Systemic therapy for advanced gastric cancer: a clinical practice guideline

M. MacKenzie MD, K. Spithoff MSc,† D. Jonker MD,‡ and the Gastrointestinal Cancer Disease Site Group*

ABSTRACT

Question

What is the optimal chemotherapy regimen in advanced gastric cancer?

Perspectives

Gastric cancer is the second leading cause of cancer mortality worldwide. Despite low incidence rates for gastric cancer in Ontario, the overall prognosis is bleak, with 5-year survival rates of approximately 23% in Canada. Even with the considerable body of research available on chemotherapy for advanced gastric cancer, uncertainty remains. There is no recognized standard treatment, and there appears to be geographic variation in practice.

Outcomes

Outcomes of interest were overall survival, objective response rate (complete plus partial responses), time to disease progression, adverse effects, and quality of life.

Methodology

After a systematic review, a practice guideline containing clinical recommendations relevant to patients in Ontario was drafted. The practice guideline was reviewed and approved by the Gastrointestinal Disease Site Group (GI DSG) and the Report Approval Panel of the Program in Evidence-Based Care. External review by Ontario practitioners was obtained through a survey, the results of which were incorporated into the practice guideline.

Practice Guideline

The GI DSG makes the following recommendations:

- To improve survival, a platinum agent should be included in any combination chemotherapy regimen.
- Within a combination chemotherapy regimen, oral capecitabine is preferred over intravenous 5-fluorouracil (5FU)—that is, epirubicin–cisplatin–capecitabine is preferred over the prior standard regimen, epirubicin–cisplatin–5FU (ECF).
- Epirubicin–oxaliplatin–capecitabine (EOX) is a reasonable alternative to ECF. The choice between ECF and EOX should be based on patient preference.
- Trastuzumab in combination with cisplatin and a fluoropyrimidine (5FU or oral capecitabine) is recommended for advanced gastric cancer positive for the human epidermal growth factor receptor 2 (HER2/*neu*).

KEY WORDS

Advanced gastric cancer, systemic therapy, practice guideline

1. QUESTION

What is the optimal chemotherapy regimen in advanced gastric cancer?

Outcomes of interest were overall survival (OS), objective response rate (complete plus partial responses), time to disease progression, adverse effects, and quality of life.

2. INTRODUCTION

Gastric cancer is a virulent disease that is the second leading cause of cancer mortality worldwide [1]. There is significant geographic variation in the incidence of gastric cancer, with incidence and mortality being particularly high in Japan, China, Korea, Chile, and Costa Rica [2]. Even though the incidence rate for gastric cancer in Ontario is one of the lowest worldwide [3], overall prognosis is bleak, with 5-year survival rates of approximately 23% in Canada [4] and 23%–25% in the United States for all stages combined [5].

Despite the considerable body of research available on chemotherapy for advanced gastric cancer,

uncertainty remains. There no recognized standard treatment for gastric cancer, and there appears to be geographic variation in practice. A Cochrane Collaboration systematic review and meta-analysis on chemotherapy in advanced gastric cancer was first published in 2005 [6] and updated in 2006 [7]. Because of the availability of numerous randomized trials since the publication of the Cochrane review, the Gastrointestinal Disease Site Group (GI DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) decided to develop a guideline on systemic therapy for advanced gastric cancer.

3. METHODS

3.1 Guideline Development

This guideline was developed by Cancer Care Ontario's PEBC using the methods of the practice guidelines development cycle [8]. The core methodology used to develop the evidentiary base is the systematic review. For this guideline, evidence was selected and reviewed by 2 members of the GI DSG and a methodologist.

This practice guideline is a convenient and up-to-date source of the best available evidence on chemotherapy for advanced gastric cancer. It was developed by systematic review, data synthesis, internal review by a clinician and a methodologist, and external review by clinical experts and Ontario practitioners. The systematic review evidence (manuscript under development) forms the basis of the recommendations developed by the GI DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent of its funding source.

3.2 Literature Search Strategy

The literature contained in the Cochrane review [6,7] was used as the primary evidentiary base up to 2004. The MEDLINE (2004 to week 4, August 2010), EMBASE (2004 to week 34, 2010), and CENTRAL (the Cochrane Library, Issue 3, 2008) databases were systematically searched to identify relevant randomized trials published after the Cochrane review that met the inclusion criteria. To identify trials that met the inclusion criteria for the present review, but that were excluded from analysis in the Cochrane review [6,7], the list of trials excluded from the Cochrane review was searched for additional relevant evidence [6].

