Gastric Cancer Therapy: Recognizing and Managing Fragmentation of Care and Evidence Gaps

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GASTRIC CANCER IS THE FIFTH most common type of malignancy and the third leading cause of cancer-related death worldwide.[1] Although gastric cancer is less common in the United States than abroad, there remains a notable lack of standardization of care across all lines of therapy, but particularly in later-line gastric cancer treatment.[2,3] Response to treatment may be highly individualized, varying even between patients with the same stage of cancer. Unfortunately, because gastric cancer is managed with a variety of therapeutic strategies, the standard of care in later-line treatment is not well characterized, and there is a need for further research to establish more comprehensive and standardized treatment strategies.[3]

For patients with advanced or metastatic disease or for patients receiving postoperative therapy, National Comprehensive Cancer Network (NCCN) guidelines currently recommend platinum-based therapies, such as cisplatin or oxaliplatin, plus fluoropyrimidine therapies, such as fluorouracil or capecitabine.[2,4] Fifteen and 8 other discrete regimens for first- and second-line treatment of gastric cancer, respectively, are also recommended by NCCN.[4] Although NCCN categorizes some treatments as preferred and classifies other treatments as alternative therapeutic options, there still remains a wide variety of choices for treatment.[4]

For patients with metastatic adenocarcinoma with human epidermal growth factor receptor 2 (*HER2*) overexpression, trastuzumab should be added in combination with a first-line chemotherapy regimen. However, importantly, NCCN recommends against administration of trastuzumab in patients receiving anthracyclines.[4] With combination drug regimens, 2-drug combination regimens are generally preferred over 3-drug combination regimens, as 2-drug combinations usually have lower rates of toxicity. However, 3-drug combination regimens may be used in patients with good performance status who can be regularly examined for adverse events.[4]

In 2016, a study conducted by Hess et al examined chemotherapy treatment patterns, costs, and outcomes of gastric cancer patients across the United States. Their results indicated that the approach to care after disease progression or recurrence is not rigorously evidence-based. Uncertainties in the existing evidence have led to large variations in treatment patterns across providers.[2]

Hess and colleagues retrospectively analyzed data collected from electronic medical records (EMRs) and administrative claims.[2] Data from the latter included records from hospital inpatient admissions, outpatient medical claims, professional claims, service and facility files, length of stay in institutional settings, copayment amounts, and pharmacy claims. EMR data were drawn from therapeutic regimens (drug molecule, generic drug name, dose, date of administration, length of therapy) and gastric/gastroesophageal-related surgical procedures.[2]

Patients included in the study were aged 18 years or older with recent diagnosis of gastric cancer between 2004 and 2012; excluded were patients who had any signs of cancer up to 6 months prior to initial diagnosis or who had gastrointestinal stromal tumor.[2]

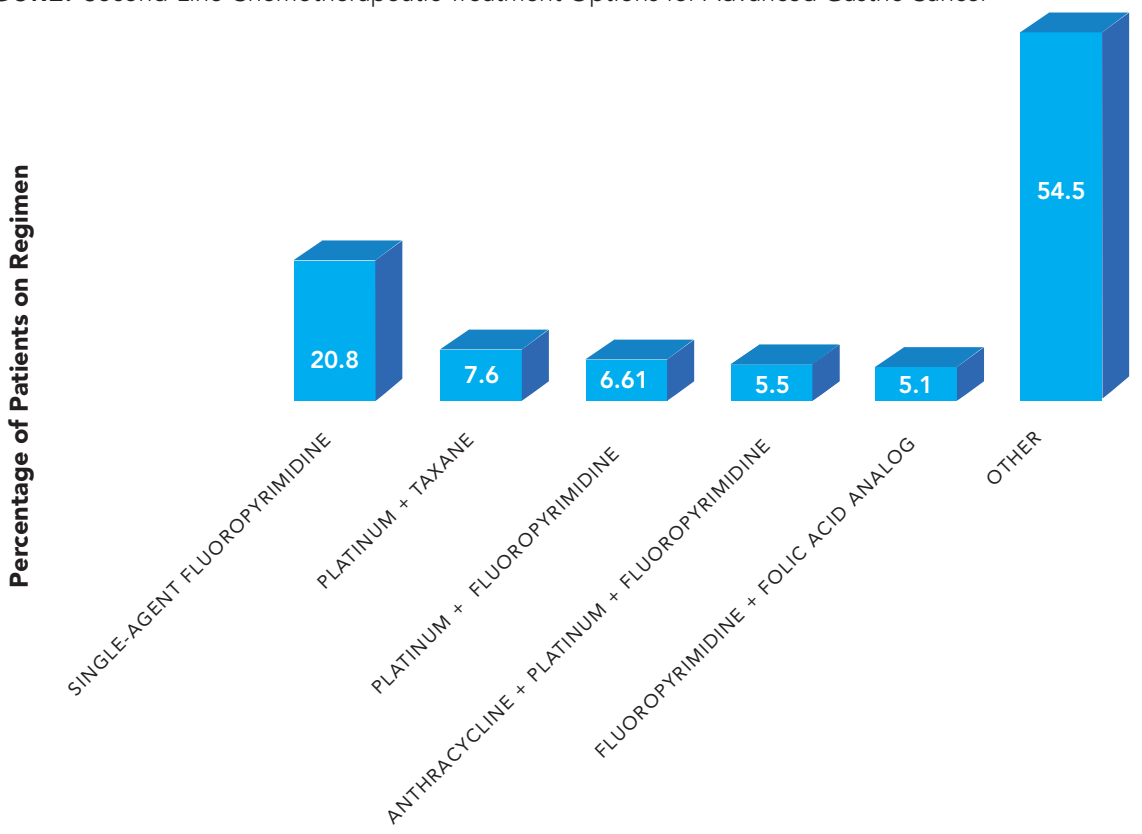
The study examined how often patients require further chemotherapy after initial treatment. Of 1982 patients who received chemotherapy treatments, as indicated by EMR data, 42.3% required second-line treatment, 18.1% required third-line treatment, and 7.9% required fourth-line treatment.[2] Of the 11,891 eligible patients in the administrative database, 5299 patients were identified as having received chemotherapy. Of these, 54.5% required chemotherapy as second-line treatment, and 30.2% required chemotherapy as third-line treatment.[2]

