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Antiangiogenic Therapy for Advanced Gastric Cancer - Update for Oncologists

Gastric cancer is a highly aggressive disease that continues to threaten public health throughout the world. Globally, more than 950,000 new cases were estimated in 2012, along with more than 720,000 deaths, making gastric cancer the fifth most common cancer worldwide and the third leading cause of cancer death.[1] The greatest burden of gastric cancer falls on Eastern Asia, where about half the world's cases occur. The American Cancer Society estimates that for the year 2015, about 24,590 cases of gastric cancer will be diagnosed in the United States and that gastric cancer will cause about 10,570 deaths.[2]

The prevalence of gastric cancer has declined in recent decades, possibly as a result of increased access to refrigeration.[3] Nevertheless, increases in obesity and gastroesophageal reflux disease, which are risk factors for cancer of the gastroesophageal junction, have added to the occurrence of gastric cancer in Western Europe and North America.[4] Recent years have shown a trend toward greater incidence of noncardia gastric cancer among American Caucasians between the ages of 25 and 39 years[5] and in the same age group in other Western countries.[6]

While affecting a single organ, gastric cancer is a heterogeneous disease. Epidemiological, pathological, and clinical data point to three main subtypes: proximal intestinal, distal intestinal, and diffuse.[7] These subtypes evolve by different genetic pathways and vary in regard to histopathology, epidemiology and outcome. Proximal intestinal gastric cancer is located in the gastric cardia, which can extend to the gastroesophageal junction. In these tumors, carcinogenic inflammation is often caused by gastric acid reflux.[8,9] Distal intestinal tumors occur between the body of the stomach and the pylorus. Chronic gastritis is often present, and this is typically a result of Helicobacter pylori infection. Diffuse gastric cancer may occur in any part of the stomach. Histopathology shows no gastritis and reveals a pattern of infiltration with the poorly differentiated signet ring cell type. Unlike intestinal gastric cancer, which emerges from a multistep carcinogenic process, diffuse gastric cancer is believed to arise de novo and is associated with downregulation of the CDH1 gene. The heterogeneity of gastric cancer is an important concern in the development of new treatments, because the three subtypes express different biomarkers and therefore have different potential therapeutic targets.

Environmental, nutritional, and genetic factors have been implicated as contributors to gastric cancer.[10] H. pylori, which infects roughly half the world's population, is classified as a type 1 carcinogen by the International Agency for Research in Cancer.[11] After infection, H. pylori enters the gastric mucosa and triggers a cascade of inflammatory steps that may lead to cancer. Persistent infection with H. pylori is associated with the development of both intestinal-type and diffuse-type gastric cancers.[12] Perhaps surprisingly, H. pylori might actually be protective for proximal stomach cancers, which exhibit a different epidemiology and a higher prevalence in Caucasian males.[13] Other risk factors for gastric cancer include smoking, obesity, and diets high in sodium and processed meats.[14] In contrast, fruits, vegetables, and micronutrients show a protective effect. A familial form of gastric cancer exists.[15]

Targeted Therapies

The standard of care for localized cancers of the upper gastrointestinal tract is surgical resection. However, most patients present with regional lymph node involvement or metastatic disease at the time of diagnosis. Gastric cancers are highly aggressive malignancies, and the prognosis for patients with metastatic or inoperable disease is poor. Median survival is less than one year for patients treated with standard cisplatin/fluorouracil-based chemotherapy.[16] In response to this bleak scenario, several novel therapy targets are being explored, some of which have already been shown to have therapeutic potential. These targets capitalize on advances in the understanding of the cellular and molecular mechanisms underlying the growth and development of gastric tumors.

