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Critical Reviews in Oncology/Hematology 95 (2015) 165–178

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Angiogenic inhibitors in gastric cancers and gastroesophageal junction carcinomas: A critical insight

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Accepted 24 February 2015

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Abstract

Advanced gastric cancer ranks second as the global leading cause of cancer-related death and improvements in systemic chemotherapy have reached a plateau. Advanced molecular sequencing techniques help identifying patients more likely to respond to targeted agents; nevertheless we are still far from major breakthroughs. Although antiangiogenic drugs have produced notable advances, redundant pathways or mechanisms of resistance may limit their efficacy. Novel compounds have been recently developed to specifically target VEGF receptors, PlGF, FGF, MET, and angiopoietin. Ramucirumab, a monoclonal antibody specifically directed against the VEGFR-2, has emerged as a novel therapeutic opportunity. REGARD and RAINBOW were the first phase III studies to report the value of this strategy in gastric cancer patients, and other ongoing trials are testing novel antiangiogenic compounds. The aim of our review is to present the state-of-the-art of novel antiangiogenic compounds in advanced gastric cancer, underlying the biology, their mechanism of action, and their clinical results.

Keywords: Angiogenesis; Advanced gastric cancer; Bevacizumab; Ramucirumab

1. Introduction

Gastric cancer (GC) is one of the most common cancers worldwide and represents a public health concern [1], with a rise in incidence and mortality for proximal

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http://dx.doi.org/10.1016/j.critrevonc.2015.02.009
1040-8428/

location close to the gastroesophageal junction (GEJ) [2]. Despite the improvements achieved for patients with early stage disease [3,4], the 5-year survival rate for those with metastatic disease remains vastly disappointing and median overall survival (OS) is limited to 12 months [5]. Standard first-line chemotherapy regimens for metastatic disease may vary across different countries. Nevertheless, numerous global trials confirmed that the use of a platinum- and fluoropyrimidine-based regimen may enhance patients' outcome along with quality of life [6–8]; similarly, three different randomized trials showed improved outcomes for patients receiving single-agent irinotecan or a taxane as second-line compared to best supportive care alone [9–11]. Recently, novel targeted therapies have emerged as a new hope for GC management. While EGFR-inhibitors [12,13] and mTOR-inhibitors [14] failed to provide any benefit, the addition of trastuzumab produced significant survival improvements in patients with HER-2 positive gastric or GEJ cancers (median survival increase of 3 months, hazard ratio (HR) 0.74, 95% CI 0.60–0.91, $p = 0.0046$) [15]. However, this therapeutic option is available for few potential candidates, as the HER2 overexpression (IHC) or amplification (FISH) is identified in less than 20% of patients. In gastrointestinal malignancies, angiogenesis is a well-known underlying promoter of tumor growth, invasion, and metastases. Based on a solid biologic background [16–18], the role of antiangiogenic drugs has been extensively investigated in gastric cancers [19]. Among many other molecules, bevacizumab, sorafenib, and sunitinib have been tested in clinical trials. Recently, ramucirumab has been reported as the first antiangiogenic drug to improve survival in pretreated patients with advanced GC. We reviewed published literature and ongoing trials through PubMed and Clinicaltrials.gov, respectively. The aims of this review are to define the biologic importance of angiogenesis in both gastric and gastroesophageal cancer, to critically recall the steps of the development of antiangiogenic therapy for patients with such diseases and to report the results of recent phase II and phase III randomized trials discussing the potential future role of these new agents in clinical practice.

2. The biology of angiogenesis in gastric and gastroesophageal carcinomas

Angiogenesisis a key process of the tumor growth as it ensures oxygen and nutrients supply to proliferating tumor cells. The increase of tumor size and the functional abnormalities of tumor vasculature, however, result in hypoxia and necrosis of tumor center [20–22]. Tissue hypoxia is a powerful inducer of VEGF expression [23] which, in turn, stimulates angiogenesis, invasive tumor growth and metastasis [24]. VEGF family comprises five distinct VEGF members including VEGF-A, placental growth factor (PlGF), VEGF-B, VEGF-C, and VEGF-D. Each of these ligands interacts with its specific receptor: VEGF-A binds VEGFR-1 and VEGFR-2 [25]; PlGF and VEGF-B bind VEGFR-1, although they seem to play a secondary role in the regulation of angiogenesis as compared to VEGF-A [26,27]. VEGF-C and VEGF-D bind to both VEGFR-2 and VEGFR-3, and are involved in the regulation of lymphangiogenesis [28]. The major signal transducer in angiogenesis is VEGFR-2 [29], which regulates endothelial cell proliferation through a number of different pathways (Fig. 1) [23,30]. The VEGFA-VEGFR2 binding triggers the receptor dimerization and the autophosphorylation of the VEGFR2 tyrosine-kinase site, which leads to the hydrolysis of phosphatidylinositol 4,5 bisphosphate. This cascade process generates inositol-3,4,5 trisphosphate and diacylglycerol, which eventually activate different downstream signaling cascades such as extracellular signal-regulated kinase 1 and 2 (ERK1/2), p38 kinase, and c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), all belonging to the mitogen-activated protein kinases (MAPKs) family [31]. VEGFA/VEGFR-2 interaction regulates proliferation, migration, permeability, invasion, and tube formation of endothelial cells. Disrupting this circle with the use of antiangiogenic drugs that block VEGFs and VEGFR-2 is therefore considered a key treatment modality in gastric cancer patients.

There are many mechanisms which guarantee an adequate blood supply to the tumor, including sprouting and intussusceptive angiogenesis, recruitment of endothelial progenitor cells, vessel co-option, vasculogenic mimicry and lymphangiogenesis [32]. A new form of neoangiogenesis in gastric cancer called the "cavity type" has been recently described, but its clinical relevance is unclear [33]. While the clinical efficacy of antiangiogenic therapy has been clearly shown in some type of solid tumors, it is still unknown whether this benefits maintained over the time. Resistance to antiangiogenic therapy is multifactorial and depends on several mechanisms including (1) switch to different angiogenic factors such as fibroblast growth factor (FGF) [34], (2) recruiting of tumor vessels via VEGF-independent mechanisms, (3) differentiation of cancer stem cells into endothelial cells, (4) development of cytogenetic abnormalities in tumor endothelial cells [35]. Differently from normal vessels, tumor capillaries are tortuous, blunt-end and chaotic in their organization causing a patchy and frequently reduced delivery of cytotoxic drugs to cancer cells [36]. As a result, blood flow does not reach each region of the tumor equally, starting from the center to the periphery [37] and the relative endothelial cell area is therefore high in the invasive tumor front, medium in tumor parenchyma and reduced in the inner portions [38]. Notably, the blood flow abnormalities also limit the access of immune effector cells in tumors [39,40]. Additionally, hypoxia induces the release of hypoxia inducible factor 1 alpha (HIF-1α), which is known to promote tumor progression and metastasis by inducing angiogenesis, immunosuppression, inflammation, resistance to cell death by apoptosis and autophagy, altered metabolism. Hypoxia ultimately causes drug resistance because various treatments, including radiation, chemotherapy, and even immunotherapies, require oxygen to be effective [41]. Many studies