Burden of Illness and Treatment Patterns of Adult Patients with Advanced or Metastatic Gastric/Gastroesophageal Junction Cancer – A Systematic Literature Review

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BACKGROUND

- Gastric cancer, including gastroesophageal junction cancer (G/GEJC), represents the fifth most common malignancy and the fourth leading cause of cancer-related death worldwide.[1]
- Survival in patients with HER2-negative advanced G/GEJC who receive standard first-line platinum-fluoropyrimidine in clinical trials is less than 1 year.[2,3] The addition of nivolumab can improve survival, however efficacy has been mostly limited to patients with a PD-L1 combined positive score (CPS) of ≥5.[4] Recent phase 3 studies demonstrated that other immunotherapy agents (e.g., pembrolizumab, tislelizumab) or zolbetuximab (in patients with CLDN18.2-positive cancer) may extend survival when combined with standard chemotherapy.[5-8]
- Approximately 30% of patients with advanced HER2 non-positive G/GEJC overexpress the fibroblast growth factor receptor 2b (FGFR2b) protein, an emerging biomarker and investigational target in gastric cancer.[9] Bemarituzumab is a first-in-class monoclonal antibody that has shown inhibition of FGFR2b signaling and cytotoxicity against tumor cells that express FGFR2b. In the phase 2 FIGHT study, treatment of FGFR2b-positive advanced G/GEJC patients with bemarituzumab plus mFOLFOX6 resulted in clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS) relative to placebo plus mFOLFOX6.[10] Bemarituzumab is currently assessed in two randomized, multicenter, double-blind phase 3 trials; the FORTITUDE-101 study evaluates bemarituzumab plus mFOLFOX6 and the FORTITUDE-102 study evaluates bemarituzumab plus nivolumab and physician's choice standard chemotherapy.
- Considering the expected increase in targeted therapies and the knowledge base regarding the burden of illness of advanced G/GEJC, there is a need to consolidate the existing evidence on treatment patterns, real-world clinical, economic, and humanistic outcomes in this patient population.

METHODS

- This SLR was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.[11] Search strategies and eligibility criteria were developed in alignment with population, intervention, comparator(s), outcome(s), and study design(s) (PICOS) elements (see Table 1).
- Data sources and search strategy: Electronic searches were performed on the Ovid® platform using 3 databases (Embase, MEDLINE, and the Cochrane Library) covering full publications without restriction on the publication date. Supplementary hand searches were performed to identify evidence from congress abstracts, health technology assessment (HTA) reports, relevant regulatory documents, and treatment guidelines. The searches were performed on 24 June 2022.
- Citation screening and full text review: Title and abstract screening and full-text review were performed against the predefined eligibility criteria by two reviewers independently. Any discrepancies in screening decisions were resolved by a third reviewer.
- Data extraction and quality assessment: Due to the high number of studies matching the PICOS criteria, data were extracted from a subset of studies. Specifically, studies eligible for extraction included populations consisting of ≥50% patients with G/GEJC, reported outcomes from key countries (i.e., the USA, Canada, Japan, South Korea, EU, and Turkey), and had a sample size of ≥150 patients. Studies published before 2012 and those including only patients with HER2-positive tumor were deprioritized for extraction. One person extracted data from included articles and a second person checked each data point for accuracy. A risk of bias assessment for full publications was performed using the Newcastle-Ottawa Scale series.[12,13]

Table 1. Study Eligibility Criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥ 18 years) with previously untreated, unresectable locally advanced or metastatic G/GEJC	Pediatric or adolescent patients, patients without G/GEJC, or >50% patients with cancer/adenocarcinoma solely of the esophagus
Interventions/ Comparators	Any 1L pharmacologic therapy	Patients receiving ≥2L treatment, studies reporting data from mixed populations (i.e., not reporting data for 1L separately)
Outcomes	Treatment patterns, epidemiological burden, real-world clinical, humanistic, and economic outcomes	N/A
Study types	Observational/RWE studies Any types of economic studies	Interventional studies, case reports or case series, reviews, editorials, letters
Publication date	No restriction to publication date	N/A