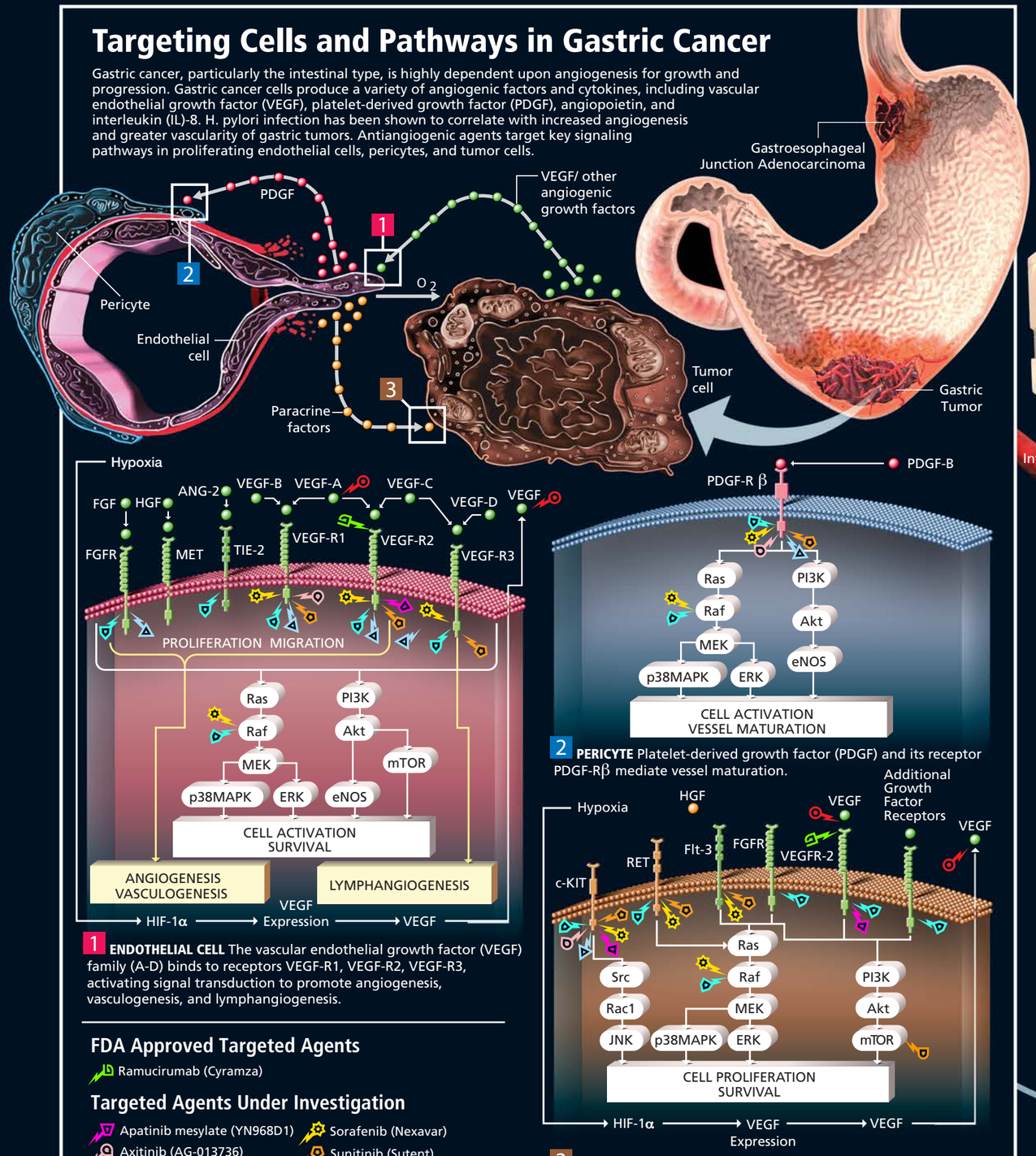
Human epidermal growth factor receptor 2 (HER2) was the first biomarker to emerge as a successful target in gastric cancer. HER2 mediates two major signaling pathways: the mitogen-activated protein kinase pathway and the phosphatidylinositol 3-kinase pathway, and thus has critical roles in cell growth, survival, and differentiation.[17] It correlates with poor clinical outcomes in breast, ovarian, prostate and other cancers, though data are inconsistent regarding its prognostic impact in gastric cancer. About 15% to 20% of patients with gastric cancer are positive for HER2 amplification or overexpression.[18] In gastric cancer, the extent of HER2 overexpression varies with the location of the carcinoma, with higher expression in the gastroesophageal and proximal areas compared to the distal parts of the stomach. Moreover, HER2 overexpression and amplification seem to be most pronounced in the intestinal form of gastric cancer.[18]

Trastuzumab

Trastuzumab, a humanized monoclonal antibody, targets the extracellular binding domain of the HER2 receptor. It has been approved by the US Food and Drug Administration (FDA) since 1998 for the treatment of breast cancer. The efficacy of trastuzumab in gastric cancer was demonstrated by the trastuzumab for gastric cancer (ToGA) investigation, an international, open-label phase III trial.[19] Participants in ToGA showed overexpression of HER2 in treatment-naïve metastatic or locally advanced unresectable gastric or gastroesophageal junction adenocarcinoma. The study's two cohorts received chemotherapy (cisplatin plus fluoropyrimidine), either alone (control) or with intravenous trastuzumab (6 mg/kg after a one-time loading dose of 8 mg/kg. The authors reported a 2.7-month improvement in median overall survival (OS) for patients who received trastuzumab (median OS 13.8 months compared with 11.1 months). Response rate, time to progression, and duration of response were significantly higher in the trastuzumab plus

Targeting Cells and Pathways in Gastric Cancer

Gastric cancer, particularly the intestinal type, is highly dependent upon angiogenesis for growth and progression. Gastric cancer cells produce a variety of angiogenic factors and cytokines, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), angiopoietin, and interleukin (IL)-8. H. pylori infection has been shown to correlate with increased angiogenesis and greater vascularity of gastric tumors. Antiangiogenic agents target key signaling pathways in proliferating endothelial cells, pericytes, and tumor cells.



1 ENDOTHELIAL CELL The vascular endothelial growth factor (VEGF) family (A-D) binds to receptors VEGF-R1, VEGF-R2, VEGF-R3, activating signal transduction to promote angiogenesis, vasculogenesis, and lymphangiogenesis.

2 PERICYTE Platelet-derived growth factor (PDGF) and its receptor PDGF-Rβ mediate vessel maturation.

3 TUMOR CELL Multiple growth factors and receptors activate signal transduction and cell cycle pathways to stimulate tumor cell growth.

