Editorial

RAINFALL before RAINBOW—an illusion or reality?

Kohei Shitara

Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwanoha, Kashiwa, Chiba, Japan

Correspondence to: Kohei Shitara. Department of Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. Email: kshitara@east.ncc.go.jp.

Provenance: This is a Guest Editorial commissioned by Section Editor Rulin Miao, MD [Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Gastrointestinal Tumor Center, Peking University Cancer Hospital & Institute, Beijing, China].

Comment on: Yoon HH, Bendell JC, Braiteh FS, *et al.* Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. Ann Oncol 2016;27:2196-203.

Received: 18 February 2017; Accepted: 21 February 2017; Published: 30 March 2017.

doi: 10.21037/tgh.2017.03.04

View this article at: http://dx.doi.org/10.21037/tgh.2017.03.04

Combination with fluoropyrimidines and platinum-based agents have been used as first-line therapy for metastatic gastric/gastroesophageal junction cancer (GC) resulting in a median progression-free survival (PFS) of 5–6 months and a median overall survival (OS) of 10–15 months. Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), significantly improved the OS of HER2-positive GC patients, which consists of around 15% of patients (1). However, other randomized studies failed to show benefits of several molecular targeting agents for GC in first-line (2-7), thus development of more effective combination is important.

Ramucirumab, a fully human immunoglobulin G1 monoclonal antibody to the extracellular binding domain of vascular endothelial growth factor receptor 2 (VEGFR-2), become one of the standard treatment for pretreated GC based on two pivotal trials (RAINBOW and REGARD). Ramucirumab monotherapy in REGARD improved OS compared with placebo (8). Additionally, ramucirumab plus paclitaxel in RAINBOW was more effective than paclitaxel alone as second-line treatment for GC (9). To move effective agents from second-line to first-line is a formula in Oncology field and efficacy of ramucirumab in first-line is anticipated.

In the issue of *Annals of Oncology*, the result of a randomized phase-2 study of first-line ramucirumab were reported (10). This trial failed to show improvement in PFS when ramucirumab was combined with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) in comparison with FOLFOX plus placebo (6.4 *vs.* 6.7 months, hazard ratios; HR 0.98). OS (median 11.7 *vs.* 11.5 months) or ORRs (45.2% versus 46.4%) as secondary endpoints were also similar. Higher proportion of patients in the ramucirumab arm discontinued study treatment because of reasons other than progressive disease (48% *vs.* 16%). Although most grade ≥3 toxicities did not differ significantly between two arms, slightly higher incidence of mild grade toxicities in ramucirumab arm might contribute to this difference of treatment discontinuation. Overall, this trial did not show any benefit of ramucirumab, so is this the end of development of ramucirumab in first-line? The answer is "NO" since there are several issued to be addressed. First, the treatment might not be delivered adequately in ramucirumab arm. According to post hoc exploratory analysis which censored treatment discontinuation due to reasons other than progressive disease (on-treatment PFS), HR favored the ramucirumab arm (0.76). This phenomenon was in line with previous randomized study of anti-VEGF-A monoclonal antibody bevacizumab plus FOLFOX for colorectal cancer, which showed better HR in on-treatment PFS (0.63) rather than analysis by usual PFS definition (0.83) due to discontinuation of entire protocol treatment by low grade toxicities such as sensory neuropathy (11). In this first-line ramucirumab trial, treatment duration of all compounds seems to be similar (10). So, not a few patients are suspected to stop entire treatment due to side effects with chemotherapy. In previous AVAGAST trial of bevacizumab in combination with fluoropyrimidines and cisplatin for GC, more

