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REVIEW

Clinical role of ramucirumab alone or in combination with paclitaxel for gastric and gastro-esophageal junction adenocarcinoma

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Abstract: Cancers of the stomach and gastro-esophageal junction represent a significant challenge in oncology. Despite some recent advances in genetic categorization and the development of novel agents, outcomes remain poor. The vascular endothelial growth factor receptor 2 monoclonal antibody ramucirumab is the first targeted therapy to improve survival in a molecularly unselected population, and represents a valuable new treatment option. This review describes the current treatment landscape for advanced disease, evaluates existing and ongoing research into ramucirumab, and discusses its current and potential future therapeutic role.

Keywords: advanced gastric cancer, ramucirumab, paclitaxel, angiogenesis inhibitors

Introduction

Gastric cancer (GC) represents a challenging global health problem. It is the fifth most common malignant disease worldwide and the third leading cause of cancer mortality.[1] Despite some recent advances in both its genetic characterization and the development of novel targeted agents the outlook for advanced disease remains bleak, with median overall survival generally not extending beyond 12 months in the majority of trials. It is increasingly recognized as a heterogeneous condition with variations in geographical prevalence and histological and genetic characteristics, all of which impact upon management. A small minority of cases are associated with hereditary genetic abnormalities including constitutional mutations in *CDH1* (causing hereditary diffuse gastric cancer) and in the mismatch repair genes which characterize Lynch syndrome.[2,3] However the majority of diagnoses worldwide are associated with recognized environmental and modifiable risk factors such as *Helicobacter pylori* infection, diet, cigarette smoking, and obesity-related gastro-esophageal reflux disease.[4,5] More than 70% of gastric cancers occur in the developing world, with the highest incidence being found in Eastern Asia.[6] The vast majority of these are adenocarcinomas, which can be further subdivided into intestinal and diffuse types according to the Lauren classification.[7] Adenocarcinomas of the distal esophagus and gastro-esophageal junction (GOJ) typically arise from the columnar epithelial metaplasia that characterizes Barrett's esophagus, and again it is modifiable risk factors, particularly gastro-esophageal reflux disease, that are predominantly implicated in its development. More recently work has been done to develop a further classification of gastric cancer based on genomic analysis and molecular subtyping. In the landmark analysis performed by the Cancer Genome Atlas, four gastric cancer subtypes were proposed: tumors positive for Epstein-Barr virus, microsatellite unstable tumors, genomically stable tumors, and

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tumors with chromosomal instability.[8] These subtypes each show distinct genomic features with potentially important clinical implications. Of relevance to angiogenic targeting, both the genomically stable and the chromosomal-instability subtypes have demonstrated amplifications of potentially therapeutically-targetable receptor tyrosine kinases, in particular the gene coding for ligand vascular endothelial growth factor (VEGF)-A. It is hoped that such work will help to further identify and refine targets for molecular and immunotherapeutic approaches going forward.

Current treatment landscape: chemotherapy

Gastric and GOJ adenocarcinomas are chemotherapy-responsive with a number of cytotoxic agents and combinations showing efficacy, and standard of care for advanced disease remains largely chemotherapy-based.[9] Despite differences in epidemiology and genetic characteristics, chemotherapy regimens have not demonstrated significant differences in efficacy. It is instructive to consider the standard chemotherapy options currently in use, as the choice of chemotherapy "backbone" is significant in the evaluation of trials of targeted agents. Although there is no international consensus on optimal first-line treatment, a standard reference regime usually consists of a fluoropyrimidine combined with a platinum agent, with the possible addition of either an anthracycline or taxane. Evidence for the use of both an anthracycline as well as alternative fluoropyrimidine and platinum substitutes is provided by the REAL-2 study, where capecitabine and oxaliplatin were found to be non-inferior to Fluorouracil (5-FU) and cisplatin respectively.[10] Although epirubicin/platinum/fluoropyrimidine triplets have not been compared with a doublet in a Phase III trial, a meta-analysis has suggested a 2-month median survival benefit with the combination of an anthracycline with a 5-FU/platinum backbone.[9] Docetaxel can also be added to a cisplatin/5-FU backbone and the triplet is associated with improved median overall survival (OS) compared with the doublet, however excessive toxicity limits its use.[11] Irinotecan is more commonly used as a second-line therapy for advanced gastric cancer (AGC), however several studies suggest that FOLFIRI (irinotecan with 5-FU) also has activity as a first-line regimen.[12,13]

