A population-based outcomes study of patients with metastatic gastric cancer receiving second-line chemotherapy: A nationwide health insurance database study

In Sil Choi1, Jee Hyun Kim2, Ju Hyun Lee2, Koung Jin Suh2, Ji Yun Lee2, Ji-Won Kim2, Se-Hyun Kim2, Jin Won Kim2,2, Jeong-Ok Lee2, Yu Jung Kim2, Soo-Mee Bang2, Jong Seok Lee2, Keun-Wook Lee1,*

1 Department of Internal Medicine, Seoul National University College of Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea, 2 Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

* hmodoctordr@snubh.org

Abstract

Purpose

The survival benefit of second-line chemotherapy in patients with metastatic gastric cancer (MGC) has recently been established. We conducted a nationwide population-based outcomes study of patients with MGC receiving second-line chemotherapy to better understand real-world treatment patterns and outcomes.

Materials and methods

Data were collected from the Health Insurance Review and Assessment Service database. We identified 509 newly diagnosed patients with MGC in 2010 who received second-line chemotherapy. These patients were divided into three groups for analyses: Group A comprised all patients who received second-line chemotherapy (N = 509); Group B comprised those who received fluoropyrimidine (Fp) plus platinum as first-line treatment, followed by irinotecan-based or taxane-based regimens as second-line chemotherapy (N = 284); and Group C comprised those who received Fp plus cisplatin as first-line treatment, followed by 5-fluorouracil (5-FU)/oxaliplatin, irinotecan-based, or taxane-based regimens as second-line chemotherapy (N = 184).

Results

Among patients who received first-line chemotherapy, 47.2% (509/1,078) continued to receive second-line chemotherapy. The most commonly used second-line chemotherapy regimens were 5-FU/irinotecan, 5-FU/oxaliplatin, and docetaxel. The median overall survival (OS) of all 509 patients was 5.2 months. The time from the start date of first-line chemotherapy to the start date of second-line chemotherapy > 6.1 months was an independent
prognostic factor for improved OS. The type of chemotherapy regimen was not a significant factor affecting OS.

**Conclusion**

The findings provide a better understanding of second-line treatment patterns and outcomes in patients with MGC and will help guide treatment decisions in real-world clinical practice.

**Introduction**

Gastric cancer (GC) is currently the fifth most commonly occurring cancer and the third leading cause of cancer-related deaths worldwide [1]. Surgical resection is a curative treatment option for localized GC; however, local and distant recurrences commonly occur. For patients with metastatic or recurrent GC, palliative chemotherapy can effectively prolong overall survival (OS) and improve the quality of life compared with best supportive care (BSC) alone [2–4]. Although fluoropyrimidine (Fp) and platinum (P)-based combination regimens are considered established first-line treatments for patients with metastatic GC (MGC) or recurrent GC, the disease of most patients receiving first-line chemotherapy eventually progresses, and the patients have a median progression-free survival (PFS) of 4–7 months. More than half of the patients do not respond to first-line chemotherapy, and among responders, the duration of response is as short as several months [5–9].

For patients with progressive disease following first-line chemotherapy, we now have evidence revealing that second-line chemotherapy with docetaxel, paclitaxel, or irinotecan results in the substantial prolongation of survival compared with BSC [10–12]. More recently, in two phase III trials of ramucirumab, which is a monoclonal antibody against vascular endothelial growth factor receptor, monotherapy or combination therapy with paclitaxel significantly improved OS compared with BSC or paclitaxel alone [13,14].

However, before obtaining recent evidence that shows the benefit of second-line chemotherapy, the proportion of patients who received further therapy after failure with first-line chemotherapy varied, largely depending on the discretion of the physician. Moreover, in the absence of standard second-line chemotherapy regimens, patients were treated with various chemotherapeutic agents [15]. Ramucirumab, a new biologic agent, was not reimbursed in many countries until quite recently. Therefore, it would be helpful to investigate real-world treatment patterns and outcomes in a large population of patients to have a better understanding of these patients and to guide treatment decisions in real-world clinical practice. To the best of our knowledge, nationwide- or population-based studies of patients with MGC or recurrent GC receiving second-line chemotherapy are very limited.

