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Evidence-based Series 2-22 EDUCATION AND INFORMATION 2011

The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer

Members of the Gastrointestinal Cancer Disease Site Group

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

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Evidence-based Series (EBS) 2-22 EDUCATION AND INFORMATION 2011, the resulting review report,
consists of the following 5 parts:

1. **Guideline Report Overview**
2. **Section 1: Clinical Practice Guideline**
3. **Section 2: Systematic Review**
4. **Section 3: Guideline Development and External Review**
5. **Document Assessment and Review Tool**

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Gastrointestinal Cancer Disease Site Group page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gastro-ebs/.

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The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Dec 2006	1966 to 2006	Full Report	Peer review publication[1] Web publication	Not Applicable
Reviewed Version Jul 2010	Document Assessment and Review Tool		Updated Web publication	Guideline ARCHIVED

[1] Jonker D, Rumble RB, Maroun J and the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Role of oxaliplatin combined with 5-fluorouracil and folinic acid in the first- and second-line treatment of advanced colorectal cancer: a systematic review and clinical practice guideline. Curr Oncol 2006;13(5):173-84.

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Evidence-based Series 2-22 ARCHIVED 2011

The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer

Guideline Review Summary

Review Date: July 12, 2010

The 2006 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), in 2006. In April 2010, the PEBC guideline update strategy was applied, and the recommendations were ARCHIVED in July 2010.

Update Strategy

The PEBC update strategy includes an updated search of the literature, the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence. See the Document Assessment and Review Tool.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

What is the role of oxaliplatin combined with 5-fluorouracil (5FU) and folinic acid (FA) in the first- and second-line treatment of advanced (non-resectable locally advanced or metastatic) colorectal cancer? Outcomes of interest were one-year survival, response rates, and quality of life.

Literature Search and New Evidence

A search for new literature with respect to this question was not conducted since it was determined that components of this guideline will be replaced by a new guideline that is currently in production, "Strategies of sequential therapy in advanced colorectal cancer". Hence, the guideline and its recommendations have been ARCHIVED.

Impact on Guidelines and Its Recommendations

The Gastrointestinal Cancer DSG **ARCHIVED** the 2006 recommendations. Therefore this guideline will no longer be updated.

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Evidence-based Series #2-22: Section 1

The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer: A Clinical Practice Guideline

D. Jonker, R.B. Rumble, J. Maroun, and members of the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gastrointestinal DSG

Please see the EBS 2-22 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2005 and 2010.

Report Date: December 8, 2006

Question

What is the role of oxaliplatin combined with 5-fluorouracil (5FU) and folinic acid (FA) in the first- and second-line treatment of advanced (non-resectable locally advanced or metastatic) colorectal cancer? Outcomes of interest were one-year survival, response rates, and quality of life.

Target Population

These recommendations apply to adult patients with advanced colorectal cancer who have high performance status (Eastern Cooperative Oncology Group [ECOG] 0-2).

Recommendations

Refer to Appendix 1 in the *Section 2: A Systematic Review* for recommended dosages and schedules.

- Combination oxaliplatin, short-term infusional 5FU, and folinic acid (FOLFOX) is an important component of therapy, and oxaliplatin should be made available for the treatment of advanced colorectal cancer.

First-line Therapy

- FOLFOX was shown to be superior to bolus 5FU/FA/irinotecan (IFL) in one trial. The FOLFOX

regimen has superior median survival and tumour response rates. Compared with IFL, FOLFOX has lower incidences of severe nausea, vomiting, diarrhea, and febrile neutropenia, but higher peripheral neuropathy.
- Short-term infusional 5FU/FA in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are both acceptable alternatives for fit patients when combination therapy is the preferred treatment. Choice of first-line therapy may rely on patient factors and preferences, for example, less neuropathy with irinotecan versus less alopecia with oxaliplatin.

Second-line Therapy
- After progression on first-line anti-thymidylate synthase monotherapy (e.g., 5FU/FA; capecitabine), irinotecan is the standard second-line therapy. FOLFOX is a reasonable alternative for patients with contraindications to the use of second-line irinotecan.
- After progression on both irinotecan and an anti-thymidylate synthase agent, FOLFOX is the preferred therapy. Recent trials suggest that, as compared to FOLFOX alone, FOLFOX combined with bevacizumab provides additional survival benefits.

Qualifying Statements
- The role of radiation therapy, either alone or in combination with chemotherapy, for locally advanced non-resectable colorectal cancer is not addressed in this guideline.
- Use of chronomodulated regimens is a topic that intersects with the use of oxaliplatin/U combinations, particularly the chronomodulation of 5FU in these combinations. Chronomodulation of oxaliplatin has not been extensively studied, and the topic of chronomodulation is beyond the scope of this guideline and will not be thoroughly addressed.
- Although data exist to support the use of bevacizumab in combination with FOLFOX in second-line treatment, no first-line treatment data are available on which to make a recommendation.

Key Evidence
First-line Therapy
- Four fully published studies have compared combination 5FU/FA/oxaliplatin with combination 5FU/FA/irinotecan. The largest of these studies, performed by the U.S/Canadian Intergroup, compared the infusional FOLFOX regimen to the bolus IFL regimen (1). This study demonstrated a 4.5 month improvement in median survival (15 months versus [vs.] 19.5 months) favouring the infusional FOLFOX regimen. Although this evidence suggests the superiority of oxaliplatin/5FU combinations over irinotecan combinations, there is further evidence to suggest that the superiority of FOLFOX in this study is related to its use within an infusional 5FU regimen. Three studies compared oxaliplatin-based and irinotecan-based regimens where 5FU was delivered in an identical fashion (2-4). The Colucci et al study (2) (comparing FOLFOX vs. FOLFIRI) did not detect any differences between treatments. Results of the SICOG 0103 trial reported by Comella et al (3) (comparing OXAFAFU vs. IRIFAFU) detect a significant benefit for OXAFAFU in one-year overall survival (39% vs. 23%; p=0.032). The results of the GERCOR study, a crossover study using short-term infusional 5FU in both treatment arms, were reported by Tournigand et al (4). That trial compared FOLFOX followed (at the time of progression) by FOLFIRI versus FOLFIRI followed by FOLFOX. The study demonstrated similar median survival (21.5 months vs. 20.6 months) and overall response rate (56% vs. 54%) in first-line treatment. FOLFOX was associated with lower 60-day mortality, a lower incidence of severe nausea, less vomiting, less diarrhea, and less febrile neutropenia but was associated with a higher

incidence of peripheral neuropathy.

- Four trials have compared first-line combination 5FU/FA/oxaliplatin to 5FU/FA alone. Only two of these trials reported one-year survival outcomes, and no difference was detected in either trial. However, all three of the trials that reported on overall response rate detected a superior benefit favouring the addition of oxaliplatin to 5FU/FA.
- A meta-analysis of seven RCTs involving 3,186 patients by Grothey et al (5) and comparing combination chemotherapy (either oxaliplatin or irinotecan in combination with 5FU) with 5FU-based therapy alone detected a significant 3.5 month increase in median survival (p=0.0083) in patients who received a first-line combination therapy (either oxaliplatin/5FU/FA or irinotecan/5FU/FA).
- Three trials have examined chronomodulated (CM) 5FU in combination with oxaliplatin versus fixed-rate 5FU in combination with oxaliplatin (6-8). A pooled analysis of the seven-year results of two underpowered trials by Levi et al (abstract only) (9) demonstrated superior ORR% (51% vs. 30%; p<0.001), complete surgical resection (23.3% vs. 12.8%; p<0.001), and median progression-free survival (PFS) (10.3 vs. 7.5; p=0.039) favouring CM therapy, without a difference in median survival (18.6 vs. 16.5 months; p=0.22) or survival at either five or seven years (5year: 12.6 vs. 15.2; 7year: 6.6 vs. 7.1). A third trial by Giacchetti et al (8) reported no significant difference in overall survival or PFS between treatment groups.

