnormalities of tumors, holds great promise for improving outcomes in this disease.

Methods: A search was performed in PubMed to identify studies that have characterized the molecular basis of gastric and esophageal adenocarcinoma, as well as clinical trials exploring targeted therapies in this disease.

Findings: Recent genomic studies have identified potentially targetable genomic alterations in gastroesophageal adenocarcinoma. Specifically, The Cancer Genome Atlas study defined 4 subgroups of gastric cancer, each harboring distinct genomic features. However, development of targeted therapies for gastroesophageal cancer has been challenging. The only biomarker-driven therapy in clinical practice, trastuzumab for the ~15% of patients with human epidermal growth factor receptor 2–positive disease, is modestly effective, extending median overall survival by 2.7 months. Clinical trials of other targeted therapies, including epidermal growth factor receptor, fibroblast growth factor receptor 2, and MET inhibitors, have had disappointing results so far.

Implications: The availability of genomic tools provides an unprecedented opportunity to develop new rational therapeutic strategies. New trial designs of targeted therapies in biomarker-selected patient populations have the potential to improve outcomes in this lethal disease. As these clinical trials are being developed, it is increasingly important to incorporate correlative studies that will allow us to identify biomarkers of response or resistance to targeted therapies. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: Gastric adenocarcinoma, esophageal adenocarcinoma, genomics, targeted therapy.

INTRODUCTION

Gastric and esophageal cancers are the fifth most commonly diagnosed cancers, and second leading cause of cancer mortality worldwide, with an estimated 1.4 million new cases and 1.1 million deaths annually.[1] While the overall incidence of gastric cancer is declining, it remains particularly prevalent in developing countries, mostly in Asia and South America. In the Western world, the incidence of esophageal adenocarcinoma and cancers of the gastroesophageal junction has increased 6-fold in recent decades.[2] Gastroesophageal cancers are typically diagnosed at an advanced stage and have a dismal 5-year overall survival of 20% to 25%.[3] Systemic therapy for these tumors relies largely on empiric chemotherapy. Several clinical trials testing combination chemotherapy regimens for metastatic gastroesophageal cancer have showed modest results. The most effective multi-agent chemotherapy regimen in a multicenter, randomized, Phase III clinical trial was shown to be EOX (epirubicin, oxaliplatin, and capecitabine), with a median overall survival of 11.2 months.[4] Additional first-line options include ECF (epirubicin, cisplatin and 5-fluorouracil), DCF (docetaxel, cisplatin, and 5-fluoroucil), and FOLFOX (5-fluoroucil and oxaliplatin).[4-6] However, overall survival with empiric chemotherapy remains <12 months and new, effective therapeutic strategies are urgently needed.

To develop new therapies, we need to advance our understanding of the biology of these tumors. During the past decade, several studies have shed light on the molecular basis of gastric and esophageal cancer. Most recently, The Cancer Genome Atlas (TCGA) project led to a comprehensive molecular classification

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of gastric cancer and the identification of genomic alterations that represent potential therapeutic targets.[7] Similar studies in esophageal cancer have described the genomic landscape of this disease and revealed candidate driver oncogenic events that can be targeted therapeutically.

METHODS

PubMed was searched using the terms *genomics* and *gastric cancer*, *genomics* and *esophageal adenocarcinoma*, *targeted therapy* and *gastric cancer*, *targeted therapy* and *esophageal adenocarcinoma* and *targeted therapy* and *gastroesophageal adenocarcinoma*. Only English-language clinical trials in humans published between 2005 and December 30, 2015 were included. ClinicalTrials.gov, the American Society of Clinical Oncology annual meeting, and American Society of Clinical Oncology Gastrointestinal Cancers Symposium abstracts from 2005 to 2015 were queried for trials.

RESULTS

Molecular Characteristics of Gastric and Esophageal Adenocarcinoma

Molecular Profiling of Gastric Cancer

The most comprehensive molecular characterization of gastric cancer was performed by the TCGA Research Network in 2014.[7] In this study, the TCGA investigators evaluated the mutations, copy-number alterations, gene expression, and DNA methylation of 295 primary gastric adenocarcinomas. This unsupervised analysis led to the identification of 4 subtypes of gastric cancer with distinct features.

Of these tumors, approximately 9% were Epstein-Barr virus–associated, 22% were hypermutated or microsatellite unstable, 20% were genomically stable, and 50% were tumors with chromosomal instability (CIN) (Figure 1). Epstein-Barr virus–associated tumors showed DNA hypermethylation and a strong predilection for *PIK3CA* mutations, with 80% of tumors harboring nonsilent *PIK3CA* mutations. Phosphoinositide 3 kinase inhibitors should therefore be

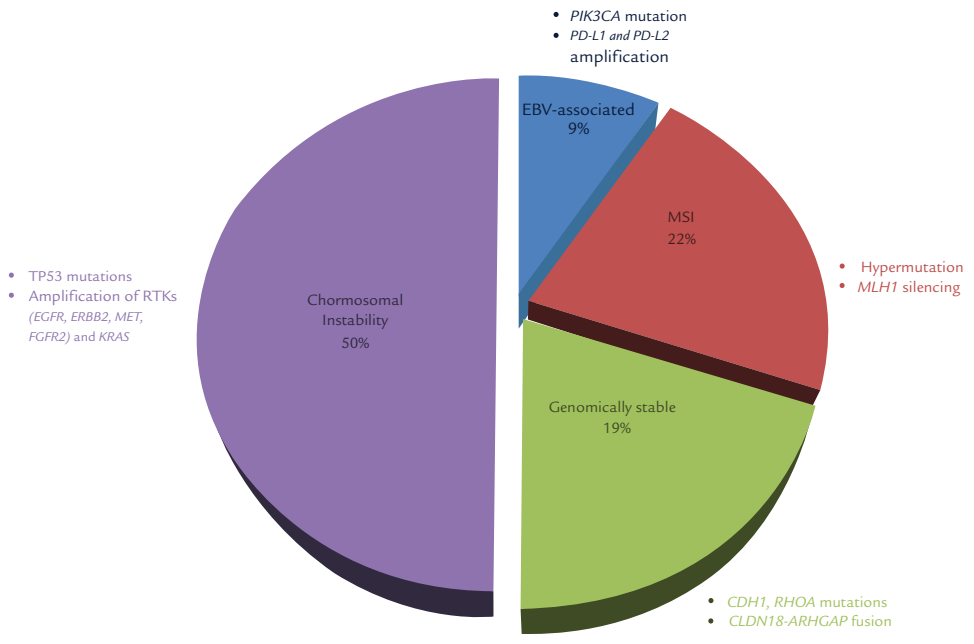

Figure 1. Comprehensive molecular characterization of gastric adenocarcinoma by The Cancer Genome Atlas Network identified 4 subgroups with distinct genomic features: tumors with chromosomal instability, 50%; tumors with microsatellite instability (MSI), 22%; genomically stable tumors, 19%; and Epstein-Barr virus (EBV)–associated tumors, 9%.