Treatment Patterns, Healthcare Resource Utilization and Costs, and Clinical Outcomes among Elderly Patients with Advanced HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma

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Introduction

- Gastric/Gastroesophageal Junction (GEJ) cancer ranks third in cancer-related deaths globally,[1] with around 60% occurring in individuals aged 65 or older,[2] adenocarcinoma accounts for approximately 95% of all cases,[3] and approximately 7.3–20.2% have human epidermal growth factor receptor 2 (HER2) overexpression.[4,5]
- Since 2010, trastuzumab, in combination of fluoropyrimidine- and platinum-based chemotherapy, has been the standard first-line (1L) treatment for HER2+ gastric/GEJ adenocarcinoma on the basis of the ToGA trial (NCT01041404). There have been no advancements in treatment options until in May 2021 when the FDA granted accelerated approval to pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the 1L treatment for these patients, based on the positive results from the ongoing KEYNOTE-811 trial (NCT03615326).[6]
- The interim analysis of the on-going KEYNOTE-811 trial data showed that pembrolizumab plus SOC provided a statistically significant and clinically meaningful improvement in PFS and a trend toward favorable OS compared with SOC.[7]

Objective

- To evaluate treatment patterns, healthcare resource utilization (HCRU) and costs, and clinical outcomes following 1L trastuzumab-contained therapy among elderly patients with advanced HER2+ gastric or GEJ adenocarcinoma before pembrolizumab's FDA approval using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.

Methods

Data Source

SEER-Medicare linked database consists of:

- The US National Cancer Institute's SEER registry (1973-2019) contains clinical, demographic, and survival data on new cancer cases from 22 US geographic areas covering approximately 48% of the US population.
- The Medicare claims database (2007-2020) includes claims related to hospital care (Part A), outpatient medical services (Part B), and outpatient drug prescriptions (Part D) among Americans aged ≥65 years or have certain disabilities.

Study Design and Sample Selection

- Patients aged ≥65 years who had a diagnosis of stage III or IV primary gastric/GEJ adenocarcinoma (ICD-O-3 codes: C15 or C16; histology codes: 8140-8389; sequence number: 00 or 01) and have initiated 1L trastuzumab-contained regimen (as a proxy for HER2+ expression date of 1L initiation defined as the **index date**) after their gastric/GEJ adenocarcinoma diagnosis between Jan 1, 2011 and Dec 31, 2019 were identified. Patients were required to have continuous enrollment in Medicare Part A, B, and D from index date until the earlier of death or end of Medicare Parts A, B, or D eligibility. Patients were excluded if they had a breast cancer diagnosis before the index date or enrolled in a clinical trial at any time in the data.
- The **baseline period** was defined as from the start of data availability to the index date (exclusive); **follow-up period** was defined as the index date (inclusive) to the earliest of end of data availability, death, or end of Medicare Parts A, B, or D eligibility.
- Initiation of second line (2L) treatment following the 1L treatment was used as a surrogate for disease progression.
- Patients were further classified into four subgroups based on the 1L treatment: trastuzumab + chemotherapy doublet cohort, trastuzumab + chemo-monotherapy cohort, trastuzumab + taxane-based doublet cohort, and trastuzumab + other therapy cohort.

Outcomes and Statistical Analysis

- Treatment patterns from 1L to third line (3L) were described.
- All-cause and disease-related (i.e., associated with a diagnosis of gastric/GEJ adenocarcinoma) HCRU and costs were summarized as number of events per person-month or per patient per month (PPPM) costs (inflated to 2022 US dollars) during three mutually exclusive periods: pre-progression (before 2L initiation), post-progression (after 2L initiation and before 30 days prior to death if applicable), and terminal care period (30 days preceding death).
- Real-world overall survival (rwOS) and time to next treatment or death (rwTNTD) were analyzed using Kaplan-Meier approach.

Results

Baseline Characteristics (Table 1)

- Among the 315 patients included, mean [SD] age was 73.9 [5.9] years. Majority of overall patients were male (77.1%), White (83.5%), and non-Hispanic (91.4%) while nearly half were from the West region (48.6%).
- Most of the patients (84.1%) were in stage IV and over half (58.7%) had gastric adenocarcinoma. The mean [SD] time to 1L treatment initiation was 2.2 [3.3] months.
- Distributions of baseline characteristics were similar among patients in the 1L trastuzumab + chemotherapy doublet cohort, trastuzumab + taxane-based doublet cohort, and trastuzumab + other therapy cohort.
- Patients in 1L trastuzumab + chemo-monotherapy cohort, relative to the overall cohort, tend to be older (mean [SD]: 77.8 [7.5] vs 73.9 [5.9] years), had a longer time to 1L initiation (mean [SD]: 4.3 [4.7] vs 2.2 [3.3] months), had fewer male patients (70%) or White patients (74.0%), and had more patients with gastric adenocarcinoma (72.0%).