FDA Approved Targeted Agents

- Ramucirumab (Cyramza)

Targeted Agents Under Investigation

- Apatinib mesylate (YN968D1)
- Axitinib (AG-013736)
- Bevacizumab (Avastin)
- Pazopanib (Votrient)
- Sorafenib (Nexavar)
- Sunitinib (Sutent)
- Regorafenib (Stivarga)

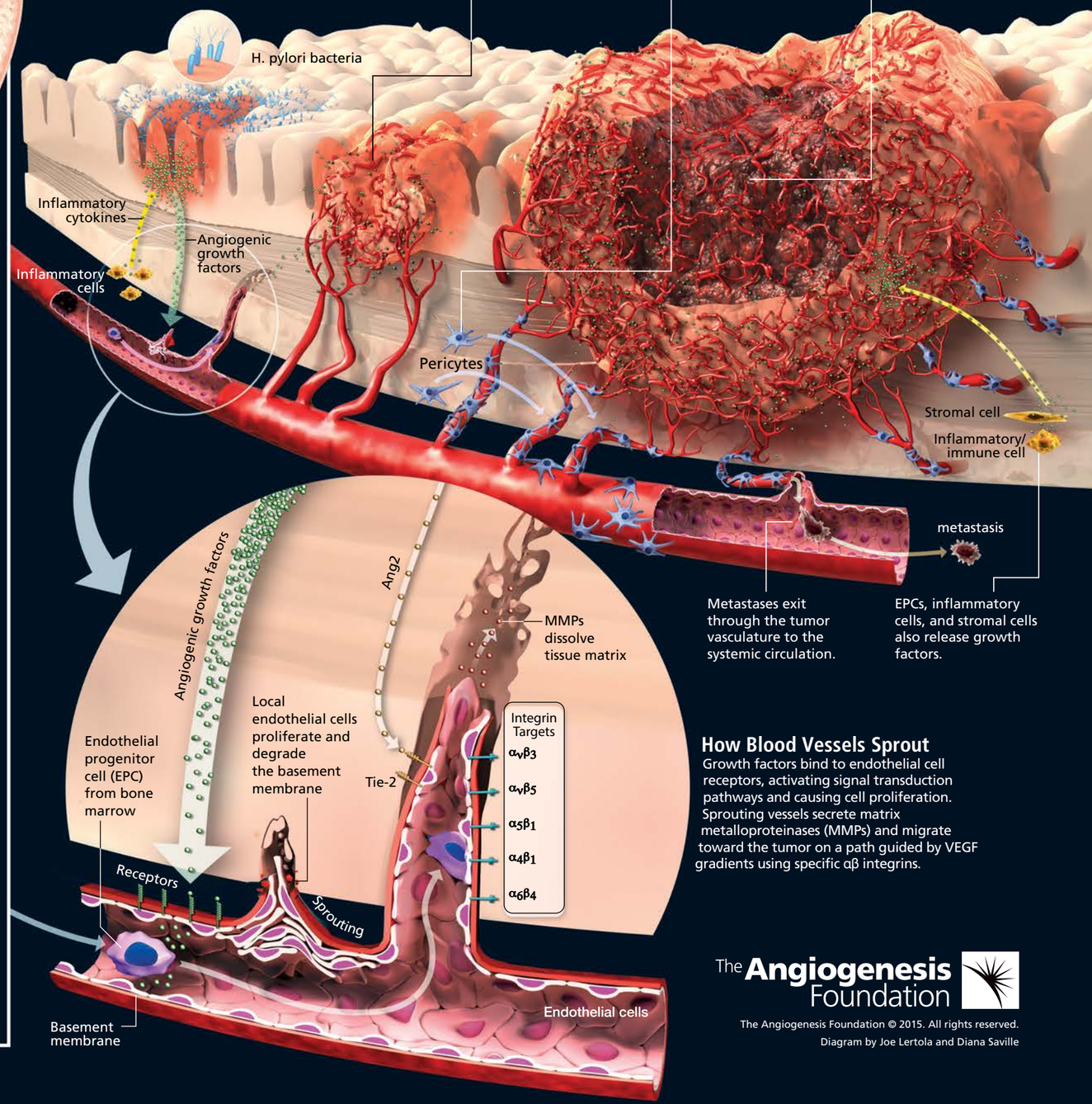
Targeting Tumor Angiogenesis

1 Cancer cells release growth factors that activate endothelial cells during the switch to the angiogenic phenotype. In gastric cancer, H. pylori infection induces an inflammatory cascade that upregulates a variety of angiogenic factors, cytokines, matrix metalloproteinases (MMPs), and adhesion molecules.

2 Angiogenic vessels form tubes and loops, thereby delivering oxygen, nutrients, and survival factors to cancer cells.

3 Vessels mature as pericytes are recruited by endothelial cells to stabilize new capillaries.

4 Unabated angiogenesis enables tumor expansion and local invasion. Abnormal blood flow leads to central hypoxia. Vessel hyperpermeability results in tumor edema.



How Blood Vessels Sprout

Growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation. Sprouting vessels secrete matrix metalloproteinases (MMPs) and migrate toward the tumor on a path guided by VEGF gradients using specific αβ integrins.

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Diagram by Joe Lertola and Diana Saville

chemotherapy group as well. In response to these findings, both the FDA and the European Medicines Agency approved trastuzumab in conjunction with chemotherapy as first-line therapy for gastric cancer involving HER2-positive disease.

