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Leucovorin Dosing for Gastrointestinal Cancer

Khai Tran
Melissa Walter

Rapid Review

Key Messages

What Is the Issue?

- Since 2008, the shortage of leucovorin has had a significant impact on fluorouracil-based chemotherapy. Many institutions worldwide provided possible options to relieve the leucovorin shortage, including using treatment without leucovorin, lowering the standard leucovorin dose, or using alternative drugs.
- If lowering the body surface area-adjusted standard dose of leucovorin does not affect efficacy and safety, then implementation of a low flat-dose protocol may prevent mistakes that result during dose calculation and save pharmacy compounding time and costs.
- Decision-makers want to know if any clinical evidence supports a low flat-dose protocol for leucovorin.

What Did We Do?

- To inform decisions about using flat-dose leucovorin in conjunction with fluorouracil-based chemotherapy, CADTH sought to identify and summarize literature comparing the clinical effectiveness of flat dosing versus weight-based leucovorin dosing. We also attempted to identify evidence-based recommendations for leucovorin dosing for colorectal or upper gastrointestinal cancer.
- A research information specialist conducted a literature search of the peer-reviewed and grey literature with a search strategy focused on leucovorin, dosing, and colorectal or gastrointestinal cancers. The search was limited to English-language documents published since 2013. One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

What Did We Find?

- We found 1 small retrospective cohort study (58 patients) comparing low flat-dose 50 mg leucovorin with body surface area-adjusted to high-dose 200 mg/m^2 to 500 mg/m^2 leucovorin in patients with colorectal cancer. The study found no statistically significant differences between the 2 doses in survival or complication rates.
- We found no evidence-based guidelines regarding leucovorin dosing for colorectal or upper gastrointestinal cancer. However, we found several guidelines with unclear methodology reporting leucovorin doses used in different fluorouracil-based regimens.

Key Messages

What Does it Mean?

- Limited evidence from this review suggests that the standard weight-based dosing of leucovorin may be reduced to a low flat-dose. However, we require a larger and well conducted trial to confirm the findings of that study.
- Decision-makers may wish to consider that reducing the dose of leucovorin may conserve the supply, reduce pharmacy compounding time and control acquisition costs.

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Abbreviations

AE	adverse event
BSA	body surface area
FOLFOX	fluorouracil, leucovorin, oxaliplatin
IV	intravenous
OS	overall survival
PFS	progression-free survival

Context and Policy Issues

Colorectal and Gastrointestinal Cancers in Canada

Colorectal cancer represents 11.3% of all 25-year prevalent cancers in Canada.[1] It is the third most common cancer type after breast and prostate cancers.[1] It is estimated that 1 in 16 men and 1 in 19 women will develop colorectal cancer during their lifetime. One in 34 men and 1 in 40 women will die from it.[2] Upper gastrointestinal cancers, including those of the esophagus and stomach, are relatively rare in Canada, but they can be deadly.[3] There were 13,555 and 5,100 Canadians diagnosed with stomach and esophagus cancers over the past 25 years, respectively.[1] Stomach and esophagus cancers represent the 14th and 19th most common cancer types in Canada, respectively.[1]

What Is the Current Practice?

There are different treatment options for colorectal and upper gastrointestinal cancer, including surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy.[4,5] Depending on the stage of colorectal cancer, different treatments may be recommended.[4] Surgery is often the first treatment for stage I and II colorectal cancer.[4] Radiation therapy and adjuvant chemotherapy may be recommended for some people of stage II and III.[4] For stage IV and metastatic colorectal cancers, for which surgery is not an option, various fluorouracil-based chemotherapy regimens are recommended.[4] Similarly, the management of gastrointestinal cancers often involves multiple therapies, such as surgery plus chemotherapy, surgery plus radiation therapy, or a combination of all 3, depending on the severity of the disease.[5]

Fluorouracil was discovered over 6 decades ago as a new class of tumour-inhibitory compounds.[6] It is a prodrug that is converted inside the cells to various metabolites that inhibit the enzyme thymidylate synthase responsible for the synthesis of thymidine, a building block of DNA.[7] Some metabolites are incorporated into ribonucleic acid (RNA) and interfere with RNA function, or they are incorporated into DNA and break the DNA into fragments.[6] It has a broad spectrum of anticancer activity against common solid tumours of the gastrointestinal system, but it does not have a robust anticancer activity when administered alone.[6]