Table 1. Baseline Characteristics of Stage III or IV HER2+ Gastric/GEJ Adenocarcinoma Patients

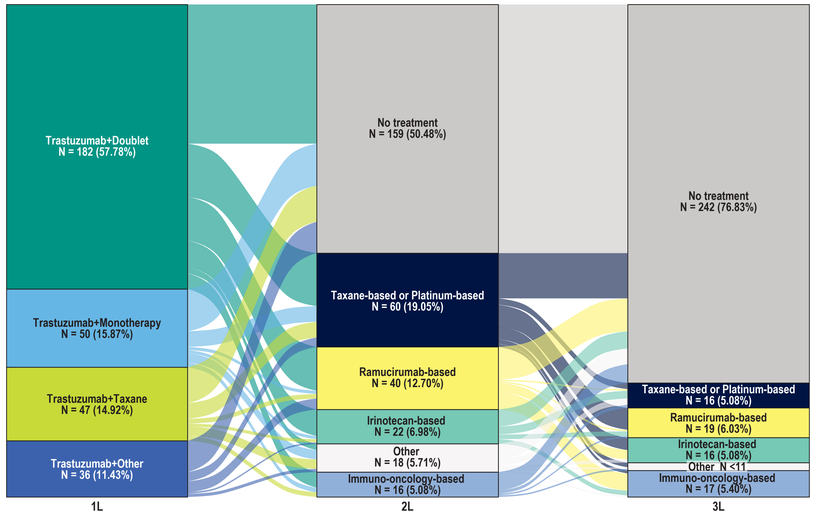
	Overall (N = 315)	Trastuzumab+ Doublet 1L[a] (N = 182)	Trastuzumab+ Monotherapy 1L[b] (N = 50)	Trastuzumab+ Taxane Based Doublet 1L[c] (N = 47)	Trastuzumab+ Other 1L[d] (N = 36)
Age (years) at 1L treatment initiation, mean ± SD	73.9 ± 5.9	73.1 ± 5.0	77.8 ± 7.5	74.3 ± 6.3	71.9 ± 5.0
Male, N (%)	243 (77.1%)	145 (79.7%)	35 (70.0%)	35 (74.5%)	>25 (>69.4%)
White race, N (%)	263 (83.5%)	150 (82.4%)	37 (74.0%)	>36 (>76.6%)	>25 (>69.4%)
Non-Hispanic, N (%)	288 (91.4%)	166 (91.2%)	44 (88.0%)	>36 (>76.6%)	>25 (>69.4%)
Geographic region, N (%)					
West	153 (48.6%)	91 (50.0%)	24 (48.0%)	19 (40.4%)	19 (52.8%)
Northeast	70 (22.2%)	40 (22.0%)	13 (26.0%)	< 11 (< 23.4%)	< 11 (< 30.6%)
South	58 (18.4%)	34 (18.7%)	< 11 (< 22.0%)	12 (25.5%)	< 11 (< 30.6%)
Midwest	34 (10.8%)	17 (9.3%)	< 11 (< 22.0%)	< 11 (< 23.4%)	< 11 (< 30.6%)
Time to 1L treatment (months), mean ± SD	2.2 ± 3.3	1.7 ± 1.8	4.3 ± 4.7	2.3 ± 5.0	2.0 ± 3.0
Primary cancer site[e]					
Gastric	185 (58.7%)	109 (59.9%)	36 (72.0%)	25 (53.2%)	15 (41.7%)
GEJ	130 (41.3%)	73 (40.1%)	14 (28.0%)	22 (46.8%)	21 (58.3%)
Stage IV at the cancer diagnosis	265 (84.1%)	163 (89.6%)	>39 (>78.0%)	32 (68.1%)	>25 (>69.4%)
National Cancer Institute Comorbidity Index (NCICI)[f], mean ± SD	1.2 ± 0.8	1.2 ± 0.8	1.2 ± 0.9	1.3 ± 0.9	1.1 ± 0.9

Notes:
[a] Trastuzumab-contained doublet treatment included the following combination treatment groupings: Trastuzumab+FOLFOX, Trastuzumab+CAPOX, Trastuzumab+XP, Trastuzumab+FP, or Trastuzumab+Carboplatin+5FU.
[b] Trastuzumab-contained monotherapy included the following combination treatment grouping: Trastuzumab or Trastuzumab+Chemo-monotherapy.
[c] Trastuzumab-contained taxane based doublet treatment included the following combination treatment groupings: Trastuzumab+Taxane based doublet therapy.
[d] Trastuzumab-contained other treatment included the following combination treatment groupings: Trastuzumab+Any triplet chemotherapy or Trastuzumab+Other therapies.
[e] Gastric cancer was defined using the ICD-O-3 code C16.x within SEER data whereas GEJ was defined using the ICD-O-3 code C15.x within SEER data.
[f] Stedman, M. R., Doria-Rose, P., Warren, J. L., Klabunde, C. N., & Mariotto, A. (2017). Comorbidity technical report: the impact of different SEER-Medicare claims-based comorbidity indexes on predicting non-cancer mortality for cancer patients. https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity-report.pdf.

