Review Article
Progress of anti-angiogenic agencies in esophageal cancer

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Received August 24, 2015; Accepted December 3, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Esophageal cancer is the eighth most common malignancy worldwide with poor prognosis. The standard first-line chemoradiotherapy or surgical resection approaches are of limited efficacy in terms of treatment. To improve outcome, tumor angiogenesis and anti-angiogenic agents have recently become important. A considerable amount of data showed that angiogenesis plays an important role in tumor growth, progression, invasion, and metastasis. The vascular endothelial growth factor (VEGF) family and its receptors have been extensively studied. The prominent role of the VEGF signaling pathway in tumor angiogenesis led to the clinical development of angiogenesis inhibitors for the treatment of several cancers, including esophageal cancer. VEGF is frequently overexpressed in patients with esophageal cancer, and it has been suggested to promote tumor progression by stimulating angiogenesis. Moreover, it is linked to poor clinical outcomes in advanced esophageal squamous cell carcinoma patients. This review summarizes recent advances in the development of anti-angiogenic agents for the treatment of esophageal cancer and discusses the results of clinical studies that researched the safety and efficacy of esophageal cancer anti-angiogenic therapies.

Keywords: Esophageal cancer, angiogenesis, vascular endothelial growth factor, molecular targets

Introduction
Esophageal cancer is a highly fatal and aggressive disease with poor overall outcome. It is the eighth most common malignancy globally, affects over 450,000 people worldwide, and its prevalence is still increasing at a rapid speed [1]. In the United States in 2014, approximately 18,170 new cases were diagnosed, and 15,450 patients died of the disease [2]. In addition, the incidence of esophageal cancer in countries such as Iran, India, South Africa, and China is 10-100 times higher than that in the United States; esophageal cancer is approximately three times more prevalent in males than in females [3]. China is one of the countries with the highest occurrence of the disease [4]. Esophageal cancer comprises two distinct histopathological types, namely, squamous cell carcinoma (SCC) and adenocarcinoma. The two types account for more than 90% of all esophageal cancer cases. In the past five decades, the epidemiology of esophageal cancer has made a fundamental change in the world. Esophageal cancer has become a major public health problem because of increasing incidence rates and need urgent attention worldwide [1].

Esophageal cancer patients have poor prognosis, and over 50% patients with unresectable disease or distant metastasis at the time of diagnosis [5]. For many decades, surgical resection has been the major treatment for potentially curable patients. However, incomplete resections have increased to 25% [6], and local recurrence is between 30% and 40%; moreover, the five-year survival rate is rarely over 25% [7].

Numerous clinical trials have addressed the preferred treatment sequence in managing locally advanced esophageal cancer. However, no standard therapy has been established. Although esophagectomy remains the basis of...
Anti-angiogenic agencies in esophageal cancer

treatment of clinically localized esophageal cancer, the systemic nature of the disease attributes to the failure of surgery alone. Systemic chemotherapy, with or without radiotherapy, can lead to improved outcomes [8-10]. In different studies reported from trials involving surgery alone or combined with multimodal (adjuvant or neoadjuvant) treatments, the five-year overall survival (OS) rates ranged up to 39% for surgery alone arms, up to 36% for neoadjuvant chemotherapy, and up to 47% for neoadjuvant chemoradiation as summarized by some authors [11]. In the treatment of esophageal cancer, combined chemotherapy and modality treatment has reached a plateau. Targeted therapy has a different toxicity profile and can be combined with cytotoxins to improve the clinical benefit. Exploring targeted therapy can improve therapeutic benefits in patients with esophageal cancer.