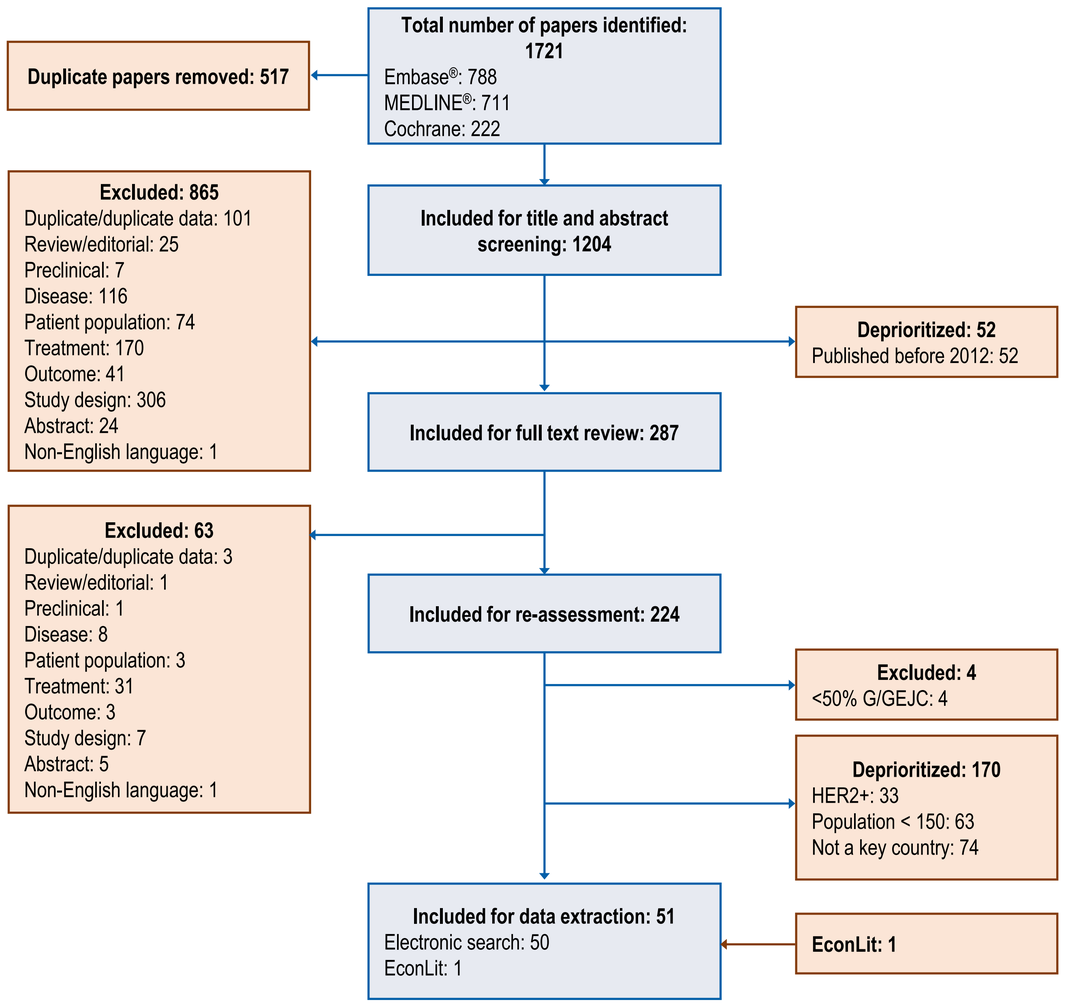
1L: first line; 2L: second line; G/GEJC: gastric or gastroesophageal cancer; PICOS: population, intervention, comparator(s), outcome(s), and study design(s); N/A: not applicable; RWE: real-world evidence.

RESULTS

Study selection

- Out of the 1,721 screened citations, 287 studies were included for full-text review. Of these, 51 studies were identified as relevant for data extraction (see Figure 1). Most studies (n = 47) reported outcomes from individual countries (23 Asian and 24 non-Asian studies), while only 4 were multi-country studies.
- Relevant outcomes were reported for the different disease burden endpoints as follows:
  - 37 publications (18 and 19 from Asian and non-Asian countries, respectively) reported data on real-world treatment patterns
  - 40 publications (20 from both Asian and non-Asian countries) reported on real-world clinical outcomes
  - 3 publications presented results of economic burden (2 from the USA and 1 international publication), and 1 publication described an economic evaluation
- The number of studies reporting data on epidemiological and humanistic outcomes was very small and thus not reported here.