While no standard treatment regimen was identified following first-line therapy, Hess et al found that certain agents used for first-line treatment were used more often in second-line treatment in a variety of combinations.[2] Using information from both databases, Hess et al found that for first-line therapy, a platinum-based treatment used alone or in combination with fluoropyrimidine was most often used (89.7% of patients from the EMR database and 88.7% of patients from the administrative database).[2] Data from the EMR database and the administrative database also showed that 131 and 351 unique drug combinations, respectively, were used for second-line therapy.[2] The distribution of patients who were indicated in the administrative database as having been on second-line treatment regimens is represented in the **FIGURE**.[2]

In addition to finding large variation in treatment regimens, Hess and colleagues also found great variability in costs. Third-party total healthcare costs for first-line treatment ranged from $7.89 to $933,828.53 with a mean of $40,810.87, and out-of-pocket total healthcare costs ranged from $0 to $33,513.16 with a mean of $926.11.[2]

All-cause total costs following chemotherapy averaged $80,148.07 from the end of chemotherapy to death or end of patient record in the database. While costs often »

FIGURE. Second-Line Chemotherapeutic Treatment Options for Advanced Gastric Cancer[2]



varied greatly, treatment was generally associated with a large patient financial burden.[2] For patients who were hospitalized after chemotherapy, the average per-patient total cost per hospital stay was $85,769.49.[2]

Looking closely at the chemotherapy regimens documented in the databases, Hess et al found that few patients were treated using evidence-based regimens.[2] Additionally, published data reveal that no randomized clinical trials assessing second-line chemotherapy regimens for gastric cancer were published after the year 2011.[5] This suggests that a lack of current clinical data may be a contributing factor to the current variability and lack of standardization of care for gastric cancer.[2]

Although there has been a notable lack of progress in recent years, past clinical trials have demonstrated improved rates of survival in second-line treatment with a single agent, such as docetaxel, irinotecan, and ramucirumab, a monoclonal antibody vascular endothelial growth factor (VEGF) inhibitor.[2] Survival outcomes have been reported for some combination therapies as well, including ramucirumab plus paclitaxel, which improved survival to a larger degree than paclitaxel monotherapy.[2] Treatment arms and overall survival rates in other phase 3 clinical trials that have assessed second-line treatment regimens in patients with advanced gastric cancer are outlined in the **TABLE**.[6-12,13]

Targeted agents are a more recent approach in advanced gastric cancer treatment, and the number of clinical trials evaluating these agents has recently increased.[3] Specific molecular targets being tested in clinical trials include epidermal growth factor receptor, VEGF, and HER2.[3] Current data show poor efficacy of these targeted agents, suggesting the need to investigate new molecular targets to improve survival rates.[3]

Until the FDA approved the use of ramucirumab in 2014, few therapeutic options existed for progressive or recurrent gastric cancer. With the introduction of ramucirumab as a treatment option and its preferred status in current NCCN guidelines, physicians had a new option for second-line treatment for advanced gastric cancer.[2,3] Ramucirumab has indications for use in metastatic non–small-cell lung cancer, metastatic colorectal cancer, and advanced gastric or gastroesophageal junction adenocarcinoma.[14] Main phase 3 trials RAINBOW and REVEL have both demonstrated the efficacy and safety of ramucirumab for advanced gastric cancer.[12]

The RAINBOW trial compared the safety and efficacy of ramucirumab in combination with paclitaxel against paclitaxel with placebo, and the REGARD trial compared ramucirumab with placebo.[7,12] Both trials found that both ramucirumab monotherapy and ramucirumab plus paclitaxel

TABLE. Results from Phase 3 Clinical Trials Assessing Second-Line Chemotherapy Regimens in Patients with Advanced Gastric Cancer[6-12,13]

