Clinical Oncology xxx (2016) 1–10

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Targeting the MET Pathway in Gastric and Oesophageal Cancers: Refining the Optimal Approach

J. Lee [*1], P. Tran [†1], S.J. Klempner [†]

[*] Department of Medicine, University of California Irvine, Orange, CA, USA
[†] Division of Hematology-Oncology, University of California Irvine, Orange, CA, USA

Received 30 July 2015; received in revised form 9 November 2015; accepted 10 December 2015

Abstract

Gastric and oesophageal cancers are a major cause of global cancer-related morbidity and mortality. Improvements in treatment for locoregional and metastatic gastric and oesophageal cancer have been incremental and the overall prognosis remains poor. Increasingly, molecular classification has identified recurrent, therapeutically relevant, somatic alterations in gastroesophageal malignancies. However, other than ERBB2 amplification, molecularly directed therapies have not translated to improved survival. Amplification of the receptor tyrosine kinase MET is found in about 5% of gastroesophageal cancers and represents an oncogenic driver and therapeutic target. Small series have shown activity of MET-directed tyrosine kinase inhibitors, but the clinical benefit of anti-MET antibodies has been disappointing. Here we discuss the MET pathway in gastroesophageal cancers, the clinical data for MET small molecule tyrosine kinase inhibitors, anti-MET antibodies and future clinical directions for targeting MET in gastric and oesophageal cancers. To our knowledge, this is the most comprehensive review of the clinical experience with MET-directed therapies in gastric and oesophageal cancers.

Key words: AMG 337; comprehensive genomic profiling; crizotinib; gastric cancer; MET; oesophageal cancer

Statement of Search Strategies Used and Sources of Information

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed) with key words 'Met', 'gastric' and 'esophageal' and prioritised information from core clinical journals. Subsequent searches using individual compound names were carried out to identify additional results. Clinical trial information was abstracted from ClinicalTrials.gov using the same search terms. Additional results were obtained from searching proceedings from the American Society of Clinical Oncology (ASCO) and American Association for Cancer Research (AACR). Genomic frequency data were obtained from The Cancer Genome Atlas using the MSKCC cbio portal (http://www.cbioportal.org/) and the Catalog of Somatic Mutations in Cancer (COSMIC) (http://cancer.sanger.ac.uk/cosmic) databases.

Introduction

Gastric cancer is the fourth most common cancer in men, the seventh in women and the third leading cause of global cancer-related death [1]. Within the USA, 24 590 new cases of gastric cancer and an estimated 10 720 deaths were projected in 2015. Oesophageal cancers represent a significant global cancer burden, accounting for 400 200 deaths in 2012. Although the US incidence of gastric and oesophageal cancer has fallen 1–1.5% per year over the last decade, death rates have not been affected [2]. Surgical resection, chemotherapy and chemoradiation are the mainstays of management for locoregional gastric and oesophageal cancer, whereas combination chemotherapy is the approach towards advanced disease. Improvements in standard of care therapies, including the incorporation of the anti-ErBB2 antibody, trastuzumab, led to marginal improvements, with a median overall survival of 10–12

Author for correspondence: S.J. Klempner, UC Irvine Health, Division of Hematology-Oncology, 101 The City Dr. Blvd, Orange, CA 92868, USA. Tel: +1-714-456-8161; Fax: +1-714-456-2242.
E-mail address: sklempne@uci.edu (S.J. Klempner).
[1] These authors contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.clon.2016.01.009
0936-6555/

months in advanced disease [3]. The improved overall survival in the phase III Trastuzumab for Gastric Cancer (ToGA) trial highlighted the potential of molecularly directed therapy [4]. Other actionable genomic alterations, such as ROS1 rearrangements, BRAF-fusions and ERBB2 mutations, have been identified, and The Cancer Genome Atlas recently confirmed a 6% frequency of alterations in the receptor tyrosine kinase c-MET [5]. Despite the recognition and pre-clinical validation of MET as an oncogenic driver and therapeutic target across multiple cancer types, translation to improved patient outcomes in gastric and oesophageal cancer has lagged (Figure 1). Here we discuss the role and therapeutic implications of MET-directed therapies in gastric and oesophageal cancer highlighting the clinical experience to date. To our knowledge, this is the most comprehensive review of the clinical experience of MET-directed therapies in gastric and oesophageal cancer to date.