Treatment Patterns (Figure 1)

- In 1L, 182 (57.8%) patients received trastuzumab + chemotherapy doublet (fluoropyrimidine + platinum), with common regimens being trastuzumab + FOLFOX (40.0%), trastuzumab + CAPOX (8.3%), and trastuzumab + FP (3.8%). Other 1L regimens were trastuzumab + chemo-monotherapy (n=50, 15.9%), trastuzumab + taxane-based doublets (n=47, 14.9%), and trastuzumab + other therapy (n=36, 11.4%).
- After 1L treatment, 156 patients (49.5%) received 2L treatment. Common 2L regimens were ramucirumab-based therapy (12.7%), irinotecan-based therapy (7.0%), and platinum-based therapy (7.0%).

Figure 1. Treatment Sequence (1L to 3L)



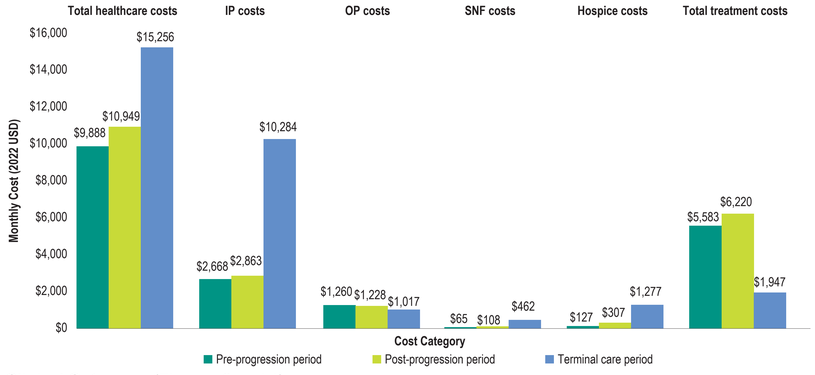
HCRU

- All-cause inpatient admissions occurred in 55.9%, 66.2%, and 53.4% of patients during pre-progression, post-progression, and terminal care period, with mean length of stay being 1.2, 1.2, and 4.3 days/person-month, respectively.
- Disease-related inpatient admissions occurred in 52.9%, 64.2%, and 46.6% of patients during pre-progression, post-progression, and terminal care period, with mean length of stay being 1.1, 1.1, and 3.9 days/person-month, respectively.
- Among patients who died (n = 223), 55.2% had hospice visits with mean (SD) and median (IQR) duration from hospice initiation to death being 52.3 (90.9) days and 23.0 (13.0, 55.0) days, respectively.

Healthcare Costs (Figure 2)

- The mean monthly all-cause total healthcare costs were $12,356, $13,545, and $19,085 (2022 USD) during the pre-progression, post-progression, and terminal care period, respectively. Approximately 80% of the all-cause total costs was attributable to disease-related costs: $9,888 (80.0%), $10,949 (80.8%), and $15,256 (79.9%) for the three periods, respectively.
- During pre-progression and post-progression periods, the disease-related total costs were mainly attributable to treatment costs and IP cost, with mean monthly treatment costs of $5,583 (56.5%) and $6,220 (56.8%), and IP costs of $2,668 (27.0%) and $2,863 (26.1%), respectively.
- During the terminal care period, IP costs ($10,284), treatment costs ($1,947), and hospice costs ($1,277) were the main components for disease-related total costs.

Figure 2. Disease-related Healthcare Costs during Pre-Progression Period, Post-Progression Period, and Terminal Care Period



Clinical Outcomes (Figures 3 and 4)

- The median rwOS [95% CI] was 15.3 [13.2, 16.9] months among the overall patients. It was similar in the trastuzumab + chemotherapy doublet cohort (16.0 [13.4, 20.6] months] and trastuzumab + other therapy cohort (15.2 [8.6, 28.7] months), shorter in the trastuzumab + chemo-monotherapy cohort (12.0 [8.3, 14.9] months), and longer in the trastuzumab + taxane-based chemotherapy doublet (16.9 [11.2, 23.8] months] (**Figure 3**).
- A similar pattern was found for rwTNTD. The median rwTNTD [95% CI] was 8.3 [6.7, 8.9] months among the overall patients, and was 8.5 [6.7, 10.0] months, 5.4 [4.2, 8.3] months, 9.2 [6.3, 11.5] months, and 8.5 [5.2, 10.4] months among patients who received 1L trastuzumab + chemotherapy doublet, trastuzumab + chemo-monotherapy, trastuzumab + taxane-based chemotherapy doublet, and trastuzumab + other therapy, respectively (**Figure 4**).