The administration of second-line chemotherapy is also now well established, with randomized studies of irinotecan, docetaxel and paclitaxel all demonstrating a survival advantage over best supportive care (BSC) alone.[14–17] The WJOG study of irinotecan versus weekly paclitaxel failed to demonstrate superiority of irinotecan, and the median OS of 9.5 months achieved in the paclitaxel arm represents the most positive result seen in any second-line chemotherapy trial.[17] It should be noted that this trial population was made up of Japanese patients of predominantly good performance status without the presence of significant peritoneal metastases, and that the uptake of further lines of post-trial treatment was high across both groups. These factors are likely to have influenced the improved outcomes seen. Optimal second-line chemotherapy is not established, with irinotecan, docetaxel and paclitaxel all used. Given its favorable toxicity profile paclitaxel is often a preferred option. The survival benefit of second-line therapy has been further confirmed in a meta-analysis of selected randomized trials, which demonstrated an improved hazard ratio (HR) for OS compared with BSC alone of 0.73 (95% CI 0.58–0.96). It is important to note that this analysis also found that patients with a preserved performance status of 0–1 had a greater magnitude of benefit (HR 0.57 [95% CI 0.36–0.91]).[18] Administration of second-line or beyond treatments in AGC can be clinically challenging: cancer and chemotherapy-related symptoms will often precipitate a deterioration in fitness and functioning, limiting tolerance to further treatment. The margin of benefit for second-line therapy appears to be greater in fitter patients and thus consideration of patient suitability, as well as the toxicities of the proposed second-line regimen are paramount.

Targeted therapy

The utilization of molecularly-targeted agents as monotherapy or in combination with chemotherapy in gastric cancer has yielded only modest results thus far. The most notable development was reported in the landmark 2010 ToGA trial evaluating trastuzumab in combination with cisplatin and capecitabine in the first-line setting.[19] Median OS was improved significantly, with the greatest margin of benefit seen in those patients over-expressing HER2 (immunohisto-chemistry 2+ or 3+, FISH positive). On the basis of this trastuzumab in combination with chemotherapy is now standard first-line treatment for HER2 positive cancers. Novel strategies to further exploit the HER2 pathway such as the antibody-drug conjugate TDM1 and the monoclonal antibody pertuzumab are under investigation, but at present there are no standard HER2 directed approaches in the second-line setting. Further trials of molecularly targeted agents have, in the main, proved disappointing. Antibody inhibitors of EGFR cetuximab and panitumumab have been investigated in large Phase III trials, failing to show a survival advantage.[20,21] Similarly, Phase III trials agents targeting the MET, and P13K/mTOR pathway have also yielded negative

results.[22–24] PARP-inhibitors have been shown to have synergistically-enhanced activity in tumors with impaired DNA repair mechanisms, such as those associated with BRCA mutation or ATM deficiency.[25,26] A randomized Phase II study in AGC compared paclitaxel plus or minus olaparib in a study population enriched to 50% for patients with low or undetectable ATM levels, with an OS benefit seen across both the whole group and a subset analysis of low ATM-expressing patients.[26] The combination was further evaluated in the Phase III GOLD study, however at the time of writing a recent company press release has indicated no statistically significant improvement in outcome.[27] BBI608 is an oral small molecule STAT3 inhibitor targeting cancer stem cell growth and survival. Preclinical and Phase I/II evidence of signal in AGC has led to the BRIGHTER study evaluating BBI608 in combination with paclitaxel in the second line.[28]