Angiogenesis is the formation of new blood vessels, and it is a hallmark in the pathology of many diseases (e.g., ischemia, atherosclerosis, and inflammatory diseases), in wound healing, and in the formation of granulation tissue. However, it is also an important step for tumor growth, invasion, and metastasis. Given that diffusion of nutrients and oxygen supply promote tumor growth, establishing a sufficient blood supply is a critical and limiting step for continued tumor progression [12]. Angiogenesis is a complex process, tightly regulated at the molecular level by involving growth factors, receptor extracellular matrix (ECM) proteins, and humoral factors [13]. The cells in the center of the tumor become more hypoxic as cancer progresses, and the tumor activates the neo-angiogenesis process by shifting homeostasis between angiogenesis inhibitors and stimulators through a process known as “angiogenic switch” [14]. As result of metabolic stresses, such as acidosis, inflammation, or hypoxia, the switch can occur at different stages of tumor development. In addition, pro- and anti-angiogenic factors play a very important role in the occurrence and development of tumors by modulating the tumor’s progression and metastasis, which are not only produced by tumor cells, but also by stromal cells of the tumor microenvironment [15].

The hypothesis that angiogenesis promotes tumor growth was first proposed by Judah Folkman in 1971 [16]. In accordance with this hypothesis, endothelial cells may be converted from a resting state into a rapid growth stage by diffusing a chemical signal that emanates from the tumor cells. The increase in production of one or multiple regulators of angiogenesis promotes transformation, such as VEGF, placental growth factor (PIGF), platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2), transforming growth factor-β, angiopoietins, and other factors [17]. These factors are mobilized from the ECM, emanate from tumor cells, or released from host cells and lead to tumors. On the other hand, angiogenesis is inhibited by several angiogenic inhibitors, such as fumagillin, endostatin, angiostatin, and matrix metalloproteinase inhibitors. The balance between angiogenesis activators and inhibitors and the eventual changes in angiogenic equilibrium determine the state of the angiogenic switch.

Strong preclinical data suggested that angiogenesis is involved in growth, invasion, and metastasis of esophageal cancer [18-22]. Anti-angiogenesis may inhibit esophageal cancer in vitro and in vivo [23-27]. Clinical evidence to support this strategy is rapidly increasing [28-32]. In the present study, we reviewed the progress of the biology and treatment of anti-angiogenesis in esophageal cancer.

Anti-angiogenesis and esophageal cancer

In esophageal cancer, pro-angiogenic pathways have been established as important and effective therapeutic targets because they are of the essence for tumor growth, progression, and metastasis [33]. Tumor angiogenesis is a highly complicated process involving a network of autocrine and paracrine signaling pathways within the tumor and surrounding stromal cells. A key driver of tumor angiogenesis is hypoxia, which stimulates the overproduction of pro-angiogenic factors relative to anti-angiogenic factors [34, 35]. One of the best characterized pro-angiogenic pathways is the VEGF signaling pathway. The VEGF family is composed of six factors (VEGF-A to VEGF-E and PIGF) and three receptors of VEGF (VEGFR-1 to VEGFR-3). VEGFR-1 (binds VEGF-A, VEGF-B, and PIGF) and VEGFR-2 (binds mainly VEGF-A) are mainly expressed by vascular endothelial cells. Lymphangiogenesis is regulated by VEGFR-3, which is mainly expressed by lymphatic endothelial cells [36-38]. Interactions between VEGF
ligands and VEGFRs stimulate several downstream signaling cascades that coordinate endothelial cell proliferation, differentiation, permeability, and migration to stimulate the generation of new blood vessels [39]. VEGF-A is the most characteristic growth factor in the VEGF family. The major targets of recent anti-angiogenic agents are VEGF-A and its receptor VEGFR-2; the interaction between them is the main interaction in angiogenesis [40]. The anti-apoptotic effect in endothelial cells is provided by VEGF, which also stimulates the growth of new blood vessels and regulates vascular permeability [41]. The prominent role of the VEGF signaling pathway in tumor angiogenesis led to the clinical development of angiogenesis inhibitors for the treatment of various cancers, including esophageal cancer. This pathway has been suggested to promote tumor progression by stimulating angiogenesis because of the overexpression in esophageal cancer patients [42] and link to poor clinical outcomes in advanced esophageal cancer patients [43]. Although research on VEGF expression in patients of esophageal cancer is limited, some studies have revealed that VEGF promotes lymphangiogenesis by acting on its corresponding receptor VEGFR [44-47]. Some trials indicated that VEGF expression functions as a marker for predicting the aggressiveness and prognosis of esophageal cancer [48, 49].