Second-line Therapy

- The ECF4584 trial (10) demonstrated improvements in time to progression and response rate with second-line FOLFOX compared to oxaliplatin alone or infusional 5FU/FA alone in patients who progressed on the IFL (irinotecan, leucovorin calcium, bolus 5FU) regimen. Combination 5FU/FA/oxaliplatin is an acceptable palliative therapy in patients who have progressed on both 5FU/FA/irinotecan. Presently, there remains more evidence supporting second-line irinotecan than 5FU/FA/oxaliplatin or oxaliplatin alone, but oxaliplatin in combination with infusional 5FU/FA is a reasonable alternative for patients considered poor candidates (ECOG 3-4) for second-line irinotecan. Interim analysis of that trial detected an overall symptom relief difference favouring treatment with FOLFOX4 (33% vs. 12%).
- Garay et al (abstract) (11) reported a significant improvement in the median time to progression (4.9 months vs. 2.6 months) and objective response rate (11.1% vs. 1.9%), favouring FOLFOX over 5FU/FA.
- Pitot et al (abstract) (12) reported a significant benefit in the objective response rate, favouring the sequence FOLFOX4→CPT-11 over CPT-11→FOLFOX4 (27% vs. 15%, p<0.0142).
- Giantonio et al (abstract) (13) compared FOLFOX4 with and without bevacizumab and found that the addition of bevacizumab to the FOLFOX regimen resulted in significant gains in both median survival (10.7 months vs. 10.2 months, p=0.0024) and PFS (7.4 months vs. 5.5 months, p=0.0003).

Box 1: Treatment options (see Appendix 1, Section 2 for recommended dosages and schedules).

1st-line treatment alternatives
• FOLFIRI (combination 5FU/FA/irinotecan) ± bevacizumab
• FOLFOX (combination 5FU/FA/oxaliplatin) ± bevacizumab
• XELOX (combination capecitabine/oxaliplatin) ± bevacizumab
• de Gramont schedule (infusional 5FU/FA)
• Raltitrexed
• Capecitabine ± bevacizumab
2nd-line treatment alternatives

• FOLFOX (combination 5FU/FA/oxaliplatin) ± bevacizumab, after 1st-line FOLFIRI
• FOLFIRI (combination 5FU/FA/irinotecan) ± bevacizumab, after 1st-line FOLFOX
• Irinotecan alone

Future Research

Results from three key studies are awaited:

- Sanofi-ECF4585: Phase III oxaliplatin/irinotecan versus irinotecan alone as second-line therapy after progression on anti-thymidylate synthase therapy.
- Roche: Phase III FOLFOX versus XELOX (combination capecitabine and oxaliplatin) as first-line therapy for advanced colorectal cancer.
- Roche: Phase III FOLFOX versus XELOX as second-line therapy after progression on 5FU/Irinotecan combination therapy for advanced colorectal cancer.

Related Guidelines

PEBC Practice Guideline Reports:

- #2-15: *Capecitabine in Metastatic Colorectal Cancer*
- #2-16: *Use of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma*
- #2-16b: *Use of Irinotecan (Camptosar®, CPT-11) Combined with 5FU & LV as First-line Therapy for Metastatic Colorectal Cancer*
- #2-17: *Use of Raltitrexed (Tomudex) in the Management of Metastatic Colorectal Carcinoma*
- #2-25: *The Role of Bevacizumab (Avastin®) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer*

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Evidence-based Series #2-22: Section 2

The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer: A Systematic Review

D. Jonker, R.B. Rumble, J. Maroun, and members of the Gastrointestinal Cancer Disease Site Group

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Developed by the Gastrointestinal DSG

Please see the EBS 2-22 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2005 and 2010.

Report Date: December 8, 2006

QUESTION

What is the role of oxaliplatin combined with 5-fluorouracil (5FU) and folinic acid (FA) in the first- and second-line treatment of advanced (non-resectable locally advanced or metastatic) colorectal cancer? Outcomes of interest were one-year survival, response rates, and quality of life.

INTRODUCTION

In Ontario, Canada, colorectal cancer is the fourth most common cancer site for both sexes combined, representing 13.1% of all new cancer cases (1). Colorectal cancer is the third most common site in men (13.3% of all new cases) and the second most common site in women (12.9% of all new cases) (1), and remains the second leading cause of cancer deaths (10.6% of all cancer deaths) (1). For both men and women, colorectal cancer ranks third as the leading cause of death, after breast and lung in women and after lung and prostate in men (1). For that reason, there is great interest in improving the treatment results for this group of patients.

Currently, the standard first-line treatment for metastatic colorectal cancer in Canada is a combination of 5FU, FA (also known as leucovorin calcium [LV]), and irinotecan, known as FOLFIRI, given by infusional delivery (Douillard regimen) (2). Infusional FOLFIRI replaced IFL, the same treatment regimen by bolus delivery. For patients unable to tolerate a combination-

therapy regimen, an alternative to FOLFIRI would be monotherapy with a first-line thymidylate synthase (TS) inhibitor (such as 5FU/LV, raltitrexed (3), or capecitabine) followed by second-line irinotecan alone (4).

Once patients are no longer responding to the combined use of a TS inhibitor and irinotecan or monotherapy, the options for treatment are limited. Oxaliplatin (L-OHP), a third-generation platinum compound has demonstrated activity in colorectal cancer. Oxaliplatin differs from both cisplatin and carboplatinum in its amino acid configuration. Oxaliplatin has an oxalato group that was removed by hydrolysis and replaced with a diaminocyclohexane (DACH) group (5). The bulky DACH side groups inhibit DNA-base excision by mismatching the repair enzymes (5). Because the repair enzymes are particularly active in colorectal cancer, oxaliplatin has the potential to be of great benefit to patients in both first- and second-line treatment. With the availability of randomized trials comparing regimens of oxaliplatin combined with 5FU/FA versus other combinations, a systematic review of the evidence and clinical practice guideline was warranted.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (6). Evidence was selected and reviewed by two members of the PEBC's Gastrointestinal Disease Site Group (GI DSG) and by a methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on oxaliplatin combined with 5FU and folinic acid in advanced colorectal cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the GI DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1966 to June (week 1) 2006), CANCERLIT (1975 to October 2002), EMBASE (week 26 2003 to week 23 2006), Guidelines International Network (http://www.guidelines-international.net/), and the Cochrane Library (Issue 1, 2006) were searched. The Medical Subject Heading [MeSH] search terms "colonic neoplasms," "rectal neoplasms," and "colorectal neoplasms" were combined with the text words "oxaliplatin," "L-OHP," "LOHP," and "FOLFOX." These results were then combined with the following terms describing specific study designs: "random" and "clinical trial." Results were limited to the English language. The conference proceedings of the 1999 to 2006 annual meetings of the American Society of Clinical Oncology (ASCO), including the 2004 through 2006 Gastrointestinal Cancer Symposiums, were also searched for reports of new or ongoing trials. The reference lists from retrieved papers were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Phase III randomized controlled trials (RCTs) of oxaliplatin combined with 5FU/FA or capecitabine as first-line or second-line therapy for advanced colorectal cancer.
2. Full publications or abstract reports of trials.
3. English-language published reports.

Synthesizing the Evidence

For the following reasons, the GI DSG decided not to pool the results of the trials found in the literature search:

- Treatments described were too heterogeneous to allow for pooling.
- Evidence from the studies obtained provided a clear indication of benefit or harm.
- Published meta-analyses of individual patient data were available. (The meta-analyses are discussed in the appropriate sections of this report.)

RESULTS

Literature Search Results

The literature search found thirty-three reports (7-39), including twenty-seven reports of RCTs of first-line treatment (7-16,18-27,31-37) involving sixteen separate RCTs (7-13,15-16,31-37), two meta-analyses on first-line treatment (28,29), and four reports on second-line treatment (17,30,38,39). Eleven of these reports were preliminary publications that provided additional information about the included trials (14,18-27). Of the thirty-three trial reports obtained, thirteen were fully published (7,8,10,11,15,16,28,30-32,34,35,37), and twenty were available in abstract form only (9,12-14,17-27,29,33,36,38,39). Of the sixteen main reports on first-line treatment, five were available as abstracts only (9,12-13,33,36). Three of the four reports on second-line treatment were available as abstracts only (17,38,39).

Sixteen of the included trial reports disclosed funding, either wholly or in part, from pharmaceutical companies (7,8,10,11,15–17,20–22,27,30,31,39). Seven reported Debiopharm as the source of funding (7,8,10,11,20–22); one reported Pharmacia (Pfizer) / Sanofi-Synthelabo (15); two reported Aventis (16,27); one reported Aventis/ Sanofi–Synthelabo (31); and three reported Sanofi–Synthelabo (17,30,39). Five of the reports disclosed a hospital, university, research group, or another non-industry entity as the source of funding (32–35,37), and twelve trials did not report the source of funding (9,12–14,18,19,23–26,36,38). The reported sources of funding for the two obtained meta-analyses were a research group grant (28) and partial industry funding (29).