We conducted this study to assess second-line treatment patterns, outcomes, and prognostic factors associated with survival outcomes in patients with MGC using a nationwide health insurance database.

**Materials and methods**

**Study population**

Data were collected from the Health Insurance Review and Assessment Service (HIRA) database. In Korea, all hospitals and clinics submit inpatient and outpatient claims data on spent cost covered by the National Health Insurance or Medical Aid programs to HIRA for reimbursement. Thus, the HIRA database contains information on all claims data submitted from all
hospitals and clinics. From the database, we retrieved data that included an unidentifiable code representing each individual, with diagnostic codes, demographic information, a list of medical procedures that were employed for diagnosis and treatment, and prescribed medications.

The diagnosis and procedure codes from the Korean Classification of Disease, fifth edition, as well as a supplementary code of “V193,” which is given to all patients with a confirmatory cancer diagnosis, were used to identify patients who were newly diagnosed with de novo MGC (stage IV). We already described in detail the process of identifying these cases in our previous study [16].

In 2010, 1,871 patients were newly diagnosed with GC with distant metastasis. Of 1,871 patients, 793 who did not receive any chemotherapy were excluded and the remaining 1,078 patients with MGC who received palliative first-line chemotherapy were identified. Among 1,078 patients, 509 who continued to receive second-line chemotherapy were finally selected as the target population of this study (Fig 1). For the selected 509 patients, the start time of second-line chemotherapy was between February 2010 and July 2013.

The 509 patients were divided into three groups according to the treatments they received (first-line and second-line therapy): Group A comprised all patients who received second-line chemotherapy after failure with first-line chemotherapy (N = 509); Group B comprised those who received Fp plus P combination therapy as first-line treatment, followed by irinotecan-based or taxane-based regimens as second-line chemotherapy (N = 284); and Group C comprised those who received Fp plus cisplatin combination therapy as first-line treatment, followed by 5-fluorouracil (5-FU)/oxaliplatin, irinotecan-based, or taxane-based regimens as second-line chemotherapy (N = 184). The detailed patients’ flow from first-line to second-line chemotherapy including chemotherapy regimens is shown in Fig 2 using Sankey diagram (http://sankeymatic.com).

Because this study was performed using publicly released data, approval of the Institutional Review Board (IRB) was waived off (IRB number: X-1802-453-901).

Statistical analysis
OS was estimated using the Kaplan-Meier method, and the statistical significance of differences in survival curves between the groups was assessed using a log-rank test. A prognostic model was established by searching variables that significantly influenced OS with \( p \) values of <0.05 in the univariable analysis. For the multivariable analysis, a Cox proportional hazards regression model was used to estimate the adjusted hazard ratio (HR) to determine the significance of specified clinical variables on OS. OS was defined as the interval from the start date of second-line chemotherapy to the date of death or last follow-up. As of October 31, 2013 (the date of data cutoff), a patient who died of any cause or who was lost to follow-up for >1 year without further information on the survival status (i.e., if the last follow-up date was before November 1, 2012) was regarded as an event case. If a patient visited a hospital or clinic at least once within 1 year before October 31, 2013 and the survival status was not reported as dead in the last claim specification, the case was regarded as a censored case. All analyses were conducted using the SAS/STAT software (version 9.4; Cary, NC, USA, SAS Institute Inc.) and IBM SPSS Statistics (version 18; Armonk, NY, USA, IBM Corp.). The statistical significance was set at \( p \) values of <0.05.

Results
Patient characteristics
In 2010, among 1,078 newly diagnosed patients with MGC who received first-line chemotherapy, 509 patients (47.2%) continued to receive second-line chemotherapy. The proportion of
Fig 1. Study population and the process of case identification.

https://doi.org/10.1371/journal.pone.0205853.g001
patients receiving second-line chemotherapy was 27.8% (76/273) among patients aged ≥70 years and 53.8% (433/805) among those aged <70 years.

