Ramucirumab: Successfully Targeting Angiogenesis in Gastric Cancer

Milind Javle¹, Elizabeth C. Smyth², and Ian Chau²

Abstract

Gastric cancer is the fourth most common cancer globally and represents the second most common cause of cancer-related mortality. Early detection, aggressive surgical resection, and postoperative adjuvant therapy have led to survival improvement for early-stage gastric cancer, particularly in Asian countries. Unfortunately, advanced gastric cancer continues to pose a formidable challenge with few gains being reported recently. Trastuzumab was the first targeted agent to be approved for the treatment of advanced gastric cancer in 2010. The failure of the AVAGAST trial was a setback for antiangiogenic therapy for this disease. Ramucirumab is a monoclonal antibody that binds to VEGF-R2 and prevents its activation. The recent REGARD trial was a randomized phase III trial of ramucirumab vs. placebo for patients with advanced, pretreated gastric cancer that met its primary endpoint of increased overall survival. The toxicity of ramucirumab was modest in this setting, with an increased risk of grade 3 or higher hypertension (8% vs. 3%, with ramucirumab and placebo, respectively). The subsequent RAINBOW trial of paclitaxel plus ramucirumab vs. paclitaxel plus placebo for advanced pretreated gastric cancer confirmed the survival advantage of this antiangiogenic agent in gastric cancer. Ramucirumab is the first FDA-approved therapy for advanced gastric cancer after prior chemotherapy. Clin Cancer Res; 20(23): 5875–81. ©2014 AACR.

Introduction

On April 21, 2014, the FDA approved ramucirumab (Cyramza; Eli Lilly and Company) for the treatment of patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy (1). Ramucirumab is the first agent to be approved by the FDA in this setting. Ramucirumab was also granted "orphan" product designation by the FDA because it is intended to treat a rare disease or condition. This designation incentivizes pharmaceutical industry to develop new therapies for relatively uncommon diseases. Ramucirumab is a recombinant monoclonal antibody of the IgG1 class that binds to vascular endothelial growth factor receptor-2 (VEGF-R2) and blocks the activation of the receptor and is the only antiangiogenic agent to be approved by the FDA for gastric or GEJ adenocarcinoma.

VEGF-Directed Therapies in Clinical Practice

The cloning of VEGF in 1989 and an appreciation of the critical role of angiogenesis in cancer has incentivized intensive research in this field over the past two decades and has led to the successful clinical translation of VEGF-directed therapies to the clinic (2). The VEGF family, consists of five ligands [VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PIGF)] and three receptor tyrosine kinases [VEGF-R1, -R2, and -R3]. Of the VEGF receptors, VEGF-R2 expression is restricted to vasculature and appears to play a key role in angiogenesis. When activated, the VEGF receptors activate a complex cascade of downstream signaling pathways that result in neovascularization, vasodilation, increased vascular permeability, and migration of bone marrow endothelial cells (3). VEGF blockade inhibits these pathways and thereby effects tumor survival, migration, and invasion. Bevacizumab was the first FDA-approved antiangiogenic agent and acts by specifically binding to VEGF-A, preventing its interaction with VEGF-R. Ziv-Aflibercept (VEGF trap) contains portions of the extracellular domains of VEGF-R1 and -R2 fused to antibody Fc fraction of IgG1, thus acting as a decoy receptor for VEGF-A, preventing its binding to VEGF-R. Other FDA-approved antiangiogenic agents acting at the receptor tyrosine kinase level include sorafenib, sunitinib, pazopanib, regorafenib, and axitinib.