Annual meeting proceedings of the American Society of Clinical Oncology (ASCO) from 2005 to 2010 were searched to identify abstract reports or publicly available presentations of relevant randomized controlled trials (RCTs). Proceedings of the ASCO gastrointestinal symposia from 2005 to 2010 were also searched. Reference lists of relevant reviews and included RCTs were screened for additional relevant trials.

4. RESULTS

The literature search identified reports of seventy-two randomized trials [9–80] that met the inclusion criteria for the present review. Given the large numbers of trials and the many different comparisons in the trials retrieved, the GI DSG made an *a posteriori* decision to focus on the individual contributions of fluoropyrimidines [20,24,25,28,32–40], platinum agents [9,23,26,30,36,41–45], anthracyclines [34,46–50,79], taxanes [22,51,52], and irinotecan [9,53]. The DSG also decided to determine whether the available evidence supports the regimens that are currently in common use in Ontario [21,24,25,36,48,55–58] and to determine the contribution of targeted therapies [59,80].

5. DSG CONSENSUS PROCESS

The draft guideline and systematic review were circulated for review and discussion by the GI DSG. The DSG consists of medical oncologists, radiation oncologists, surgical oncologists, a methodologist, and a patient representative. The GI DSG approved the draft guideline and systematic review in November 2009.

6. INTERNAL REVIEW

Before the report was sent for external review, it was reviewed and approved by the PEBC Report Approval Panel, which consists of 2 members, including an oncologist with expertise in clinical and methodology issues. The Report Approval Panel raised these key issues:

- Justification for the recommendation concerning anthracycline-containing regimens was requested.
- Based on the ToGA (Trastuzumab in Gastric Cancer) trial, the lack of a full recommendation on trastuzumab was queried.
- To address those comments, the GI DSG
- included a qualifying statement that ECF [epirubicin–cisplatin–5-fluorouracil (5FU)] is the standard of care in Ontario and, thus, is the most relevant comparator in the Ontario context, but that the DSG acknowledges that other options are based on levels of evidence that are similar to those for ECF.
- noted that the results of ToGA are available only in abstract form, and the PEBC has a policy against making recommendations based solely on a single abstract.

7. EXTERNAL REVIEW

The PEBC external review process is two-pronged: a targeted peer review aims to obtain direct feedback

on the draft report from a small number of specified content experts, and a professional consultation acts to facilitate dissemination of the final guidance report to Ontario practitioners.

7.1 Methods

7.1.1 Targeted Peer Review

During the guideline development process, 4 targeted individuals from Ontario, Manitoba, and British Columbia who are considered clinical or methodological experts on the topic were asked to serve as peer reviewers. All 4 individuals agreed, and the draft report and a survey questionnaire were sent by e-mail for their review. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and asking whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey and draft guideline were sent February 24, 2010. Follow-up reminders were sent at 2 weeks (e-mail) and at 4 weeks (telephone call). The GI DSG reviewed the results of the survey (see Table I).

7.1.2 Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All medical oncologists in the PEBC database who treat gastric cancer were contacted by e-mail and directed to the survey Web site where they were provided with access to the survey, the guideline recommendations, and the evidentiary base. Participants were asked to rate the overall quality of the guideline and whether they would use or recommend it. Written comments were invited. The notification message was sent March 10, 2010. The consultation period ended April 21, 2010. The GI DSG reviewed the results of the survey (see Table II).

7.2 Results

7.2.1 Summary of Written Comments from the Targeted Peer Review

Concerns were raised that the platinum meta-analysis included many small and phase II trials. A statement that the platinum meta-analysis included many small and phase II trials was therefore added to the recommendation about platinum agents.

7.2.2 Summary of Written Comments from the Professional Consultation

Requests were made for recommendations on how to treat less-fit patients. Unfortunately, there are no data about how less-fit patients should be treated, and therefore recommendations could not be made. There was also a request to follow up on the role of trastuzumab in gastric cancer. The role of trastuzumab will be followed up, and a statement to that effect appears in one of the qualifying statements appended to the recommendations.