The baseline patient characteristics are shown in Table 1. Group A included all patients who received second-line chemotherapy (N = 509). Of 509 patients, 85.1% of patients were aged <70 years, with a median age of 55 (range, 25–82) years. Most patients were previously treated with Fp (88.2%) and P (82.9%), and the most commonly prescribed first-line chemotherapy regimens were 5-FU/oxaliplatin (26.5%), S-1/cisplatin (23.6%), and capecitabine/cisplatin (12.8%). For second-line chemotherapy, various regimens were prescribed; they could be classified as irinotecan-based regimens, taxane-based regimens, 5-FU/oxaliplatin, and others. Irinotecan-based regimens included irinotecan monotherapy, irinotecan/Fp, and irinotecan/cisplatin. In contrast, taxane-based regimens included taxane monotherapy (docetaxel or paclitaxel), taxane/Fp, and taxane/cisplatin. Of these regimens, the most commonly used second-line chemotherapy regimens were 5-FU/irinotecan (35.6%), 5-FU/oxaliplatin (19.8%), and docetaxel (13.4%). As mentioned in the Materials and Methods section, Group B included patients who received first-line Fp/P combination therapy followed by second-line irinotecan-based or taxane-based chemotherapy (N = 284). The most commonly used first-line chemotherapy regimens in Group B were not much different from those in Group A. However, for second-line chemotherapy, more patients received 5-FU/irinotecan (56.3%), and there were no patients who received 5-FU/oxaliplatin. Group C included patients who received Fp/cisplatin combination therapy as first-line treatment followed by 5-FU/oxaliplatin, irinotecan-
based, or taxane-based regimens as second-line chemotherapy (N = 184). Most patients received S-1/cisplatin (63.0%) or capecitabine/cisplatin (33.7%) as first-line chemotherapy. As was the case in Groups A and B, 5-FU/irinotecan (35.3%) was the most commonly prescribed regimen as second-line chemotherapy, followed by docetaxel (24.5%) and 5-FU/oxaliplatin (22.3%).

The median OS of all 509 patients (Group A) from the start of second-line chemotherapy was 5.2 months (95% confidence interval [CI], 4.7–5.7; S1 Fig.). Because a wide variety of regimens were prescribed as first- and second-line chemotherapy in Group A, we did not

Table 1. Patient characteristics.

| Parameters                      | Group A (N = 509) | Group B (N = 284) | Group C (N = 184) |
|---------------------------------|-------------------|-------------------|-------------------|
| Age                             |                   |                   |                   |
| < 70 years                      | 433 (85.1%)       | 255 (89.8%)       | 164 (89.1%)       |
| ≥ 70 years                      | 76 (14.9%)        | 29 (10.2%)        | 20 (10.9%)        |
| Sex                             |                   |                   |                   |
| Male                            | 356 (69.9%)       | 198 (69.7%)       | 134 (72.8%)       |
| Female                          | 153 (30.1%)       | 86 (30.3%)        | 50 (27.2%)        |
| First-line chemotherapy         |                   |                   |                   |
| 5-fluorouracil/Oxaliplatin      | 135 (26.5%)       | 115 (40.5%)       | -                 |
| S-1/Cisplatin                   | 120 (23.6%)       | 89 (31.3%)        | 116 (63.0%)       |
| Capecitabine/Cisplatin          | 65 (12.8%)        | 50 (17.6%)        | 62 (33.7%)        |
| 5-fluorouracil/Irinotecan       | 33 (6.5%)         | -                 | -                 |
| Docetaxel/Cisplatin             | 29 (5.7%)         | -                 | -                 |
| Capecitabine/Oxaliplatin        | 27 (5.3%)         | 26 (9.2%)         | -                 |
| S-1                             | 24 (4.7%)         | -                 | -                 |
| Others                          | 76 (14.9%)        | 4 (1.4%)          | 6 (3.3%)          |
| Previously exposed drugs        |                   |                   |                   |
| Fluoropyrimidine                | 449 (88.2%)       | 284 (100.0%)      | 184 (100.0%)      |
| Platinum                        | 422 (82.9%)       | 284 (100.0%)      | 184 (100.0%)      |
| Taxane                          | 61 (12.0%)        | -                 | -                 |
| Irinotecan                      | 36 (7.1%)         | -                 | -                 |
| 2nd-line chemotherapy regimens  |                   |                   |                   |
| 5-fluorouracil + Irinotecan     | 181 (35.6%)       | 160 (56.3%)       | 65 (35.3%)        |
| 5-fluorouracil + Oxaliplatin    | 101 (19.8%)       | -                 | 41 (22.3%)        |
| Docetaxel                       | 68 (13.4%)        | 55 (19.4%)        | 45 (24.5%)        |
| Docetaxel + Cisplatin           | 40 (7.9%)         | 28 (9.9%)         | 17 (9.2%)         |
| Irinotecan                      | 14 (2.8%)         | 10 (3.5%)         | 6 (3.3%)          |
| Paclitaxel                      | 14 (2.8%)         | 5 (1.8%)          | 1 (0.5%)          |
| Paclitaxel + Cisplatin          | 12 (2.4%)         | 11 (3.9%)         | 1 (0.5%)          |
| Docetaxel + 5-fluorouracil      | 8 (1.6%)          | 7 (2.5%)          | 3 (1.6%)          |
| Paclitaxel + 5-fluorouracil     | 7 (1.4%)          | 5 (1.8%)          | 4 (2.2%)          |
| Irinotecan + Cisplatin          | 4 (0.8%)          | 3 (1.1%)          | 1 (0.5%)          |
| Others                          | 60 (11.8%)        | -                 | -                 |

