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Review Article

Ramucirumab in patients with advanced gastric and gastroesophageal junction cancer: Learnings from East Asian data

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ABSTRACT

Advanced gastric and gastroesophageal junction cancers remain a major cause of concern considering their high incidence in Taiwan, poor outcomes essentially due to diagnosis at the advanced stage, and poor prognosis. These evidences along with the heterogeneity associated with the disease reflect that there is a requirement of new and robust active treatment options for advanced gastric and gastroesophageal junction cancers. Because tumor angiogenesis plays a key role in the pathogenesis and progression of these cancers, recent studies indicate that anti-angiogenesis is a promising approach for the treatment of the disease. The recent phase III trials REGARD and RAINBOW showed survival benefits (improved median overall and progression-free survival) and acceptable safety profiles with ramucirumab alone and ramucirumab plus paclitaxel, respectively in patients with disease progression on or after first-line chemotherapy. Further, these data unveil that ramucirumab plus paclitaxel could be regarded as a new standard second-line treatment for patients with advanced or metastatic gastric or gastroesophageal junction cancers in Taiwan.

1. Introduction

Gastric cancer, presently, is the fifth most common malignancy and the third leading cause of cancer mortality globally (723,000 deaths in 2012, 8.8% of total cancer deaths).[1] Geographical differences in the incidence of gastric cancer can be evinced from the fact that almost half of the new cases occurred in the East Asia in 2012. Besides, East Asia has the highest mortality rates for gastric cancer (24 per 100,000 in men, 9.8 per 100,000 in women).[1] The Taiwan Cancer Registry reported gastric cancer as the ninth most common cancer and the seventh leading cause of cancer-related deaths in 2014 in Taiwan, with 3786 new cases and 2350 deaths, respectively. In Taiwan, approximately 30% of newly diagnosed gastric cancer patients present metastatic lesions.[2] In accordance with globally established guidelines, combination with fluoropyrimidine and platinum is the preferred first-line option in Taiwan for patients with HER2-negative or low-expression tumors, although a weekly infusion of high-dose fluorouracil and leucovorin, the HDFL regimen, tends to be a favored schedule.[3,4] The real-world treatment patterns collected through physicians' review of 122 Taiwanese patient charts indicated that approximately two-thirds of the patients with metastatic gastric cancer received active second-line therapy versus best supportive care after failure of first-line therapy. The selection of second-line treatment of the patients was majorly based on physicians' experiences, followed by hospital guidelines or insurance reimbursement, hence, heterogeneity in the regimen was observed. The most frequent regimens for second-line therapy were still a fluropyrimidine and a platinum agent, or single agent fluropyrimidine.[5]

Survival benefits have been observed with taxanes or irinotecan in patients relapsing shortly or progressing after first-line therapy. A prospective, randomized phase III study showed that irinotecan as a second-line chemotherapy significantly prolongs overall survival compared to best supportive care, concluding that second-line chemotherapy can now be considered for the treatment of patients

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with metastatic or locally advanced gastric cancer.[6] Further, selected second-line chemotherapy in a study in Korean patients with advanced gastric cancer showed significant and clinically meaningful improvement in overall survival when added to best supportive care; however, the prognosis was dismal with median survival less than 6 months since the initiation of second-line chemotherapy.[7] Ford et al., as well, demonstrated a significant improvement in overall survival with docetaxel added to active symptom control; though it was observed that toxicity was the major reason for not completing the treatment.[8] Besides, in the light of reimbursement constraints in Taiwan taking into account that neither irinotecan nor taxanes are presently reimbursed by the National Health Insurance in Taiwan, other fluoropyrimidine-containing regimens or infusion of fluorouracil and leucovorin with or without cisplatin are usually considered in second-line situation. For these reasons, there is a huge requirement of new, better, and robust active second-line treatment options for advanced gastric cancer in Taiwan.

1.1. Vascular endothelial growth factor–targeted therapy

Recent developments have indicated that inhibition of angiogenesis signaling pathways may be an exciting and at the same time, a highly effective approach to treat cancer.[9] Available data have shown that pharmacologic blockade of angiogenesis can be considered as one of the promising therapies for advanced gastric cancer management.[10] Lately, studies have supported the contribution of a pro-angiogenic factor—vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2)–mediated signaling and tumor angiogenesis to the proliferation and metastasis of cancer cells, highlighting the importance of molecular therapies targeting this pathway in gastric cancer.[11,12] Various approaches to inhibit the VEGF-VEGFR signaling axis comprise VEGF ligand–targeted therapy, inhibition of VEGFR and their downstream targets, and specific VEGFR-2-targeted therapy.[12]

1.2. Place of ramucirumab in advanced gastric cancer management

Ramucirumab, a recombinant human immunoglobulin G1 monoclonal antibody specific for VEGFR-2,[13] is approved in Taiwan since January 2016, as a monotherapy or in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction cancer with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. However, currently ramucirumab is yet to be reimbursed by Taiwan National Health Insurance.

