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Ramucirumab: Successfully Targeting Angiogenesis in Gastric Cancer

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Abstract

Gastric cancer is the fourth most common cancer globally and represents the second most common cause of cancer mortality. Early detection, aggressive surgical resection and postoperative adjuvant therapy has 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 anti-angiogenic 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, pre-treated 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.

Introduction

On April 21, 2014, the Food and Drug Administration (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 (VEGFR-2) and

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blocks the activation of the receptor and is the only anti-angiogenic agent to be approved by the FDA for gastric or GE junction 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 led to the successful clinical translation of VEGF-directed therapies to the clinic (2). The VEGF family, consists of five ligands [VEGFA, VEGFB, VEGFC, VEGFD 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 anti-angiogenic agent and acts by specifically binding to VEGF-A preventing its interaction with VEGF-R. Ziv-Ablibercept (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 anti-angiogenic agents acting at the receptor tyrosine kinase level include sorafenib, sunitinib, pazopanib, regorafenib and axitinib.

Front-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 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 anti-angiogenic 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 9–11 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 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 demonstrate defficacy in improving survival in randomized trials however the margin of benefit is small with improvements in absolute overall survival of less than two 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 overall survival advantage in the international AVAGAST trial despite significant improvements in progression free survival 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 measurable 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 overall survival. 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 overall survival in the treatment group was 5.2 months, 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 progression free survival (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 anti-angiogenic agents, such as bevacizumab.

Mechanism of Action

Ramucirumab is direct inhibitor of VEGFR-2, 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 et al, 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 non-immunized healthy human donor (18). 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) which inhibits VEGF/VEGF-R2 interaction at IC₅₀ of 0.8 to 1 nM, compared with 3–4 nM for the parent Fab fragments (20). The crystal structure of the 1121B Fab fragment has been identified; this complex 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 ligand (Fig. 1)(21). Ramucirumab has potential advantages over bevacizumab as it is selective for VEGF-R2, whereas bevacizumab

by targeting VEGF-A impacts VEGF-R1, R2 and the non-catalytic co-receptors neuropilin 1 and 2 (22). Ramucirumab thus leaves the 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 of ramucirumab was studied in 37 patients with advanced solid malignancies (24). In preclinical studies, ramucirumab concentrations of >20 ug/ml were associated with anticancer activity. Therefore, in the clinical study pharmacokinetic (PK) analyses were directed toward identifying doses associated with trough concentrations of > 20 ug/ml. Although there was a linear increase in C 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- ∞ increased linearly from 2–8 mg/kg dose, beyond which the increase was non-linear. There was significant inter-patient variability noted and $t_{1/2}$ ranged from 200–300 hours at doses of 8–16 mg/kg. C min levels of > 20 ug/ml were achieved in all patients beyond 6 mg/kg. These data supported 8 mg/kg as the phase 2 dose for ramucirumab. The effects of ramucirumab on VEGF-A, sVEGFR-R2 and sVEGFR-R1 were measured after the first infusion cycle. Post treatment 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 per cent 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 DLTs were observed in this study: grade 3 hypertension in two patients, DVT, grade 3 proteinuria and grade 3 nausea and vomiting in one patient each. The MTD of ramucirumab was determined to be 13 mg/kg weekly, however as discussed above pharmacokinetic 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 advanced gastroesophageal cancer patients 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 day 1 and 15 plus paclitaxel 80 mg/kg day 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. 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 overall survival compared to those treated with paclitaxel alone (9.63m vs. 7.26m, HR 0.807, 95% CI 0.678–0.962; $p=0.0169$). Response rate and progression free survival were also comparably 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 progression-free survival, Asian patients did not derive a similar OS benefit as compared with non-Asian patients. The reasons for a discrepant outcome from anti-angiogenic therapy in Asian vs. Caucasian patients are not known. One possibility is that Asian gastric cancer patients 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 3rd and subsequent lines of therapy in Japanese patients were 75% compared to <40% in non-Asian patients (27). Similar findings were also in the AVAGAST study which investigated capecitabine, cisplatin ± bevacizumab for patients with advanced gastric cancer. In this study, patients from Europe or North America derived more benefit from anti-angiogenic 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 US 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 progression free survival was not met (6.4 months vs. 6.7 months, HR 0.98, $p=0.89$) and overall survival was also similar in both arms (11.7 months vs. 11.5 months, with FOLFOX + ramucirumab or FOLFOX + placebo, respectively) (29). Cessation of treatment for reasons other than disease progression was significantly higher in ramucirumab treated patients and this may have impacted on progression free survival as analyses censored at treatment discontinuation for non-progression demonstrated a trend towards improved PFS for ramucirumab treated patients and those with non-esophageal tumors. A reasonable question that arises in this setting is if platinum analogues are the best chemotherapeutic backbone to which anti-angiogenic therapy should be added (30–32). These data are consistent with the negative results of the AVAGAST trial of bevacizumab plus cisplatin-fluoropyrimidine chemotherapy (28). As paclitaxel has been demonstrated to have intrinsic anti-angiogenic 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%) (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 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 treatment naive advanced gastroesophageal cancer patients, 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 to 16% in the placebo arm) and this may have impacted 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 anti-angiogenic 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 breast cancer patients 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. Additionally, the rates of venous thromboembolism appear to be higher in AVAGAST 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 anti-angiogenic therapy in gastric cancer are summarized in Table 1. Table 2 compares the mechanism of action and efficacy of ramucirumab and bevacizumab.