**Group A:** All patients who received second-line chemotherapy (N = 509)

**Group B:** Patients who received fluoropyrimidine plus platinum as first-line treatment, and then second-line chemotherapy with irinotecan-based or taxane-based regimens (N = 284)

**Group C:** Patients who received fluoropyrimidine plus cisplatin as first-line treatment, and then second-line chemotherapy with 5-fluorouracil/oxaliplatin, irinotecan-based, or taxane-based regimens (N = 184)

https://doi.org/10.1371/journal.pone.0205853.t001

Based, or taxane-based regimens as second-line chemotherapy (N = 184). Most patients received S-1/cisplatin (63.0%) or capecitabine/cisplatin (33.7%) as first-line chemotherapy. As was the case in Groups A and B, 5-FU/irinotecan (35.3%) was the most commonly prescribed regimen as second-line chemotherapy, followed by docetaxel (24.5%) and 5-FU/oxaliplatin (22.3%).

The median OS of all 509 patients (Group A) from the start of second-line chemotherapy was 5.2 months (95% confidence interval [CI], 4.7–5.7; S1 Fig.). Because a wide variety of regimens were prescribed as first- and second-line chemotherapy in Group A, we did not
analyze and compare the survival outcomes among patients receiving particular chemotherapy regimens.

**Prognostic factors affecting survival outcomes following second-line chemotherapy (Group B, N = 284)**

All patients in Group B received Fp/P combination therapy as first-line treatment, followed by second-line irinotecan-based or taxane-based chemotherapy. The univariable analyses for prognostic factors affecting OS revealed that an age of ≥ 70 years was significantly associated with shorter survival time (4.3 vs. 5.1 months; \( p = 0.048 \)) (Table 2). The median time from the start date of first-line chemotherapy to the start date of second-line chemotherapy (TF1T2) was 6.1 months (range, 0.2–32.3 months). The median OS of patients with a TF1T2 of ≥ 6.1 months was longer than that of patients with a TF1T2 of < 6.1 months, although the difference was not statistically significant (5.4 vs. 4.5 months; \( p = 0.079 \)) (Table 2, Fig 3A). The chemotherapy regimen was not a significant factor affecting OS (irinotecan-based vs. taxane-based regimens; 5.1 vs. 4.8 months; \( p = 0.706 \)) (Table 2, Fig 3B). In addition, there was no significant difference in OS between patients receiving monotherapy and combination therapy (irinotecan monotherapy vs. irinotecan-based combination therapy vs. taxane monotherapy vs. taxane-based combination therapy; \( p = 0.865 \)). However, because of a very small number of patients receiving irinotecan monotherapy, the result needs to be read with discretion (S2 Fig.). In the multivariable analyses, both age and TF1T2 were independent prognostic factors that correlated with OS following second-line chemotherapy: age of ≥ 70 years (HR 1.59, 95% CI 1.06–2.39; \( p = 0.024 \)) and TF1T2 of ≥ 6.1 months (HR 0.77, 95% CI 0.60–0.99; \( p = 0.039 \)).