Outcomes

Phase III RCTs of Oxaliplatin Combined with Fluorouracil and Folinic Acid as First-line Therapy for Advanced Colorectal Cancer

Twenty-seven reports (7-16,18-27,31-37) of RCTs on first-line treatment, representing sixteen individual trials (7-13,15-16,31-37) were obtained (Table 1). Five reports of these sixteen trials were available in abstract form only (9,12,13,33,36).

One-Year Survival

Only seven of the sixteen trials reported one-year survival data (8,10,11,15,31,32,35). One of the trials (8) compared two regimens that both contained 5FU, FA, and oxaliplatin: one in a standard infusion, and the other in a chronomodulated regimen. Both arms reported similar one-year survival rates (66% versus [vs.] 63%, $p > 0.05$). Of the other six trials, only two detected statistically significant one-year survival differences: one for FOLFOX4 over IFL (71% versus 58%, p=0.002) (15), and another for OXAFAFU over IRIFAFU (39% vs. 23%; p=0.032) (31).

Response Rates

Only two of the sixteen trials did not report data on response rates (9,12). Nine of the 14 trials reported statistically significant differences ($p<0.05$) in response rates between treatment arms: three for chronomodulated regimens of 5FU, FA, and oxaliplatin over standard infusion regimens of the same agents (7,8,11); and the others for LV5FU2 and oxaliplatin over LV5FU2 alone (10); for FUFOX over FUFA (13); for FOLFOX4 over IFL and for IROX over IFL (15); for both

low- and high-dose OXAFAFU over IRIFAFU (31); for FOLFOXIRI over FOLFIRI (33); and for OXAFAFU over FAFU (34). One trial that reported on response rates did not report a p value (36). Three trials reported no significance difference between treatment arms: FOLFOX and FOLFIRI (32), FOLFOX4 and IROX (15), and the crossover trial by Tournigand et al. (16) that compared the sequences FOLFIRI→FOLFOX6 and FOLFOX6→FOLFIRI.

Quality of Life (QOL)

Only two of the sixteen trials reported data on QOL (10,34). Of these latter two trials, neither reported a significant difference in QOL scores between the trial arms: LV5FU2 plus oxaliplatin versus LV5FU2 (10), or OXAFAFU versus FAFU (33).

As reported in the RCTs located by the literature search, first-line treatment with oxaliplatin was associated with significantly more peripheral and sensory neuropathy and neutropenia beyond the adverse effects expected with the other drugs given in the regimen.

Meta-analyses of First-line Trials

A meta-analysis by Grothey et al. (28) included fully published or publicly presented results from seven RCTs involving 3186 patients. It detected a significant 3.5-month increase in median survival (p=0.0083) in patients who received a first-line combination therapy (either oxaliplatin/5FU/FA or irinotecan/5FU/FA) as compared with patients who received monotherapy. The results of the meta-analysis indicated that, for maximum overall survival benefit, patients on a first-line combination therapy containing oxaliplatin should be offered combination therapy with irinotecan as second-line treatment, and vice versa. It appears that second-line treatment may compensate for less-active first-line treatment, since patients who had access to all three active drugs (oxaliplatin, irinotecan, and 5FU) showed the longest overall survival. However, this conclusion is confounded by the fact that patients who lived longer were more likely to have been treated with all three drugs. In addition, patients with lower performance status may have been excluded from second-line treatments using oxaliplatin and irinotecan. In addition, oxaliplatin was not available to all patients, especially in older trials. The meta-analysis detected longer median survival times in more recent trials—trials more likely to use oxaliplatin in first- and second-line treatment.

An abstract report by Lévi et al. (29) pooled the seven-year results of two individually-underpowered trials comparing chronomodulated (CM) infusion to flat infusion in the first-line treatment of MCC (7,8). Significant benefits were detected in overall response rate (ORR%: 51% vs. 30%; p<0.001), complete surgical resection (23.3% vs. 12.8%, p<0.001), and median progression-free survival (PFS: 10.3 months vs. 7.5 months; p=0.039) favouring CM therapy; however, no difference was detected in median survival (18.6 months vs. 16.5 months, p=0.22). Pooled data did not detect any difference in survival at either five or seven years (5-year survival: 12.6% vs. 15.2%; 7-year survival: 6.6% vs. 7.1%). The results may have been confounded by an imbalance between the studies with regard to recurrent metastatic disease following surgery for liver metastases (10% of patients receiving flat infusion vs. 22% of patients receiving CM infusion, p<0.001), and in addition, by significant treatment crossover from the flat infusion to the CM infusion arm (26% of patients), which affected median survival (14.7 months non-crossover vs. 18.5 months crossover; p=0.043). The pooled results from those two trials confirmed that, as compared with flat infusion, CM infusion significantly improved the ORR% and PFS.

Phase III RCTs of Oxaliplatin Combined with Fluorouracil and Folinic Acid as Second-line Therapy for Advanced Colorectal Cancer.

Four reports (17,30,38,39) describing four RCTs of second-line treatment were obtained (Table 2). Three of these trial reports were available in abstract form only (17,38,39).

One-Year Survival

None of the second-line treatment reports obtained provided data on one-year survival.

Response Rates

Three of the four reports (17,30,39) provided data on response rates. All three trials reported statistically significant differences between the trial arms, two for FOLFOX4 over LV5FU2 (17,30) (11.1% vs. 1.9%, $p<0.05$ [17]; 9.9% vs. 0%, $p<0.0001$ [30]), and the third for the sequence FOLFOX4→CPT-11 over CPT-11→FOLFOX4 (27% vs. 15%, $p<0.0142$) (39).

Quality of Life

None of these abstract reports provided data on QOL. As indicated under the heading "Quality of Life" in the first-line therapy section of this review, treatment with oxaliplatin was associated with significantly more peripheral and sensory neuropathy and neutropenia beyond the adverse effects expected from other drugs given in the regimen.

Table 1. Phase III trials of oxaliplatin combined with fluorouracil and folinic acid as first-line therapy for advanced colorectal cancer.

Study (Ref)	Regimen	# pts	ORR (% pts) [CR+PR]	Disease stabilization (% pts)	Median TTP (months)	Median PFS (months)	Median Survival (months)	Median Follow-up Time (months)	One year survival (%)
Lévi et al (7) [France]	5FU/FA/oxaliplatin	47	32 [2+13]	45	NR	8	14.9	30	NR
	CM 5FU/FA/oxaliplatin	45	53 [3+21] p=0.038	33 p=NR	NR	11 p=NR	19 p=0.03		NR
Lévi et al (8) [France]	5FU/FA/oxaliplatin	93	29 [3+24]	NR	4.9	7.9	16.9	36	66
	CM 5FU/FA/ oxaliplatin	93	51 [5+42] p<0.0001	NR	6.4 p=0.006	9.8 p=ns	15.9 p=ns		63 p=ns
Buechele et al (9) [abstract] [Germany]	5FU/FA/ oxaliplatin	NR	NR	NR	NR	NR	NR	NR	NR
	5FU/FA	NR	NR	NR	NR	NR	NR		NR
de Gramont et al (10) [France]	LV5FU2/ oxaliplatin	210	50.7 [3+102]	31.9	NR	9	16.2	27.7	69
	LV5FU2	210	22.3 [1+45] p=0.0001	51.0 p=NR	NR	6.2 p=0.0001	14.7 p=0.05		61 p=ns
Giacchetti et al (11) [France]	CM 5FU/FA/oxaliplatin	100	53 [3+50]	24	NR	8.7	19.4	47	75*
	CM 5FU/FA	100	16 [0+16] p<0.0001	45 p=NR	NR	6.1 p=0.48	19.9 p=ns		71* p=ns
Giacchetti et al (12) [France] [abstract] EORTC trial	CM 5FU/FA/oxaliplatin	282	NR	NR	NR	NR	NR	>36	NR
	5FU/FA/oxaliplatin	282	NR	NR	NR	NR Log rank p=ns	NR Log rank p=ns		NR