Immune checkpoint inhibition

As with other solid organ tumors there has been an increasing interest in immunotherapeutic treatment approaches in advanced gastric cancer, primarily focused on the use of checkpoint inhibitors to induce immune-mediated cytotoxic responses. The KEYNOTE 012 Phase I study investigated the anti–PD1 antibody pembrolizumab in a number of solid organ cancers, with updated results from the AGC cohort presented at ASCO (American Society of Clinical Oncology) 2015.[29] Eligible patients were screened for PDL-1 expression and a total of 39 patients were enrolled, with most having received ≥2 previous lines of systemic therapy. An overall response rate (ORR) of 22% and a 6-month OS rate of 69% was reported, with an apparent correlation between PDL-1 expression and survival. This activity in heavily pretreated patients has led to further evaluation, with trials of pembrolizumab currently in progress both in first-line combination with chemotherapy (NCT02335411) and in second-line comparison with paclitaxel (NCT02370498). Interestingly, evaluation of combination blockade of both PD-1 and VEGFR2 in murine models appeared to show a synergistic effect without excessive toxicity.[30] Importantly, angiogenic inhibition via VEGFR2 blockade did not appear to interfere with the immunological activation induced by PD-1 targeting. An open-label Phase I study is currently evaluating the combination of pembrolizumab and ramucirumab in a cohort of advanced, pre-treated gastric cancer patients (NCT02443324). The optimal use of immune-modulating drugs in AGC has yet to be established, and the results of ongoing trials investigating their use as monotherapies, combinations, or as maintenance therapy are awaited with interest.

Targeting angiogenesis

Sustained angiogenesis is a hallmark of cancer and has been an attractive therapeutic target for some years. It is a complex process, controlled by a balance of inducers and inhibitors and involving numerous pathways and receptors. A key inducer is the VEGF and its receptor tyrosine kinases, consisting of VEGF-A-E and placental growth factors 1 and 2, with the differing isoforms binding to and activating three receptors, VEGFR-1–3. Angiogenesis in cancer is primarily mediated by the VEGFR-2–VEGF-A interaction causing receptor dimerization, tyrosine kinase phosphorylation and activation of a number of downstream signaling pathways leading to increased cell proliferation, migration and vascular permeability.[31] So far clinical experience of anti-angiogenic agents across a number of tumor types has been variable, with the most extensively trialed agent being the VEGF-A monoclonal antibody bevacizumab. Monotherapy with bevacizumab appears to be effective only in selected highly VEGF-dependent tumors and combinations with chemotherapy have otherwise proven necessary, with an OS effect demonstrated in selected studies in colorectal, gynecological and breast cancers.[32–34] Rare but serious toxicities including thromboembolism, hemorrhage, gastrointestinal perforation, hypertension, and proteinuria are well recognized. In advanced gastric and GOJ cancers, bevacizumab was evaluated in the first-line setting in the AVAGAST study, comparing cisplatin/fluoropyrimidine with the antibody or placebo.[35] Despite significant improvements in response rate (RR) and progression free survival (PFS), the numerically longer median OS seen (12.1 vs 10.1 months) was not statistically significant. A subgroup analysis suggested some geographical variation, with patients in the Pan-American subgroup showing a statistically significant benefit in OS whereas those in the European and Asian subgroups did not. This suggestion of differential response to treatment based on geographical area was further supported by the Chinese Phase III AVATAR study, which did not meet its primary survival endpoint.[36] A biomarker analysis of the AVAGAST study demonstrated that high baseline circulating VEGF-A levels and low tumour NRP1 expression appeared to correlate with bevacizumab benefit in non-Asian patients. In Asian patients however this trend was not seen: this group showed lower levels of VEGF-A overall and even those with higher levels still did not gain benefit from bevacizumab.[37] These findings are further complicated by regional differences in tissue sample analysis. Further evidence for the efficacy of angiogenesis inhibition in improving outcome in gastric cancer may be found in a recently reported Chinese Phase III

study of apatinib, a novel, highly potent VEGFR-2 tyrosine kinase inhibitor (TKI) as third-line treatment for advanced GC, which reported statistically significant median improvements in PFS and OS of 2.6 and 6.4 months respectively.[38] However given the regional variability demonstrated in GC outcomes it is unknown whether this benefit would be comparable in a non-Asian population.