The ToGA results validated the use of targeted therapies for gastric cancer, but continued research is still necessary, especially given that the survival benefits of trastuzumab shown in the ToGA trial were modest, most gastric cancers do not overexpress HER2, and resistance to trastuzumab is countering its benefits.[17] Numerous clinical trials are being planned or are under way to evaluate additional anti-HER2 agents in metastatic gastric cancer. These include pertuzumab, a HER2-targeted monoclonal antibody; lapatinib, a small tyrosine kinase inhibitor of EGFR and HER2; and the irreversible small molecule pan-HER TKIs dacomitinib and afatinib. Another promising approach is the coupling of trastuzumab with a potent microtubule inhibitor (DMI). This antibody-drug conjugate is being investigated in a multicenter adaptive phase II/III trial with HER2 positive advanced gastric cancer after progression following first line treatment (NIH study trial registration number NCT01641939; ClinicalTrials.gov).

Angiogenesis in Gastric Cancer

The pursuit of targeted therapies in gastric cancer has extended far beyond growth factor receptors. Targets under investigation include angiogenic pathways, adhesion molecules, and mediators of intracellular signal transduction. Tumor angiogenesis is a particularly important therapeutic target. Drugs that inhibit angiogenesis are now clinically validated for a number of tumor types, including colorectal, lung, liver, kidney, breast, and brain cancers.

Angiogenesis is critical for tumor growth, progression, invasion, and metastasis. Vascular endothelial growth factor (VEGF), the primary mediator of tumor angiogenesis, initiates the formation of new blood vessels and the sprouting of existing vessels.[20] High expression of VEGF in gastric tumors correlates with poor prognosis.[21]

VEGF-mediated angiogenesis varies among the different types of gastric cancer. It is more robust in intestinal-type tumors than diffuse gastric tumors. Moreover, the tumors of gastric cancer patients positive for H. pylori infection show greater vascularity than those of patients who have undergone eradication of H. pylori; thus, H. pylori influences angiogenic activity in gastric cancer.[22] Angiogenesis appears to be somewhat less robust in diffuse-type gastric tumors and more dependent upon expression of basic fibroblast growth factor (bFGF)-2, particularly in scirrhous-type tumors.[22] Other proangiogenic factors highly expressed in gastric cancer include interleukin (IL)-8, platelet-derived growth factor (PDGF), and angiopoietin-1 and -2.

Members of the VEGF family, as well as PDGF and bFGF, also stimulate the growth of lymphatic vessels (lymphangiogenesis) in gastric tumors, a process associated with lymphatic invasion by tumor cells, lymph node metastasis, and increased microvessel density.[22] Two approaches have been used to modulate angiogenic signaling in cancer therapy. One strategy uses monoclonal antibodies to deplete angiogenic factors, and the other method targets angiogenic receptors with small molecule inhibitors of receptor tyrosine kinases.

Bevacizumab

Bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody, is the first clinically validated antiangiogenic cancer drug. It has been evaluated for use in gastric cancer in combination with chemotherapy in both front-line and relapsed settings. Researchers at Memorial Sloan Kettering Cancer Center assessed bevacizumab in two phase II studies of gastric cancer. In one study involving 47 chemotherapy-naïve patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma, treatment with a combination of bevacizumab, cisplatin, and irinotecan yielded a response rate of 67% and a median time-to-progression (TTP) and median overall survival (OS) of 8.3 months and 12.3 months, respectively.[23] The TTP achieved in this study represents a 75% improvement over historical controls.

Subsequently, the same researchers performed a single-arm phase II study of bevacizumab in combination with a modified regimen of docetaxel, cisplatin, and fluorouracil (mDCF).[24] The mDCF regimen was developed to improved tolerability of the three-drug combination; it included a shortened de Gramont-like fluorouracil schedule to reduce mucositis and diarrhea, reduced bimonthly doses of cisplatin and docetaxel, and administration of cisplatin and docetaxel on separate days.[24] The study enrolled 44 patients with previously untreated metastatic gastroesophageal adenocarcinoma (22 gastric, 20 gastroesophageal junction, and 2 esophageal) to receive mDCF plus bevacizumab 10 mg/kg every two weeks. Thirty-two patients were alive and progression-free at 6 months, and median 6-month progression-free survival (PFS) was improved to 79% from a historical rate of 43% with non-modified DCF. The overall response rate was 67% and the median PFS and OS were 12 months and 16.8 months, respectively. Notably, 37% of patients in the study remained alive at 2 years. Another interesting finding was that both PFS and OS were significantly diminished for diffuse-type gastric cancer.

A third phase II study evaluated bevacizumab in combination with docetaxel and oxaliplatin.[25] This study enrolled 38 patients with previously untreated locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal to receive (7.5 mg/kg) in combination with docetaxel and oxaliplatin on day 1 of a 21-day treatment cycle. (The original planned bevacizumab dose of 15 mg/kg was reduced to 7.5 mg/kg after the occurrence of two gastrointestinal perforations in the first 5 patients.)[25] The median PFS for the 38 eligible patients 6.6 months, while median OS was 11.1 months. Objective tumor responses were seen in 16 patients (42%), including 2 CR (5%) and 14 PR (37%).