The vast majority of anti-angiogenic agents that are clinically tested are based on the strategies that either interfere with pro-angiogenic ligands or block the signaling of pro-angiogenic receptor tyrosine kinases. The disruption of angiogenesis with novel molecules is an emerging and exciting area of clinical investigation in multiple cancer types, including esophageal cancer.

This review summarizes recent advances in anti-angiogenic agents for the management of esophageal cancer. The different agents will be grouped by the main molecular target and divided by the mechanism of action.

**VEGFR tyrosine kinase inhibitor (TKI)**

TKI are small molecules that diffuse through the cell membrane to inhibit the phosphorylation of the relevant kinase, thereby inhibiting intracellular signal transduction. The ability to suppress the activity of other kinases is the advantage of TKI over monoclonal antibodies. However, this effect will also result in increased toxicity. The increased toxicity is probably why combination of TKI with chemotherapy has not found its way to practice. The following section will discuss the TKIs tested in esophageal cancer.

**Sunitinib**

Sunitinib is a multitargeted TKI of VEGFR-2, PDGFRb, FLT-3, and KIT that plays a role in tumor angiogenesis and tumor cell proliferation. It is usually used in the management of gastrointestinal stromal and renal tumors. Sunitinib has insufficient clinical value in gastric or gastroesophageal junction (GEJ) cancer patients [50]. In addition, sunitinib combined with chemotherapy in the treatment of patients with gastric and esophageal cancers is currently under investigation [51, 52]. Schmitt et al. reported a phase II study of sunitinib plus paclitaxel in the treatment of esophageal cancer patients. A total of 28 patients with advanced esophageal or GEJ cancer from six centers received 37.5 mg of sunitinib everyday and 90 mg/m² paclitaxel on days 1, 8, and 15 every four weeks. In this study, the results showed that the 24-week progression-free survival (PFS) of the patients with advanced esophageal or GEJ cancer treated with sunitinib and paclitaxel was not better than that of the patients of historical controls. The combination of sunitinib plus paclitaxel failed to show an improvement in PFS in second-line therapy in patients with esophageal and GEJ cancers [51]. Wu et al. recently reported another phase II study that focused on the administration of sunitinib for treating patients with relapsed/refractory GEJ/esophageal cancer. In their study, 25 patients were treated with 37.5 mg of sunitinib daily. The authors concluded that sunitinib is well tolerated, but only partial patients benefit from it [52].

**Sorafenib**

Sorafenib is a new small-molecule multikinase inhibitor with activity against RAF kinase, VEGFR 1-3, and PDGFRb, leading to anti-angiogenic effects. Clinically, sorafenib has FDA approval for metastatic hepatocellular cancer and renal cell cancer.

In a phase II study, patients with GEJ and gastric cancer were treated with sorafenib in combination with docetaxel and cisplatin. The
results showed that response rate (RR) was 41% and OS was 13.6 months. Although the OS is promising, the PFS was not better than the observed PFS with combination chemotherapy, suggesting that the observed OS benefit was due to second-line therapy [53]. However, in another phase II study, sorafenib was investigated in patients with metastatic or relapsed esophageal cancer and GEJ adenocarcinoma (NCT00917462).

**Monoclonal antibody of anti-VEGF**

**Bevacizumab**

Bevacizumab is a recombinant, humanized monoclonal antibody that blocks angiogenesis by inhibiting VEGF-A. Bevacizumab has been approved for the treatment of several solid tumors by the US FDA, including non-small cell lung cancer, colorectal cancer, recurrent glioblastoma, and metastatic renal cell cancer [54-58]. Bevacizumab in combination with different chemotherapy regimens in esophageal cancer has been largely researched in several clinical trials [30, 59-62].