Leucovorin (or folinic acid) is a folate analogue used to increase the anticancer activity of fluorouracil.[6] It forms a stable ternary complex that increases and prolongs the inhibition of thymidylate synthase by fluorouracil.[6] In vitro studies suggested that extracellular levels of leucovorin should be at least 10 micromolar for optimal enhancement of fluorouracil cytotoxicity.[6] Therefore, clinical studies of leucovorin and fluorouracil for the treatment of cancer patients have generally used large, body surface area (BSA)-adjusted doses of leucovorin (200 to 500 mg/m^2) to attain plasma levels of 10 micromolar or higher.[6]

Why Is it Important to Do This Review?

A shortage of leucovorin first occurred in 2008 and worsened between 2009 and 2012 due to manufacturing delays, thus limiting the supply around the world.[8-10] This shortage had a significant impact on fluorouracil-based chemotherapy.[11] As a result, many health care organizations were required to use alternative measures, such as reducing the leucovorin dose, using treatment without leucovorin, or switching to levoleucovorin, an active isomer.[12,13] Levoleucovorin has demonstrated a similar efficacy and toxicity

profile as leucovorin, but concerning cost, leucovorin remains the drug of choice.[13,14] Findings from several randomized and nonrandomized studies suggest no difference in efficacy and safety outcomes between body surface area (BSA)-adjusted low-dose (20 mg/m^2 to 25 mg/m^2) and BSA-adjusted high-dose (200 mg/m^2 to 500 mg/m^2) leucovorin in fluorouracil-based therapy of colorectal cancer.[15-21] However, it is unclear whether offering a flat dose of leucovorin is as safe and effective as BSA-adjusted dosing. From the health system resource management perspective, standardization with flat dosing instead of weight-based dosing may reduce mistakes during dose calculation, simplify treatment protocols, and save pharmacy compounding time and costs.

Objective

The current report aims to summarize evidence regarding the clinical effectiveness of flat dosing versus weight-based dosing of leucovorin for colorectal or upper gastrointestinal cancer. The report also aims to summarize the recommendations from evidence-based guidelines regarding dosing of leucovorin for colorectal or upper gastrointestinal cancer.

Research Questions

1. What is the clinical effectiveness of flat dosing versus weight-based dosing of leucovorin for colorectal or upper gastrointestinal cancer?
2. What are the evidence-based guidelines regarding dosing of leucovorin for colorectal or upper gastrointestinal cancer?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International Health Technology Assessment Database, the websites of Canadian and major international health technology agencies, and a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were leucovorin, dosing, and gastrointestinal cancers. The search was completed on October 16, 2023 and limited to English-language documents published since January 1, 2013.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first screening level, the reviewer reviewed the titles and abstracts and retrieved potentially relevant articles for inclusion. Table 1 presents the inclusion criteria for final selection of full-text articles.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with colorectal or upper gastrointestinal cancer
Intervention	Q1: Flat dose of leucovorin administered with fluorouracil Q2: Leucovorin administered with fluorouracil
Comparator	Weight-based dosing of leucovorin administered with fluorouracil
Outcomes	Q1: Clinical benefits and harms (e.g., safety, mortality, treatment response,) Q2: Recommendations regarding dosing of leucovorin with fluorouracil (e.g., weight-based vs flat dosing, optimal dose)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, evidence-based guidelines

Exclusion Criteria

We excluded articles that did not meet the selection criteria outlined in Table 1, articles published in language other than English, articles published before 2013, or guidelines with unclear methodology.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included publication using the Downs and Black checklist[22] for the nonrandomized study. Summary scores were not calculated for the included study; rather, the strengths and limitations of the included publication were described narratively.

Summary of Evidence

Quantity of Research Available

We identified a total of 401 citations from the literature search. Following screening of titles and abstracts, we excluded 397 citations and retrieved 4 potentially relevant reports from the electronic search for full-text review. We did not find any potentially relevant publications from the grey literature search. Of the 4 potentially relevant articles, we excluded 3 publications (2 for irrelevant intervention, and 1 published in language other than English), and included 1 publication, which is a retrospective matched cohort study that met the inclusion criteria. Appendix 1 presents the PRISMA[23] flow chart of the study selection. We did not identify any relevant evidence-based guidelines that could be included in this report. However, we identified 13 guidelines with unclear methodology, in which the doses of leucovorin used in different fluorouracil-based regimens for the management of colorectal and gastrointestinal cancers were presented in Table 8 of Appendix 5.