**Prognostic factors affecting survival outcomes following second-line chemotherapy (Group C, N = 184)**

All patients in Group C received Fp/cisplatin combination therapy as first-line treatment, followed by 5-FU/oxaliplatin, irinotecan-based, or taxane-based regimens as second-line chemotherapy. In the univariable analyses for prognostic factors associated with OS, age was not a significant prognostic factor related to OS (age of < 70 vs. ≥ 70 years; 5.3 vs. 5.4 months; \( p = 0.639 \)). TF1T2 of ≥ 6.1 months (vs. < 6.1 months) was significantly associated with

| Table 2. Prognostic factors related to survival outcomes in Group B (N = 284). |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| N                          | Univariable analysis        | Multivariable analysis      |                             |
|                            | Overall survival (months; median) | Hazard ratio | 95% confidence interval | p          |
| Sex                        |                             |                             |                             |
| Male                       | 198                         | 5.0                         | -                           | 1.00       | -           |
| Female                     | 86                          | 4.8                         | 0.460                       | 0.90       | 0.69–1.17   | 0.413       |
| Age (year)                 |                             |                             |                             |
| < 70                       | 255                         | 5.1                         | -                           | 1.00       | -           |
| ≥ 70                       | 29                          | 4.3                         | 0.048                       | 1.59       | 1.06–2.39   | 0.024       |
| Duration from first-line to second-line chemotherapy | | |                             |
| ≤ 6.1 months               | 144                         | 4.5                         | -                           | 1.00       | -           |
| > 6.1 months               | 140                         | 5.4                         | 0.079                       | 0.77       | 0.60–0.99   | 0.039       |
| Chemotherapy regimens      |                             |                             |                             |
| Irinotecan-based therapy   | 173                         | 5.1                         | -                           | 1.00       | -           |
| Taxane-based therapy       | 111                         | 4.8                         | 0.706                       | 0.99       | 0.77–1.27   | 0.925       |

https://doi.org/10.1371/journal.pone.0205853.t002
improved OS (6.7 vs. 4.7 months; \( p = 0.030 \)) (Table 3, Fig 4A). There was no significant difference in OS between patients receiving each chemotherapy regimen (5-FU/oxaliplatin vs. irinotecan-based vs. taxane-based regimens; 7.0 vs. 5.3 vs. 5.1 months; \( p = 0.469 \)) (Table 3, Fig 4B).

In the multivariable analyses, TF1T2 was the only independent prognostic factor associated

![Fig 3. Kaplan–Meier survival curves for overall survival in Group B (N = 284). (A) Survival curves for overall survival according to the median time from the start date of first-line chemotherapy to the start date of second-line chemotherapy (TF1T2). (B) Survival curves for overall survival of patients receiving irinotecan-based (N = 173) vs. taxane-based chemotherapy (N = 111).](https://doi.org/10.1371/journal.pone.0205853.g003)

| Table 3. Prognostic factors related to survival outcomes in Group C (N = 184). |
|---------------------------|---------------|----------------|-------------|---------------|----------------|-------------|---------------|----------------|---------------|
| N                        | Univariable analysis |              | Hazard ratio | 95% confidence interval | Multivariable analysis |              |              |              |              |
|                          | Overall survival (months; median) | \( p \) |              |              |              |              |              |              |              |
| Sex                      |                |              |              |              |              |              |              |              |              |
| Male                     | 134            | 5.3          | -            | 1.00         | -            | -            | -            | -            | -            |
| Female                   | 50             | 6.2          | 0.295        | 0.84         | 0.60–1.18    | 0.324        | -            | -            | -            |
| Age (year)               |                |              |              |              |              |              |              |              |              |
| \(< 70\)                 | 164            | 5.4          | -            | 1.00         | -            | -            | -            | -            | -            |
| \(\geq 70\)              | 20             | 5.3          | 0.639        | 1.20         | 0.74–1.95    | 0.453        | -            | -            | -            |
| Duration from first-line to second-line chemotherapy |                |              |              |              |              |              |              |              |              |
| \(\leq 6.1\) months      | 93             | 4.7          | -            | 1.00         | -            | -            | -            | -            | -            |
| \(> 6.1\) months         | 91             | 6.7          | 0.030        | 0.68         | 0.50–0.93    | 0.015        | -            | -            | -            |
| Chemotherapy regimens    |                |              |              |              |              |              |              |              |              |
| Irinotecan-based therapy | 72             | 5.3          | -            | 1.00         | -            | -            | -            | -            | -            |
| Taxane-based therapy     | 71             | 5.1          | 0.823\(^\dagger\) | 0.91         | 0.64–1.30    | 0.616\(^\dagger\) | -            | -            | -            |
| 5-fluorouracil/oxaliplatin | 41          | 7.0          | 0.259\(^\dagger\) | 0.72         | 0.48–1.08    | 0.110\(^\dagger\) | -            | -            | -            |