First-Line Therapy for Gastric Cancer

Although the gastric cancer has been declining in the Western hemisphere, worldwide this cancer ranks fourth in...
incidence and second in cancer-related mortality (4). Survival outcomes differ between Western and Eastern populations, with an improved survival noted in the Eastern patients. This may be accounted for earlier stage at presentation, secondary to screening strategies in high incidence areas, more aggressive surgical resection, and intrinsic differences in tumor biology. Western patients with gastric cancer are more likely to have proximal tumors and diffuse or signet ring histology, both of which are associated with a poor prognosis (5). These differences may also result in variable responses to targeted therapy, including antiangiogenic agents. Fluoropyrimidines and platinum analogs with the addition of either a taxane or anthracycline for fit patients have been the mainstay of first-line therapy for advanced-stage gastric cancer for almost a decade. However, the prognosis for these patients remains poor with a median survival of 9 to 11 months demonstrated in most studies (6, 7). The first FDA-approved biologic therapy for advanced gastroesophageal cancer was the anti-HER2 monoclonal antibody trastuzumab, the addition of which to fluoropyrimidine–cisplatin chemotherapy for HER2-positive patients substantially increased survival in the first-line setting [median overall survival (OS) 16 months for HER2 IHC3+ or FISH-positive patients]. However, only a minority (less than one quarter) of patients are eligible for this treatment (8). Second-line or salvage chemotherapy with paclitaxel, docetaxel, or irinotecan has recently demonstrated efficacy in improving survival in randomized trials; however, the margin of benefit is small with improvements in absolute OS of less than 2 months (9–11). In contrast to the success of HER2-directed therapy, the use of targeted therapy in non-molecularly selected patients with esophagogastric cancer has not been proven beneficial. Large randomized trials have failed to demonstrate any improvement in survival for patients treated with agents targeting the EGFR and mTOR pathway (12–16). The anti-VEGF monoclonal antibody bevacizumab also failed to yield an OS advantage in the international AVAGAST trial despite significant improvements in progression-free survival (PFS) and response rate (16).

Clinical Trial Resulting in Approval

The REGARD study was a double-blind, placebo-controlled, phase III study conducted in 355 patients with gastric or GEJ adenocarcinoma, who had received prior fluoropyrimidine or platinum-based therapy, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (17). All patients were required to have measureable or evaluable disease. Patients were randomized in a 2:1 ratio to either ramucirumab (8 mg/kg every 2 weeks intravenously) or placebo. The primary study endpoint was OS. A total of 355 patients were randomized, of which 238 received ramucirumab. This international study was conducted in 119 centers and 69% of the study population was from Western countries; 76% of the study subjects were Caucasian. Median OS in the treatment group was 5.2 vs. 3.8 months in the placebo group [hazard ratio (HR), 0.77; P = 0.047]. This difference remained significant after adjusting for other prognostic variables including performance status, tumor location, and peritoneal disease. There was also a modest improvement in PFS, with a median PFS of 2.1 months in study arm vs. 1.3 months in placebo arm (HR, 0.483; P < 0.0001). Responses were infrequent with ramucirumab; however, disease control rate was significantly higher in the study group (49%) as compared with the control group (23%). Ramucirumab was generally well tolerated, although with a higher risk of grade 3 hypertension (8% vs. 3% in study and placebo groups, respectively). There was, however, no increased risk of thrombo-embolic events, fistula formation, or gastrointestinal perforation with ramucirumab, as was seen with other antiangiogenic agents, such as bevacizumab.

Mechanism of Action

Ramucirumab is direct inhibitor of VEGF-R2, where it binds to the extracellular VEGF-binding domain with high degree of specificity and affinity, at picomolar dose range. It thus prevents the binding of the VEGF ligand to the VEGF-R2 receptor. Lu and colleagues (18) isolated several high-affinity human Fab antibody fragments directed against VEGF-R2 from an antibody phage display library constructed from the pooled B lymphocytes of nonimmunized healthy human donor. They subsequently identified clone 1121, which showed a >30-fold higher binding affinity to VEGF-R2. Furthermore, clone 1121 was more potent in inhibiting VEGF-stimulated VEGF-R2 phosphorylation in endothelial cells (19). Further development via genetic modification led to compound IMC-1121B (ramucirumab) that inhibits VEGF–VEGF-R2 interaction at IC50 of 0.8 to 1 nmol/L, compared with 3 to 4 nmol/L for the parent Fab fragments (20). The crystal structure of the 1121B Fab fragment has been identified: this complexes with domain 3 of VEGF-R2 at the N terminus and blocks VEGF signaling in two ways: by sterically preventing the ligand from binding to VEGF-R2, and by changing the receptor conformation so that it cannot bind to ligand (Fig. 1; ref. 21). Ramucirumab has potential advantages over bevacizumab as it is selective for VEGF-R2, whereas bevacizumab by targeting VEGF-A affects VEGF-R1, -R2, and the noncatalytic coreceptors neuropilin-1 and -2 (22). Ramucirumab thus leaves VEGF-R2. Furthermore, it leads to compound IMC-1121B (ramucirumab) that inhibits VEGF–VEGF-R2 interaction at IC50 of 0.8 to 1 nmol/L, compared with 3 to 4 nmol/L for the parent Fab fragments (20). The crystal structure of the 1121B Fab fragment has been identified: this complexes with domain 3 of VEGF-R2 at the N terminus and blocks VEGF signaling in two ways: by sterically preventing the ligand from binding to VEGF-R2, and by changing the receptor conformation so that it cannot bind to ligand (Fig. 1; ref. 21). Ramucirumab has potential advantages over bevacizumab as it is selective for VEGF-R2, whereas bevacizumab by targeting VEGF-A affects VEGF-R1, -R2, and the noncatalytic coreceptors neuropilin-1 and -2 (22). Ramucirumab thus leaves VEGF-R1 receptor alone, which behaves like a decoy receptor, providing additional potency to the VEGF-R2 inhibitory effect. An additional benefit results due to VEGF-R2 expression on macrophages, which get suppressed by ramucirumab (23). Inhibition of these macrophages results in decreased tumor immune infiltration, cytokine and chemokine release, which thereby decrease tumor growth and proliferation.