Ramucirumab

Early studies

Ramucirumab is a fully humanized monoclonal antibody specifically directed against VEGFR-2. The compound was isolated from a large phage display antibody library with specificity to VEGFR-2, and following several rounds of in-vitro selection a high affinity variant was selected for further development. The final ramucirumab product binds to and alters the conformation of the receptor, preventing VEGF binding and inhibiting subsequent VEGF induced signaling. Three Phase I trials have been completed, of which one has been published.[39] In this study ramucirumab showed early evidence of efficacy in 37 patients, of whom 4 had advanced gastric or esophageal cancer. Patients were treated once weekly with a range of escalating doses between 2 mg and 16 mg per kg. Five dose limiting (> grade 3) toxicities were observed: 2 incidences hypertension and 1 incidence each of DVT, proteinuria and vomiting. On the basis of this the maximum tolerated dose was determined to be 13 mg/kg weekly. In this study 15% of patients showed a partial response and 30% had a partial response or stable disease lasting greater than 24 weeks.

Second-line treatment

Phase III evaluation of ramucirumab has demonstrated statistically and clinically significant efficacy both as monotherapy and in combination with paclitaxel in previously treated advanced gastric and GOJ cancers. REGARD was a double-blind placebo-controlled Phase III study involving 355 patients with gastric or GOJ adenocarcinoma.[40] Participants were randomized in a 2:1 fashion to receive either ramucirumab 8 mg/kg IV or placebo 2 weekly following progression after first-line chemotherapy. There was no crossover allowed and primary endpoint was OS. Eligible patients were required to show progressive disease within 4 months of first-line treatment and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Key exclusion criteria included significant gastrointestinal bleeding within 3 months of randomization, any arterial thromboembolism such as myocardial infarction, transient ischemic attack, or cerebrovascular accident within 6 months of randomization or uncontrolled hypertension. The study recruited at 29 centers globally across the Americas, Asia, Europe, and Africa with approximately 69% of patients recruited from Europe, North America, or Australasia. Ramucirumab treatment led to a significantly longer median OS compared to placebo (5.2 vs 3.8 months) with 6 month PFS also improved from 31.6% to 41.8%. It is notable that this reflects almost exactly the survival benefit attributable to systemic chemotherapy in the same setting.[15,16] After adjustment for factors such as performance status, site of primary tumor and presence of peritoneal metastases, the survival benefit for ramucirumab remained significant. Although RRs were low at only 4%, the overall rate of stable disease was over twice that of placebo (45% vs 21%) leading to significantly improved disease control rates.

Concurrently with REGARD,[40] the double-blind randomized Phase III RAINBOW study recruited 665 patients with advanced GC or GOJ adenocarcinoma to receive either paclitaxel 80 mg/m^2 on days 1, 8 and 15 of a 28-day cycle plus either ramucirumab at 8 mg/kg or placebo intravenously on day 1 and 15.[41] Again this was a large global study run across 27 countries with 60% of patients drawn from Europe, North America, and Australasia; 33% from Asia; and 7% from South and Central America. Eligibility criteria were similar to those in REGARD with the additional stratification factor of time to progression on first-line therapy. OS was significantly prolonged with the addition of ramucirumab (9.63 vs 7.26 months) with additional significant improvements in PFS and RR. A subset analysis by geographical region showed that overall survival benefit was not significant for those from Asia when compared to non-Asian participants, however it is important to note that this differential related only to OS and not PFS. The use of subsequent lines of therapy was comparable between treatment arms at 45.7% for ramucirumab and 46% for placebo, but was substantially higher in Asian patients (almost 70% vs almost 40%) and may go some way to explaining the differential in OS seen. A subsequent efficacy analysis contrasting Japanese with European, American and Australian patients found no median OS benefit in the Japanese population, but did see statistically significant improvements in PFS, ORR and OS at 6 months.[42] Again there was a higher uptake of subsequent lines of treatment amongst the Japanese group of patients. Table 1 illustrates the efficacy outcomes of RAINBOW and REGARD in comparison to selected Phase III trials of both chemotherapy and targeted agents in second-line advanced GC treatment.