	TREATMENT ARMS	NUMBER OF PATIENTS	OS, MONTHS
COUGAR-02	Docetaxel	84	5.2
	BSC	84	3.6
REGARD	Ramucirumab + BSC	238	5.2
	Placebo + BSC	117	3.8
WJOG 4007	Paclitaxel	108	9.5
	Irinotecan	111	8.4
Korean	Docetaxel or Irinotecan	133	5.3
	BSC	69	3.8
AIO	Irinotecan	21	4.0
	BSC	19	2.4
TCOG GI-0801	Irinotecan + Cisplatin	64	N/A; PFS: 4.17
	Irinotecan	66	N/A; PFS: 3.03
RAINBOW	Ramucirumab + Paclitaxel	330	9.6
	Placebo + Paclitaxel	335	7.4

BSC indicates best supportive care; OS, overall survival; PFS, progression free survival.

combination therapy demonstrated superior overall survival (OS) rates versus comparator treatments. In RAINBOW, median OS was 9.6 months with ramucirumab plus paclitaxel versus 7.4 months with placebo plus paclitaxel ($P = .017$). In REGARD, median OS was 5.2 months with ramucirumab alone versus 3.8 months with placebo ($P = .047$).[7,12,15,16]

Progression-free survival (PFS) was also measured in both trials. In the RAINBOW trial, PFS was 4.4 months for the ramucirumab plus paclitaxel treatment combination, and 2.9 months for the placebo plus paclitaxel treatment ($P < .0001$).[12] In the REGARD trial, PFS was 2.1 months in the ramucirumab group and 1.3 months in the placebo group ($P < .0001$).[7,15,16]

Overall, chemotherapy has proven to be more beneficial than best supportive care for alleviating symptoms and prolonging survival for patients with advanced gastric cancer.[15,16] These clinical studies should be used as a reference point for making treatment decisions for gastric cancer, and data from these clinical studies can be used to evaluate cost-effectiveness of different regimens and the order of care strategies, and to inform the best treatment options.[2] In managing lines of therapy, oncologists should use the most up-to-date available evidence to maximize outcome and survival in patients with advanced gastric cancer. ■

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-E356. doi: 10.1002/ijc.29210.

2. Hess LM, Michael D, Mytelka DS, Beyrer J, Liepa AM, Nicol S. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer.* 2016;19(2):607-615. doi: 10.1007/s10120-015-0486-z.

3. Bilici A. Treatment options in patients with metastatic gastric cancer: current status and future perspectives. *World J Gastroenterol.* 2014;20(14):3905-3915. doi: 10.3748/wjg.v20.i14.3905.

4. Gastric cancer. National Cancer Comprehensive Network website. www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Updated March 21, 2017. Accessed April 2017.

5. Karve S, Lorenzo M, Liepa AM, Hess LM, Kaye JA, Calingaert B. Treatment patterns, costs, and survival among Medicare-enrolled elderly patients diagnosed with advanced stage gastric cancer: analysis of a linked population-based cancer registry and administrative claims database. *J Gastric Cancer.* 2015;15(2):87-104. doi: 10.5230/jgc.2015.15.2.87.

6. Ford HE, Marshall A, Bridgewater JA, et al; COUGAR-02 Investigators. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol.* 2014;15(1):78-86. doi: 10.1016/S1470-2045(13)70549-7.

7. Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383(9911):31-39. doi: 10.1016/S0140-6736(13)61719-5.

8. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol.* 2013;31(35):4438-4444. doi: 10.1200/JCO.2012.48.5805.

9. Kang JH, Lee SI, Lim DH, 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(13):1513-1518. doi: 10.1200/JCO.2011.39.4585.

10. Thuss-Patience PC, Kretzschmar A, Bichev D, 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(15):2306-2314. doi: 10.1016/j.ejca.2011.06.002.

11. Shimada K, Higuchi K, Hosaka N, et al; The Tokyo Cooperative Oncology Group. Randomized phase III trial of irinotecan plus cisplatin versus irinotecan alone after S-1 based chemotherapy failure for patients with advanced and recurrent gastric cancer (AGC) (TCOG GI-0801) [abstract 61]. *J Clin Oncol.* 2013;31(suppl 4). doi: 10.1200/jco.2013.31.4_suppl.61.

12. Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. 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(11):1224-1235. doi: 10.1016/S1470-2045(14)70420-6.

13. Kim SM, Park SH. Chemotherapy beyond second-line in advanced gastric cancer. *World J Gastroenterol.* 2015;21(29):8811-8816. doi: 10.3748/wjg.v21.i29.8811.

14. Cyramza [package insert]. Indianapolis, IN: Eli Lilly & Co; 2017.

15. Yuan M, Shi Z, Wang Z, et al. The significance of multi-line chemotherapy for advanced gastric cancer: a retrospective analysis. *Mol Clin Oncol.* 2017;6(4):606-612. doi: 10.3892/mco.2017.1163.

16. 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 multicentre, double-blind, randomised phase 3 trial. *Lancet.* 2014;384(9944):665-673. doi: 10.1016/S0140-6736(14)60845-X.