Summary of Study Characteristics

Appendix 2 provides details regarding the characteristics of the included primary study[24] (Table 2).

Study Design

The included primary study by Shank et al. (2017)[24] was a single-centre, retrospective matched cohort study. Patients were identified from the electronic pharmacy order system if they were prescribed IV (IV) leucovorin. Patient demographic characteristics were collected from each patient's electronic medical record. The low-dose cohort patients received a flat-dose leucovorin treatment between 1 January 2012 to 31 December 2012. The matched cohort patients received at least 1 BSA-adjusted leucovorin dose from 1 January 2009 to 31 December 2011. The study was published in 2017.

Country of Origin

The included study[24] was conducted by authors from US.

Patient Population

The study[24] involved adult patients with stage III or stage IV colon cancer or first-line metastatic colorectal cancer receiving fluorouracil-containing therapy. A total of 58 patients were included in the study. Patients' baseline characteristics were balanced between groups. The median age was around 57 years with a range between 32 to 80 years. Approximately 76% of patients had metastatic disease. Most patients (72.4%) in both groups received surgical resection of primary tumour. The most common regimen was FOLFOX alone (52%) or in combination with bevacizumab (38%). The FOLFOX regimen consists of oxaliplatin, fluorouracil, and leucovorin. Few patients received FOLFIRI regimen alone (3%) or in combination with bevacizumab (7%). The FOLFIRI regimen consists of irinotecan, fluorouracil, and leucovorin.

Interventions and Comparators

Patients in the BSA-adjusted leucovorin group received a treatment regimen of FOLFOX or FOLFIRI, in which the dose of leucovorin range between 200 mg/m^2 and 500 mg/m^2 per dose IV.[24] Patients in the flat-dose group also received a treatment regimen of FOLFOX or FOLFIRI, but the BSA-adjusted dose was replaced by a flat dose of 50 mg IV leucovorin.[24]

Outcomes

The efficacy outcomes considered in the study[24] were progression-free survival (PFS), determined by radiographic evidence of progression, and overall survival (OS). The date of death was collected from medical records. Safety outcomes were adverse events (AEs), whose rates were calculated for each group per cycle. The authors also reported the rates of dose reduction or delay in therapy in patients with severe AEs.

Summary of Critical Appraisal

Table 3 in Appendix 3 presents the strengths and limitations of the included primary study.[24]

For reporting, the authors of the included study[24] clearly described the objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of

interest, and the main findings. The authors reported actual P values for the primary outcomes and reported AEs of the intervention.

For external validity, the treatment settings (i.e., hospitals) in the included study[24] were representative of the treatment received by most of the patients. However, the patients may not represent the entire population from which they were selected, as the authors of the study[24] conducted a chart review of a small sample size from a single hospital.

For internal validity related to bias, the authors[24] used statistical tests appropriately to compare variables and assessed the main outcome measures using an accurate and reliable method.

For internal validity related to confounding, most baseline characteristics of the treatment groups appeared balanced, thus reducing the risk of confounding bias. The study's authors did not report whether sample size calculation was performed, and it is unclear whether the non-significant differences in specific outcomes were because the studies were underpowered for those outcomes.

Summary of Findings

Appendix 4 presents the study findings, which were summarized by outcome: PFS (Table 4); OS (Table 5); supportive care for patients with different AEs (Table 6); and other AEs (Table 7).

Clinical Effectiveness of Flat Dosing Versus Weight-Based Dosing of Leucovorin for Colorectal or Upper Gastrointestinal Cancer

Progression-Free Survival

Median PFS was 9.5 months (95% confidence interval [CI] 4.8 to 14.2) in the flat-dose group compared with 8.8 months (95% CI 6.2 to 11.4) in the BSA-adjusted dose group. Between group comparison showed no statistically significant difference (P = 0.254).[24]

Overall Survival

Median OS was 28 months in the flat-dose group compared with 36.2 months in the BSA-adjusted dose group. There was no statistically significant difference in median OS between groups (P = 0.923).[24]

Supportive Care in Patients With Different Adverse Events

The authors of the study[24] assessed 4 AEs including thrombocytopenia, neutropenia, diarrhea, and mucositis that were severe enough to require dose reduction or delay therapy of the combination of leucovorin and fluorouracil. There were no statistically significant differences between the flat-dose and the BSA-adjusted dose cohorts in the percentage of patients requiring dose reduction or delay in treatment greater than 5 days. There were also no statistically significant differences between groups in hospitalizations due to various conditions such as infection, obstruction, neutropenic fever, and dehydration.