Together, these studies provided the phase II experience needed to support an examination of bevacizumab in a larger phase III study called AVAGAST (AVAstin in advanced GASTric cancer).[26] This international trial enrolled 774 treatment-naïve patients with inoperable, locally advanced, or metastatic gastric or gastroesophageal junction cancer from the Asia-Pacific region (49%), Europe (32%), and the Americas (19%).[17] Patients were randomly assigned to receive capecitabine and cisplatin plus either bevacizumab 7.5 mg/kg or placebo. The addition of bevacizumab to chemotherapy failed to produce an improvement in OS, the trial's primary endpoint. Median OS in the intent-to-treat population was 10.1 months for chemotherapy plus placebo and 12.1 months for chemotherapy plus bevacizumab (P=0.1002). Secondary endpoints, however, did show significant improvement in the bevacizumab arm compared with placebo, with a median PFS of 6.7 months versus 5.3 months (P=0.0037) and an overall response rate of 38%

versus 29.5% (*P*=0.0121) for the bevacizumab and placebo arms, respectively.

A striking and not definitively explained finding of AVAGAST is that different outcomes were seen in patient populations from different geographic regions. European and American patients had shorter PFS and OS than Asian patients but derived more benefit from the addition of bevacizumab to chemotherapy. In patients from the Asian subcontinent, bevacizumab did not generate improvements in either PFS or OS with bevacizumab. These discrepancies might reflect differences in clinical presentation, prior treatment, or differences in the cancer subtypes involved.

AVAGAST included an analysis of a prespecified panel of tumor angiogenic factors to shed light on their utility as predictive biomarkers for anti-VEGF therapy. Tumor samples were analyzed at baseline for the markers VEGF-A, VEGFR-1 and -2, EGFR, and neuropilin (NRP), a coreceptor for VEGF-A.[27] In addition, plasma samples were analyzed for levels of VEGF-A. One finding was that a low level of NRP expression in a tumor was associated with shorter OS in the placebo arm. Adding bevacizumab to chemotherapy seemed to mitigate this prognostic marker, as patients with low tumor NRP had a numerically improved OS treatment hazard ratio compared with those with high tumor NRP (HR 0.75 and 1.07 for low and high NRP, respectively). Patients with higher baseline levels of plasma VEGF-A appeared to benefit from the addition of bevacizumab to chemotherapy.[27] While this is an area of intensive research, there are presently no clinically validated biomarkers that can predict which patients will benefit from treatment with an antiangiogenesis agent.

Further information about bevacizumab in gastric cancer is emerging from a phase II/III trial now taking place in the UK (http://www.ctu.mrc.ac.uk/our_research/research_areas/cancer/studies/st03/). The phase II segment of the trial, which is already completed, confirmed the safety and feasibility of combining bevacizumab with chemotherapy in patients with operable esophagogastric adenocarcinoma. The phase III segment is now being conducted to evaluate the efficacy of this combination. Based on phase II data, patients with lower esophageal, Siewert Type I, II, or III OGJ adenocarcinomas will not receive bevacizumab. Patients in the control arm will receive standard ECX (sECX), consisting of three cycles of oral epirubicin 50 mg/m2 IV day 1, cisplatin 60 mg/m2 IV day 1, and capecitabine 1250 mg/m2 daily in two divided doses on days 1–21 preoperatively, followed by surgery, and then followed by three postsurgical cycles of sECX at the same doses. Patients in the investigational arm (sECX + bevacizumab) will receive the same treatment, except that on day 1 of each cycle of chemotherapy they will receive bevacizumab 7.5 mg/kg IV. In addition, after the three cycles of postsurgical chemotherapy are completed, they will receive 6 doses of maintenance bevacizumab 7.5mg/kg IV once every 21 days. The total duration of therapy in the investigational arm will be 52 weeks. This clinical trial began patient recruitment in 2007 and is expected to announce results in 2017.

Ramucirumab

Ramucirumab, a fully human immunoglobulin G1 monoclonal antibody, followed trastuzumab to become established as a biologic agent approved for the treatment of gastric cancer. Ramucirumab specifically and potently inhibits VEGF receptor-2 (VEGFR-2), which is considered the primary driver of angiogenesis within the VEGF family, by binding to its extracellular binding domain. It has demonstrated efficacy and tolerability in several studies.

The phase III Ramucirumab Monotherapy for Previously Treated Advanced Gastric or Gastro-Oesophageal Junction Adenocarcinoma (REGARD) study compared ramucirumab to best supportive care in randomized second-line gastric or gastro-esophageal junction adenocarcinoma patients.[28] The study included 355 patients from 30 countries at 120 centers. The primary end point was overall survival. Secondary end points were progression-free survival and quality of life. Participants were randomly assigned to receive a placebo or ramucirumab 8 mg/kg every two weeks in conjunction with best supportive care.

The study results showed significant benefits for patients receiving ramucirumab. The median overall survival time was 5.2 months in the study group compared to 3.8 months for the control group, (*P*=0.042). The ramucirumab group also showed an advantage in progression-free survival, with 12-week progression-free survival of 40%, versus 16% for the control group. Overall toxicity in the ramucirumab group was low.

In response to these results, the US Food and Drug Administration approved ramucirumab in 2014 for use as a single agent in gastric and GEJ cancer after progression on a platinum or fluropyrimidine-containing regimen.[29] This is the first approval of a biologic agent in an unselected gastroesophageal population.