Table 1 Randomized Phase III trials in the second-line treatment of advanced esophago-gastric cancer

Trial	Eligible patients	Target	Treatment	N	Response rate (%)	Median PFS (months)	Median OS (months)
Chemotherapy							
Thuss-Patience et al[14]	Advanced GC/GOJ	n/a	BSC	19	NR	NR	2.4
			Irinotecan	21	0	2.5	4.0
COUGAR-02[16]	Advanced GC/GOJ/esophageal adenocarcinoma	n/a	BSC	84	NR	NR	3.6
			Docetaxel	84	7	NR	5.2
Kang et al[15]	Advanced GC	n/a	BSC	62	NR	NR	3.8
			Chemotherapy, either:	126	13	NR	5.3
			Docetaxel or	66			5.2
			Irinotecan	60			6.5
WJOG 4007[17]	Advanced GC	n/a	Irinotecan	111	13.6	2.3	8.4
			Paclitaxel	108	20.9	3.6	9.5
Targeted agents							
REGARD[40]	Advanced GC/GOJ	VEGFR2	Placebo/BSC	117	2.6	1.3	3.8
			Ramucirumab/BSC	238	3.4	2.1	5.2
RAINBOW[41]	Advanced GC/GOJ	VEGFR2	Paclitaxel/placebo	335	16	2.9	7.4
			Paclitaxel/ramucirumab	330	28	4.4	9.6
TyTAN[51]	HER2 positive advanced GC	HER2	Paclitaxel	129	9	4.4	8.9
			Paclitaxel/lapatinib	132	27	5.4	11.0
COG[52]	Advanced esophageal/GOJ adenoca or SCC	EGFR	Placebo	224	16.0*	1.1	3.6
			Gefitinib	225	25.5*	1.6	3.7
GRANITE-1[24]	Previously treated advanced GC	mTOR	Placebo + BSC	217	2.1	1.4	4.3
			Everolimus + BSC	439	4.5	1.7	5.4

Note: *Disease control rate (partial response or stable disease).
Abbreviations: BSC, best supportive care; GC, gastric cancer; NR, not reported; n/a, not available; GOJ, gastro-esophageal junction; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

Safety

Ramucirumab was generally was well tolerated, reflected in the high dose intensity achieved across both Phase III second-line trials. In REGARD hypertension was more common, however rates of other adverse events including hemorrhage, venous thromboembolism, perforation and fistula formation were similar across both arms. Overall 2% (n=5) of deaths in the treatment arm were assessed as being related to the drug, consisting of two intestinal perforations, one myocardial infarction, one gastric hemorrhage and one pneumonia. Quality of life data was collected at 6 weekly intervals in REGARD but the percentage of patients returning this information at the first assessment point was low across both arms due to treatment discontinuations.[40] Of these respondents a non-significantly larger number reported stable or improved global quality of life. Importantly, time to deterioration of performance status was significantly improved. In RAINBOW grade ≥3 adverse events were recorded in 82% of patients in the ramucirumab/paclitaxel arm vs 63% in the paclitaxel arm, with hypertension, proteinuria, bleeding and gastrointestinal perforation all more commonly seen. Grade ≥3 neutropenia was also increased (41% vs 19%), however the incidence of febrile neutropenia was low in both arms (3% vs 2%). Despite the increase in toxicity rates seen, the incidence of discontinuation or death due to treatment related adverse events was comparable between both arms. Quality of life data showed more patients reporting a maintained or improved quality of life with the addition of ramucirumab, suggesting that its addition did not increase the incidence of side effects in a clinically meaningful way.[41] Table 2 illustrates the comparative side effect profile of ramucirumab and the ramucirumab/paclitaxel combination in comparison to selected trials of second-line chemotherapy.