Study (Ref)	Regimen	# pts	ORR (% pts) [CR+PR]	Disease stabilization (% pts)	Median TTP (months)	Median PFS (months)	Median Survival (months)	Median Follow-up Time (months)	One year survival (%)
Grothey et al (13)	FUFA (Mayo)	124	22.6	NR	NR	5.3	16.1	27.3	NR
[abstract]	FUFOX	114	48.3 p<0.0001	NR	NR	7.9 p<0.0001	20.4 p=NR		NR
Goldberg et al (15)	FOLFOX 4 (A)	267	45	NR	8.7	NR	19.5		71*
Intergroup N9741	IFL (B)	264	31	NR	6.9	NR	15.0	NR	58*
	IROX (C)	264	35 AvB;p<0.05 BvC; p<0.05 AvC; p=ns	NR	6.5 AvB; p<0.05 BvC; p<0.05 AvC; p=ns	NR	17.4 AvB; p<0.05 BvC; p<0.05 AvC; p=ns		65* AvB: p=0.002 BvC: p=ns AvC; p=ns
Tournigand et al (16)	FOLFIRI → FOLFOX6	109	56 [3 + 58] 1st line 15 [0 + 12] 2nd line	23-1st line 48-2nd line	NR	8.5-1st line 4.2-2nd line	21.5	43.9	NR
GERCOR	FOLFOX6 → FOLFIRI	111	54 [5 + 54] 1st line 4 [0 + 3] 2nd line p=ns	27-1st line 30-2nd line p=NR	NR	8.0-1st line 2.5-2nd line	20.6 p=ns		NR
Comella P et al (31)	IRIFAFU	135	31 [16+26]	27	7.9	5.8	15.6	24	23
SICOG	OXAFAFU hd	71	41 [7+22]	21	10.5	7.0	17.6		39
	OXAFAFU ld	68	47 [13+19] p=0.029	22	7.9		23+		p=0.032
Colucci G et al (32)	FOLFIRI	178	34 [8+48]	42	7	NR	14	31	55
GOIM	FOLFOX4	182	36 [9+53] p=0.60	38	7	NR	15		62 p>0.05

Study (Ref)	Regimen	# pts	ORR (% pts) [CR+PR]	Disease stabilization (% pts)	Median TTP (months)	Median PFS (months)	Median Survival (months)	Median Follow-up Time (months)	One year survival (%)
Falcone (33)	FOLFOXIRI	122	66	NR	NR	9.8	22.6	15.2	NR
	FOLFIRI	122	41 p=0.0002	NR	NR	6.9 p=0.0006	16.7 p=0.032		NR
Hospers GAP et al (34)	OXAFAFU	151	33.8	43	NR	6.7	13.8	31.8	NR
	FAFU	151	18.5 p=0.004	50.3	NR	5.6	13.3		NR
Souglakos (35)	FOLFOXIRI	137	43 [9+50]	NR	8.4	NR	21.5	26	67
	FOLFIRI	146	33.6 [5+44] p=NS	NR	6.9 p=NS	NR	19.5 p=NS		64 p=NS
Stanculeanu DL et al (36) [abstract]	FOLFOX4	22	64 [2+12]	27.3	NR	NR	NR	NR	NR
	FOLFIRI	18	44 [1+7]	44.4	NR	NR	NR		NR
	IROX	17	53 [2+7] p=NR	35.3	NR	NR	NR		NR
Tournigand C et al (37) GERCOR	FOLFOX4	311	58.5	NR	NR	9	19.3	31	NR
	FOLFOX7	309	59.2 p=ns	NR	NR	8.7	21.2		NR

Note: 5FU, fluorouracil; B, bolus; CI, continuous infusion; CM, chronomodulated delivery rate; CR, complete response; EORTC, European Organization for Research and Treatment of Cancer; FA, folinic acid; LV5FU2, leucovorin calcium, 5FU; FUFA, 5FU, folinic acid; FUFOX, 5FU, folinic acid, oxaliplatin; FOLFOX, folinic acid, fluorouracil, oxaliplatin; FOLFIRI, folinic acid, 5FU, irinotecan; OXAFAFU, oxaliplatin, folinic acid, 5FU; IRIFAFU, irinotecan, folinic acid, 5FU; GERCOR, Groupe Coopérateur Multidisciplinaire en Oncologie; IFL, irinotecan, fluorouracil, leucovorin calcium (folinic acid); inf, intravenous infusion; IROX, irinotecan, oxaliplatin; NR, not reported; ns, not significant; PFS, progression-free survival; PR, partial response; pts, patients; Ref, references; TTP, time-to-progression.
* estimated from survival curve.

Table 2. Phase III trials of oxaliplatin combined with fluorouracil and folinic acid as second-line therapy for advanced colorectal cancer.

Study (Ref)	Regimen	# pts	ORR (% pts) [CR+PR]	Disease stabilization (% pts)	Median TTP (months)	Median PFS (months)	Median Survival (months)	Median Follow-up Time (months)	One year survival (%)
Rothenberg et al (30) [EFC4584]	LV5FU2 (A)	256	0	NR	2.7	NR	NR	NR	NR
	Oxaliplatin (B)	266	NR	NR	1.6	NR	NR		NR
	FOLFOX4 (C)	267	9.9 p<0.0001	NR	4.6 A vs C p<0.0001 A vs B p=0.03	NR	NR		NR
Garay et al (17) [abstract]	FOLFOX4	105	11.1	NR	4.9	NR	NR	NR	NR
	LV5FU2	101	1.9 p<0.05	NR	2.6 p<0.05	NR	NR		NR
Giantonio BJ et al (38) ECOG [abstract]	FOLFOX4+Bev (A)	290	NR	NR	NR	7.4	12.5	NR	NR
	FOLFOX4 (B)	289	NR	NR	NR	5.5	10.7		NR
	Bev	243	NR	NR	NR	3.5 A vs B p=0.0003	10.2 A vs B p=0.0024		NR
Pitot HC et al (39) N9841 [abstract]	CPT-11→ FOLFOX4	245	15	NR	4.0	NR	14.7	NR	NR
	FOLFOX4→ CPT-11	246	27 p<0.01	NR	5.2	NR	13.5		NR

Note: Bev, bevacizumab; CR, complete response; FA, folinic acid; LV5FU2, leucovorin calcium, 5FU; FUFA, 5FU, folinic acid; FUFOX, 5FU, folinic acid, oxaliplatin; FOLFOX, folinic acid, fluorouracil, oxaliplatin; FOLFIRI, folinic acid, 5FU, irinotecan; OXAFAFU, oxaliplatin, folinic acid, 5FU; IRIFAFU, irinotecan, folinic acid, 5FU; GERCOR, Groupe Coopérateur Multidisciplinaire en Oncologie; IFL, irinotecan, fluorouracil, leucovorin calcium (folinic acid); inf, intravenous infusion; IROX, irinotecan, oxaliplatin; NR, not reported; ns, not significant; PFS, progression-free survival; PR, partial response; pts, patients; Ref, references; TTP, time-to-progression.
* estimated from survival curve

DISCUSSION

The combination regimens using infusional 5FU (FOLFOX or FOLFIRI) both represent acceptable treatment alternatives for first-line therapy in fit patients.

Oxaliplatin is active in colorectal cancer, and the evidence supports its use in combination with infusional 5FU/FA (FOLFOX). Oxaliplatin without 5FU/FA does not appear to have meaningful activity. The FOLFOX regimen has definite advantages over bolus IFL in terms of toxicity, objective response rates (45% vs. 31%), median time-to-progression (TTP) (8.7 months vs. 6.9 months), median survival (19.5 months vs. 15.0 months), and one-year survival (71% vs. 58%) as demonstrated in the N9741 study (15).

The superior one-year survival seen in the N9741 study may have two possible explanations. The 5FU was given as an infusion in the FOLFOX arm, but as a bolus in the IFL arm, and infusional 5FU has demonstrated superiority over bolus 5FU in terms of toxicity and tumour response rate. This fact alone may therefore account for the differences seen in the two regimens. It may also account for the lack of difference seen between FOLFOX and FOLFIRI in the GERCOR study, because both regimens used infusional 5FU (16).

The second possible explanation for superior survival in the FOLFOX arm relates to the high rate of second-line irinotecan use. In the FOLFOX arm, 53% of the patients received second-line irinotecan, but only 17% of patients on the IFL arm received second-line oxaliplatin. It is becoming increasingly clear that subsequent therapy can have a substantial effect on survival. From the evidence reviewed, it appears that the number of active drugs available to a study arm may positively affect survival, because when more drugs are made available to patients, median survival is increased. This finding does not rule out other factors, such as variations in study population and other variations in treatment over time, but it is highly supportive of the conclusion that access to all three active drugs (5FU/FA, oxaliplatin, irinotecan) is important to optimize patient outcomes (27). It is also evident that when combination therapy is to be used, infusional 5FU should be used rather than bolus. This recommendation to use 5FU in an infusional schedule is now abundantly clear from single-agent studies, from combination studies in advanced disease, and from the adjuvant setting in early colorectal cancer. The role of bolus 5FU in the management of colorectal cancer is becoming increasingly limited.