The REGARD study was followed by RAINBOW, a phase III trial conducted at 170 centers in 27 countries in North and South America, Europe, Asia, and Australia. The study group consisted of patients with advanced gastric or gastroesophageal adenocarcinoma and disease progression on or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline).[30] Patients were randomly assigned to recieve ramucirumab plus paclitaxel or a placebo plus paclitaxel. Overall survival was significantly longer in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (median 9.6 months [95% CI 8.5-10 ·8] vs 7.4 months [95% CI 6.3-8.4], hazard ratio 0.807 [95% CI 0.678-0.962]; *P*=0.017). Based on these results ramucirumab has become the first targeted agent to be approved by the US FDA for advanced gastric cancer after prior chemotherapy.

Tyrosine Kinase Inhibitors

Another approach to targeting the VEGF pathway in addition to monoclonal antibodies is the use of tyrosine kinase inhibitors (TKIs) that inhibit the VEGF receptor. TKIs that are now being explored in gastric cancer include sunitinib, sorafenib, pazopanib, axitinib, apatinib mesylate, and regorafenib.

Sunitinib was evaluated as a single agent in a phase II trial involving 78 patients with advanced gastric and gastroesophageal junction cancer. In this trial, two patients had partial responses and 25 patients had stable disease for ≥6 weeks.[31] Sunitinib has also been evaluated in combination with chemotherapy in a phase II trial that randomized 107 patients to docetaxel with or without sunitinib.[32] The time to progression was not significantly different (3.9 months in the sunitinib arm versus 2.6 months for the comparison group), but there was an increased response rate of 41.4% compared to 14.3% with sunitinib.

Sorafenib showed positive results in a phase II study that evaluated it in combination with chemotherapy (median PSF of 5.8 months and median overall survival of 13.6 months).[33] However, other studies have not matched these response rates.[34, 35]

Two trials are now evaluating pazopanib. The phase II PaFLO trial (FLO ± pazopanib as first-line treatment in advanced gastric cancer) is recruiting first-line advanced gastric cancer patients to receive 5-fluorouracil, leucovorin, and oxaliplatin with or without pazopanib.[36] Another first-line phase II trial in the recruitment stage will add pazopanib to capecitabine and oxaliplatin in patients with advanced gastric cancer.[37]

Another agent under investigation is axitinib (AG-013736), a substituted indazole derivative. Axitinib potently inhibits all known VEGFRs at subnanomolar concentrations.[38] In studies with gastric cancer cells in vitro and in vivo, axitinib inhibited cell proliferation and retarded tumor growth.[39] In the same study, axitinib had a synergistic inhibitory effect when combined with 5-fluorouracil. The highest inhibitory effects occurred with the combination of axitinib and cisplatin, which produced an inhibitory ratio of >80% compared to control.

A phase I study assessed the administration of a combination of cisplatin/capecitabine and a standard starting dose of axitinib (5 mg twice/day) to patients with previously untreated advanced gastric cancer. Eight of the 12 patients studied had either a partial response or stable disease.[40] The median response duration was 9.1 months, and median progression-free survival was 3.8 months. Adverse events in this study group were manageable.

Apatinib mesylate, another small-molecule TKI targeting VEGFR-2, has been investigated in a phase III randomized, double-blind, placebo-controlled trial in patients with chemorefractory gastric cancer.[41] In this study, 273 Chinese patients who had progressed on second-line therapy were randomly assigned in a 2:1 ratio to receive apatinib or placebo. Apatinib was associated with increased median overall survival (195 days with apatinib versus 140 days with placebo, HR = 0.71, $P < 0.016$) and improved progression-free survival (53 days vs. 78 days, HR = 0.44, $P < 0.0001$). The toxicity profile of apatinib was found to be acceptable.

Regorafenib, an oral agent that inhibits multiple kinases involved in angiogenesis, tumor microenvironment, and oncogenesis, has yielded positive results in an international phase II trial. Regorafenib was compared with placebo in patients with advanced esophago-gastric carcinoma who had experienced failure of first- or second-line chemotherapy. Progression-free survival was significantly longer with regorafenib than placebo. Moreover, the tolerability of regorafenib was sufficient to warrant the initiation of a phase III evaluation.[42]

Side Effects of Antiangiogenic Agents

Antiangiogenic agents are generally well tolerated and associated with fewer treatment interruptions and discontinuations due to cumulative toxicities than conventional chemotherapy. Nonetheless, VEGF is essential for the health and maintenance of numerous organ systems, and its pharmacological disruption can lead to off-target side effects. Most of the adverse effects of VEGF inhibitors are modest and manageable, but some have been associated with serious, life-threatening complications.[43] Monoclonal antibodies and tyrosine kinase inhibitors used for VEGF inhibition have similar adverse effects that necessitate careful patient monitoring; these include hypertension, arterial thromboembolic events, proteinuria, wound healing complications, hemorrhaging, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome.

A recent meta-analysis involving 72 studies (n = 38,078) reporting on 11 different VEGF inhibitors added to data on adverse effects associated with VEGF inhibition treatment in cancer patients.[44] The authors concluded that the risks of fatal and nonfatal myocardial infarction, hypertension, arterial thromboembolism, and proteinuria were all higher among VEGF inhibitor recipients.