Other Adverse Events

The authors of the study[24] documented the percentage of patients with AEs that did not result in dose reduction or delay in treatment without providing any statistical comparisons between groups. The events in the flat-dose group versus BSA-adjusted dose group included neuropathy (21.3% versus 13.2%), nausea

(3.5% versus 8.3%), constipation (2.1% versus 0), confusion (0.7% versus 0), fever (0.7% versus 2.1%), and pulmonary embolism (0 versus 0.7%).

Guidelines Regarding Dosing of Leucovorin for Colorectal or Upper Gastrointestinal Cancer
We did not identify any evidence-based guidelines regarding dosing of leucovorin for colorectal or gastrointestinal cancer; therefore, no summary can be provided.

However, we identified 13 guidelines with unclear methodology, in which the doses of leucovorin used in different fluorouracil-based regimens for treatment of colorectal or gastrointestinal cancer were presented in Table 8 of Appendix 5.

Limitations

There is limited evidence regarding comparing a low flat dose with a high BSA-adjusted dose of leucovorin, as 1 relevant study with a sample size of 58 patients was identified from the past 10 years. No evidence was identified regarding such comparison for treating upper gastrointestinal cancer. The included study also had several limitations, including a small sample size (underpowered), retrospective design (risk of selection bias), and inability to measure patient-reported outcomes such as quality of life. It was unclear whether the non-statistically significant differences between groups in survival and safety outcomes were true or whether the study was not powered to detect differences. Selection bias would have occurred if the cohort selected was not representative of all possible patients with the condition of interest in the larger population. The AEs were not graded; thus, the interpretation of AE severity may have varied among providers. Supportive care interventions may also have varied over the study period and from provider preference. Evidence for a flat-dose leucovorin is limited, and evidence-based guidelines informed by a systematic review of evidence and an assessment of the benefits and harms of dose modifications were unavailable.

Conclusions and Implications for Decision- or Policy-Making

We reviewed the clinical evidence of 1 pilot study with small sample size (n = 58), comparing a flat-dose (50 mg) with a BSA-adjusted dose (200 to 500 mg/m^2) of leucovorin in patients with colon or metastatic colorectal cancer receiving fluorouracil-containing therapy. We did not identify any evidence-based guideline regarding the dosing of leucovorin for the treatment of colorectal or upper gastrointestinal cancer. We provide a summary table (Table 8 in Appendix 5) presenting the doses of leucovorin used in the fluorouracil-based regimens for treating colorectal or upper gastrointestinal cancers in guidelines with unclear methodology.

For clinical evidence, the included study[24] did not detect differences in efficacy (i.e., PFS, OS) or adverse event rates between flat-dose and BSA-adjusted dose groups in patients with colorectal cancer. However, this was a pilot study, which may not be sufficiently powered to detect differences. A larger and well conducted trial would be needed to confirm the findings of this study.

Notably, a systematic review and meta-analysis exists[25] comparing low-dose (20 mg/m^2 to 50 mg/m^2) versus high-dose (200 mg/m^2 to 500 mg/m^2) BSA-adjusted leucovorin in patients with metastatic colorectal cancer. The results of the meta-analyses revealed a nonsignificant difference between groups in median survival time, tumour response rate, and hematological and nonhematological toxicities.[25] In addition, the large QUASAR RCT[26] (N = 4,927) comparing a low flat-dose (25 mg) with a high flat-dose (175 mg) of leucovorin in patients with stage I to stage III colorectal cancer reported no significant difference in recurrence and survival rates after 3 years of follow-up. Since those studies did not compare flat dosing with BSA-adjusted dosing of leucovorin, they did not meet our inclusion criteria, and we excluded them from the analysis in this report; however, they may provide some insight on the potential effectiveness of low, flat-dose leucovorin. For example, if the average BSAs of adult men and women are 1.9 m^2 and 1.6 m^2, respectively,[27] then a low dose of 20 mg to 50 mg/m^2 would translate to a flat dose of 38 mg to 95 mg for men and 32 mg to 80 mg for women with metastatic colorectal cancer. Thus, the findings in those studies may provide additional support to the decision to reduce the dose of leucovorin for treatment of colorectal or gastrointestinal cancers in patients receiving fluorouracil-containing therapy.

