Ramucirumab for advanced gastric or GEJ adenocarcinoma in previously treated patients with disease progression

See Commentary on page 427

Ramucirumab was approved by the US Food and Drug Administration for use as a single agent in the treatment of patients with advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after treatment with fluoropyrimidine- or platinum-containing chemotherapy.[1,2] Ramucirumab is a recombinant human IgG1 monoclonal antibody directed at vascular endothelial growth factor receptor 2 (VEGFR2). By binding VEGFR2, ramucirumab blocks binding of the VEGFR ligands VEGF-A, VEGF-C, and VEGF-D and thus inhibits ligand-stimulated activation of VEGFR2, including ligand-induced proliferation and migration of endothelial cells. Ramucirumab was shown to inhibit angiogenesis in vivo in animal models. The approval was based on the finding of improved overall survival (OS) in the international double-blind phase 3 REGARD trial (study I4T-IE-JVBD).[2,3] Ramucirumab is the first biological treatment given as a single drug that has produced survival benefit in advanced gastric or GEJ adenocarcinoma progressing after first-line treatment, and the study findings validate VEGFR2 signaling as an important target in advanced gastric cancer.

In the trial, 355 patients with previously treated advanced or metastatic gastric or GEJ adenocarcinoma were randomized between October 2009 and January 2012 to receive IV infusion of ramucirumab 8 mg/kg every 2 weeks plus best supportive care (n = 238) or placebo plus best supportive care (n = 117). Randomization was stratified by weight loss over the previous 3 months (≥10% vs <10%), geographic region, and location of the primary tumor (gastric or GEJ). Eligible patients had to have disease progression either within 4 months after the last dose of first-line therapy for locally advanced or metastatic disease or within 6 months after the last dose of adjuvant therapy and had to have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with a bilirubin level of ≥1.5 mg/dL, uncontrolled hypertension, or who would be having major surgery within 28 days or who were receiving chronic antiplatelet therapy other than once daily aspirin were excluded.

The ramucirumab and placebo groups were generally balanced for age (median, 60 years in both), sex (71% and 68% male), ethnicity (76% and 78% white, 16% and 15% Asian), ECOG performance status (0 in 28% and 26%, 1 in 72% and 73%), weight loss in previous 3 months (≥10% in 17% in both), measurable disease (92% and 91%), primary tumor (gastric in 75% and 74%), and progression-free

What's new, what's important

Ramucirumab is a recombinant monoclonal antibody of the IgG1 class that binds to vascular endothelial growth factor receptor (VEGFR-2) and blocks activation of the receptor. The US Food and Drug Administration has approved ramucirumab for advanced gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma, as a single-agent after prior fluoropyrimidine- or platinum-containing chemotherapy. It is given intravenously at 8 mg/kg every 2 weeks.

This approval was based on improvement in overall survival in a randomized (2:1), double-blind, multicenter study that enrolled 355 patients with previously treated advanced or metastatic, gastric, or GEJ adenocarcinoma. Patients received ramucirumab plus best supportive care (BSC) or placebo plus BSC. The median overall survival was 5.2 months in the ramucirumab group, and 3.8 months in the placebo group ($P = .047$). Median progression-free survival was also longer in the ramucirumab group compared with the placebo group, ($P < .001$).

The most common adverse reactions (all grades) observed in ramucirumab-treated patients were hypertension and diarrhea. The grade 3-4 adverse reactions reported at a higher incidence in the ramucirumab arm included hypertension and hyponatremia. The most common serious adverse events with ramucirumab were intestinal obstruction (2.1%) and anemia (3.8%). It is important to know that other important risks described in labeling include hemorrhage, arterial thrombotic events, infusion-related reactions, gastrointestinal perforation, impaired wound healing, clinical deterioration in patients with cirrhosis, and reversible posterior leukoencephalopathy.

Ramucirumab is a reasonable option for patients with advanced gastric cancer or GEJ adenocarcinoma, as a single-agent after prior fluoropyrimidine- or platinum-containing chemotherapy.

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How I treat metastatic gastroesophageal adenocarcinoma – second-line therapy

Patients with metastatic gastric or esophageal adenocarcinoma represent a challenging group of patients to treat. Many patients have a poor performance status, and second-line chemotherapy is not always appropriate. I typically use only single-agent chemotherapy in the second-line setting, with the goal of reducing symptom burden and prolonging life. I minimize the use of imaging in this patient population – preferring to use history, physical exam, and tumor markers when feasible.