The combination of oxaliplatin and irinotecan is also active, but it has lower tumour response rates and one-year survival rates than does FOLFOX, and therefore has no advantages (15).

The inconvenience of infusional 5FU pump programs, in combination with the drug's unavailability in certain regions, has led to interest in oral capecitabine as a possible replacement for infusional 5FU in oxaliplatin and irinotecan combinations. The few phase II trials reported thus far have demonstrated response rates and toxicity that appear comparable to those seen with infusional 5FU combinations. In the future, capecitabine may supersede the 5FU pump and the need for central venous access devices; however, this development will depend on the results of ongoing phase III trials. Until the results of those trials are available, infusional 5FU regimens—either alone or in combination—are standard therapy.

The question of whether to use a CM regimen of infusional 5FU is a compelling area of study, but no such regimen has been widely evaluated outside of a few specialized centres. This question extends beyond a simple review of 5FU/oxaliplatin combinations. The pooled analysis of the two underpowered studies by Lévi et al. (7,8) suggests that CM could both reduce toxicity and positively affect endpoints such as ORR% and TTP. The intervention is worthy of further study, although the complexity of the therapy may put it beyond feasibility in many locales.

The ECF4584 trial (30) demonstrated improvements in response rate, TTP (median: 4.6 months vs. 1.6 months, $p<0.0001$), and symptom control with second-line FOLFOX as compared with oxaliplatin alone or infusional 5FU/FA alone in patients who progressed on the

IFL regimen. No overall survival analysis was performed. For patients who have progressed on both an anti-TS agent and irinotecan, FOLFOX is the preferred therapy.

In patients with tumour progression on first-line 5FU/FA, FOLFOX is active, with an ORR% that appears to compare favourably with FOLFIRI, the standard regimen. Currently, more evidence supports second-line irinotecan than supports FOLFOX or oxaliplatin alone, but for patients considered poor candidates for second-line irinotecan, FOLFOX is a reasonable alternative. Further clarification of the role of oxaliplatin after progression on first-line 5FU awaits more-mature data from the Sanofi-sponsored ECF4585 trial.

As treatment regimens for advanced colorectal cancer continue to evolve, recent trials (38,40) have investigated the addition of bevacizumab to the FOLFOX regimen. An abstract report by Hochster et al. (40) of the TREE-2 study—a first-line cohort study comparing FOLFOX plus bevacizumab, OXAFAFU plus bevacizumab, and capecitabine and oxaliplatin (CAPOX) plus bevacizumab—found that FOLFOX plus bevacizumab resulted in the longest median survival with acceptable adverse events. In the TREE-2 study, the median survivals for the treatment arms without bevacizumab were 19.2 months (FOLFOX), 17.9 months (OXAFAFU), and 17.3 months (CAPOX) as compared with 26 months (FOLFOX + bevacizumab), 20.7 months (OXAFAFU + bevacizumab), and 27.0 months (CAPOX + bevacizumab) (41). The overall median survival was 18.2 months (no bevacizumab) as compared with 24.4 months (bevacizumab added) (41). When the overall survival data from the TREE-1 trial (no bevacizumab) was compared with the TREE-2 trial data (bevacizumab added), the results were 12 months, 67.5% versus 79.1%; 18 months, 50.1% versus 64.7%; 24 months, 35.8% versus 50.7%—all in favour of the treatments including bevacizumab (41).

The second-line RCT reported by Giantonio et al. (38), which compared FOLFOX4 with and without bevacizumab, found that the addition of bevacizumab to the FOLFOX regimen resulted in significant gains in both median survival (10.7 months vs. 10.2 months, p=0.0024) and PFS (7.4 months vs. 5.5 months, p=0.0003). Based on these two trials, we conclude that the addition of bevacizumab to an infusional 5FU, FA, and oxaliplatin regimen may provide benefits beyond those that would be possible with infusional 5FU, FA, and oxaliplatin without bevacizumab.

Preliminary results of the NO16966 trial, a phase III 2x2 factorial trial comparing capecitabine and oxaliplatin (XELOX) to FOLFOX4 with or without bevacizumab, were presented at the 2006 Congress of the European Society of Medical Oncology after the literature search for this review was completed (43). The two primary objectives of the trial were to demonstrate that XELOX is not inferior to FOLFOX and that chemotherapy with bevacizumab is superior to chemotherapy with placebo, using the primary endpoint of PFS After a median follow-up of 18.6 months, the hazard ratio for progression was 1.05 (95%CI, 0.94-1.18), and the criterion for non-inferiority was met. Patients in the XELOX arms experienced more grade 3/4 diarrhea and grade 3 hand-foot syndrome than did patients in the FOLFOX arms, but less grade 3/4 neutropenia, febrile neutropenia, and granulocytopenia. Final efficacy data are awaited to confirm these results and to clarify the effects of the addition of bevacizumab to chemotherapy in this setting.

ONGOING TRIALS

The National Cancer Institute's database of ongoing clinical trials (http://www.cancer.gov/search/clinical_trials/) was searched on October 24, 2006 for relevant reports. A listing of relevant trials appears in Appendix 2.

CONCLUSIONS

The evidence review found one first-line therapy trial (15) that demonstrated infusional 5FU/FA/oxaliplatin (FOLFOX) to be superior to bolus 5FU/FA/irinotecan (IFL), with more favourable median survival and tumour response rates. Compared with IFL, FOLFOX has lower

incidences of severe nausea, vomiting, diarrhea, and febrile neutropenia, but higher peripheral neuropathy. Therefore, for first-line treatment, short-term infusional 5FU/FA in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are both acceptable alternatives for fit patients when combination therapy is the preferred treatment. The choice of first-line therapy may rely on patient factors and preferences, for example, less neuropathy with irinotecan versus less alopecia with oxaliplatin.

For second-line treatment after progression on first-line anti-thymidylate synthase monotherapy (e.g., 5FU/FA; capecitabine), irinotecan is standard therapy. FOLFOX is a reasonable alternative for patients with contraindications to the use of second-line irinotecan. After progression on both irinotecan and an anti-thymidylate synthase agent, FOLFOX is the preferred therapy.

The role of radiation therapy, either alone or in combination with chemotherapy, for locally advanced non-resectable colorectal cancer was not addressed in this guideline. In addition, the use of chronomodulated regimens is a topic that intersects with the use of oxaliplatin/5FU combinations, particularly chronomodulation of 5FU in these combinations. Chronomodulation of the agent oxaliplatin itself has not been extensively studied, and because the topic of chronomodulation is beyond the scope of this guideline, it was not addressed.

In conclusion, we acknowledge that the combination of oxaliplatin with short-term infusional 5FU and folinic acid (FOLFOX) is an important component of first and second-line treatment of advanced colon cancer, and we recommend that oxaliplatin should be made available for the treatment of advanced colorectal cancer.

CONFLICT OF INTEREST

The members of the GI DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. Two of the guideline authors reported no conflicts of interest. One of the guideline authors reported research involvement with the pharmaceutical company that manufactures the chemotherapy agent recommended in this guideline. No other GI DSG member declared any conflicts with respect to this report.

JOURNAL REFERENCE

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Appendix 1. Dosing by trial.

