

A Prospective Trial Evaluating the Safety of a Shortened Infusion of Ramucirumab in Patients with Gastrointestinal Cancer

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TRIAL INFORMATION

- **UMIN Clinical Trial Registry:** UMIN000029318
- **Sponsor(s):** Aichi Cancer Research Foundation
- **Principal Investigators:** Seiichiro Mitani, Naoya Hashimoto
- **IRB Approved:** Yes

LESSONS LEARNED

- A shortened infusion of ramucirumab (from 60 to 20 minutes) was safe and feasible without infusion-related reactions.
- Twenty-minute infusions of ramucirumab can be an option for patients with no infusion-related reactions during the first 60-minute treatment.

ABSTRACT

Background. Ramucirumab is usually administered over 60 minutes, during which it is unlikely to cause infusion-related reactions (IRRs). This prospective study evaluated the safety of a shortened infusion of ramucirumab.

Methods. Patients who received their first dose of ramucirumab in a 60-minute infusion without developing IRRs were eligible and received their second ramucirumab dose for 20 minutes. The primary study endpoint was incidence of IRR during the first short-term infusion, and the secondary endpoints were incidence of IRR at any time and adverse events other than IRR.

Results. Of the 40 patients enrolled (median age, 68.5 years), 20 (55%) were male, 27 (67.5%) had stage IV gastric cancer, 25 (62.5%) received ramucirumab in combination with taxane-based chemotherapy, and 24 (60%) received only a single administration of ramucirumab prior to their enrollment. Notably, no IRR was observed during the first short-term infusion (IRR rate, 0%; 95% confidence interval [CI], 0%–0.72%). Among the 149 short-term infusions performed, there were no instances of IRRs or unexpected adverse events related to the treatment (Table 1).

Conclusion. For patients without development of IRRs upon the first ramucirumab administration, shortening infusion

time (from 60 to 20 minutes) is safe and feasible. *The Oncologist* 2019;24:159–e66

DISCUSSION

To the best of our knowledge, this is the first prospective study to demonstrate the safety of a shortened infusion of ramucirumab. We aimed to evaluate the safety of a short-term infusion of ramucirumab. Our study met its primary endpoint, demonstrating that IRR rate during the first short-term infusion was 0% (95% CI, 0%–0.72%). Additionally, among a total of 149 short-term infusions, no IRR was observed. The frequency of ramucirumab-related adverse events was consistent with that in previous reports, and no unexpected adverse events related to the study treatment were observed. These results demonstrated that a short-term infusion of ramucirumab was safe. This can allow patients, particularly outpatients, to conveniently receive chemotherapy and reduce medical staff workload. We strongly believe our findings will be beneficial to both patients and medical staff.

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Table 1. Results of a short-term infusion of ramucirumab (*n* = 40)

Factors	Results
Ramucirumab dosage, median (range), mg/kg	405 (205–610)
Incidence of infusion-related reaction at first short-term infusion, % (95% CI)	0 (0–0.07)
Number of short-term infusions per patient, median (range)	3 (1–9)
Total number of short-term infusions	149
Incidence of adverse events, %	
Proteinuria	Grade 1–2, 15.0; Grade 3, 5.0; Grade 4, 0
Hemorrhage	Grade 1–2, 10.0; Grade 3, 2.5; Grade 4, 0
Hypertension	Grade 1–2, 7.5; Grade 3, 0; Grade 4, 0
Gastrointestinal perforation	Grade 1–2, 0; Grade 3, 0; Grade 4, 0
Thromboembolic events	Grade 1–2, 2.5; Grade 3, 0; Grade 4, 0

TRIAL INFORMATION

Disease	Advanced cancer/solid tumor only
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Safety
Secondary Endpoint	Safety
Secondary Endpoint	Toxicity
Additional Details of Endpoints or Study Design	Eligibility criteria included the following: (a) histologically proven gastrointestinal cancer; (b) first ramucirumab infusion administered over 60 minutes without development of an IRR; (c) no severe respiratory or cardiovascular comorbidities; and (d) no history of allergy or IRR to other chemotherapeutic agents. Our study was designed to have a maximum IRR rate of 15%, with α and β errors of .05 and .20, respectively, considering that the minimum sample size was 40 patients.
Investigator's Analysis	Shortened infusion of ramucirumab is a safe and feasible method.