Assessment of ramucirumab in the first-line setting

Ramucirumab has also been assessed in the first-line setting in a US double-blind Phase II trial involving 168 advanced esophageal or gastric adenocarcinoma patients, randomizing to FOLFOX chemotherapy plus either ramucirumab or placebo.[43] Despite a statistically significant improvement in disease control rate, the primary endpoint of improvement in median PFS was not met (6.4 vs 6.7 months, HR 0.98, 95% CI 0.69–1.37, P=0.89) and no improvement in OS was seen. Treatment was generally well tolerated, with the most common grade >3 adverse events being neutropenia, fatigue and peripheral neuropathy. The rates of these events were similar between both arms of the trial however cessation of

Table 2 Selected grade 3–4 adverse events from second-line trials in advanced gastric cancer

Trial	WJOG 4007[17]		Kang et al[15]		COUGAR-02[16]	RAINBOW[41]		REGARD[40]
Treatment	Paclitaxel	Irinotecan	Docetaxel	Irinotecan	Docetaxel	Paclitaxel	Paclitaxel/ ramucirumab	Ramucirumab
N	108	111	60	66	81	329	327	236
Toxicities (%)								
Neutropenia	28	39.1	15	18	15	18	41	–
Febrile neutropenia	2.8	9.1	2	2	7	2	3	–
Anemia	21.3	30	30	32	6	10	9	6
Thrombocytopenia	0.9	1.8	2	3	–	2	5	–
Diarrhea	0.9	4.5	3	8	–	2	4	–
Nausea	1.9	4.5	5	3	–	2	3	–
Vomiting	2.8	0.9	–	–	–	4	3	3
Anti-angiogenic toxicities of interest (%)								
Venous TE						3	2	1
Arterial TE						1	1	0
Hypertension						3	15	8
Hemorrhage						2	4	3
GI perforation						1	0	<1

Abbreviations: GI, gastrointestinal; TE, thromboembolism.

treatment for reasons other than disease progression was significantly higher in the ramucirumab arm, potentially negatively impacting upon PFS. The published abstract data does not give details on the possible reasons for the higher rates of discontinuation in the ramucirumab arm. The authors of the study have highlighted less severe adverse events occurring in the ramucirumab arm, including thrombocytopenia (56%), decreased appetite (42%), dehydration (28%), and hypokalemia (20%). All of this was in keeping with the known safety profile of ramucirumab however, and no new safety signals were identified. An exploratory analysis of PFS censored at treatment discontinuation for reasons other than progressive disease showed a HR which favored the ramucirumab arm in the GC and GOJ subgroup only (9.3 vs 7.6 months, HR 0.53, 95% CI 0.29–0.97, P=0.036). Further evaluation in the first-line setting is ongoing with the Phase III RAINFALL study (NCT02314117) recently opened to recruitment, comparing capecitabine and cisplatin with or without the combination of ramucirumab in a previously untreated AGC population. This will provide valuable information about ramucirumab efficacy in combination with a more 'standard' fluoropyrimidine/platinum doublet used in both first-line metastatic and neoadjuvant/perioperative settings. At present ramucirumab has not been assessed in the multimodality treatment of operable gastric cancer. The Phase III ST03 trial assessed the combination of bevacizumab with perioperative epirubicin, cisplatin and capecitabine chemotherapy, with data presented at the 2015 European Cancer Conference showing no improvement in curative resection rates or survival outcomes.[44] An elevated postoperative anastomotic leak rate in the bevacizumab group resulted in recruitment being closed to such patients towards the end of the trial. Given their known toxicity profile careful consideration will be required when considering use of anti-angiogenic agents in operative gastric cancer in the future.