8. UPDATE AFTER EXTERNAL REVIEW

After completion of external review, the results of the ToGA trial [59] were published in full. That publication necessitated an update of the entire literature search, which was completed in September 2010. The updated literature search is reflected in the information provided in the Abstract, Methods, and Results sections,

TABLE I Responses to items on the targeted peer reviewer questionnaire

Question	*Reviewer ratings [*n *(%)]*				
	Lowest quality (1)	(2)	(3)	(4)	*Highest quality* (5)
Rate the guideline development methods.					4 (100)
Rate the guideline presentation.					4 (100)
Rate the guideline recommendations.					4 (100)
Rate the completeness of reporting.					4 (100)
Does this document provide sufficient information to inform your decisions? If not, what areas are missing?					4 (100)
Rate the overall quality of the guideline report.					4 (100)
	Strongly disagree (1)	(2)	*Neutral* (3)	(4)	*Strongly Agree* (5)
I would make use of this guideline in my professional decisions.					4 (100)
I would recommend this guideline for use in practice.					4 (100)

TABLE II Responses to items on the professional consultation survey

General questions (overall guideline assessment)	*Survey rating [n (%)][a]*				
	Lowest quality (1)	(2)	(3)	(4)	*Highest quality* (5)
1. Rate the overall quality of the guideline report.				2 (40)	2 (40)
	Strongly disagree (1)	(2)	(3)	(4)	*Strongly agree* (5)
2. I would make use of this guideline in my professional decisions.				2 (40)	2 (40)
3. I would recommend this guideline for use in practice.				2 (40)	2 (40)

[a] Ratings do not add up to 100% because 1 of the 5 reviewers provided comments, but no ratings.

and in the practice guideline that follows. The DSG reviewed and approved the updated version.

9. PRACTICE GUIDELINE

This report reflects integration of the feedback obtained through the external review process, with final approval given by the GI DSG and the Report Approval Panel of the PEBC.

9.1 Recommendations and Key Evidence

Recommendation: To improve survival, a platinum agent should be included in any combination chemotherapy regimen.

This recommendation is based on results of a meta-analysis of eight randomized controlled trials (RCTs) [9,23,25,26,30,42–44] that indicated a significant survival benefit for chemotherapy including a platinum agent compared with the same chemotherapy without a platinum agent [hazard ratio (HR): 0.74; 95% confidence interval (CI): 0.65 to 0.84; $p < 0.00001$]. Many of those RCTs were small or phase II trials (or both).

Recommendation: Within a combination chemotherapy regimen, oral capecitabine is preferred over intravenous 5FU—that is, epirubicin–cisplatin–capecitabine (ECX) is preferred over the earlier standard ECF regimen.

This recommendation is based on results of a meta-analysis of two RCTs [35,36] that indicated a significant survival benefit for chemotherapy including capecitabine compared with chemotherapy including 5FU (HR: 0.87; 95% CI: 0.78 to 0.99; $p = 0.03$).

In Ontario, ECF has been the conventional standard chemotherapy regimen, and it remains an acceptable therapy, particularly for patients who experience difficulty taking oral medication.

Based on a database review of Ontario patients, ECF was considered the conventional regimen (58.5% receive it). Adoption of the ECF regimen relates to a single large well-conducted study demonstrating superiority in overall survival for ECF compared with a reasonable-control regimen consisting of 5FU–doxorubicin–methotrexate–leucovorin [55]. Earlier development of chemotherapy regimens for gastric cancer occurred mainly in a nonsequential, underpowered manner. This well-conducted trial credibly established a reasonable standard, although the contribution of each drug within the regimen remains controversial. Meta-analysis demonstrates significant benefit for a platinum agent within a combination regimen and trends toward benefit for fluoropyrimidines and anthracyclines, further supporting the ECF triple combination.

Recommendation: Epirubicin–oxaliplatin–capecitabine (EOX) is a reasonable alternative to ECF. The choice between ECF and EOX should be based on patient preference.