DRUG INFORMATION

Drug 1	
Generic/Working Name	Ramucirumab
Trade Name	Cyramza
Company Name	Eli Lilly
Drug Type	Antibody
Drug Class	Vascular endothelial growth factor receptor (VEGFR)
Dose	8 milligrams (mg) per kilogram (kg)
Route	IV
Schedule of Administration	Intravenous administration of ramucirumab over 20 minutes every 2 weeks in combination with paclitaxel, nanoparticle albumin-bound paclitaxel, irinotecan with fluorouracil and leucovorin (FOLFIRI), or irinotecan.

PATIENT CHARACTERISTICS

Number of Patients, Male	22
Number of Patients, Female	18
Stage	Only metastatic or advanced; stage IV: 40 (100%)
Age	Median (range): 68.5 (32–85)

Number of Prior Systemic Therapies	Median (range): 1 (1–2)
Performance Status: ECOG	0 — 16 1 — 23 2 — 1 3 — 0
Cancer Types or Histologic Subtypes	Gastric cancer, 27; colorectal cancer, 13

PRIMARY ASSESSMENT METHOD

Number of Patients Screened	42
Number of Patients Enrolled	40
Number of Patients Evaluable for Toxicity	40
Evaluation Method	Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

ADVERSE EVENTS

All Cycles							
Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades
Hypertension	92	0	8	0	0	0	8
Upper gastrointestinal hemorrhage	97	0	0	3	0	0	3
Oral hemorrhage	97	3	0	0	0	0	3
Epistaxis	92	8	0	0	0	0	8
Proteinuria	80	5	10	5	0	0	20
Thromboembolic event	97	0	3	0	0	0	3

Abbreviation: NC/NA, no change from baseline/no adverse event.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator's Assessment	Shortened infusion of ramucirumab is a safe and feasible method.

Ramucirumab is a fully human immunoglobulin G monoclonal antibody against vascular endothelial growth factor receptor-2 (VEGFR-2), a receptor for VEGF-A, VEGF-C, and VEGF-D [1]. Ramucirumab has been shown to be effective in several cancer types, including gastric, colorectal, and non-small cell lung cancer [2–5]. In general, although antibody therapies are less toxic compared with cytotoxic agents, they have peculiar toxicity profiles. A typical adverse event is infusion-related reaction (IRR). The symptoms of IRR include fever, chills, headache, pruritus, rash, cough, collapse, angioedema, and, in rare cases, life-threatening events such as respiratory disturbance or circulatory failure. Its mechanism is considered to be different from IgE-mediated hypersensitivity due to type 1 allergic reaction [6]. Because infusion duration of antibody therapies may affect IRR occurrence, monoclonal antibodies are gradually administered. Ramucirumab has been administered for over 60 minutes, but no robust evidence supports this duration. Ramucirumab is a fully human protein, and IRR occurrence due to its use has been reported to be markedly low (0.4%–5.8%) [2, 3]. Several studies have shown that rapid infusion of other antibodies was safe.

Salar et al. reported rapid administration of rituximab, which is more closely associated with IRR, and proposed that a 90-minute infusion schedule was well tolerated and safe [7]. Sehn et al. also examined that a 90-minute rituximab administration for more than 1,200 cases and reported that no grade 3 or 4 infusion reactions were observed [8]. As for bevacizumab, trastuzumab, and panitumumab, similar studies have been performed and indicated that it is possible to shorten infusion time [9–12]. Therefore, we hypothesized that it is possible to shorten the infusion duration of ramucirumab for patients without IRR during the first administration.