Geographical variability

Both REGARD and RAINBOW were major international studies incorporating patients from a wide variety of geographical areas and ethnicities. They thus provide robust and nuanced data regarding variability in response to guide treatment decisions. The REGARD study showed a similar survival benefit in Asian and non-Asian patients whereas in RAINBOW overall survival was not improved in Asian patients, however RRs and PFS were. It is instructive to compare this to the AVAGAST study where neither RR, PFS or OS were improved for Asian patients by the addition of bevacizumab. An additional RAINBOW subgroup analysis gives further information about geographical differences in outcome between Japanese patients in comparison to "Western" patients from Australia, Europe, Israel and the USA.[42] Again Japanese patients demonstrated a PFS benefit but no OS benefit. Importantly the Japanese group had a better performance status, shorter time to progression after first-line therapy, a lower burden of metastatic disease and went on to receive further lines of chemotherapy than their Western counterparts. In a further exploratory analysis the magnitude of effect on OS seen was greater across both geographical groups for patients who did not go on to receive any further lines of treatment. The survival benefit of ramucirumab for Japanese

and East Asian patients does appear to be less pronounced than for Western patients, however this is in the context of a fitter patient group receiving multiple lines of subsequent treatment, likely diluting any OS effect seen. The finding of lower levels of VEGF-A in the Asian cohort of AVAGAST patients has been implicated in the comparatively poorer results seen in comparison to Western patients, but it is not clear at this point whether geographic region is a surrogate for differences in disease biology influencing sensitivity to specific anti-angiogenic agents. Whether the specificity of ramucirumab to VEGFR-2 circumvents these possible biological or geographical differences remains to be seen.

Optimal combination treatment

A further question arises on the suitability of a platinum analog as the backbone to additional anti-angiogenic treatment, particularly as the combination of ramucirumab with FOLFOX in the first-line setting did not meet its survival endpoint. Again comparison can be made to the negative results of the AVAGAST trial of bevacizumab plus cisplatin–fluoropyrimidine chemotherapy. There is now both in-vivo and in-vitro evidence that paclitaxel displays innate anti-angiogenic properties, mediated through direct effects on endothelial cell function as well as inhibition of VEGF-induced neovascularization.[45] An improved synergy with ramucirumab as a result of this may have contributed to the positive results seen in the RAINBOW trial. The results of the RAINFALL trial of first-line treatment in combination with cisplatin and capecitabine may prove informative on the suitability of combining ramucirumab with platinum-based chemotherapy backbones.

Biomarkers and resistance

A significant challenge in the utilization of anti-angiogenic therapy so far has been the lack of validated biomarkers with which to predict response to treatment. Plasma VEGF-A levels have an established prognostic value across a number of cancer types and both VEGF-A and NRP1 have been implicated in bevacizumab response, however such analysis so far has been hypothesis-generating only.[37,46] An exploratory analysis of the REGARD data presented at ASCO 2015 examined potential candidate biomarkers from both tumour and serum with no significant predictive biomarkers for efficacy identified, however the analysis was limited by small sample numbers.[47] Prospective biomarker analysis in post-registration studies of ramucirumab may yield more clinically applicable results going forwards. Resistance to anti-angiogenic therapy is complex and can be mediated by both VEGF-axis and stromal dependent mechanisms, as well as numerous other molecular signaling pathways.[48] Early-phase clinical approaches targeting both VEGF and associated signaling pathways implicated in angiogenic resistance such as Tie2, Notch and TGF-β are ongoing.[48]

Disparity between differing anti-angiogenic approaches

After the disappointment of negative trials of bevacizumab in AGC, the success of ramucirumab in the REGARD and RAINBOW studies represents a justification and platform for further investigation of angiogenesis-targeting in this disease. The underlying reasons for disparity in efficacy between the two agents are unclear. Bevacizumab targets VEGF-A only, whereas ramucirumab binds to VEGFR-2 specifically with high affinity to block all known VEGFs, and this improved target inhibition may lead to a more effective blockade of angiogenesis. Consideration must also be given to the design of the respective studies of the two agents. In AVAGAST bevacizumab was administered at 7.5 mg/kg every 3 weeks, a slightly lower dose than that which was used in previous Phase II studies and as such may have attenuated efficacy. The chemotherapies used as a backbone to the two agents may also be relevant, as the intrinsic anti-angiogenic effects of paclitaxel and its potential synergy with ramucirumab may have contributed to improved outcomes. Importantly the patient population of the trials differed, with 16% more Asian patients in the AVAGAST study than in RAINBOW.