Author (reference)	mg/m^2/day [frequency]
First-line treatment	
Lévi et al (7), 1994 IOCC trial	5FU 600, FA 300, oxaliplatin 20 d1-5 q21d (16d intermission) via programmable pump. Arm A: constant infusion Arm B: CM infusion (max delivery of 5FU/FA: 0400 hours, oxaliplatin 1600 hours).
Lévi et al (8), 1997 IOCC trial	5FU 600, FA 300, oxaliplatin 20 d1-5 q21d (16d intermission). Arm A: constant infusion Arm B: CM infusion
Buechele et al (9), 2000 Germany	Oxaliplatin 50 2h inf + FA 500 2hr inf + 5FU 2000 24hr inf d1,8,15,22 q36d *versus* Bolus 5FU/FA (Mayo Clinic regimen)
de Gramont et al (10), 2000	Oxaliplatin 85 2h inf d1 + 5FU 400 B then 600 CI d1,2 + FA 200 CI d1,2 q2wk *versus* 5FU 400 B then 600 CI d1,2 + FA 200 CI d1,2 q2wk (LV5FU2 regimen)
Giacchetti et al (11), 2000	Oxaliplatin 125 6h inf d1 + 5FU 700 + FA 300 CM d1-5 q3wk *versus* 5FU 700 + FA 300 CM d1-5 q3wk
Giacchetti et al (12), 2002 EORTC trial	CM oxaliplatin 25 [peak@16:00], CM 5FU 750 [peak@4:00], CM FA 300 [peak@4:00]. All three drugs are given every d for 4d, repeat q2wk *versus* Oxaliplatin 100 2hr inf d1, 5FU 1500 22hr inf (every day for 2 days), FA 600 2hr inf (every day for 2 days), repeat q2wk [FOLFOX 2]
Grothey et al (13), 2002 Germany	Oxaliplatin 50 2hr inf + 5FU 2000 24hr inf + FA 500 24hr inf d1,8,15,22 q5wk (FUFOX) *versus* 5FU 425 B + FA 20 d1-5 q29d (Mayo)
Colucci et al (14), 2003 GOIM trial	Oxaliplatin 85 d1, FA 100 2hr inf d1,2, 5FU 400 B inf followed by 5FU 600 22 hr inf d1,2 q2wk *versus* Irinotecan 180 d1, FA 100 2hr inf d1,2 5FU 400 B inf followed by 5FU 600 22hr inf d1,2 q2wk.
Goldberg et al (15), 2004 Intergroup N9741 trial	Oxaliplatin 85 d1 followed by 5FU 400 B + 600 22hr inf d1,2, FA 200 d1,2 q2wk [de Gramont FOLFOX 4] *versus* Irinotecan 125 + 5FU 500 + FA 20 d1,8,15,22 q6wk [Saltz IFL] *versus* Oxaliplatin 85 d1 + irinotecan 200 d1, q3wk [Wasserman IROX]
Tournigand et al (16), 2004 GERCOR trial	1st line FOLFIRI: irinotecan 180 2h inf d1, FA 200 2h inf d1, 5FU 400 B inf d1, followed by 5FU 2400-3000 48h inf d2, q2wk until progression → followed by 2nd line FOLFOX (as below) *versus* 1st line FOLFOX6: oxaliplatin 100 2h inf d1, FA 200 2h inf d1, 5FU 400 B inf d1, followed by 5FU 2400-3000 48h inf d2, q2wk until progression → followed by 2nd line FOLFIRI (as above)
Comella P et al (31), SICOG	IRIFAFU: Irinotecan 200 mg/m^2 d1 IV, FA 250 mg/m^2 IV, followed by 5FU 850 mg/m^2 d2 *versus* OXAFAFU hd: Oxaliplatin 100 mg/m^2 d1, followed by FA 250 mg/m^2 and 5FU 1050 mg/m^2 d2 *versus* OXAFAFU ld: Oxaliplatin 85 mg/m^2 d1, FA 250 mg/m^2 and 5FU 850 mg/m^2 d1
Colucci G et al (32)	FOLFIRI: Irinotecan 180 mg/m^2 d1, FA 100 mg/m^2 2-hour infusion, 5FU 400

GOIM	mg/m^2 IV bolus injection, followed by 5FU 600 mg/m^2 22-hour infusion d1,2. *versus* FOLFOX4: Oxaliplatin 85 mg/m^2 d1, irinotecan 180 mg/m^2 d1, FA 100 mg/m^2 2-hour infusion, 5FU 400 mg/m^2 IV bolus injection, followed by 5FU 600 mg/m^2 22-hour infusion d1,2.
Falcone A et al (33) GONO	FOLFOXIRI: oxaliplatin 85, day 1; irinotecan 165, day 1; 5FU 3200 48-hour infusion starting on day 1; l-FA 200, day 1; every 2 weeks. *versus* FOLFIRI: irinotecan 180, day 1; l-LV 100, days 1 and 2; 5FU 400 bolus, days 1 and 2; followed by 5FU 600 22-hour infusion, days 1 and 2; every 2 weeks. At progression on FOLFIRI, a FOLFOX regimen was recommended.
Hospers GAP et al (34)	OXAFAFU: Oxaliplatin 85 mg/m^2, 2 hour infusion, FA 200 mg/m^2, 1 hr infusion, 5-U 2600 mg/m^2, 24 hour infusion d1, q2week. *versus* FAFU: 5FU 425 mg/m^2 d1-5, FA 20 mg/m^2 d1-5, q4week.
Souglakos J et al (35) HORG	FOLFOXIRI: oxaliplatin 65, day 2; irinotecan 150, day 1; FA 200, days 2 and 3; 5FU 400 bolus, followed by 5FU 600 22-hour infusion, days 2 and 3. *versus* FOLFIRI: irinotecan 180, day 1; FA 200, days 2 and 3; 5FU 400 bolus, followed by 5FU 600 22-hour infusion, days 2 and 3.
Stanculeanu DL et al (36)	FOLFOX4: Oxaliplatin 85 mg/m^2 d1, FA 200 mg/m^2 d1,2, 5FU 400 mg/m^2 bolus injection d1,2, followed by 5FU 600 mg/m^2 22 hour infusion d1,2 q15d. *versus* FOLFIRI: Irinotecan 180 mg/m^2, FA 400 mg/m^2, 5FU 400 mg/m^2 bolus injection, followed by 5FU 2400 mg/m^2 46 hour infusion q15d. *versus* IROX: Irinotecan 300 mg/m^2 d1, oxaliplatin 85 mg/m^2 d2, q3week.
Tournigand C et al (37) GERCOR	FOLFOX4: Oxaliplatin 85 mg/m^2 2 hour injection d1, FA 2 hour infusion (either 100 mg/m^2 l-LV or 200 mg/m^2 of dl-LV), 5FU 400 mg/m^2 bolus injection, followed by 5FU 600 mg/m^2 22hour infusion d1,2 q2weeks *versus* FOLFOX7(6 cycles)→LV5FU2(12 cycles)→FOLFOX7(6 cycles): FOLFOX7: Oxaliplatin 130 mg/m^2 2 hour injection, d1, FA 2 hour injection (either 200 mg/m^2 l-LV or 400 mg/m^2 dl-LV), followed by 5FU 2400 mg/m^2 46 hour infusion, q2weeks. LV5FU2: FA 2 hour injection (either l-LV 200 mg/m^2 or dl-LV 400 mg/m^2), 5FU 400 mg/m^2 bolus injection, followed by 5FU 3000 mg/m^2 46 hour infusion q2weeks
Second-line treatment	
Rothenberg et al (30), 2003 EFC 4584 trial	*Treatment given as second-line to IFL* Oxaliplatin 85 2hr inf d1, 5FU 400 B inf, followed by 5FU 600 22hr inf d1,2, q2wk (FOLFOX4) *versus* 5FU 400 B inf, followed by 5FU 600 22hr inf d1,2, FA 200 q2wk (LV5FU2)
Garay et al (17), 2003 Sanofi/Memorial Sloan Ketttering Cancer Centre trial	*Treatment given as second-line to 5FU + irinotecan ±FA* Oxaliplatin 85 2hr inf d1, 5FU 400 B inf, followed by 5FU 600 22hr inf d1,2, q2wk (FOLFOX4) *versus* 5FU 400 B inf, followed by 5FU 600 22hr inf d1,2, FA 200 q2wk (LV5FU2) • Crossover trial

Giantonio BJ et al (38) ECOG	FOLFOX4+Be: Bevacizumab 10 mg/kg IV biweekly, oxaliplatin 85 mg/m^2 d1, FA 200 mg/m^2 IV 2 hours, 5FU 400 mg/m^2 bolus injection, followed by 5FU 600 mg/m^2 22 hour infusion d1,2 *versus* FOLFOX4: Oxaliplatin 85 mg/m^2 d1, FA 200 mg/m^2 IV 2 hours, 5FU 400 mg/m^2 bolus injection, followed by 5FU 600 mg/m^2 22 hour infusion d1,2. *versus* Be: Bevacizumab 10 mg/kg IV biweekly.
Pitot HC et al (39) N9841	Irinotecan→FOLFOX4 *versus* FOLFOX4→Irinotecan: Irinotecan: 350 mg/m^2 d1, q3week (reduced to 300 mg/m^2 for ECOG PS =2, age ≥70, or prior pelvic radiation). FOLFOX4: Oxaliplatin 85 mg/m^2, FA 200 mg/m^2, 5FU 400 mg/m^2 bolus injection, followed by 600 mg/m^2 22 hour infusion d1,2 q2week.