Pharmacokinetics

The pharmacokinetics (PK) of ramucirumab was studied in 37 patients with advanced solid malignancies (24). In preclinical studies, ramucirumab concentrations of >20 μg/ml were associated with anticancer activity.
Therefore, in the clinical study PK analyses were directed toward identifying doses associated with trough concentrations of >20 μg/mL. Although there was a linear increase in $C_{\text{max}}$ there was relatively disproportionate decrease in clearance at higher doses, suggesting that steady state was reached around the 8 mg/kg dose level. AUC $0\rightarrow\infty$ increased linearly from 2 to 8 mg/kg dose, beyond which the increase was nonlinear. There was significant inter-patient variability noted and $t_{1/2}$ ranged from 200 to 300 hours at doses of 8 to 16 mg/kg. $C_{\text{min}}$ levels of >20 μg/mL were achieved in all patients beyond 6 mg/kg. These data supported 8 mg/kg as the phase II dose for ramucirumab. The effects of ramucirumab on VEGF-A, sVEGFR-R2, and sVEGFR-R1 were measured after the first infusion cycle. Posttreatment VEGF-A elevation was seen in all samples, this was not dose-dependent. There was a decrease in sVEGFR-R2 and sVEGFR-R1 levels with continuing therapy.

**Clinical Activity**

In the phase I trial for patients with advanced solid tumors ($n = 37$), ramucirumab demonstrated encouraging early evidence of efficacy at a range of dose levels (24). Fifteen percent of patients with measurable disease demonstrated a confirmed partial response to ramucirumab including those with metastatic melanoma, gastric, ovarian cancer, and uterine leiomyosarcoma. In total, 30% of patients had a partial response or stable disease lasting ≥24 weeks. Five dose-limiting toxicity (DLTs) were observed in this study: grade 3 hypertension in 2 patients, deep vein thrombosis (DVT), grade 3 proteinuria, and grade 3 nausea and vomiting in 1 patient each. The MTD of ramucirumab was determined to be 13 mg/kg weekly; however, as discussed above, PK studies revealed that PK clearance was saturated at 8 mg/kg.

Following the successful completion of the REGARD trial for gastric cancer, two additional trials have been reported in this disease. The RAINBOW trial was a global, phase III, randomized, placebo-controlled trial in patients with advanced gastroesophageal cancer who had progressed on or within 4 months of first-line platinum and fluoropyrimidine-based chemotherapy (25). Treatment consisted of either ramucirumab 8 mg/kg or...
placebo days 1 and 15 plus paclitaxel 80 mg/kg days 1, 8, and 15 of a 28-day cycle. All patients were required to have an ECOG PS of ≤1. Six hundred and sixty-five patients were randomized, with a median age of 61 years. The majority of patients (60%) were North American or European, approximately one third were Asian. The primary endpoint of the study (OS) was met; patients treated with ramucirumab + paclitaxel had a statistically significant and clinically meaningful improvement in OS compared with those treated with paclitaxel alone [9.63 vs. 7.26 months; HR, 0.807; 95% confidence interval (CI), 0.678–0.962; \( P = 0.0169 \)]. Response rate and PFS were also comparatively improved in the experimental arm of the study. Patients treated with ramucirumab were more likely to report stable or improved quality of life scores of a more sustained duration, indicating that the marginally increased toxicity associated with combination therapy did not impact on overall quality of life (26). In a subgroup analysis, despite improved response rates and PFS, Asian patients did not derive a similar OS benefit as compared with non-Asian patients. The reasons for a discrepant outcome from antiangiogenic therapy in Asian vs. Caucasian patients are not known. One possibility is that Asian patients with gastric cancer have a relatively less aggressive disease biology and often receive third- and fourth-line therapies. Thus, the effect of second-line trial with ramucirumab vs. placebo could be diluted by subsequent regimens in these patients. The rates for third and subsequent lines of therapy in Japanese patients were 75% compared with <40% in non-Asian patients (27). Similar findings were also in the AVAGAST study that investigated capecitabine, cisplatin ± bevacizumab for patients with advanced gastric cancer. In this study, patients from Europe or North America derived more benefit from antiangiogenic therapy than the Asian patients (28).

