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Ramucirumab: a new option in advanced gastric cancer

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Introduction

Gastric and gastro-oesophageal junction adenocarcinoma are the fourth most common malignant disease and second cause of cancer mortality (1).

Surgery remains the last curative choice but a significant number of patients presents with advanced disease or relapses after initial surgery (2-5). In this setting, the reference treatment is represented by chemotherapy that determines a significantly higher survival compared to supportive care alone (6-14). Although 5-fluorouracil and platinum-based chemotherapy is standard treatment for advanced gastric cancer, the median survival is still poor, less than 1 year (6-14).

After the first line therapy, the improvement in survival with irinotecan or taxani- based chemotherapy is limited with a median survival of about 3 months, so there is great interest for new agents targeting (15-18).

Ramucirumab in gastric cancer

The family of VEGF consists of VEGF-A, B, C, D, E, and placental growth factor (PGF). Each member binds to different VEGF receptors (VEGFR): VEGF-A binds to VEGFR-1 and 2, while VEGF-B and platelet-derived growth factor (PGF) bind to VEGFR-1, and VEGF-C and D bind to VEGFR-2 and 3. VEGFR2 plays a critical function in physiological and pathological angiogenesis and it is widely considered the main receptor driving angiogenesis (19). Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2) play a crucial role in the pathogenesis of gastric cancer , in particular in the growth and the subsequent process of metastasis, representing, therefore, an indicator of poor prognosis (20-29).

Ramucirumab (IMC-1121B) is a fully human, Ig G1 monoclonal antibody blocking with high affinity (approximately 50 pM) the extracellular VEGF-binding domain of VEGFR-2 and inhibiting downstream signaling involved in the formation and maintenance of aberrant blood vessels that supply blood to tumors (30). Ramucirumab is administered intravenously. Pharmacokinetic data support dosing every 1, 2, or 3 weeks with a Maximum Tolerated Dose (MTD) weekly identified as 13 mg/kg; Dose-Limiting Toxicities (DLT) observed in Cycle 1 weekly dosing were hypertension (at 10 mg/kg/wk&16 mg/kg/wk): deep vein thrombosis (at 16 mg/kg/wk). No DLT and no MTD were identified in every-2-week and every-3-week study. **REGARD**, an international, randomised, multicentre, placebo-controlled, phase III trial is the first positive study with anantiangiogenic treatment in patients with advanced GC progressing after first line chemotherapy. A total of 355 patients were assigned, in a 2:1 ratio, to receive ramucirumab 8 mg/kg or placebo. Median overall survival was 5.2 months in the ramucirumab group and 3.8 months in the placebo group (HR 0.776; p=0•047) and median progression free survival was 2.1 months vs 1.3 months with placebo (HR 0.483;

p<0.0001); the duration of disease control was significantly longer in the ramucirumab group than in the placebo group (median 4.2 months vs 2.9 months; *p*=0.036) (31).

Ramucirumab was well tolerated. Rate of hypertension was higher in the ramucirumab group than in the placebo group (16% vs. 8%), whereas rates of other adverse events were mostly similar between groups. Five (2%) deaths in the ramucirumab group and two (2%) in the placebo group were considered to be related to study drug (32).

RAINBOW is the largest clinical trial of second-line therapy and its results are not only statistically significant but clinically meaningful. It is a randomized, multicenter, double-blind, placebo controlled phase III clinical trial of weekly paclitaxel (80 mg/kg on days 1, 8, 15, every 4 weeks) with or without Ramucirumab (8 mg/kg i.v. infusion on days 1 and 15 every 4 weeks) in patients with metastatic GC refractory or progressive after first-line therapy with platinum and fluoropyrimidine. The study, which randomized a total of 665 patients, had as primary endpoint OS while secondary endpoints included: PFS, time to progression (TTP), objective response (OR), quality of life and safety (33). Median overall survival was 9.6 months for the combination and 7.4 months for paclitaxel alone. The overall survival curves split early, by 2 months of treatment, and remained separated beyond 1 year. The difference between arms ultimately translated into a 19% reduction in the risk of death (p=0.0169) with ramucirumab.Median progression-free survival was 4.4 months and 2.9 months, respectively, a 27% reduction in risk (p<0.0001). The objective response rate associated with the combination was 28% vs. 16% with paclitaxel alone (p=0.0001). At 6 months, the progression-free survival rate was 36% vs. 17%, and at 9 months was 22% vs. 10%, respectively. In addition, the disease control rate was much better with ramucirumab, 80% vs. 64%, respectively (p<0.0001). Ramucirumab was well tolerated, although adverse events of grade ≥3 were somewhat greater with combination treatment and included neutropenia (40.7% vs. 18.8%), leukopenia (17.4% vs. 6.7%), hypertension (14.1% vs. 2.4%) and fatigue (7.0% vs. 4.0%); however the incidence of febrile neutropenia was comparable between the two treatment arms (3.1% vs. 2.4%) . These adverse events did not lead to increased treatment discontinuation in the ramucirumab arm, nor were rates of treatment-related deaths different between the two arms (4.0% with ramucirumab/paclitaxel vs. 4.6% with paclitaxel alone). Other adverse events were anaemia (9.2% vs. 10.3%), abdominal pain (5.5% vs. 3.3%) and asthenia (5.5% vs. 3.3%) (33).

In conclusion,VEGFR-2 signaling is an important therapeutic target in advanced gastric cancer and ramuricumab is the first biological antiangiogenic treatment showing efficacy in advanced gastric cancer, particularly in pretreated patients. In this setting, according to REGARD and RAINBOW trials, ramucirumab improves survival compared to best supportive care and adds a significant benefit to the efficacy of chemotherapy.

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