than half of patients continued fluoropyrimidines and bevacizumab after completion of 6 cycles of cisplatin combination (2), and rates of treatment discontinuation due to adverse events were similar between two arms (21% in bevacizumab *vs.* 19% in placebo). Second, this study included both esophageal adenocarcinoma and GC. The HR for PFS favored the ramucirumab arm in GC subgroup (HR 0.53), but not in the esophageal cancer subgroup (10). Although the exact reason of different outcome between esophageal and GC is not clear, previous independent two meta-analyses showed prognostic impact of VEGFR expression in GC but this was not observed in esophageal adenocarcinoma (12,13). Biomarker analysis in REGARD study also showed a trend of worse outcome in GC patients with higher VEGFR2 expression, although predictive impact of ramucirumab efficacy remains unclear due to small sample size (14). Further study is necessary to compare detailed tumor profile between esophageal adenocarcinoma and GC. Finally, an exploratory exposure-response analysis indicated that patients with higher ramucirumab exposure had longer OS as same as previous analysis in REGARD and RAINBOW (15). At this time, exact impact of higher dose of ramucirumab to improve efficacy is unknown, and higher dose of trastuzumab did not result in superior outcome of HER2 positive GC patient than standard doses (16), despite the fact that exposure–response analysis showed patients with the high exposure had better OS than patient with low exposure with trastuzumab (17). These questions should be answered in ongoing randomized phase 3 trials to evaluate capecitabine/5-fluorouracil and cisplatin with or without ramucirumab as first-line therapy in patients with metastatic GC (RAINFALL, NCT02314117), which used cisplatin based regimen and intensive dose of ramucirumab (at a dose of 8 mg/kg day 1 and day 8 of a 3 weeks cycle). We should stay tuned for RAINFALL, whether it can show benefit of ramucirumab in first-line as same as antecedent RAINBOW in second-line.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
2. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011;29:3968-76.
3. Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14:490-9.
4. Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC--A Randomized Phase III Trial. J Clin Oncol 2016;34:443-51.
5. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14:481-9.
6. Shah MA, Bang YJ, Lordick F, et al. Effect of Fluorouracil, Leucovorin, and Oxaliplatin With or Without Onartuzumab in HER2-Negative, MET-Positive Gastroesophageal Adenocarcinoma: The METGastric Randomized Clinical Trial. JAMA Oncol 2016. [Epub ahead of print].
7. Cunningham D, Tebbutt NC, Davidenko I, et al. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. J Clin Oncol 2015;33:abstr 4000.
8. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-9.

9. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-35.
10. Yoon HH, Bendell JC, Braiteh FS, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. Ann Oncol 2016;27:2196-203.
11. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-9.
12. McCormick Matthews LH, Noble F, Tod J, et al. Systematic review and meta-analysis of immunohistochemical prognostic biomarkers in resected oesophageal adenocarcinoma. Br J Cancer 2015;113:107-18.
13. Liu L, Ma XL, Xiao ZL, et al. Prognostic value of vascular endothelial growth factor expression in resected gastric cancer. Asian Pac J Cancer Prev 2012;13:3089-97.
14. Fuchs CS, Tabernero J, Tomášek J, et al. Biomarker analyses in REGARD gastric/GEJ carcinoma patients treated with VEGFR2-targeted antibody ramucirumab. Br J Cancer 2016;115:974-82.
15. Tabernero J, Ohtsu A, Muro K, et al. Exposure-response (E-R) relationship of ramucirumab (RAM) from two global, randomized, double-blind, phase 3 studies of patients (Pts) with advanced second-line gastric cancer. J Clin Oncol 2015:abstr 121.
16. Shah MA, Xu R, Bang YJ, et al. Abstract CT108: HELOISE: phase IIIB randomized multicenter study comparing two trastuzumab (H) dose regimens combined with chemotherapy (CT) as first-line (1L) therapy in patients (pts) with HER2-positive metastatic gastric/gastroesophageal junction adenocarcinoma (mGC/GEJC). Proceedings: AACR 107th Annual Meeting 2016. April 16-20, 2016, New Orleans, LA.
17. Cosson VF, Ng VW, Lehle M, et al. Population pharmacokinetics and exposure-response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer. Cancer Chemother Pharmacol 2014;73:737-47.

doi: 10.21037/tgh.2017.03.04
Cite this article as: Shitara K. RAINFALL before RAINBOW—an illusion or reality? Transl Gastroenterol Hepatol 2017;2:26.

