Successful Desensitization to Ramucirumab in Signet Cell Gastric Adenocarcinoma

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Gastric cancer is currently the fourth cause of cancer-related deaths. This multifactorial disease continues to be a major public health problem [1]. In 2020, GLOBOCAN reported 1 089 103 new cases and 768 793 associated deaths [2]. The principal risk factors for gastric cancer include family history, alcohol consumption, smoking, *Helicobacter pylori* and Epstein-Barr virus infection, and a diet based on smoked food [1,2].

In 2010, the World Health Organization (WHO) established a new classification of gastric cancer, as follows: conventional gastric cancer, early-onset gastric cancer, gastric stump cancer, and hereditary diffuse gastric cancer [1].

Ramucirumab is a fully humanized monoclonal antibody that inhibits vascular endothelial growth factor receptor 2 (VEGFR-2). It is used as targeted therapy in the second-line treatment of gastric and gastroesophageal cancers, either as monotherapy or in combination with paclitaxel [3]. While the drug is well tolerated, some patients have experienced thromboembolic events, hemorrhage, and gastrointestinal perforation [3].

Overall survival is longer for the combination of ramucirumab with paclitaxel (median, 9.63 months) than for paclitaxel alone [4]. In recent years, an increase in hypersensitivity reactions (HSRs) to monoclonal antibodies (mAbs) has been observed, leading to discontinuation of first-line therapies owing to concerns about severe HSRs, anaphylaxis, or death [5-7]. Reactions to mAbs occur with the first or second exposure and are characterized by rigor, fever, joint pain, and hypotension in severe cases [8].

The patient was a 73-year-old man with no relevant medical history and a recent diagnosis of stage IV (cT4cN1M1b) signet-cell gastric adenocarcinoma. The immunohistochemistry profile revealed the disease to be HER-2–negative, pMMR, PD-L1 3%. The patient was initially treated with FOLFOX (leucovorin calcium-folinic acid, fluorouracil, and oxaliplatin) plus nivolumab as first-line therapy. The disease continued to progress rapidly after 4 cycles of chemotherapy. Following a discussion with the patient, second-line chemotherapy with paclitaxel plus ramucirumab was proposed.

Fifteen minutes after the first dose of ramucirumab, the patient developed generalized rash, dyspnea, oxygen desaturation (87%), and severe abdominal pain. The symptoms resolved with intramuscular epinephrine 0.50 mg, intravenous hydrocortisone 100 mg, and 250 mL of saline solution. The patient was then referred to the allergy clinic for further evaluation.

Two weeks later, a skin prick test performed with 10 mg/mL yielded a negative result. We were unable to measure tryptase or IL-6 levels owing to the late referral to our clinic after the anaphylactic reaction. The basophil activation test was not performed because it was not available at our hospital.

Intradermal skin tests at 0.1 mg/mL and 1 mg/mL were positive (7×7 mm and 10×10 mm, respectively) compared to the negative control (glycerinated solution 1×1 mm). We performed the intradermal test using 1:10 and 1:100 dilutions, although we cannot confirm that the HSR was associated with an IgE-mediated mechanism. Additionally, to rule out an irritant reaction, the skin test must be performed with a control, which was not possible in this case.

Since ramucirumab was the first-line treatment, we decided to perform a desensitization protocol. The patient received 875 mg of ramucirumab intravenously following a 3-bag, 12-step regimen over 5.67 hours (Table) based on the standardized Brigham and Women's Hospital desensitization protocol developed by Castells et al [9]. Premedication included dexamethasone 8 mg, diphenhydramine 10 mg, fosaprepitant 150 mg, and palonosetron 0.25 mg administered intravenously. The protocol was performed successfully every 3 weeks without HSRs for 4 cycles. The patient gave his written informed consent for the use of his medical data in this report.

The first line for management of metastatic gastric cancer involves a double-therapy regimen with a platinum salt plus a fluoropyrimidine [4]. In the RAINBOW trial, a second-line regimen with ramucirumab plus paclitaxel was proposed as an effective alternative treatment) [4]. Japanese guidelines recommended this regimen as the standard for second-line treatment in gastric cancer.