Conclusions

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 anti-angiogenic 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 post-operative 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.

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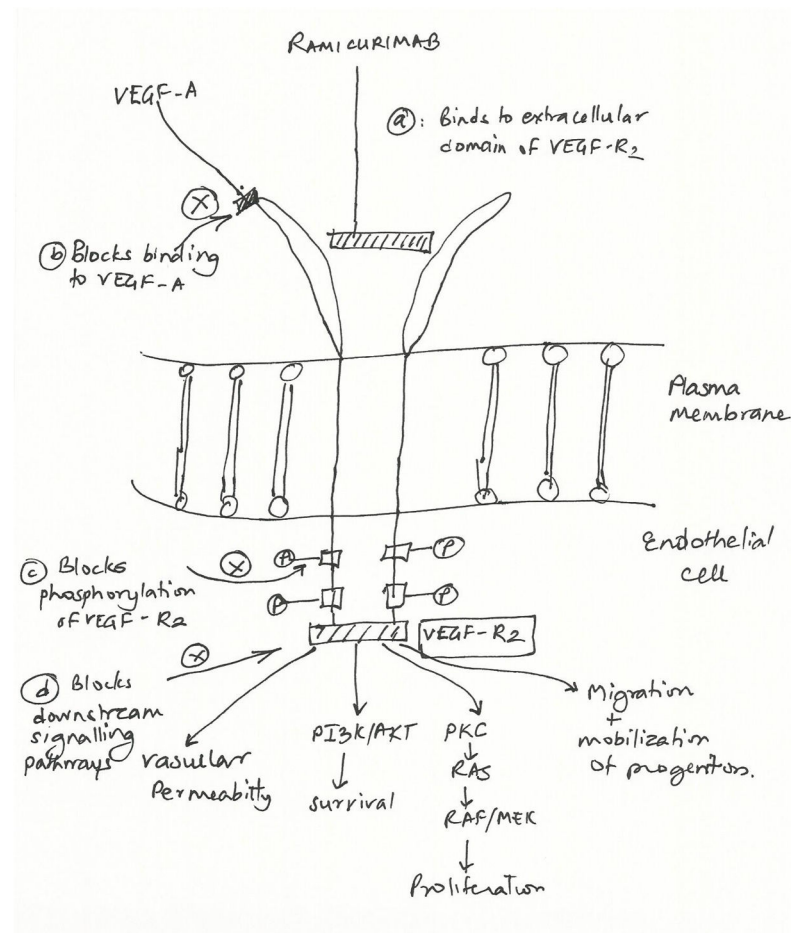


Figure 1.

Mechanism of action of ramucirumab. Ramucirumab binds specifically to VEGFR2 (1), blocks VEGF/VEGFR2 interaction (2), and (3) inhibits VEGF-stimulated receptor phosphorylation in endothelial cell resulting in disruption of downstream signaling (4). AKT, protein kinase B; MEK, mitogen-activated protein kinase kinase; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 1
Selected grade 3 toxicities of antiangiogenic therapy in randomized gastroesophageal cancer trials

	AVAGAST(16)		FOLFOX(29)		RAINBOW(25)		REGARD(17)	
	CX + Bevacizumab	CX	FOLFOX + Ramucirumab	FOLFOX	Paclitaxel + Ramucirumab	Paclitaxel	Ramucirumab	Placebo
Neutropenia	35%	37%			41%	18%		
Febrile neutropenia	5%	4%			3%	2%		
Thrombocytopenia			6%	3%				
Neuropathy			6%	9%	8%	5%		
Nausea	7%	10%						
Vomiting	6%	9%			3%	4%	3%	3%
Diarrhoea	8%	4%			4%	2%		
Decreased appetite	8%	11%	6%	0%	3%	4%	3%	3%
Dehydration			9%	1%				
Toxicities of special interest								
Venous thromboembolism	6%	9%	4%	5%	2%	3%	1%	4%
Arterial thromboembolism	1%	2%	2%	0%	1%	1%	0%	0%
Hypertension	6%	<1%	16%	4%	15%	3%	8%	3%
Haemorrhage	2%	2%	6%	6%	4%	2%	3%	3%
GI Perforation	2%	<1%			1%	0%	<1%	<1%

CX, cisplatin/capecitabine; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin

All percentages rounded to nearest whole number

Table 2

Antiangiogenic agents in gastroesophageal cancer

	Bevacizumab	Ramucirumab
Mechanism of action	Binds to circulating VEGF	Binds to the extracellular VEGF-binding domain of VEGFR-2
Actions	Inhibits VEGF-R1, VEGF-R2, NRP-1 and 2	Inhibits VEGFR-2 on endothelial cells and macrophages
Clinical Efficacy	Improved ORR and PFS without an improved OS in 1 st line(16)	Improved ORR, PFS and OS in 2 nd line as single agent and in combination with paclitaxel(17, 34) Improved DCR but not PFS or OS in 1 st line in combination with FOLFOX(29)

DCR, disease control rate; OS, overall survival; NRP, neuropilin; PFS, progression free survival; VEGF, vascular endothelial growth factor; VEGF-R, vascular endothelial growth factor receptor.