Figure 3. Kaplan-Meier Curve of Overall Survival from 1L Treatment Among Stage III or IV HER2+ Gastric/GEJ Adenocarcinoma Patients and by Treatment Subgroups

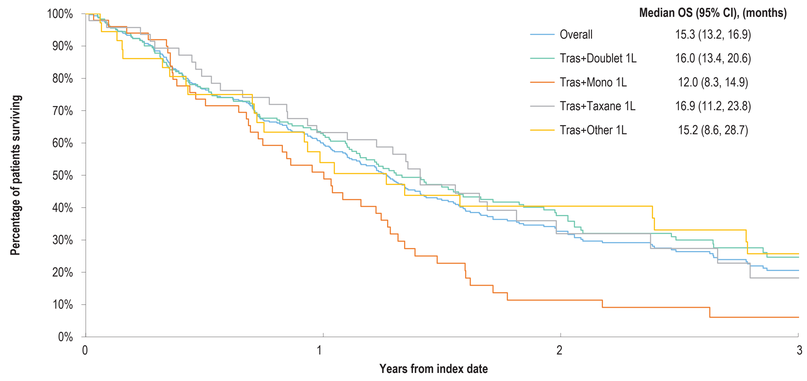
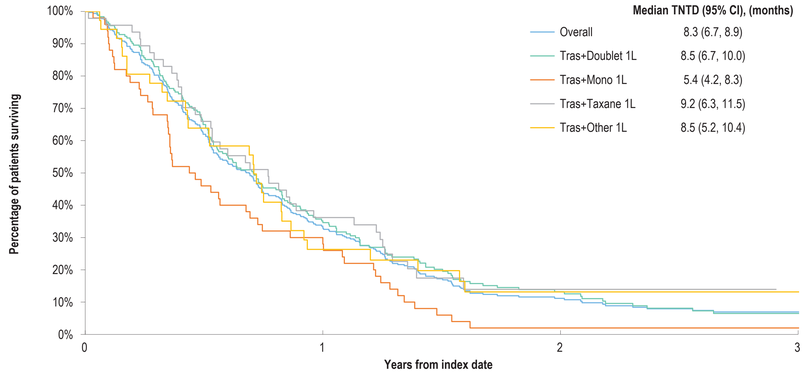


Figure 4. Kaplan-Meier Curve of Time to Next Treatment or Death Among Stage III or IV HER2+ Gastric/GEJ Adenocarcinoma Patients and by Treatment Subgroups



Discussions

Strengths

- This study conducted a thorough examination of the real-world treatment patterns, clinical outcomes following the 1L treatments, and HCRU and healthcare pre- and post-progression as well as during terminal care period using the linked SEER-Medicare database.

Limitations

- The identification of HER2+ status, disease progression, and cancer-related characteristics relied on various diagnosis, procedure, and drug codes, therefore, is subject to misclassification bias due to coding inaccuracies.
- Key oncological clinical characteristics at baseline such as performance status were not available.
- The study findings may not be generalizable to present-day situations because of a 3-year lag in the data and individuals not meeting the study's eligibility criteria (e.g., patients aged <65 years, with difference insurance, and the entire HER2+ patient population).

Conclusions

- This study reported substantial economic burden on the Medicare system before the introduction of pembrolizumab where costs were driven by treatment costs as well as inpatient care before terminal care period and by inpatient care at the end of life. Strategies to decrease inpatient hospitalizations especially in the terminal care period may help to reduce the economic burden.
- Trastuzumab has been the standard 1L treatment for HER2+ gastric/GEJ adenocarcinoma since 2011. However, there have been no advancements in treatment options until the FDA granted approval to 1L pembrolizumab use for these patients in May 2021, based on the positive results from the KEYNOTE-811 trial (NCT03615326). Our study found a median real-world OS of 15.3 months with 1L trastuzumab-containing regimens from 2011–2019. On the other hand, an interim analysis of the KEYNOTE-811 trial showed an OS of 20.0 months with pembrolizumab in combination with trastuzumab and chemotherapy,[7] indicating potential survival benefits with evolving treatment options.
- Additionally, less than half of the patients in our study received 2L treatment following 1L. Our findings highlight the need for more treatment options in HER2+ gastric/GEJ adenocarcinoma.

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