2. Therapeutic efficacy of ramucirumab

The approval of ramucirumab in Asian jurisdictions, including Taiwan, stands on the back of two phase III randomized trials comparing (1) ramucirumab versus placebo (REGARD) and (2) ramucirumab in combination with paclitaxel versus placebo plus paclitaxel (RAINBOW) in patients with advanced gastric or gastroesophageal junction adenocarcinoma following failure of standard first-line chemotherapy.

An international, randomized, double-blind, placebo-controlled phase III (REGARD) study investigated ramucirumab plus best supportive care versus placebo plus best supportive care in the second-line setting in 355 patients (Taiwan, n = 3) with metastatic or unresectable, locally advanced recurrent gastric or gastroesophageal junction cancer (NCT00917384). The median overall survival in patients receiving ramucirumab and those receiving placebo was 5.2 months (interquartile range [IQR]: 2.3–9.9) and 3.8 months (1.7–7.1), respectively (hazard ratio [HR] = 0.776; 95% CI: 0.603–0.998; p = 0.047). A 52% reduction in the risk of disease progression or death was seen with ramucirumab, with median progression-free survival of 2.1 months (IQR: 1.3–4.2) in patients receiving ramucirumab and 1.3 months (1.1–2.1) in those receiving placebo (HR = 0.483; 95% CI: 0.376–0.620; p < 0.0001). Significantly longer duration of disease control was observed in the ramucirumab group (median 4.2 months [IQR: 2.8–8.1]) than in the placebo group (2.9 months [2.7–4.3]; p = 0.036). A larger proportion of patients in the ramucirumab group than in the placebo group reported stable or improved European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30) global health status scores, although this difference was not significant (p = 0.23). However, median time to deterioration in Eastern Cooperative Oncology Group performance status to a score of 2 or worse was 5.1 months for ramucirumab and 2.4 months for placebo (HR = 0.59; 95% CI: 0.41–0.83; p = 0.002). Furthermore, the patients with grade 3 or higher adverse events receiving ramucirumab compared to those receiving placebo were 57% and 58%, respectively. Hypertension was more common in patients receiving ramucirumab (16%), although grade 3 or higher hypertension was noted in only 8% of patients given ramucirumab. These efficacy and safety results demonstrated ramucirumab as the first biological treatment given as a monotherapy with survival benefits in patients with advanced gastric or gastroesophageal junction adenocarcinoma progressing after first-line chemotherapy.[14]

The subgroup analysis of the REGARD study involved 26 East Asian patients, of which 3 patients were from Taiwan. This analysis showed consistent benefits in terms of overall survival and progression-free survival favoring ramucirumab as a monotherapy in the East Asian patients with metastatic gastric cancer following failure of the first-line chemotherapy (Table 1). These benefits were achieved with an acceptable safety profile. However, the incidence of grade ≥3 adverse events was higher in the ramucirumab arm compared to the placebo arm (72% versus 50%). Grade ≥3 adverse events occurring in at least 10% of patients and at a higher rate in the subgroup of these patients receiving ramucirumab compared to those receiving placebo included abdominal pain, decreased appetite, and pneumonia.[15]

The second phase III, international, randomized, double-blind, placebo-controlled (RAINBOW) trial assessed ramucirumab plus paclitaxel versus placebo plus paclitaxel in the second-line setting in 665 patients (Taiwan, n = 30) with metastatic or unresectable, locally advanced gastric or gastroesophageal junction adenocarcinoma (NCT01170663). The median overall survival was significantly longer in patients receiving ramucirumab plus paclitaxel (9.6 months, 95% CI: 8.5–10.8) compared to those receiving placebo plus paclitaxel (7.4 months, 95% CI: 6.3–8.4; HR = 0.807; 95% CI: 0.678–0.962; p = 0.017). The median progression-free survival with ramucirumab plus paclitaxel was significantly longer than with placebo plus paclitaxel (4.4 months, 95% CI: 4.2–5.3 versus 2.9 months, 95% CI: 2.8–3.0; HR = 0.635; 95% CI: 0.536–0.752; p < 0.0001). A significantly greater proportion of patients achieved an objective response receiving ramucirumab plus paclitaxel (28%, 95% CI: 23–33) in comparison to those receiving placebo plus paclitaxel (16%, 95% CI: 13–20), respectively, p = 0.0001. A numerically greater proportion of patients in the ramucirumab group reported improved or stable scores from baseline to discontinuation in terms of EORTC QLQ-C30 and EuroQoL five-dimension parameters. Grade 3 or higher adverse events that occurred in more than 10% of patients in the ramucirumab plus paclitaxel group versus placebo plus paclitaxel group included neutropenia (41% versus 19%), leukopenia (17% versus 7%), hypertension (14% versus 2%), and fatigue (12% versus 5%).[16]

The subgroup analysis of the RAINBOW study involved a total of