In contrast, when ramucirumab was administered in the first-line setting in conjunction with FOLFOX chemotherapy for patients with advanced gastroesophageal cancer, no survival benefit was demonstrated. In this U.S. study, 168 patients were randomized to FOLFOX chemotherapy plus either ramucirumab (8 mg/kg) or placebo. Despite a statistically significant difference in the disease control rate (85% vs. 67%; \( P = 0.008 \)) in favor of ramucirumab, the primary endpoint of an improvement in PFS was not met (6.4 vs. 6.7 months; HR, 0.98; \( P = 0.89 \)) and OS was also similar in both arms (11.7 vs 11.5 months; with FOLFOX + ramucirumab or FOLFOX + placebo, respectively; ref. 29). Cessation of treatment for reasons other than disease progression was significantly higher in ramucirumab-treated patients and this may have affected PFS, as analyses censored at treatment discontinuation for nonprogression demonstrated a trend toward improved PIS for ramucirumab-treated patients and those with nonesophageal tumors. A reasonable question that arises in this setting is whether platinum analogues are the best chemotherapeutic backbone to which antiangiogenic therapy should be added (30–32). These data are consistent with the negative results of the AVAGAST trial of bevacizumab plus cisplatin-

<table>
<thead>
<tr>
<th>Table 1. Selected ≥ grade 3 toxicities of antiangiogenic therapy in randomized gastroesophageal cancer trials</th>
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<tbody>
<tr>
<td><strong>AVAGAST (16)</strong></td>
</tr>
<tr>
<td>CX + bevacizumab</td>
</tr>
<tr>
<td>Neutropenia 35%</td>
</tr>
<tr>
<td>Febrile neutropenia 5%</td>
</tr>
<tr>
<td>Thrombocytopenia 6%</td>
</tr>
<tr>
<td>Neuropathy 6%</td>
</tr>
<tr>
<td>Nausea 7%</td>
</tr>
<tr>
<td>Vomiting 6%</td>
</tr>
<tr>
<td>Diarrhea 8%</td>
</tr>
<tr>
<td>Decreased appetite 8%</td>
</tr>
<tr>
<td>Dehydration 9%</td>
</tr>
<tr>
<td>Toxicities of special interest</td>
</tr>
<tr>
<td>Venous thromboembolism 6% 9%</td>
</tr>
<tr>
<td>Arterial thromboembolism 1% 2%</td>
</tr>
<tr>
<td>Hypertension 6% &lt;1%</td>
</tr>
<tr>
<td>Hemorrhage 2% 2%</td>
</tr>
<tr>
<td>GI perforation 2% &lt;1%</td>
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NOTE: All percentages rounded to nearest whole number.
Abbreviations: CX, cisplatin/capecitabine; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; GI, gastrointestinal.
The role of ramucirumab in the second-line setting for advanced gastric cancer after prior chemotherapy is now established after the REGARD and RAINBOW trials. These trials also highlight the need to individualize therapy for gastric cancer based on tumor location and ethnic background. A greater benefit with antiangiogenic strategies can be expected in Caucasian patients as compared with Asian patients having distal gastric cancer. Future investigations will address the potential role of ramucirumab in the first-line setting for advanced gastric cancer and for early-stage disease as postoperative adjuvant therapy. Plasma VEGF-A and neuropilin-1 are emerging as potential predictive biomarkers for bevacizumab in gastric cancer while biomarkers in case of ramucirumab have yet to be identified.