Most of the non-evidence-based guidelines (Table 8 in Appendix 5) present different fluorouracil-based regimens with BSA-adjusted dose of leucovorin ranging from 200 to 500 mg/m^2. With the few regimens containing only fluorouracil and leucovorin, the leucovorin dose was used at 20 mg/m^2 to 25 mg/m^2. The Australian eviQ guidelines present a treatment protocol using a modified FOLFOX6 regimen, in which the dose of oxaliplatin and leucovorin have been modified from the original clinical trial doses (i.e., 100 mg/m^2 to 85 mg/m^2 for oxaliplatin and 200 mg/m^2 to 50 mg flat-dose for leucovorin). Evidence supporting the recommendations to reduce leucovorin dosing in those guidelines was unclear. Despite limited evidence on the clinical effectiveness of low flat-dose leucovorin identified in this report, collective evidence from the systematic review and meta-analysis[25] and some non-evidence-based guidelines suggest that flat low-dose leucovorin regimens appear to be feasible approaches for colorectal cancer treatment with the purpose to relieve the leucovorin shortage and to reduce pharmacy compounding time and acquisition costs.

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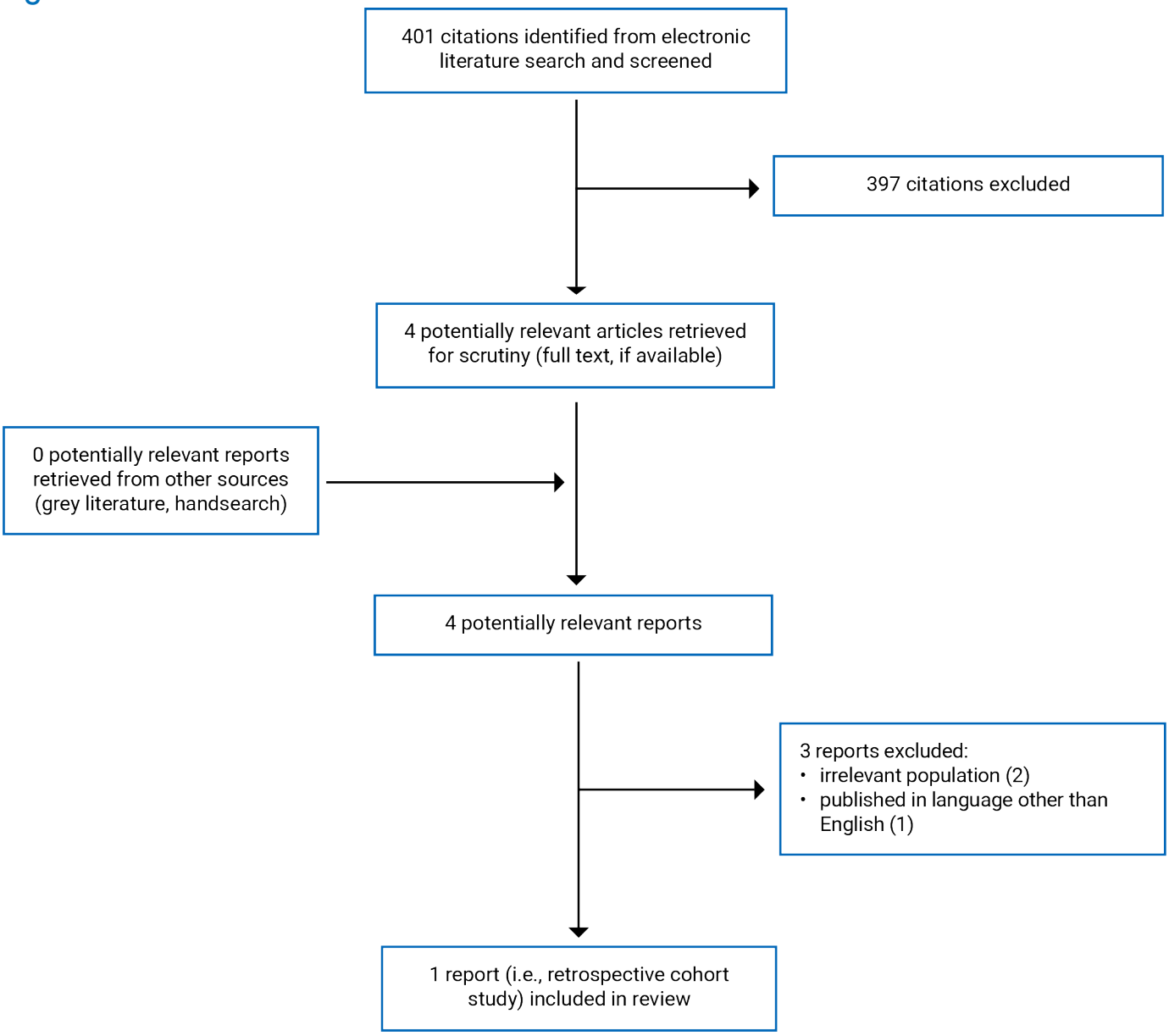
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