Increased blood pressure occurs in almost 100% of patients who take VEGF inhibitors, with a subset who develop severe hypertension.[45] In most instances this can be managed with the administration of standard antihypertensive medications. A meta-analysis examined the overall incidence and relative risk (RR) of hypertension associated with ramucirumab.[46] The authors addressed 11 studies with a total of 3,851 patients with multiple cancers. The overall incidence of all-grade hypertension was 20.0 % (95% CI 15.0-26.0) with 8.6% (95 % CI 6.3–11.7) being high-grade hypertension. The risk of developing hypertension was greater in ramucirumab-treated patients (RR for all grades 2.77, 95 % CI 1.94–3.94, $P < 0.001$, RR for high-grade 3.58, 95 % CI 2.45–5.23, $P < 0.001$).

In phase III trials of bevacizumab for metastatic colorectal cancer, grade 3 hypertension rates of 11–16% were reported; these are generally considered a benchmark for this agent.[47] In the AVAGAST trial, the rate of grade 3 or greater hypertension was approximately 4% in both treatment arms.[26] The true incidence of hypertension in clinical studies of bevacizumab, however, may vary considerably depending on the chemotherapy agents paired with bevacizumab and the hypertension criteria used. The underlying mechanism of hypertension in patients receiving antiangiogenesis therapy is thought to involve decreases in levels of nitric oxide in blood vessel walls due to VEGF inhibition, resulting in vasoconstriction. Anti-VEGF therapy also induces a functional decrease in the number of arterioles and capillaries. This effect may contribute to increased peripheral vascular resistance and elevated blood pressure.

Congestive heart failure (CHF) has been reported sporadically in clinical trials of bevacizumab for advanced solid tumors. A meta-analysis of five randomized controlled trials of bevacizumab involving 3,784 metastatic breast cancer patients reported a statistically significant increase in the incidence of clinically significant CHF among bevacizumab-treated patients (1.6%) compared with control/placebo (0.4%; RR = 4.74; $P = 0.001$).[48] There were no apparent differences in CHF incidence between low- and high-dose bevacizumab. The value of this meta-analysis may be limited by differences in trial design, patient selection, and monitoring of cardiac function, as well as limited information about underlying cardiovascular risk factors.

A more recent phase II study evaluated cardiac safety of bevacizumab with and without trastuzumab with two docetaxel-based regimens in early breast cancer.[49] At least one cardiac adverse event (congestive heart failure, cardiomyopathy, or left ventricular dysfunction) was reported in 26.1% of patients given docetaxel/doxorubicin/cyclophosphamide (n = 92) and 17.6% of those who received docetaxel/carboplatin/trastuzumab (n = 34); there were no cardiac deaths. ≥ Grade 3 clinical CHF was observed in 4.3% in the docetaxel/doxorubicin/cyclophosphamide plus bevacizumab stratum and 0% in the docetaxel/carboplatin/trastuzumab plus bevacizumab stratum. A ≥ grade 3 treatment-emergent adverse event (any kind) related to study treatment was observed in 59.8% in the TAC with bevacizumab and 52.9% in the TCH plus bevacizumab stratum. The researchers concluded that addition of bevacizumab to a docetaxel-based regimen with trastuzumab did not increase cardiotoxicity.

Other cardiotoxicity data pertaining to bevacizumab were reported in AVEREL, a phase III trial that assessed bevacizumab in combination with docetaxel and trastuzumab as a first-line therapy

for locally recurrent/metastatic breast cancers positive for HER2.[50] Cardiac events of grade 3 or greater occurred in 2.9% of patients given docetaxel and trastuzumab without bevacizumab (n=206), versus 5.1% of patients who received bevacizumab with docetaxel and trastuzumab (n=215). The authors concluded that the safety profile of bevacizumab combined with docetaxel and trastuzumab was consistent with the known safety profiles of the component agents. Moreover, detailed review of the cardiac data did not reveal deleterious effects of bevacizumab.

Gastric cancer has been linked with a high incidence of venous thromboembolism. In a phase II study in patients with metastatic gastric cancer treated with a combination of bevacizumab, irinotecan, and cisplatin, thromboembolic events occurred in 6 of 24 patients (25%).[51] This included two cases of deep vein thrombosis and 4 cases of incidental pulmonary emboli identified via routine CT scans. In the more recent phase II study of bevacizumab in combination with mDCF, 17 of 44 patients (39%) developed venous thromboembolism, which included 10 patients who were asymptomatic. All patients received anticoagulant therapy and were able to remain on study therapy. However, these results cannot be considered conclusive because in the random assignment phase III study, there was no reported increased incidence of thromboembolism with the addition of bevacizumab to chemotherapy in gastric cancer compared with chemotherapy alone.[52]

An animal study addressed thromboembolism in a murine model. The researchers induced thrombus in the inferior vena cava of mice and then treated them with the antiangiogenic agents axitinib (50 mg/kg per day), 2-methoxyestradiol (2ME, 150 mg/kg per day), or vehicle control. Both agents resulted in reduced thrombus resolution ($P<0.002$) and vein recanalization ($P<0.001$) compared with vehicle-treated controls. The researchers recommended that this potential prolongation of venous occlusion by antiangiogenic agents be taken into consideration in trials of these agents and when managing the complications of venous thromboembolic events in patients with cancer.[53]