Figure 1. PRISMA Flow Diagram



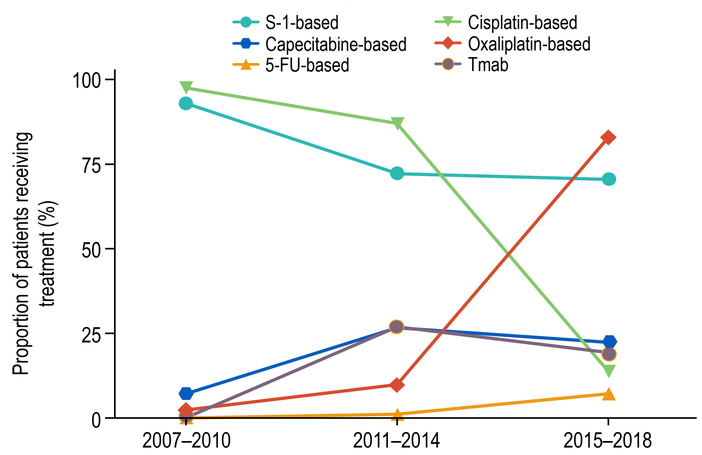
G/GEJC: gastric/gastroesophageal junction cancer; HER2+: human epidermal growth factor receptor 2 positive; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RESULTS (Cont'd)

Treatment patterns

- Based on the largest studies (≥1,000 patients), the evidence is summarized as follows:
- In Japan, based on data from 10,581 patients who received 1L treatment between 2014–2019, the most common therapy was S-1 plus oxaliplatin (SOX, 40.9%), followed by S-1 plus cisplatin (23.8%), and capecitabine plus oxaliplatin (XELOX, 12.0%).[14] Other studies had similar findings, although changes in treatment patterns over time were reported. Specifically, the use of S1-based regimens decreased from 93% (2007–2010) to 70% (2015–2018), while the use of other fluoropyrimidines increased (5-FU from 0% to 7% and capecitabine from 7% to 22%). Similarly, the use of cisplatin decreased from 98% to 14% while the use of oxaliplatin increased (2% to 83%) (see Figure 2).[15] Of patients who initiated 1L therapy, about half (51%) received 2L therapy and a quarter (23%) received 3L therapy.[14]

Figure 2. Treatment Patterns in Japanese Patients with Advanced GC



Source: Nakayama et al., 2022
GC: gastric cancer; Tmab: trastuzumab. Categories are not mutually exclusive.

- In the US, based on data from ≥1,500 patients that received 1L treatment between 2011–2018, the most often administered therapy was a fluoropyrimidine-platinum doublet ± docetaxel or epirubicin (62%).[16] Overall, platinum (79%), fluoropyrimidine (66–91%), and taxane (35%) agents were the most commonly used.[17,18] Of patients diagnosed with advanced or metastatic G/GEJC, about 75%, 32%, and 14% received 1L, 2L, and 3L therapy, respectively.[17]

Real-world clinical outcomes

- Based on the largest studies (≥1,000 patients), the evidence is synthesized as follows:
- Real-world clinical outcomes for OS were reported from 10 large-scale studies. The median OS ranged from 9.6 to 16.8 months in 5 studies conducted in Asian countries whereas it ranged from 7.3 to 10.8 months based on 5 studies conducted form the rest of the world (ROW) countries (see Table 2).[15,16,17,19-25] A trend of increasing OS was identified in most of the studies that assessed changes over time.[20,22,23]
- Prognostic factors were reported in 27 studies (13 Asian and 14 ROW publications). The most often reported prognostic factors were ECOG performance status (n = 17 publications), age (n = 9), number of metastatic sites (n = 7), peritoneal and bone metastases (n = 9), prior gastrectomy (n = 7), high alkaline phosphatase level (n = 8), and HER2 status (n = 7).

Table 2. Median Overall Survival and Progression-free Survival of G/GEJC Patients Reported by Large-scale Studies

