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Editorial

Clinical Implication of Liver Metastasis in the Treatment of Gastric Cancer

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▸ See the article "Exploratory Analysis of Patients With Gastric/Gastroesophageal Junction Adenocarcinoma With or Without Liver Metastasis From the Phase 3 RAINBOW Study" in volume 23 on page 289.

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The RAINBOW study is a phase 3 trial comparing the combination therapy of ramucirumab plus paclitaxel with paclitaxel monotherapy as palliative second-line treatment in patients with gastric or gastroesophageal junction adenocarcinoma [1]. A significant increase in both the median overall survival (OS, 9.6 vs 7.4 months) and progression-free survival (PFS, 4.4 vs. 2.9 months) was observed in patients who received ramucirumab plus paclitaxel. Based on this pivotal study, ramucirumab plus paclitaxel is the standard second-line treatment. The liver is one of the most common sites of metastasis of gastrointestinal cancer [2]. According to a study based on the Surveillance, Epidemiology, and End Results database, it is known that about 45% of metastatic gastric cancers are accompanied by liver metastasis (LM) [3]. In addition to peritoneal carcinomatosis, LM is an established poor prognostic factor of gastric cancer [4].

In this issue of the *Journal of Gastric Cancer*, Ogata et al. [5] investigated the impact of LM and the potential role of the VEGF family as biomarkers for treatment through a secondary analysis of data from the RAINBOW study. The most interesting finding of this study was that ramucirumab plus paclitaxel improved the poor prognostic effect of LM, especially on PFS. Overall, patients with LM showed inferior PFS compared to those without LM, which was mainly prominent in the paclitaxel plus placebo group. The difference in PFS was offset in the paclitaxel plus ramucirumab group. This trend was similar to the results of the comparison of the median PFS of ramucirumab plus paclitaxel and placebo plus paclitaxel among patients with and without LM. The risk reduction for disease progression with ramucirumab plus paclitaxel in patients without LM was 24%, whereas a risk reduction of 53% was observed in patients with LM. The overall response rate (ORR) to ramucirumab plus paclitaxel was also higher in patients with LM than in those without LM (38% vs. 19.4%). In the RAINBOW study, the ORR was 28%. These findings make it possible to suggest that patients with LM may respond better to ramucirumab plus paclitaxel. Unfortunately, biomarkers have not yet been established to predict treatment response to ramucirumab with or without paclitaxel. The authors also failed to identify potential biomarkers in the VEGF family. Furthermore, the effect of ramucirumab plus paclitaxel, which seemed to overcome the negative impact of LM on PFS, was not confirmed for OS. Notably, these results were derived from a post hoc analysis and should be interpreted with caution. The results of the subgroup analysis in the RAISE study, which demonstrated the role of ramucirumab-containing chemotherapy as

a second-line treatment for metastatic colorectal cancer, conflicted with the results of this study. In the RAISE trial, there was no significant benefit in either OS or PFS in the subgroup of patients with liver-only metastases [6].

How can we apply this result when choosing a second-line treatment for patients with gastric cancer? Ramucirumab plus paclitaxel is not the only choice to be selected as a second-line setting. Trastuzumab deruxtecan has recently become available as a second-line treatment for human epidermal growth factor receptor 2-positive gastric cancer in the United States and Europe [7-9]. Immune checkpoint inhibitors can also be used in clinical settings. Cytotoxic chemotherapies such as irinotecan or docetaxel and ramucirumab monotherapy are viable options. Although the results of this study cannot be used to establish a biomarker for individualizing the type of second-line chemotherapy, it is worth considering that ramucirumab plus paclitaxel may alleviate the negative effects of LM in patients with gastric cancer.

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