

[EDITORIAL]

Ramucirumab Plus Paclitaxel: A Possible New Chemotherapy Regimen for Neuroendocrine Carcinoma of the Stomach

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In this issue of Internal Medicine, Matsubara et al. reported a case of neuroendocrine carcinoma (NEC) of the stomach that was successfully treated with a combination of ramucirumab and paclitaxel as a third-line treatment (1). This is the first case report on the effectiveness of this regimen for NEC. Gastric NEC is a rare disease, and is refractory to chemotherapy. Advanced NEC in other organs has been treated with platinum-based regimens, such as cisplatin plus etoposide or cisplatin plus irinotecan, as first-line chemotherapy (2). Although there is no evidence-based second-line chemotherapy, amrubicin has been shown to be effective (3).

There is some evidence to suggest that carboplatin can be used instead of cisplatin, and some other drugs, such as gemcitabine, oxaliplatin could be candidates for NEC with an adenocarcinoma component. As the authors commented, no adenocarcinoma component was detected in repeated biopsy specimens (1). Thus, the good response to ramucirumab plus paclitaxel was not due to heterogeneity of the NEC with some adenocarcinoma component. In this case, the Ki-67 labeling index was >90%, indicating that the proliferative activity of the tumor cells was very high.

Ramucirumab is a monoclonal antibody against vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which inhibits VEGF-A, -C, -D binding and endothelial cell proliferation. Anti-angiogenic therapy shows a great anti-tumor effect on aggressive cancers, especially when combined with cytotoxic agents. The combination of ramucirumab with paclitaxel is a standard second-line chemotherapy regimen for advanced gastric cancer (4), and is recommended in the clinical practice guidelines. The important point in the paper of Matsubara et al. (1) is that they confirmed the high expression of VEGFR2 based on an immunohistochemical analysis of a gastric biopsy specimen. NEC is usually a hypervascular tumor; thus, anti-angiogenic therapy

may be expected to have some effect. The tissue expression of VEGFR2 might be a good biomarker of the efficacy of ramucirumab, not only in gastric NEC, but also in gastric, colorectal, and non-small cell lung cancers.

Kim et al. (5) compared gastric NEC and gastric adenocarcinoma in terms of relapse-free survival, and found that the rate of relapse-free survival in advanced gastric NEC is similar to that in gastric adenocarcinoma. I agree with the discussion and decision of Matsubara et al. (1), who attempted to extrapolate the efficacy of the ramucirumab plus paclitaxel regimen in gastric cancer to gastric NEC and decided to initiate the regimen as a third-line chemotherapy. The regimen was approved by their institutional review board, and the patient himself was delighted to receive this regimen. The doses of ramucirumab (8 mg/kg, biweekly) and paclitaxel (80 mg/m², weekly in a 28-day cycle) were in accordance with the standard method in gastric cancer. Ramucirumab is used in combination with irinotecan, folinate, and 5-fluorouracil for colorectal cancers, and with docetaxel for non-small cell lung cancer. The efficacy of the ramucirumab plus paclitaxel regimen might be primary site-specific.

An investigator-initiated randomized controlled trial is needed to verify the efficacy and safety of the ramucirumab plus paclitaxel regimen for gastric NEC.

The author states that he has no Conflict of Interest (COI).

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