Evidence-Based Series 2-26 Version 2 BEING UPDATED

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy for Advanced Gastric Cancer

Members of the Gastrointestinal Cancer Disease Site Group

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Evidence-based Series (EBS) 2-26 Version 2 is currently BEING UPDATED. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 2-26 Version 2 is comprised of 4 sections. You can access the summary and full report here:


Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Summary and Review Tool

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## Guideline Report History

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Evidence-Based Series 2-26 Version 2: Section 1

Systemic Therapy for Advanced Gastric Cancer: Guideline Recommendations

M. Mackenzie, K. Spithoff, D. Jonker, and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: June 29, 2010

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2009 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

QUESTION
What is the optimal chemotherapy regimen in advanced gastric cancer? Outcomes of interest are overall survival (OS), objective response rate (ORR; complete plus partial response), time-to-disease progression (TTP), adverse effects, and quality of life.

TARGET POPULATION
Adult patients with advanced (non-resectable; either locally advanced or metastatic) gastric cancer. These recommendations apply to patients with adenocarcinoma of the gastroesophageal junction but not to squamous cell carcinomas.

INTENDED USERS
This guideline is intended for use by clinicians and health care providers involved in the management or referral of adult patients with advanced gastric cancer.

RECOMMENDATIONS AND KEY EVIDENCE

A platinum agent should be included in any combination chemotherapy regimen to improve survival.

- This recommendation is based on results of a meta-analysis of eight randomized controlled trials (RCTs) (1-8) 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], 0.65-0.84; p<0.00001) (Section 2, Figure 2). Many of these RCTs were small and/or Phase II trials.

Oral capecitabine is preferred over intravenous 5-fluorouracil (5FU) within a combination chemotherapy regimen (i.e., epirubicin, cisplatin, and capecitabine [ECX] is a preferred regimen over the prior standard, epirubicin, cisplatin, and 5FU [ECF]).

- This recommendation is based on results of a meta-analysis of two RCTs (9,10) which indicated a significant survival benefit for chemotherapy including capecitabine compared with chemotherapy including 5FU (HR, 0.87; 95% CI, 0.78-0.99; p=0.03) (Section 2, Figure 1).
- ECF has been the conventional standard chemotherapy regimen in Ontario and remains an acceptable therapy, particularly for those with difficulty taking oral medication.
- ECF was considered the conventional standard based on a database review of Ontario patients, demonstrating that 58.5% receive this regimen. The adoption of this regimen relates to a single, large well-conducted study demonstrating OS superiority compared to a reasonable-control regimen consisting of 5FU, doxorubicin, methotrexate, and leucovorin (F/A/MTX/L) (11). Much of the prior development of chemotherapy regimens for gastric cancer has occurred in a non-sequential, underpowered, and slightly disorganized manner. This well-conducted trial credibly established a reasonable standard, though the contribution of each drug within the regimen remains controversial. Meta-analysis demonstrates significant benefit from a platinum agent within a combination regimen and trends for benefit from fluoropyrimidines and anthracyclines, further supporting this triple combination.

Epirubicin, oxaliplatin, and capecitabine (EOX) is a reasonable alternative to ECF. The choice between ECF and EOX should be based on patient preferences. For patients with HER-2 positive status, the addition of trastuzumab (Herceptin) to cisplatin plus fluoropyrimidine (5-fluorouracil or capecitabine) is a reasonable treatment option.

- This recommendation is based on results of the REAL-2 trial (12) that demonstrated improved OS for EOX compared to ECF (Hazard Ratio (HR) 0.80; 95% CI 0.66-0.97; p=0.02) but no difference in progression-free survival or ORR. The EOX regimen resulted in significantly higher rates of grade 3/4 diarrhea, peripheral neuropathy, and lethargy, but lower rates of grade 3/4 neutropenia and alopecia. It should be noted that this comparison was a secondary outcome and the improvement in survival cannot be clearly attributed to the change in the fluoropyrimidine versus the change in platinum within the regimen.
- The recommendation for HER-2 positive patients is based on the results of a large, multicenter, international phase III trial (ToGA) by Bang et al 2010 (17) that demonstrated a significant benefit in both OS (HR=0.74; 95% CI: 0.60-0.91; p=0.0046; median survival 13.8 versus 11.1 months) and ORR (OR=1.70; 95% CI: 1.22-2.38; p=0.0017; 47% versus 35%) for the addition of trastuzumab to cisplatin plus fluoropyrimidine (5-fluorouracil or capecitabine). The toxicity profile was similar between the regimens, with no difference in the overall rates of grade 3/4 and cardiac adverse events.
Despite ECF being accepted as the conventional standard in Ontario, there is still no single well established standard of care; this is particularly the case in patients with HER-2 overexpression. While there is no direct comparison between trastuzumab/cisplatin/fluoropyrimidine and ECF, the evidence suggestive of a benefit for the addition of epirubicin to cisplatin and 5-fluorouracil is weak and is based on small studies (14,15) that suffer from various deficiencies (i.e. unreported baseline characteristics, no mention of randomization method, or results never published in a peer-reviewed journal). In fact, a post-hoc sub-analysis of these 2 studies did not yield a significant survival benefit for the addition of epirubicin (HR=0.70; 95% CI: 0.43-1.16; p=0.15) (Figure 3b). Furthermore in a recent randomized phase II trial by Yun et al 2010 (16), the authors reported no significant differences in response rate and PFS between ECX and CX. Taken together, the available evidence showing the impact of epirubicin in a regimen is generally less robust than the evidence evaluating only a fluoropyrimidine plus a platinum. For these reasons, CF may be considered reasonable comparator to HCF or HCX.

QUALIFYING STATEMENTS

- ECF is the standard of care in Ontario and is, therefore, the most relevant comparator in that context. However, the Gastrointestinal Cancer Disease Site Group (GI DSG) acknowledges that other options for the management of gastric cancer, including CF (cisplatin + 5FU), XC (cisplatin + capecitabine), and DCF (docetaxel, cisplatin, and 5FU) are based on levels of evidence similar to the evidence for ECF.
- In reviewing clinical trials, it is prudent to recognize that differences in gastric cancer incidence, surgical care, molecular profile (e.g., rates of human epidermal growth factor receptor 2 [HER2] positivity), and possibly etiology exist between Western and Asian regions. 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.

FUTURE RESEARCH

- Future RCTs should examine new molecular targets in patients with advanced gastric cancer accounting for the genetic and molecular variation this disease.

RELATED GUIDELINES


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REFERENCES