Choice of agent is empirical providing that the patient's tumor does not express HER2-neu. I typically use agents that have a different mechanism of action from the first-line treatment agents the patient has received, and I often prefer agents that are well tolerated. If I use a doublet first-line treatment, carboplatin-gemcitabine is well tolerated without alopecia, which female patients prefer to avoid. Second-line agents can then be 5-fluorouracil, a taxane, or CPT11. Paclitaxel and taxotere have activity, but a different set of toxicities. I tend to use less doxorubicin in gastric cancer because of the drug's higher side-effect profile compared with other agents. CPT11 is another option I use less commonly – and when I do use it, I decrease the dose by 25% for the first cycle to see if there will be diarrhea or cytopenias and use a weekly schedule that results in less cytopenia. It seems rare that patients can tolerate chemotherapy beyond 2 lines of therapy

— Kevin B Knopf, MD, MPHR

interval after previous treatment (<6 months in 65% and 71%). Previous treatment included a platinum–fluoropyrimidine combination in 84% and 75% of patients, a fluoropyrimidine plus another systemic drug in 5% and 15%, a fluoropyrimidine alone in 7% and 6%, and a platinum drug plus another systemic drug in 4% in both. Overall, 85% had disease progression during or following first-line therapy for metastatic disease.

The median number of study drug doses was 4 (range, 1-34) for ramucirumab and 3 (range, 1-30) for placebo. After discontinuation of study drug, systemic treatment was used more frequently in the placebo group than in the ramucirumab group. Median OS in the ramucirumab group compared with the placebo group was 5.2 compared with 3.8 months (hazard ratio [HR], 0.78; $P = .047$). The difference remained similar and significant on multivariate analyses adjusting for other risk factors, including stratification factors. HRs for OS favored ramucirumab in most of the subgroups. The risk of death was significantly reduced with ramucirumab in men (HR, 0.68; 95% confidence interval [CI], 0.50-0.92) and nonsignificantly increased in women (HR, 1.43; 95% CI, 0.85-2.41); however, the difference by gender was not significant ($P = .063$).

Median progression-free survival was also significantly prolonged in the ramucirumab group (2.1 vs 1.3 months; HR, 0.48; $P < .001$) compared with the placebo group. Complete response was observed in 1 (<1%), compared with 0 patients, partial response in 7 (3%) compared with 3 patients (3%), and stable disease in 108 (45%) compared with 24 patients (21%), yielding disease control rates of 49% and 23% ($P < .0001$). Duration of disease control was significantly longer in the ramucirumab group (median, 4.2 vs 2.9 months; $P = .036$).

The prescribing information for ramucirumab notes that recently reported findings of another study (I4T-IE-JVBE; www.cancer.gov/clinicaltrials) in 665 patients with previously treated advanced or metastatic gastric or GEJ adenocarcinoma indicate a survival advantage for the combination of paclitaxel plus ramucirumab, compared with paclitaxel plus placebo.

The most common adverse events of any grade that occurred more frequently in the ramucirumab group were hypertension (16% vs 8% in the placebo group), diarrhea (14% vs 9%), headache (9% vs 3%), and hyponatremia (6% vs 2%). The most common grade 3 or 4 adverse events occurring more frequently in the ramucirumab group were hypertension (8% vs 3%), abdominal pain (6% vs 3%), and hyponatremia (3% vs 1%). The most common serious adverse events in ramucirumab patients were anemia (4%) and intestinal obstruction (2%). Red blood cell transfusions were required in 11% of the study group, compared with 9% of the placebo group. Other clinically relevant adverse events reported in 1% to 5% of patients who received ramucirumab were neutropenia (5% vs 1% in placebo patients), epistaxis (5% vs 1%), rash (4% vs 2%), and arterial thromboembolic events (2% vs 0%). On laboratory assessment, proteinuria occurred in 8% vs 2% of patients and resulted in discontinuation of ramucirumab in 2 patients. Gastrointestinal perforation occurred in 0.8% and infusion-related reactions in 0.4% of ramucirumab patients.

Five deaths in the ramucirumab group (2%) – 2 due to intestinal perforation, 1 to myocardial infarction,1 to gastric hemorrhage, and 1 to pneumonia – and 2 deaths in the placebo group (2%), due to intestinal perforation and pulmonary embolism, were considered to be related to study drug treatment.

The recommended dose of ramucirumab is 8 mg/kg every 2 weeks as an IV infusion over 60 minutes, with treatment continued until disease progression or unacceptable toxicity. Premedication with an IV histamine H1 antagonist (eg, diphenhydramine hydrochloride) is required before each infusion. Patients who experience a grade 1 or 2 infusion reaction should also be premedicated with dexamethasone

(or equivalent) and acetaminophen. Dose modifications or interruptions are required for infusion-related reactions, hypertension, proteinuria, and wound healing complications. Ramucirumab should be permanently discontinued in patients who experience arterial thromboembolic events, gastrointestinal perforation, grade 3 or 4 bleeding, or reversible posterior leukoencephalopathy syndrome. Blood pressure should be routinely monitored in patients receiving ramucirumab, and treatment should be withheld before surgery.

Ramucirumab is marketed as Cyramzaby Eli Lilly and Company. It carries a boxed warning for hemorrhage, including severe and fatal hemorrhagic events. It also has warnings and precautions for arterial thromboembolic events (including serious and fatal events), hypertension, infusion-related reactions, gastrointestinal perforation, impaired wound healing, clinical deterioration in patients with cirrhosis (including new onset or worsening encephalopathy, ascites, or hepatorenal syndrome in patients with Child-Pugh B or C cirrhosis), and reversible posterior leukoencephalopathy syndrome. Ramucirumab may cause fetal harm.

References

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