A phase II study reported on the application of bevacizumab in combination with oxaliplatin and capecitabine in the treatment of 38 patients with metastatic or unresectable GEJ cancers. All of the patients received 850 mg/m² capcitabine twice a day from day 1 to day 14 and 130 mg/m² oxaliplatin with 15 mg/kg bevacizumab on day 1 every three weeks. The RR was estimated at 51.4%. The median PFS and median OS were 7.2 and 10.8 months, respectively. The therapeutic regimen was well tolerated with expected drug toxicity and side effects. The results suggested that bevacizumab in combination with capcitabine and oxaliplatin can be safely administered to patients with metastatic GEJ cancer [30]. Okines et al. reported a multicenter, randomized, phase II/III study. A total of 200 perioperative patients with gastroesophageal adenocarcinoma received capcitabine with bevacizumab. Other patients received the same treatment but without bevacizumab. The results indicated that bevacizumab combined with perioperative capcitabine chemotherapy is well tolerated with acceptable toxicity and side effects. No negative effects were observed on the outcomes of surgery [30].

The Avastin for Advanced Gastric Cancer (AVAGAST) trial was a randomized, double-blind, phase III trial. In this study, patients with previously untreated unresectable locally advanced or metastatic GEJ cancers or gastric adenocarcinomas received a combination of cisplatin and fluoropyrimidine with or without bevacizumab. The combined chemotherapy regimen in patients with advanced gastric cancer did not significantly increase the OS. In AVAGAST, the outcomes of geographic differences were investigated, and only 12 Chinese patients were involved. AVATAR was designed for Chinese patients with advanced gastric cancer. It is a randomized, double-blind, phase III study similar to AVAGAST. Shen et al. recently discussed the AVATAR study of 202 Chinese patients with inoperable locally advanced or metastatic gastric or GEJ cancer, who were treated with cisplatin plus capecitabine in combination with or without bevacizumab. The results indicated that the combined chemotherapy regimen containing bevacizumab in Chinese patients with advanced gastric cancer did not improve the treatment outcomes. Both OS and PFS were similar between the two groups [60].

**Ramucirumab**

Ramucirumab is a monoclonal antibody with high binding affinity for the extracellular domain of VEGFR-2 [63]. As second-line therapy, ramucirumab has been recently approved for patients with advanced gastric cancer or GEJ adenocarcinoma by the US FDA [64]. Based on the published phase I trial, the safety profile of ramucirumab is similar to that of bevacizumab with activity against several solid tumor malignancies, including colorectal and gastric cancers [65]. In a phase III study, 355 patients with advanced gastric or GEJ adenocarcinoma were treated with ramucirumab or placebo. The results indicated that ramucirumab, as a single drug, could improve outcomes in the treatment of patients with GEJ adenocarcinoma or advanced gastric progression after first-line chemotherapy [31]. More recently, the benefit of ramucirumab in the refractory setting has been confirmed in the RAINBOW trial, an international, multicenter, randomized phase III trial. This trial involved 170 centers in 27 countries. A total of 665 patients with GEJ cancer and gastric adenocarcinoma were randomly
Anti-angiogenic agencies in esophageal cancer

divided into two groups, in which 330 patients received paclitaxel plus ramucirumab, whereas 335 patients received paclitaxel plus placebo. The addition of ramucirumab to standard chemotherapy was demonstrated to improve OS from 7.36 months to 9.63 months (HR = 0.807, P = 0.0169). The study also met its secondary endpoints of PFS (2.86 months vs. 4.40 months, HR = 0.635, P = 0.0001) and RR (16% vs. 28%, P = 0.0001). When the survival outcomes were analyzed by geographical region, ramucirumab exhibited similar activity in both Asian (33.5% of the study population) and Western patients (66.5% of the study population). The effect of ramucirumab on OS in the former group was markedly weakened by the more favorable tumor phenotype and the increased use of treatments after study cessation. The authors concluded that paclitaxel combined with ramucirumab significantly improves OS compared with paclitaxel plus placebo. For the treatment of patients with advanced gastric cancer, ramucirumab can be identified as a new standard second-line therapeutic regimen [32].