Note: 5FU, 5-fluorouracil; B, bolus; CI, continuous infusion CM, chronomodulated; d, day; EORTC, European Organization for Research and Treatment of Cancer; FA, folinic acid; FOLFOX, folinic acid, fluorouracil, oxaliplatin; GERCOR, Groupe Coopérateur Multidisciplinaire en Oncologie; GOIM, Gruppo Oncologico Italia Meridionale; h, hour; hd, high dose; ld, low dose; IFL, irinotecan, fluorouracil, leucovorin calcium (folinic acid); inf, infusion; IOCC, International Organization against Cancer; IROX, irinotecan, oxaliplatin; IV, intravenously; q, every; SICOG, Southern Italy Cooperative Oncology Group; wk, week, Be, bevacizumab; PS, performance status.

Appendix 2. Ongoing trials.

Protocol ID	Trial Description
NCRI-FOCUS2; EU-20303; MRC-CR09	**Phase III randomized study of leucovorin calcium and fluorouracil with or without oxaliplatin versus capecitabine with or without oxaliplatin in patients with metastatic colorectal adenocarcinoma** (summary last modified September 27, 2006) • A randomized, multicentre study • A total of 460 patients (115 per treatment arm) will be accrued for this study within two years • NCRI and Medical Research Council Clinical Trials Unit sponsorship

CLOSED TRIALS: Listed in the PDQ; not yet reported.	
PROLOGUE-SANOFI-ARD5099; SANOFI-ARD5099	**Phase III randomized study of oxaliplatin and bevacizumab (Avastin™) with fluorouracil and leucovorin calcium or capecitabine in patients with advanced colorectal cancer** (summary last modified July 21, 2006) • A randomized, open-label, multicentre study • A total of 375 patients (125 per treatment arm) will be accrued for this study • Sponsorship by Prologue Research International, Inc.
SWOG-S0303	**Phase III randomized study of fluorouracil, leucovorin calcium, and oxaliplatin versus capecitabine and oxaliplatin with or without bevacizumab in patients with locally advanced, metastatic, or recurrent colorectal cancer** (summary last modified August 16, 2006) • A randomized, multicentre study • A total of 2,200 patients (1,100 per treatment arm) within three years will be accrued • Southwest Oncology Group (SWOG) sponsorship
CALGB-80203	**Phase III randomized study of fluorouracil and leucovorin calcium with irinotecan or oxaliplatin and with or without cetuximab in patients with previously untreated metastatic adenocarcinoma of the colon or rectum** (summary last modified September 26, 2006)**.** • A randomized, open-label, multicentre study • Approximately 2,200 patients (550 per treatment arm) will be accrued for this study within 4.6 years • Cancer and Leukemia Group B sponsorship
NO16966; NCT00069095	**A 2x2 (4-way) randomized phase 3 study of capecitabine in combo with oxaliplatin (XELOX) with or without bevacizumab vs. fluorouracil/leucovorin with oxaliplatin (FOLFOX-4) with or without bevacizumab as first-line treatment for patients w/ metastatic colorectal cancer** (summary last modified October 16, 2006) • A randomized, multicentre trial • Accrual data not reported • Hoffmann - La Roche, Ltd. Sponsorship Preliminary results were presented at ESMO 2006 and are included in the Discussion section of the systematic review (43).
NO16967; NCT00069108	**Open-label randomized phase 3 study of capecitabine in combo with XELOX versus fluorouracil/leucovorin with oxaliplatin (FOLFOX4) as treatment for pts with metastatic colorectal cancer, who have received prior treatment with CPT-11 in combo w/ fluorouracil/leucovorin as first line therapy** (summary last modified October 16, 2006) • A randomized, multicentre trial • Accrual data not reported • Hoffmann - La Roche, Ltd. sponsorship
SANOFI-EFC4584; BRCC-00036	**Phase III randomized study of fluorouracil and leucovorin calcium versus oxaliplatin alone versus fluorouracil, leucovorin calcium, and oxaliplatin in patients with metastatic colorectal carcinoma** (summary last modified) A randomized, open-label, multicentre study A total of 786 patients (262 per arm) were to be accrued for this study within 12 months Interim results have been published and are included in the systematic review (30) Pharmaceutical sponsorship (Sanofi-Synthelabo Research)
FRE-GERCOR-C97-3/CPTF308; EU-97044; FRE-C97-3/CPTF301; FRE-C97-3/CPTF308; RP-FRE-C97-	**Phase III randomized study of leucovorin calcium plus fluorouracil with either irinotecan or oxaliplatin in patients with recurrent metastatic colorectal cancer** (summary last modified May 2000) • A randomized, multicentre study. • This study will accrue a total of 109 patients per arm over approximately 18 months. • Clinical trials group/pharmaceutical sponsorship (Groupe Coopérateur Multidisciplinaire en

3/CPTF308	Oncologie)
EORTC-05963	**Phase III randomized study of chronomodulated versus non-chronomodulated administration of fluorouracil, leucovorin calcium, and oxaliplatin as first-line treatment in patients with locoregionally recurrent or metastatic colorectal cancer** (summary last modified May 2002) • A randomized, multicentre trial • Projected accrual is 554 patients (no time frame specified) • Clinical trials group sponsorship (EORTC Chronotherapy Group)
MRC-CR08-FOCUS; EU-20038; ISRCTN79877428	**Phase III randomized study of fluorouracil with leucovorin calcium and either irinotecan or oxaliplatin in patients with unresectable metastatic colorectal cancer** (summary last modified November 21, 2005) • A randomized, open-label, multicentre study. Patients are randomized to one of five treatment arms • A total of 2,100 patients (700 in arm I, 350 each in arm II-V) will be accrued for this study • Sponsored by Saint Bartholomew's Hospital • Preliminary results have been published in abstract form (42)
FRE-GERCOR-OPTIMOX-2000; EU-20034	**Phase III randomized study of oxaliplatin, leucovorin calcium, and fluorouracil in patients with metastatic colorectal cancer** (summary last modified July 2, 2003) • A randomized, open-label, multi-centre trial • Projected accrual is 460 patients (230 per treatment arm) over 18 months • Clinical trials group sponsorship (GERCOR)

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Evidence-based Series #2-22: Section 3

The Role of Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in the First and Second-line Treatment of Advanced Colorectal Cancer: Guideline Development and External Review: Methods and Results

D. Jonker, R.B. Rumble, J. Maroun, and members of the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gastrointestinal DSG

Please see the EBS 2-22 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2005 and 2010.

Report Date: December 8, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and

evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series:

Historically all the components and methodologies of the practice guidelines were packaged into one report. However, in response to feedback from Ontario clinicians and members of the PEBC panels, the end product has been restructured to better meet the information needs and preferences of that core audience. The high-quality methods and the credible developers are now part of the Evidence-based Series.

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Gastrointestinal Disease Site Group (GI DSG) of Cancer Care Ontario's Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on oxaliplatin combined with 5-fluorouracil (5FU) and folinic acid (FA) in advanced colorectal cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus Process

Note: The GI DSG consensus process was based on an earlier draft of the present document. That draft did not contain any of the evidence regarding the addition of bevacizumab to regimens of infusional 5FU/FA plus oxaliplatin. References 15, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41 were added to the document after the consensus process took place.

The present systematic review found one first-line therapy trial (15) that demonstrated infusional 5FU/FA/oxaliplatin (FOLFOX) to be superior to bolus 5FU/FA/irinotecan (IFL), with more-favourable median survival and tumour response rates. Compared with IFL, FOLFOX has lower incidences of severe nausea, vomiting, diarrhea, and febrile neutropenia, but a higher incidence of peripheral neuropathy. Therefore, for first-line treatment, short-term infusional 5FU/FA in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is acceptable for fit patients when combination therapy is the preferred treatment. Choice of first-line therapy may rely on patient factors and preferences—for example, less neuropathy with irinotecan versus less alopecia with oxaliplatin.

For second-line treatment after progression on first-line anti-thymidylate synthase (TS) monotherapy (for example, 5FU/FA, capecitabine), irinotecan is standard therapy. For patients with contraindications to the use of second-line irinotecan, FOLFOX is a reasonable alternative. After progression on both irinotecan and an anti-TS agent, FOLFOX is the preferred therapy.

The role of radiation therapy, either alone or in combination with chemotherapy, for locally advanced unresectable colorectal cancer was not addressed in this guideline. In addition, the use of chronomodulated (CM) regimens is a topic that intersects with the use of oxaliplatin/5FU combinations, particularly CM 5FU in those combinations. Chronomodulation of oxaliplatin has not been extensively studied and was not addressed, because the topic is beyond the scope of this guideline.