This recommendation is based on results of the REAL-2 (Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2) trial [36], which demonstrated improved overall survival for EOX compared with ECF (HR: 0.80; 95% CI: 0.66 to 0.97; $p = 0.02$), but no difference in progression-free survival or objective response rate. The EOX regimen resulted in significantly higher rates of grades 3 and 4 diarrhea, peripheral neuropathy, and lethargy, but lower rates of grades 3 and 4 neutropenia and alopecia. It should be noted that this comparison was a secondary outcome and that the improvement in survival cannot be definitively attributed to the change in fluoropyrimidine compared with the change in platinum within the regimen.

Recommendation: Trastuzumab in combination with cisplatin plus a fluoropyrimidine (5FU or oral capecitabine) is recommended for advanced gastric cancer positive for the human epidermal growth factor receptor 2 (HER2/*neu*).

This recommendation is based on the results of the ToGA trial, which compared chemotherapy (5FU or

capecitabine, cisplatin) with or without trastuzumab in HER2-positive advanced gastric cancer. The study demonstrated a significant survival benefit for the addition of trastuzumab to chemotherapy (HR: 0.74; 95% CI: 0.60 to 0.91; $p = 0.0046$; median survival: 13.8 months vs. 11.1 months) [59].

The meta-analysis suggests that the relative benefit of the addition of trastuzumab to cisplatin plus a fluoropyrimidine appears greater than that for the addition of epirubicin to cisplatin plus a fluoropyrimidine.

9.2 Qualifying Statements

In Ontario, ECF is the standard of care, and that regimen is, therefore, the most relevant comparator in that context. However, the GI DSG acknowledges that other options for the management of gastric cancer, including cisplatin–5FU, cisplatin–capecitabine, and docetaxel–cisplatin–5FU are based on levels of evidence similar to those for ECF.

In reviewing clinical trials, it is prudent to recognize that there are differences between Western and Asian regions in the incidence of gastric cancer, in surgical care, in molecular profile (rates of HER2/*neu* positivity, for instance), and possibly in causative factors. Thus, some caution is warranted in interpreting the findings of a trial conducted exclusively or largely in one region as being applicable to the other. However, the extent to which regional differences may affect interpretation is speculative.

The HER2 testing in the ToGA trial was conducted at a central expert laboratory, and involved both immunohistochemical (IHC) testing and fluorescence *in situ* hybridization (FISH). Although patients were considered positive in the presence either of 3+ staining by IHC or of FISH positivity (*HER2*:*CEP17* ratio of 2 or more), *post hoc* subgroup analyses showed that the benefit from trastuzumab appeared to be less associated with FISH positivity than with IHC staining intensity. Specifically, there was no apparent overall survival benefit in FISH-positive patients who were IHC 0 to 1+ (HR: 1.07; 95% CI: 0.70 to 1.62; median survival: 10.0 months vs. 8.7 months). In that light, it is likely that the only patients who benefit from trastuzumab are those with either IHC 3+ or 2+ and FISH positivity (HR: 0.65; 95% CI: 0.51 to 0.83; median survival: 16.0 months vs. 11.8 months). Furthermore, the highly controlled setting of the central laboratory within the trial is important. For benefit in community practice to approximate that seen in the trial, laboratory expertise and quality assurance are essential.

10. PRACTICE GUIDELINE DATE

This clinical practice guideline is based on work completed in September 2010. The full version of this guideline and the associated systematic review is located at www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=75973. The systematic review will be published separately. The report will be updated as new evidence informing the question of interest emerges.

11. ACKNOWLEDGMENTS

This work was sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

12. CONFLICT OF INTEREST DISCLOSURES

Members of the GI DSG involved in the development of this systematic review and clinical practice guideline were polled for potential conflicts of interest. Two authors (KS, DJ) declared no conflicts of interest. One author (MM) declared consultant fees and honoraria less than $5000 from Roche Pharmaceuticals for assistance to attend 2 conferences and participation in an advisory board regarding Herceptin (Genentech, San Francisco, CA, U.S.A.) and gastric cancer.

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Correspondence to: Mary MacKenzie, London Regional Cancer Program, 790 Commissioners Road East, London, Ontario N6A 4L6.
E-mail: mary.mackenzie@lhsc.ca

* London Health Sciences Centre, London, ON.
† Cancer Care Ontario's Program in Evidence-Based Care, Hamilton, ON.
‡ The Ottawa Hospital, Ottawa, ON.