Discussion and future directions

There is now a well-established role for a number of second-line chemotherapies in AGC and consideration is required of where ramucirumab will fit into existing treatment pathways. With the exception of trastuzumab in the minority of HER2 positive patients, trials of targeted agents in AGC have been disappointing, and the addition of an effective treatment option for a molecularly unselected population is welcome. Based on REGARD and RAINBOW the US Food and Drug Administration approved ramucirumab as second-line monotherapy in April 2014 before extending its approval to include combination with paclitaxel chemotherapy in November 2014, with European Medicines Agency approval for the same following in December 2014. Ramucirumab alone or in combination with paclitaxel now provides an alternative treatment option to other established chemotherapies in the second-line setting such as docetaxel or irinotecan. The greater magnitude of clinical benefit seen in ramucirumab with paclitaxel makes this an attractive approach for patients

suitable for combination therapy who are also willing to accept the potential possibility of more treatment-related side effects. When considering the carefully-selected patients in both REGARD and RAINBOW, they represent a younger, fitter population than routinely encountered in the "real world" second-line treatment of AGC. Thus it remains to be seen what percentage of those who fail first-line therapy will be suitable for and will gain benefit from ramucirumab in routine clinical use, where issues around toxicity and tolerability may potentially prove more challenging.

Furthermore, in the absence of directly comparative trials the routine use of ramucirumab is likely to be limited by restricted access when compared to the more easily available and inexpensive chemotherapy options, particularly in resource-limited health care systems. Specific to the UK, the National Institute for Health and Care Excellence is currently appraising the use of second-line ramucirumab in AGC, with a decision expected in early 2016.[49] A number of ongoing trials may aid in developing and defining its clinical treatment role further. Its utility in the first-line setting will be evaluated in the RAINFALL study, which will also give valuable information regarding its effectiveness when combined with a standard up-front platinum–fluoropyrimidine doublet. Importantly, RAINFALL allows for continuation of the fluoropyrimidine/ramucirumab component of the treatment as "maintenance" after 6 cycles of cisplatin, a treatment approach that is more in-keeping with advanced colorectal cancer practice. Another area of interest is in the continuation of anti-angiogenic agents after progression in the first line. Again there is evidence in colorectal cancer that continuation of bevacizumab beyond progression with a second-line chemotherapy is associated with improved PFS.[50] Given the positive results seen with ramucirumab in second-line gastro-esophageal cancer a similar continuation approach may be indicated and represents an interesting potential future avenue of research. The statistically significant improvement in RR seen in combination with paclitaxel may suggest a role in early stage disease as a neoadjuvant or perioperative chemotherapy adjunct however given concerns regarding class-effect toxicities of anti-angiogenic drugs on surgical outcomes this may not be an indication that is pursued further.

It is hoped that as the molecular pathways of gastric cancer become better understood through the application of more sophisticated genomic analysis and integrative approaches for the identification of therapeutic targets and predictive biomarkers the promise of a more "personalized" approach to treatment may come to be realized. In future there may be a number of novel treatment options, each available to only a highly selected, molecularly enriched population. Ramucirumab is at an advantage at present as with the lack of a predictive biomarker it exerts a second-line effect in a molecularly unselected population, however ongoing trials of novel targeted agents and biomarker research may refine its role in the future. A further promising area of treatment development is in the use of immunotherapy, with a number of trials in progress (NCT02335411, NCT02370498, NCT02443324). Should these prove positive they have the potential to change the treatment landscape for AGC quite profoundly, and the relative efficacy of ramucirumab in comparison to these agents or indeed in conjunction with them remains to be seen. The results of a number of trials of ramucirumab in combination with differing chemotherapies, immune-therapies and targeted agents are all awaited with interest. Further post registration studies also have the potential to provide valuable safety and efficacy data based on real world usage, and highlight safety issues which may not have been identified in studies thus far. Given more general and legitimate concerns over increasing costs in cancer care, cost-effectiveness analysis should also be incorporated where possible into future clinical trials.

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