VEGFR-2 inhibitors are the only agents approved by the United States Food and Drug Agency for gastric cancer, either as monotherapy or in combination with paclitaxel, as in the present case. The REGARD trial assessed the safety and

Table. Three-Bag, 12-Step Desensitization Protocol for Ramucirumab.

3 Bags/12 steps		Volume per bag		Concentration per bag, mg/mL	Amount of bag infused	Dose administered per bag
Bag 1		50 mL		0.035 mg/mL	9.38 mL	0.328 mg
Bag 2		50 mL		0.35 mg/mL	18.75 mL	6.56 mg
Bag 3		250 mL		3.47 mg/mL	250 mL	868.112 mg
Step	**Bags**	**Rate**	**Time**	**Volume infused**	**Dose administered**	**Cumulative dose**
1	1	2.5 mL/h	15 min	0.625 mL	0.0218 mg	0.0218 mg
2	1	5 mL/h	15 min	1.25 mL	0.0437 mg	0.0655 mg
3	1	10 mL/h	15 min	2.5 mL	0.0875 mg	0.153 mg
4	1	20 mL/h	15 min	5 mL	0.175 mg	0.328 mg
5	2	5 mL/h	15 min	1.25 mL	0.437 mg	0.765 mg
6	2	10 mL/h	15 min	2.5 mL	0.875 mg	1.64 mg
7	2	20 mL/h	15 min	5 mL	1.75 mg	3.39 mg
8	2	40 mL/h	15 min	10 mL	3.5 mg	6.89 mg
9	3	10 mL/h.	15 min	2.5 mL	8.68 mg	15.57 mg
10	3	20 mL/h	15 min	5 mL	17.35 mg	32.92 mg
11	3	40 mL/h	15 min	10 mL	34.7 mg	67.62 mg
12	3	80 mL/h	174.4 min	232.5 mL	807.38 mg	875 mg

efficacy of ramucirumab in patients with advanced gastric or gastroesophageal junction adenocarcinoma who did not respond after first-line chemotherapy, demonstrating clinically significant overall survival as monotherapy for second-line treatment [3].

The use of mAbs has increased exponentially and is now a cornerstone of targeted therapies for cancer and inflammatory diseases. This increase has been accompanied by an increase in HSRs [5]. HSRs typically occur within the first or second exposure, and those caused by mAbs have often been underrecognized and underreported owing to the nonavailability of definitive tests at the time of the reactions [8].

Although it is generally understood that a positive skin test result requires prior immunological sensitization, the patient we report experienced a reaction during the first infusion and subsequently tested positive, suggesting the possibility of prior sensitization, as demonstrated with cetuximab [5,8,9]. However, the exact mechanism for this reaction remains unknown, since the literature provides very little information on the immunological mechanisms in biological therapies.

While skin prick tests with a 1:1 dilution have been demonstrated to be safe, such concentrations should not be used for intradermal testing. Following recommendations, we performed intradermal tests with 1:100 and 1:10 dilutions. It is essential to conduct skin tests on healthy controls to rule out an irritant reaction; however, given the high cost of ramucirumab, we were unable to perform such tests on healthy individuals.

In terms of phenotype, the patient had symptoms suggesting an IgE-mediated mechanism, since he presented rash, dyspnea, abdominal pain, and oxygen desaturation. Nevertheless, this may also be a cytokine-mediated mechanism associated with severe desaturation, since the reaction occurred during the first administration and is therefore most likely not IgE-mediated.

Our experience highlights the need to diagnose HSRs to monoclonal antibodies in clinical practice. Diagnosis should be based on an appropriate clinical history and skin tests, before desensitization protocols are administered in the management of HSRs to mAbs, so that patients can benefit from otherwise effective treatments while mitigating the risks associated with severe allergic reactions [10]. We demonstrated that ramucirumab can be safely reintroduced with a desensitization protocol after an immediate reaction. Further research is needed with healthy controls to standardize the optimal concentrations for skin tests to recognize IgE-mediated reactions.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Data Availability

The study data are available from the authors upon reasonable request.

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