Proteinuria, the presence of excess protein in the urine, is one of the most common side effects of anti-VEGF therapy. Although the precise mechanisms are not fully understood, renal toxicity and proteinuria during anti-VEGF therapy may be the result of dysfunction of the glomerular endothelium and localized thrombotic microangiopathy related to disruption in VEGF supply.[54]

Potential renal adverse effects of antiangiogenic agents were addressed in an 8-year observational study of antiangiogenic-treated-cancer patients who underwent renal biopsies for renal adverse effects from 2006 to 2013. In this study, 73 patients experienced renal thrombotic microangiopathy (TMA) and 27 patients had variable glomerulopathies, which mainly consisted of minimal change disease and/or collapsing-like focal segmental glomerulosclerosis (MCN/cFSGS). MCN/cFSGS-like lesions developed mainly with tyrosine-kinase inhibitors, whereas TMA was seen with anti-VEGF ligands. The researchers concluded that TMA and MCN/cFSGS are the most frequent forms of renal involvement under anti-VEGF therapy.[55]

Gastrointestinal perforation is another worrisome adverse effect associated with antiangiogenic therapy. The mechanism of developing gastrointestinal perforation is unclear, but bevacizumab is associated with impaired wound healing[56, 57] that may be related to altered function of the gut microvasculature. In gastric cancer, when bevacizumab was administered with irinotecan and cisplatin, two patients developed a perforation and one patient had a "near" perforation (6% rate, 95% CI 1-18%).[58] This prompted an evaluation of the incidence of gastrointestinal perforation in patients with metastatic gastric cancer receiving chemotherapy, which demonstrated a rate of perforation with chemotherapy alone of 1.1% (95% CI 0.5–1.9%).[59] These findings were inconsistent with the subsequent phase II study of bevacizumab, and the incidence of gastrointestinal perforation was not increased in the group that received bevacizumab in the phase III random assignment AVAGAST study.[26] In the phase II study of bevacizumab in combination with oxaliplatin and docetaxel, gastrointestinal perforation appeared to occur early in the course of therapy, which is similar to the pattern observed in patients with metastatic colorectal cancer treated with bevacizumab.[33]

Gastrointestinal perforation in association with bevacizumab was addressed in 2014 in a meta-analysis involving 26,833 patients from 33 randomized controlled trials.[60] In this analysis, bevacizumab-containing therapy significantly increased the risk of developing all-grade (RR 3.35, 95% CI 2.35–4.79, $P<0.001$) and fatal gastrointestinal perforation (RR 3.08, 95% CI: 1.04–9.08, $P=0.042$). Risk differences did not correlate with bevacizumab dosage, treatment duration, treatment line, type of clinical trial, or median age. However, when stratified by tumor types, a significantly increased risk of gastrointestinal perforation with bevacizumab was observed in colorectal cancer (RR 2.84, 95% CI 1.43–5.61, $P=0.003$), gynecologic cancer (RR 3.37, 95% CI 1.71–6.62, $P<0.001$) and prostate cancer (RR 6.01, 95% CI 1.78–20.28, $P=0.004$). The risk of gastrointestinal perforation with bevacizumab was increased when bevacizumab was administered in conjunction with taxanes (RR 3.09, 95% CI 1.92–4.96, $P<0.001$) or oxaliplatin (RR 2.85, 95% CI 1.07–7.57, $P=0.036$).

Conclusion

A growing body of clinical data validates the use of antiangiogenic therapeutics, administered alone or with chemotherapy, in the management of advanced gastric cancer. Nevertheless, many challenges remain. A critical need exists to discover new biomarkers that can predict the efficacy and toxicity of targeted therapies. Strategies to curb the development of resistance are also needed. Clinical trials offer the best opportunities for patients with advanced gastric cancer to receive promising new therapies and help to further define the role of antiangiogenic agents in the management of advanced gastric cancer.

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SYLLABUS / PROGRAM CONTENT REQUIREMENTS

TARGET AUDIENCE
This activity is designed for oncologists and primary care physicians who treat patients with gastric cancer.

LEARNING OBJECTIVES
At the completion of this activity, participants should be able to:

- Summarize the current clinical progress of targeted therapies in the management of advanced gastric cancer in early and late stage clinical trials.
- Explain current clinical challenges in the management of advanced gastric cancer.
- Interpret the outcome data from recent well-designed scientific and clinical studies of protocols studying new-targeted therapies.
- Integrate side effect management into the long term management of patients with advanced gastric cancer.
- Improve understanding of current targeted therapies with the associated pathways and mechanisms in the treatment of advanced gastric cancer.

ACTIVITY GOAL
This activity is designed to address the following ABMS / IOM competencies:
Patient Care and Medical Knowledge

FACULTY / SPEAKERS WITH TITLES

William W. Li, M.D., President, the Angiogenesis Foundation

Harry H. Yoon, M.D., Assistant Professor of Oncology, Mayo Clinic College of Medicine

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FACULTY DISCLOSURE SUMMARY

William W. Li, M.D.
President, the Angiogenesis Foundation, Editor-in-Chief

Dr. Li has nothing to disclose with regard to commercial interests.

Harry H. Yoon, M.D.
Assistant Professor of Oncology, Mayo Clinic College of Medicine, Editor

Dr. Yoon has received research grant support from Lilly Oncology and Genentech/Roche. He has also acted on advisory boards for Lilly Oncology and FivePrime.

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