In conclusion, the GI DSG acknowledges that the combination of oxaliplatin with short-term infusional 5FU and FA (FOLFOX) is an important component of first- and second-line treatment of advanced colon cancer, and the DSG recommends that oxaliplatin be made available for the treatment of advanced colorectal cancer.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the GI DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review September 15, 2004)

Target Population

- These recommendations apply to adult patients with advanced colorectal cancer who have high performance status (ECOG 0-2).

Recommendations

Refer to Appendix 1 for recommended dosages and schedules.

- Combination oxaliplatin, short-term infusional 5-fluorouracil and folinic acid (FOLFOX) is an important component of therapy and should be made available for the treatment of advanced colorectal cancer.

First-Line therapy

- Infusional 5FU/FA/oxaliplatin (FOLFOX) is superior to bolus 5FU/FA/irinotecan (IFL). FOLFOX has superior median survival and tumour response rates. Compared with IFL, FOLFOX has lower incidences of severe nausea, vomiting, diarrhea, and febrile neutropenia, but higher peripheral neuropathy.
- Short-term infusional 5FU/FA in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are acceptable alternatives for fit patients when combination therapy is the preferred treatment. Choice of first-line therapy may rely on patient factors and preferences, for example less neuropathy with irinotecan versus less alopecia with oxaliplatin.

Second-line therapy

- After progression on first-line anti-thymidylate synthase monotherapy (e.g., 5FU/FA; capecitabine), irinotecan is standard second-line therapy. FOLFOX is a reasonable alternative for patients with contraindications to the use of second-line irinotecan.
- After progression on both irinotecan and an anti-thymidylate synthase agent, FOLFOX is the preferred therapy.

Treatment Alternatives (refer to Appendix 1 for recommended dosages and schedules)

First-line therapy

- FOLFIRI (combination 5FU/LV/irinotecan)
- FOLFOX (combination 5FU/FA/oxaliplatin)
- de Gramont schedule (infusional 5FU/LV)

- Raltitrexed
- Capecitabine

Second-line therapy
- FOLFOX (combination 5FU/FA/oxaliplatin), after 1st-line FOLFIRI
- FOLFIRI (combination 5FU/FA/irinotecan), after 1st-line FOLFOX
- Irinotecan alone

Future Research

Final results from three key studies are awaited:
- Sanofi-ECF4585: Phase III oxaliplatin/irinotecan versus irinotecan alone as second line therapy after progression on anti-thymidylate synthase therapy.
- Roche: Phase III FOLFOX versus XELOX as first line therapy for advanced colorectal cancer.
- Roche: Phase III FOLFOX versus XELOX as second-line therapy after progression on 5FU/Irinotecan combination therapy for advanced colorectal cancer.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 63 practitioners in Ontario (11 medical oncologists, nine radiation oncologists, and 42 surgeons. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on September 15, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GI DSG reviewed the results of the survey.

Results

Twenty-nine responses were received out of the 63 surveys sent (46% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 18 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	100	-	-
There is a need for a clinical practice guideline on this topic.	89	11	-
The literature search is relevant and complete.	78	22	-
The results of the trials described in the report are interpreted according to my understanding of the data.	89	11	-
The draft recommendations in this report are clear.	78	17	6
I agree with the draft recommendations as stated.	83	11	6
This report should be approved as a practice guideline.	89	6	6
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	67	11	11

Summary of Written Comments

Four respondents (18%) provided written comments. The main points contained in the written comments were:

- There are ongoing issues regarding access to the drug oxaliplatin.
- The guidelines seem to be directed to the medical oncologists who provide the treatments. For other caregivers in the cancer system this key message needs to be delivered: cancer treatment is in a state of continuous development with increasing efficacy, therefore assessment by a medical oncologist is important for all patients.
- Some of the stated recommendations are currently in use, and being accepted with enthusiasm by both clinicians and patients.
- This guideline has not included any information regarding the role of radiation in the local management of rectal tumours. However, the guideline makes good sense with respect to the recommended chemotherapy regimens. Could a recommendation, or at least a comment, be added somewhere in the document regarding radiation timing, and radiation in combination with the recommended chemotherapy regimens.

Modifications/Actions

The Gastrointestinal Cancer DSG made the following modifications to the clinical practice guideline in response to the comments obtained during practitioner feedback:

- With respect to the ongoing issues regarding oxaliplatin access, the GI DSG acknowledges that this is a major barrier to putting these recommendations into practice, and it is the hope of the GI DSG that by recommending oxaliplatin this will raise awareness of the issue and facilitate making this drug available to patients.
- With respect to the issue of radiation therapy, the GI DSG added the following Qualifying Statement to both Section 1 and the main document, "The role of radiation therapy, either alone or in combination with chemotherapy, for locally advanced non-resectable colorectal cancer is not addressed in this guideline."

Funding

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Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

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DOCUMENT ASSESSMENT AND REVIEW TOOL

Number and title of document under review	EBS #2-22 The role of oxaliplatin combined with 5-fluorouracil and folinic acid in the first and second-line treatment of advanced colorectal cancer
Date of current version	December 8, 2006
Clinical reviewer	Dr. J. Biagi
Research coordinator	Rovena Tey
Date initiated	April 15, 2010
Date and final results/outcomes	**July 12, 2010 (ARCHIVED)**
Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document? Answer Yes or No, and explain if necessary:	1. YES • However, the recommendations in this guideline do not take into account newer treatment strategies (e.g., biologics) that might be used in combination. • Guideline 2-22 can be **ARCHIVED** because components of this guideline will be replaced by a new guideline that is currently in production, "Strategies of sequential therapy in advanced colorectal cancer" • The new guideline is expected to be completed in 2011 and will update the literature search to address the research Qs from guideline 2-22 • In the meantime, Guideline 2-22 will still be available to view on the CCO website If No, then the document should be **ARCHIVED**1 with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. If Yes, the document can be **ENDORSED**2 with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. If Yes, the document should be taken off the website as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. List below any new, relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered.	

5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).	
5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.	
Go to 6.	
6. Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?	6. If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7. If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. An **UPDATE**[4] will be posted on the website, indicating an update is in progress.
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.	
DSG Approval Date:	**July 12, 2010**

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

STEPS | **Outcomes** | **Action**

STEP 1: Initiation of the Document Assessment & Review process

RC emails DSG reviewer(s) the protocol

STEP 2: First teleconference to determine:
- **the clinical relevance of the guideline,**
- **if a new literature search is needed, and**
  - **if Yes, the search criteria.**

Discuss questions **#1-5**

#1. Is there still a **NEED** for a guideline covering one or more of the **topics** in this document?

No → **Archive**[1]

Yes

#2. Are all the current recommendations based on the current questions definitive* or sufficient[§], and have less than 5 years elapsed since the latest search?

Yes to all → **Endorse**[2]

Please note: **No teleconference needed, IF** the answers lead to one of these outcomes, **PLUS** the reviewer(s) complete & return the form **with the answers & explanations.**

No

#3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if

Yes → **Warning**[¶]

No

#4. Do current resources allow for an updated literature search to be conducted at this time?

No → **Deferral**[3]

Yes

#5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

→ **New search**

Teleconference with the reviewer(s) will focus the discussion on **#5**: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria

STEP 3: A new literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date

RC conducts new search

FLOW CHART (cont.)

STEPS	Outcomes	Action

STEP 4: Second teleconference to determine the ultimate status of the document

Review questions **#6-9**

#6. Are the volume and content of the newly identified evidence such that **a new document is necessary** to address the topic?

Yes → **Archive**

No

#7. Does the newly identified evidence **support the existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary?

Yes to all → **Endorse**

No

#8. Does any of the newly identified evidence, on initial review, **contradict** the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?

Yes → **Warning**

No

#9. Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?

Yes → **Deferral**

No

#10. An update should be initiated as soon as possible. List the expected date of completion of the update.

Yes → **Update**[4]

Please note: No teleconference needed, IF the reviewer(s) complete and return the form **with answers & explanations.**

Teleconference with the reviewer(s) to discuss the **type of update, priority, and resources.**

STEP 5: Final outcome approval; Document Assessment & Review questions #11

#11. Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.

RC emails draft for DSG approval

DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

***DEFINITIVE RECOMMENDATIONS** – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§SUFFICIENT RECOMMENDATIONS – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶WARNING – A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.