\(^\dagger\) Irinotecan-based therapy versus taxane-based therapy versus 5-fluorouracil/oxaliplatin;
\(^\dagger\) Irinotecan-based therapy versus taxane-based therapy;
\(^\dagger\) Irinotecan-based therapy versus 5-fluorouracil/oxaliplatin

[https://doi.org/10.1371/journal.pone.0205853.t003]
with OS following second-line chemotherapy: TF1T2 of ≥ 6.1 months (HR 0.68, 95% CI 0.50– 0.93; \( p = 0.015 \)).

**Discussion**

Recent evidence has demonstrated that second-line chemotherapy improves OS in patients with MGC or recurrent GC [10–14]. However, we still do not have much information regarding the subset of patients who could benefit most from second-line chemotherapy as well as chemotherapy regimens that could be accepted as standard second-line treatment. In addition, not all newly approved agents are available for clinical practice due to economic cost. In this regard, it would be helpful to investigate second-line treatment patterns, outcomes, and prognostic factors associated with survival outcomes in a large population of patients receiving treatments in real-world clinical practice.

We conducted a nationwide population-based study to assess real-world treatment patterns and outcomes in patients with MGC receiving second-line chemotherapy using a nationwide health insurance database. In 2010, of 1,078 newly diagnosed patients with MGC who received first-line chemotherapy, 509 (47.2%) continued to receive second-line chemotherapy. For second-line chemotherapy in these patients who were mostly exposed to Fp and P previously, 5-FU/irinotecan, 5-FU/oxaliplatin, and docetaxel were the most commonly prescribed regimens, and the median OS of these patients receiving second-line chemotherapy was 5.2 months. As this study was a retrospective population-based study, not prospective randomized controlled study, we were not able to compare the OS between the patients who received and those who did not receive second-line chemotherapy because it was impossible to set the start date of the OS interval in those who did not receive second-line chemotherapy. The median OS of our patient population who received second-line chemotherapy (5.2 months) was quite similar to the OS reported in previous phase III clinical trials [10–13]; in these phase III...
studies, second-line chemotherapy clearly resulted in the substantial prolongation of median OS (range, 4.0–5.2 months) compared with best supportive care (median OS: range, 2.4–3.8 months). In addition, we had already reported the result of an outcomes research including all patients (N = 1078) in the same patient cohort with the current study [16]. In the previous study, we showed that the OS of patients who received second-line or more chemotherapy was longer than the OS of patients who received first-line chemotherapy only, and the number of lines of chemotherapy was an independent prognostic factor for OS in all patients as well [16]. Although direct comparison of OS between patients who received and those who did not receive second-line chemotherapy is not possible in population-based outcomes research like ours, we thought the above results suggest indirect evidences of real benefit of second-line chemotherapy in patients with MGC.

