Antiangiogenic Therapy in Gastroesophageal Cancer

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KEYWORDS

• Angiogenesis • Gastric cancer • Esophageal cancer • Immunotherapy
• Checkpoint inhibitor

KEY POINTS

- Antiangiogenesis therapy is one of only 2 biologically targeted approaches (the other being anti–human epidermal growth factor receptor 2 [HER2] therapy) shown to improve overall survival over standard of care in advanced adenocarcinoma of the stomach or gastroesophageal junction (GEJ).
- Therapeutic targeting of vascular endothelial growth factor receptor 2, either its extracellular domain (ramucirumab) or tyrosine kinase domain (apatinib), has been demonstrated to improve overall survival in patients with previously treated advanced gastric/GEJ adenocarcinoma.
- To date, no antiangiogenesis therapy has demonstrated an overall survival benefit in patients with chemo-naïve or resectable esophagogastric cancer or in patients whose tumors arise from the esophagus.
- Promising clinical investigations include the combination of antiangiogenesis therapy with immune checkpoint inhibition and anti-HER2 therapy.

INTRODUCTION

Gastric and esophageal cancers are the fifth and eighth most common malignancies worldwide, respectively, with a combined global incidence of 1.4 million cases yearly.[1] In the United States, an estimated 43,280 new cases and 26,420 deaths from gastroesophageal cancer will occur in 2016.[2] Prognosis remains poor for this patient population with a 5-year-overall survival (OS) rate of 29% and 20% for gastric and esophageal cancer, respectively, underscoring the need for novel therapies.[3]

Angiogenesis is primarily mediated by the interaction between vascular endothelial growth factor (VEGF) and its receptors and is critical for tumor growth, progression,

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invasion, and metastasis.[4] Angiogenesis inhibitors have demonstrated generally modest clinical benefit over the standard of care across multiple tumor types (Fig. 1).

Antiangiogenesis therapy is one of only 2 biologically targeted approaches (the other being anti–human epidermal growth factor receptor 2 [HER2] therapy) shown to improve OS over the standard of care in patients with adenocarcinoma of the stomach or gastroesophageal junction (GEJ). In this review, the authors discuss the most current clinical data regarding the anticancer activity of antiangiogenesis monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) in gastroesophageal cancer. The authors briefly review areas of ongoing clinical/translational research and future directions.

ANGIOGENESIS PATHWAY

The VEGF family consists of 5 members: VEGF-A (thereafter called VEGF), VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) (Fig. 2). Members of the VEGF family show different affinities for one of the 3 VEGF tyrosine kinase receptors: VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3. Several coreceptors, such as heparan sulfate proteoglycans and neuropilins, have been implicated in promoting the activation of VEGFRs.[5] VEGFR-1 can bind VEGF, VEGF-B, and placental growth factor. VEGFR-2 is activated primarily by VEGF but also by proteolytically cleaved forms of VEGF-C and VEGF-D. VEGFR-3 is activated only by VEGF-C and VEGF-D. VEGFR-1 is expressed on endothelial cells, monocytes/macrophages, hematopoietic stem cells, and certain non-endothelial cell types.[6] VEGFR-2 is expressed exclusively on endothelial and hematopoietic cells[7]; a notable exception includes non–small cell lung cancer (NSCLC) whereby tumor cell expression of VEGFR-2 has been detected.[8] Ligand binding to the receptor leads to receptor homo-dimerization/hetero-dimerization and autophosphorylation, which triggers an intracellular signaling cascade.[9]

The progression from normal esophagus to Barrett esophagus, dysplasia, and adenocarcinoma is characterized by neovascularization, with microvessel density, vascular immaturity, and VEGF expression increasing along the cancer progression sequence.[10] VEGFR-2 is strongly expressed on new endothelial cells feeding the Barrett mucosa. VEGF-mediated angiogenesis is more robust in intestinal-type gastric tumors than diffuse-type, and tumors positive for *H pylori* infection show greater vascularity than those from patients who underwent *H pylori* eradication.[11] In gastric cancers, VEGF expression in tumors and/or sera/plasma concentrations have been correlated with stage,[12] vessel involvement,[13] metastasis,[12–14] and shorter survival.[14,15] Adverse associations have also been found in human esophageal cancer, suggesting the importance of the VEGF axis in the progression of this disease.[16]

INHIBITION OF THE VASCULAR ENDOTHELIAL GROWTH FACTOR AXIS VIA MONOCLONAL ANTIBODIES

Therapeutic inhibition of the VEGF/VEGFR-2 interaction has demonstrated benefit in patients with advanced gastroesophageal adenocarcinoma whose tumor has progressed on prior therapy (Fig. 3).

Anti–Vascular Endothelial Growth Factor Monoclonal Antibody

Single-arm clinical trials in gastric/GEJ adenocarcinoma combining bevacizumab (a recombinant humanized anti-VEGF mAb) with cisplatin/irinotecan,[17] modified docetaxel/cisplatin/fluorouracil,[18] and docetaxel/oxaliplatin[19] showed promising activity.

The first randomized examination of bevacizumab in gastroesophageal cancer avastin in gastric cancer study (AVAGAST) enrolled 774 treatment-naïve patients with inoperable, locally advanced, or metastatic gastric or GEJ cancer from Asia