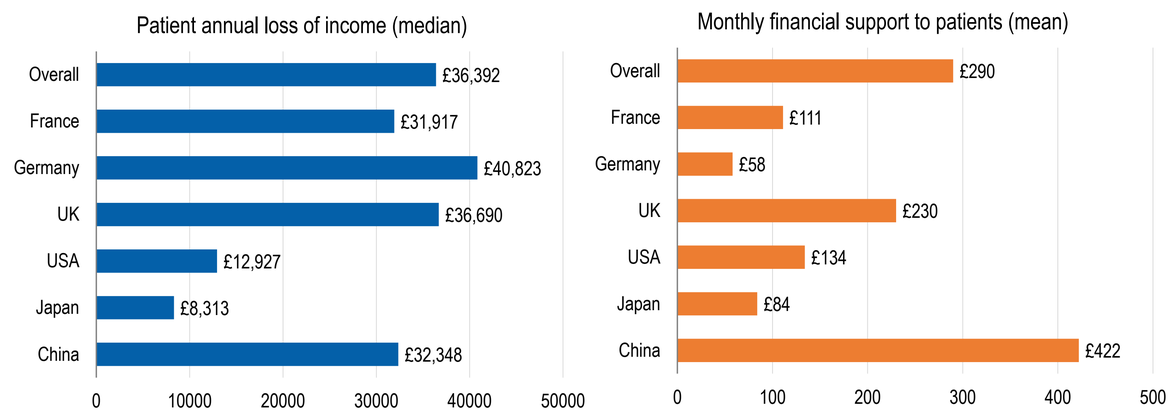
Country	Median OS (months)	Median PFS (months)	Follow-up years
Asia	9.6–16.8	5.3–7.5	2000–2018
Korea[19-21]	9.6–12.2	5.3–7.0	2000–2015
Japan[15,22]	12.4–16.8	7.3–7.5	2005–2018
Non-Asia	7.3–10.8	5.1–6.1	2008–2021
USA[16,17]	9.7–10.7	5.1–5.3	2010–2018
Other[23-25]	7.3–10.8	5.8–6.1	2008–2021

G/GEJC: gastric/gastroesophageal cancer; OS: overall survival; PFS: progression-free survival.
Other: Netherlands, Spain, and Chile.

Economic burden

- Economic burden was reported in 2 publications from the US. One study evaluated healthcare resource use (HCRU) and Medicare costs for 2012 in elderly patients diagnosed with advanced G/GEJC between 2000 and 2007 that received 1L chemotherapy with fluoropyrimidine and/or a platinum agent. The study reported mean total costs of $36,810 and $40,628 for patients who received additional treatment and who received only supportive care after 1L therapy, respectively. Costs associated with G/GEJC-related 1L treatment and supportive care amounted to $17,829 and $23,756 in these patient groups, respectively.[26] Another study that assessed HCRU of patients diagnosed with advanced G/GEJC between 2004 and 2015 and received systemic therapy found that in the first 6-month period after chemotherapy initiation the most commonly used healthcare services and treatments were hospitalization (56.3%), emergency room (ER) visits (55.6%), hospital admission from an ER visit (32.4%), antiemetics (91.6%), and opioids (55.9%).[27]
- Finally, an international chart review study assessed the impact of advanced G/GEJC and esophageal cancer (EC) on work productivity in patients of working age and their caregivers as well as the financial impact of the disease (see Figure 3). There were 176 (62%) patients in paid employment at the time of diagnosis, and only 40 (14%) remained in employment at the time of data analysis, resulting in 77% of patients being unemployed, on long-term sick leave, or retirement due to cancer. The reduction of working hours per month due to cancer was 83% resulting in a median annual loss of income of £36,392. In addition, 18.5% of caregivers experienced a decrease in annual income.[28]

Figure 3. Financial Impact of Advanced G/GEJC/EC in France, Germany, UK, USA, Japan, and China



Source: Xiao et al, 2022
(A) Patient annual income loss due to cancer (median); (B) Monthly financial support to patients provided by caregivers (mean).
EC: esophageal cancer; G/GEJC: gastric/gastroesophageal cancer.

KEY FINDINGS

- A large number of publications reporting on the burden of illness of locally advanced unresectable or metastatic G/GEJC in previously untreated patients was identified. Of these, 51 studies were extracted for this SLR.
- Treatment patterns were reported in 37 publications. Fluoropyrimidine-platinum combinations were the most commonly used regimens; S-1 was almost exclusively used in Asian countries.
- A considerable number of studies on real-world clinical effectiveness of therapies were identified. Across studies, patients with advanced unresectable or metastatic G/GEJC had poor survival outcomes; the median OS across large studies ranged from 7.3 to 16.8 months.
- ECOG performance status, age, and the number of metastatic sites were the three most often reported prognostic factors associated with clinical outcomes.
- Advanced G/GEJC has a significant financial impact on patients and caregivers in the US and in other countries.
- None of the identified publications reported outcomes by FGFR2b status.

DISCLOSURES AND REFERENCES

Disclosures:
ZC, AY, and IM are employees of Amgen and hold Amgen stocks. CE was paid consultant to conduct the SLR. JA has provided consultancy for Amgen. This study was supported by Amgen Inc.

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