Canonical MET Signalling

The receptor tyrosine kinase MET belongs to the receptor tyrosine kinase class VI known as hepatocyte growth factor (HGF) receptor family, structurally composed of an extracellular Sema, PSI and IPT domains, a transmembrane domain, the intracellular juxtamembrane and tyrosine kinase domains [6]. Extracellular binding of the ligand HGF results in receptor phosphorylation at tyrosine residues 1349 and 1356 within the C-terminal cytoplasmic region, activating downstream intracellular signalling pathways, such as PI3K-AKT, Src, Ras-MAPK, Cdc42/Rac, Grb2, STAT3, Gab1, PLC-ɣ and Shp2 (Figure 2) [6,7]. Recruitment of the adaptor protein Gab1 is most crucial for HGF/MET pathway activation [8,9]. The MET/HGF signalling pathway is negatively regulated via ubiquination of Met by Cbl, a ubiquitin that binds to the phosphorylated tyrosine Y1003 located within exon 14, resulting in degradation of MET [10,11].

In physiological conditions, the MET/HGF pathway plays a key role in hepatocyte and placental formation, limb muscle and nervous system formation, as well as tissue regeneration, protection and homeostasis in various tissues and cells, including hepatocytes, keratinocytes, podocytes, pancreatic β-cells and more [6,12–15]. Pathological MET activation promotes survival, invasion and metastasis [16]. Additionally, HGF is an important mediator in the tumour–stromal interaction and mediates innate resistance to RAF inhibitors [17,18]. Finally, the MET/HGF pathway plays a key role in cancer stem cells by regulation of self-renewal and epithelial–mesenchymal transition [19,20].

Overexpression of MET leads to constitutive downstream activation and increased sensitivity to sub-threshold levels of HGF across multiple tumour types [21]. Amplification of MET on chromosome 7q31 has been described in many cancer types, including gastroesophageal, colorectal carcinoma, endometrial carcinoma, medulloblastoma, non-small cell lung cancer (NSCLC) and glioma (Figure 1) [22–28]. MET interacts with other key oncogenic signalling pathways, including human epidermal growth factor receptor 2 (HER2) superfamily members, epidermal growth factor receptor (EGFR) and HER3. Transforming growth factor-α (TGFα), HER3-mediated activation of MET signalling and ligand-independent MET phosphorylation and activation via EGFR have been shown (Figure 2B) [29–31]. Somatic splice site alteration leading to exon 14 skipping results in MET protein stability through decreased ubiquination and degradation resulting in prolonged stimulation and has been shown in multiple tumour types [32]. MET mutation in the intracellular kinase domain has been identified in tumours, although the therapeutic relevance is not known [33]. Finally, missense mutations of MET have been found in germline of families with a history of hereditary papillary

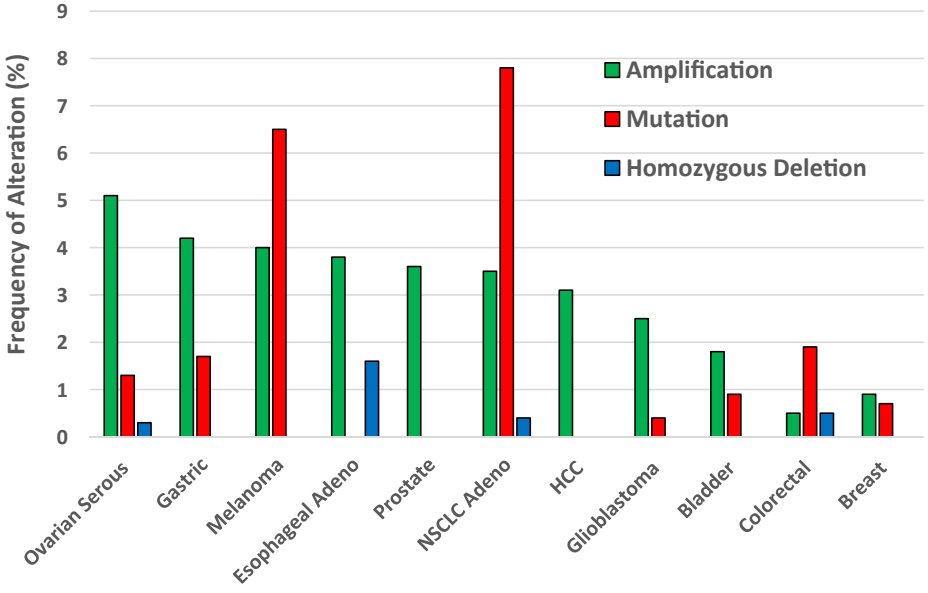

Fig 1. MET is altered across multiple tumour types with amplification being the most common genomic aberration. NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; adeno, adenocarcinoma. Data from The Cancer Genome Atlas, accessed June 2015.

Please cite this article in press as: Lee J, et al., Targeting the MET Pathway in Gastric and Oesophageal Cancers: Refining the Optimal Approach, Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.01.009