Other agents

FORETINIB (GSK1363089)

Foretinib (GSK1363089A) is a potentially useful small-molecule and oral multikinase TKI of mesenchymal-epithelial transition (MET) and VEGFR-2. MET and VEGFR kinases were inhibited by foretinib at 0.4 and 0.8 nmol/L, respectively. In human tumor xenografts, foretinib has shown antitumor activity, and a phase I study showed that three of 40 patients had a partial response [66, 67]. As a single agent, patients with metastatic gastric adenocarcinoma in a phase II study received two dosing regimens of foretinib to investigate its effect and safety. Foretinib was well tolerated and demonstrated potential in esophagogastric tumor treatment, but it has never been tested with radiotherapy in this setting [68].

Aflibercept

Aflibercept is a recombinant fusion protein composed of the extracellular domains from human VEGFR-1 and VEGFR-2 fused with the Fc region of IgG1. Aflibercept inactivates circulation and has binding affinity to VEGF and PIGF. It has a higher affinity binding for VEGF-A than bevacizumab and prevents the interaction with VEGFR-1 and VEGFR-2 [69]. In a phase II randomized clinical trial, aflibercept was investigated in patients with gastric cancer (NCT01747551). Recent data suggested that aflibercept is active in colorectal cancer patients even after failure of bevacizumab (VELOUR trial).

Nintedanib

Nintedanib is a triple angiokinase inhibitor that simultaneously inhibits signaling pathways activated by VEGF, PDGF, and FGF. In a prospective phase I study, nintedanib was administered to patients with advanced, refractory colorectal cancer. Moreover, its efficacy and safety were investigated. As an agent, nintedanib shows antitumor activity and maintains an acceptable safety profile [70]. In November 2014, nintedanib was approved in Europe for the treatment of patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma in combination with docetaxel after first-line chemotherapy.

Apatinib

Apatinib (YN968D1) is a small-molecule TKI that selectively inhibits VEGFR-2 with an intriguing biologic rationale [71] that is able to circumvent cancer cell resistance to other antitumor agents [72]. Preclinical experiments showed that apatinib has the potential to become a therapeutic drug for malignancies. Apatinib is a new treatment option providing hope for patients with gastric cancer who have previously failed second-line chemotherapy [71]. A phase I study in China showed that apatinib demonstrates antitumor activity in gastric cancer patients [73]. A phase II study involving 144 patients with metastatic gastric cancer who experienced treatment failure after at least two cycles of chemotherapy were randomly divided into three groups. The three groups were treated with 850 mg of apatinib once a day, 425 mg of apatinib twice a day, or placebo. The results showed that patients with metastatic gastric cancer who received apatinib had significantly longer PFS and OS than placebo. The author found that apatinib could increase PFS and OS in the patients with metastatic gastric cancer who had experienced treatment failure after at least two cycles of chemotherapy [74]. Liu et al. recently reported phase II/III studies involving
303 gastric cancer patients. The results showed that PFS is strongly correlated with OS; to the gastric cancer patients who have undergone third-line or later-line chemotherapy, PFS may be a useful early endpoint [75]. However, the aforementioned agents have not been evaluated in esophageal cancer.

Conclusion

Esophageal cancer is characterized by resistance to current first-line therapies and poor clinical outcome, highlighting the urgent need for more effective and innovative treatment strategies. Our understanding of cancer biology with the addition of the development of targeted drugs will positively influence the treatment of esophageal cancer. The current ongoing clinical trials of targeted drugs in esophageal cancer patients have been mostly based on molecular targets identified in other malignancies.

The most recent clinical studies support that specifically attacking VEGFR remains effective in esophageal cancer. These pivotal trials may prove to shift current therapy and will likely gain approval as a drug of interest. Simultaneously, the patients who will benefit the most from such therapy can be identified from the results of disease biology.

Given that the mechanism of angiogenesis in esophageal cancer has been elucidated, the use of anti-angiogenesis agents plays a crucial role in treatment. However, more multicenter, randomized studies and research on synergistic effects with surgery and radiotherapy are needed in the future.

Disclosure of conflict of interest

None.

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References


Anti-angiogenic agencies in esophageal cancer


Anti-angiogenic agencies in esophageal cancer


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