Disclosure of Potential Conflicts of Interest
I. Chau is a consultant/advisory board member for Eli Lilly. No potential conflicts of interest were disclosed by the other authors.

Table 2. Antiangiogenic agents in gastroesophageal cancer

<table>
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<tr>
<th>Mechanism of action</th>
<th>Bevacizumab</th>
<th>Ramucirumab</th>
</tr>
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<tbody>
<tr>
<td>Actions</td>
<td>Inhibits VEGF-R1, VEGF-R2, NRP-1 and -2</td>
<td>Inhibits VEGF-R2 on endothelial cells and macrophages</td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td>Improved ORR and PFS without an improved OS in first line (16)</td>
<td>Improved ORR, PFS, and OS in second line as single agent and in combination with paclitaxel (17, 34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved DCR but not PFS or OS in first line in combination with FOLFOX (29)</td>
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</tbody>
</table>

Abbreviations: DCR, disease control rate; NRP, neuropilin.

fluoropyrimidine chemotherapy (28). As paclitaxel has been demonstrated to have intrinsic antiangiogenic properties independent of cytotoxic activity, potential synergy with ramucirumab in combined blockade of angiogenic activity may have contributed to improved survival outcomes in the RAINBOW trial (33).

Toxicity Considerations
Ramucirumab is tolerable as a single agent and in combination with cytotoxic chemotherapy such as with platinum analogues and taxanes. However, combination regimens are associated with higher toxicity in general (17, 34, 35). In the RAINBOW trial, ramucirumab plus paclitaxel was associated with significantly increased rates of ≥grade 3 neutropenia than paclitaxel plus placebo (40.7% vs. 18.8%, respectively). However, this did not translate into higher rates of febrile neutropenia (3.1% vs. 2.4%; ref. 34). Higher rates of ≥grade 3 neuropathy (8.3% vs. 4.6%) and diarrhea were also associated with the combination regimen in this study. These results are consistent with the phase III randomized REVEL study in non–small cell lung carcinoma (NSCLC), in which patients who were randomized to ramucirumab plus docetaxel experienced increases rates of neutropenia as compared with those treated with docetaxel alone (36). In the first-line study of ramucirumab plus FOLFOX chemotherapy for patients with treatment-naïve advanced gastroesophageal cancer, increased rates of thrombocytopenia, decreased appetite, and dehydration occurred in the combination therapy arm as compared with FOLFOX alone (35). In this study, 48% of patients treated with ramucirumab discontinued treatment due to an adverse event or because of patient/physician decision (compared with 16% in the placebo arm) and this may have affected the efficacy analysis for this trial. As ramucirumab did not increase rates of FOLFOX-related toxicities in a colorectal cancer trial, an interaction with the patient population may be responsible for these findings (37).

Specific toxicities of concern for patients undergoing antiangiogenic therapy include hypertension, hemorrhage, and thromboembolic disease. In randomized trials, the rate of significant (≥grade 3) hypertension associated with ramucirumab ranges from 6% (REVEL) to 16% (FOLFOX-gastric). Comparably, grade 3 or higher hypertension is noted in 15% of patients with breast cancer treated with paclitaxel and bevacizumab (38). In gastric cancer, in the AVAGAST study, bevacizumab was associated with a 6% incidence of grade 3 or higher hypertension. In addition, the rates of venous thromboembolism appear to be higher in the AVAGAST trial than noted in the ramucirumab trials, this may also be related to cisplatin-based chemotherapy, which is associated with higher risk of thromboembolic events (39). Finally, although overall rates of hemorrhage (including epistaxis) are higher for ramucirumab-treated patients with gastric cancer, the incidence of significant hemorrhage including gastrointestinal hemorrhage is low, and ramucirumab appears to be a safe treatment choice for these patients. The toxicities related to antiangiogenic therapy in gastric cancer are summarized in Table 1. Table 2 compares the mechanism of action and efficacy of ramucirumab and bevacizumab.
Authors' Contributions

Conception and design: M. Javle, E.C. Smyth, I. Chau

Development of methodology: M. Javle

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Javle, E.C. Smyth, I. Chau

Writing, review, and/or revision of the manuscript: M. Javle, E.C. Smyth, I. Chau

Study supervision: M. Javle

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