In patients who received Fp/P combination therapy as first-line treatment, followed by second-line irinotecan-based or taxane-based chemotherapy (Group B), there was no significant difference in OS between patients receiving irinotecan-based or taxane-based chemotherapy. Moreover, in patients who received Fp/cisplatin combination therapy as first-line treatment, followed by second-line 5-FU/oxaliplatin, irinotecan-based, or taxane-based chemotherapy (Group C), no significant difference in OS was observed between patients receiving 5-FU/oxaliplatin, irinotecan-based, or taxane-based chemotherapy. There have been some concerns about introducing oxaliplatin after failure with cisplatin-containing regimens owing to the possibility of cross-resistance between the two agents. However, in our study, the median OS of patients receiving 5-FU/oxaliplatin as second-line chemotherapy after failure with Fp/cisplatin was numerically longer than that of patients receiving irinotecan-based or taxane-based chemotherapy. Therefore, in concordance with previous reports [17–20], oxaliplatin can be a valuable treatment option even after failure with cisplatin, and some patients with MGC or recurrent GC can benefit from 5-FU/oxaliplatin regimen in a second-line setting. In our previous study of 229 patients with MGC receiving third-line chemotherapy in the same patient cohort with the current study, the median OS of patients who received 5-FU/oxaliplatin as third-line chemotherapy was shown to be similar to that of patients who received third-line taxane or irinotecan-based chemotherapy, suggesting the benefit of 5-FU/oxaliplatin in a third-line setting after treatment failure with cisplatin [20]. In Groups B and C, TF1T2 was a consistent independent prognostic factor affecting OS, and TF1T2 of ≥ 6.1 months (vs. < 6.1 months) was significantly associated with improved OS. However, we could not perform in-depth analysis in terms of chemo-responsiveness and tumor progression to first-line chemotherapy which must have had influences on TF1T2 because PFS or tumor response to prior chemotherapy could not be accurately assessed in this population-based retrospective study. In spite of that, TF1T2 needs to be considered and incorporated as a stratification factor when designing future clinical trials involving patients with MGC receiving second-line chemotherapy.

This retrospective study had several limitations. First, we retrieved the exact survival status from the database in only 63.9% of patients (N = 325). We assumed that patients without any claim submitted from hospitals/clinics within 1 year before the data cutoff date must have died of MGC or other causes, considering the natural course of patients with MGC who have progressive disease following palliative second-line chemotherapy. For these patients, we considered the last date of their visit to the hospitals/clinics as the date of death; therefore, the survival duration might be underestimated for some patients. However, the median OS of our patient population (5.2 months) was not much different from the OS reported in previous studies [10–13]. Second, we could not evaluate all known prognostic factors associated with survival outcomes, such as the performance status of patients, laboratory values, and tumor burdens (metastatic number and sites), because the HIRA database did not have information...
on these clinical variables. Furthermore, as we mentioned above, the efficacy of second-line chemotherapy in connection with PFS or tumor response to first-line chemotherapy could not be assessed by this population-based database. Third, to select MGC cases more precisely in this study, we included only MGC cases with de novo metastatic disease, excluding recurrence cases after prior curative gastrectomy, and thus, only a relatively small number of patients (509 patients) were finally selected as the target population, although this was a nationwide population-based study [16]. In addition, most patients with stage II or III disease after primary gastrectomy receive adjuvant chemotherapy with Fp- and/or P-containing regimens in Korea. Therefore, if recurrence cases after prior curative gastrectomy were included in this analysis, the results could be somewhat different.

To summarize, in this population-based study evaluating real-world treatment patterns and outcomes in patients with MGC receiving second-line chemotherapy, we observed that 47.2% of patients continued to receive second-line chemotherapy after failure with first-line chemotherapy. The median OS of these patients was 5.2 months from the start of second-line chemotherapy, and a longer TF1T2 was an independent prognostic factor for improved OS following second-line chemotherapy. The type of chemotherapy regimen was not a significant factor affecting OS. To the best of our knowledge, this is one of the few nationwide, population-based studies of patients with MGC receiving second-line chemotherapy. Overall, this study will help guide treatment decisions in real-world clinical practice and design prospective clinical trials for these patients.

**Supporting information**

S1 Fig. Kaplan–Meier survival curves for overall survival in the entire population (Group A, N = 509) from the start of second-line chemotherapy.

(TIF)

S2 Fig. Kaplan–Meier survival curves for overall survival of patients receiving monotherapy vs. combination therapy (Group B, N = 284).

(TIF)

**Author Contributions**

**Conceptualization:** Jong Seok Lee, Keun-Wook Lee.

**Data curation:** Ju Hyun Lee, Keun-Wook Lee.

**Formal analysis:** Ju Hyun Lee, Keun-Wook Lee.

**Investigation:** In Sil Choi, Ju Hyun Lee, Keun-Wook Lee.

**Methodology:** In Sil Choi.

**Writing – original draft:** In Sil Choi.

**Writing – review & editing:** Jee Hyun Kim, Koung Jin Suh, Ji Yun Lee, Ji-Won Kim, Se-Hyun Kim, Jin Won Kim, Jeong-Ok Lee, Yu Jung Kim, Soo-Mee Bang, Jong Seok Lee, Keun-Wook Lee.