The primary endpoint, IRR rate during the first short-term infusion, was 0% (95% confidence interval, 0%–0.72%). Additionally, among the 149 short-term infusions, no IRR was observed. In total, 13 patients (32.5%) developed adverse events related to ramucirumab. One (2.5%) and two (5.0%) patients developed grade 3 upper gastrointestinal hemorrhage and proteinuria, respectively. The incidence of these adverse events was consistent with that in previous reports. Therefore, our findings demonstrated that a short-term infusion of ramucirumab was safe. In

cases with no IRR upon the first administration of ramucirumab over 60 minutes, a shorter 20-minute infusion can be used for the subsequent administrations. When ramucirumab is administered in combination with other cytotoxic drugs, it requires considerable time, increasing the burden on patients and medical staff. A shorter infusion can be beneficial to patients and medical staff.

There were a few limitations to the present study. First, data on pharmacokinetics of ramucirumab were not obtained. However, in a previous report, shortening the infusion duration did not affect the blood concentration of panitumumab [12], another fully human antibody. Second, this study included patients with differing treatment regimens, resulting in differences in terms of premedication. Our results should be validated in a larger sample sufficiently representing each regimen; however, this is the first study demonstrating that a 20-minute ramucirumab infusion

is safe and feasible for patients with gastrointestinal cancer despite these limitations. The shortened infusion time can reduce the burden of both patients and medical staff. Further studies are warranted to confirm the safety of short-term ramucirumab infusion.

DISCLOSURES

Seiichiro Mitani: Eli Lilly & Co. (H); **Hiroya Taniguchi:** Eli Lilly & Co. (H); **Toshiki Masuishi:** Eli Lilly & Co. (H); **Shigenori Kadowaki:** Eli Lilly Japan K.K. (RF, H); **Kei Muro:** Eli Lilly & Co., Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ono Pharmaceutical Co., Ltd., Taiho, Bayer (H), Gilead Sciences, Ono Pharmaceutical Co., Ltd., Merck Sharp & Dohme, Shionogi, Kyoma Hakko Kirin, Daiichi Sanyo (RF). The other authors reported no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

- Lu D, Jimenez X, Zhang H et al. Selection of high affinity human neutralizing antibodies to VEGFR2 from a large antibody phage display library for antiangiogenesis therapy. *Int J Cancer* 2002;20:393–399.
- Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.
- Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomized, multicenter, placebo-controlled, phase 3 trial. *Lancet* 2014;383:31–39.
- Tabernero J, Takayuki Y, Cohn AL et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomized, double-blind, multicenter, phase 3 study. *Lancet Oncol* 2015;16:499–508.
- Garon EB, Ciuleanu TE, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicenter, double-blind, randomised phase 3 trial. *Lancet* 2014;23:665–673.
- Cheifetz A, Smedley M, Martin S et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003;98:1315–1324.
- Salar A, Casao D, Cervera M et al. Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. *Eur J Haematol* 2006;77:338–340.
- Sehn LH, Donaldson J, Filewich A et al. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood* 2007;109:4171–4173.
- Reidy DL, Chung KY, Timoney JP et al. Bevacizumab 5 mg/kg can be infused safely over 10 minutes. *J Clin Oncol* 2007;25:2691–2695.
- Yanmaz MT, Guner SI, Satilmis B et al. Thirty-minutes infusion rate is safe enough for bevacizumab; no need for initial prolong infusion. *Med Oncol* 2014;31:276.
- Abe H, Umeda T, Kawai Y et al. Adjuvant trastuzumab can be infused safely over 30 minutes [in Japanese]. *Gan To Kagaku Ryoho* 2010;37:1887–1891.
- Stephenson JJ, Gregory C, Burris H et al. An open-label clinical trial evaluating safety and pharmacokinetics of two dosing schedules of panitumumab in patients with solid tumors. *Clin Colorectal Cancer* 2009;8:29–37.

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