**References**

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136: E359–386. [https://doi.org/10.1002/ijc.29210](https://doi.org/10.1002/ijc.29210) PMID: 25220642
Second-line chemotherapy for metastatic gastric cancer

2. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjödén PO, Haglund U, et al. Randomised comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol. 1997; 8:163–168.

3. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer. 1995; 71:587–591. PMID: 7533517

4. Wagner AD, Syn NLX, Moehler M, Grothe W, Yong WP, Tai BC, et al. Chemotherapy for advanced gastric cancer. Cochrane Database of Syst Rev. 2017, Issue 8. Art.No.:CD004604.

5. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008; 358: 36–46. https://doi.org/10.1056/NEJMoa073149 PMID: 18172173

6. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009; 20 (4): 666–673. https://doi.org/10.1093/annonc/mdn717 PMID: 19153121

7. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III Comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010; 28:1547–1553. https://doi.org/10.1200/JCO.2009.25.4706 PMID: 20159816

8. Al-Batran SE, Hartmann JT, Probst S, Schmalenborg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008; 26:1435–1442. https://doi.org/10.1200/JCO.2007.13.9378 PMID: 18349393

9. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008; 9: 215–221. https://doi.org/10.1016/S1470-2045(08)70053-4 PMID: 18282605

10. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011; 47: 2306–2314. https://doi.org/10.1016/j.ejca.2011.06.002 PMID: 21742485

11. Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol. 2012; 30: 1513–1518. https://doi.org/10.1200/JCO.2011.39.4585 PMID: 22412140

12. Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014; 15: 78–86. https://doi.org/10.1016/S1470-2045(13)70549-7 PMID: 24332238

13. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-esophageal junction adenocarcinoma ( REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014; 383:31–39. https://doi.org/10.1016/S0140-6736(13)61719-5 PMID: 24094768

14. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-esophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014; 15:1224–1235. https://doi.org/10.1016/S1470-2045(14)70420-6 PMID: 25240821

15. Ji SH, Lim DH, Yi SY, Kim HS, Jun HJ, Kim KH, et al. A retrospective analysis of second-line chemotherapy in patients with advanced gastric cancer. BMC Cancer. 2009; 9:110. https://doi.org/10.1186/1471-2407-9-110 PMID: 19358705

16. Lee KW, Lee JH, Kim JW, Kim JW, Ahn S, Kim JH. Population-based outcomes research on treatment patterns and impact of chemotherapy in older patients with metastatic gastric cancer. J Cancer Res Clin Oncol. 2016; 142(3):687–697. https://doi.org/10.1007/s00432-015-2075-2 PMID: 26567125

17. Tsuji K, Yasui H, Onozawa Y, Boku N, Doyama H, Fukutomi A, et al. Modified FOLFOX-6 therapy for heavily pretreated advanced gastric cancer refractory to fluorouracil, irinotecan, cisplatin and taxanes: a retrospective study. Jpn J Clin Oncol. 2012; 42(8):686–690. https://doi.org/10.1093/jjco/hys084 PMID: 22693245

18. Kim YS, Hong J, Sym SJ, Park SH, Park J, Cho EK, et al. Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX-4) combination chemotherapy as a salvage treatment in advanced gastric cancer. Cancer Res Treat. 2010; 42(1):24–29. https://doi.org/10.4143/crt.2010.42.1.24 PMID: 20369048
19. Kim DY, Kim JH, Lee SH, Kim TY, Heo DS, Bang YJ, et al. Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol. 2003; 14(3):383–387. PMID: 12598342

20. Choi IS, Choi M, Lee JH, Kim JH, Suh KJ, Lee JY, et al. Treatment patterns and outcomes in patients with metastatic gastric cancer receiving third-line chemotherapy: A population-based outcomes study. PLoS ONE 13(6):e0198544. https://doi.org/10.1371/journal.pone.0198544