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Table 2: Characteristics of Included Primary Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Shank et al. (2017)[24] US **Funding source:** The authors indicated that they received no financial support for the research, authorship, and/or publication of this article	A single-centre, retrospective matched cohort study	Adult patients with stage III or stage IV colon cancer or first-line mCRC receiving fluorouracil-containing therapy. Median age (IQR), years: • Flat dose: 57 (36 to 80) • BSA-adjusted: 56 (32 to 79) % Male/female: • Flat dose: 41/59 • BSA-adjusted: 48/52 Stage at diagnosis: • 2: 3.4% in both groups • 3: 20.7% in both groups • 4: 75.9% in both groups Received surgical resection of primary tumour: • Flat dose: 72.4% • BSA-adjusted: 72.4% Patients with metastatic disease: • Flat dose: 76% • BSA-adjusted: 76% Initial regimen: • Most patients received FOLFOX[a] alone (52%) or in combination with bevacizumab (38%). • Few patients receiving FOLFIRI[b] alone (3.4%) or in combination with bevacizumab (7%)	**Intervention:** Flat-dose leucovorin 50 mg IV (n = 29) **Comparator**: BSA-adjusted leucovorin 200 mg/m^2 to 500 mg/m^2 per dose (n = 29)	Outcomes: • PFS (determined by radiographic evidence of progression) • OS • AEs Follow-up: NR

AE = adverse event; BSA = body surface area; IQR = interquartile range; IV = IV; mCRC = metastatic colorectal cancer; NR = not reported; OS = overall survival; PFS = progression-free survival.

[a]FOLFOX: Oxaliplatin 85 mg/m^2 IV on day 1, fluorouracil 400 mg/m^2 IV bolus over 1 hour on day 1, followed by 2,400 mg/m^2 IV over 46 to 48 hour as a continuous infusion, and leucovorin 200 to 500 mg/m^2 IV on day 1 repeated every 2 weeks.

[b]FOLFIRI: Irinotecan 180 mg/m^2 IV on day 1, fluorouracil 400 mg/m^2 IV bolus over 1 hour on day 1, followed by 2,400 mg/m^2 IV over 46 to 48 hour as a continuous infusion, and leucovorin 200 mg/m^2 to 500 mg/m^2 IV on day 1 repeated every 2 weeks.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of Clinical Study Using the Downs and Black Checklist[22]

Strengths	Limitations
Shank et al. (2017)[24]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • Actual P values were reported for the main outcomes. • Safety outcomes including adverse events of the intervention were reported. **External validity:** • The study was conducted in a hospital setting. The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. **Internal validity – bias:** • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. **Internal validity – confounding:** • The baseline characteristics of the treatment groups appeared to be balanced, thus reducing the risk of confounding bias.	**External validity:** • The retrospective cohort study with small sample size was conducted from a single hospital. The patients may not be representative of the entire population from which they were treated. **Internal validity – bias:** • Risk of selection bias is a main limitation of a retrospective cohort study. **Internal validity – confounding:** • The study did not report whether sample size was calculated.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 4: Summary of Findings by Outcome — Progressive Free Survival

Dose of leucovorin	Median PFS	95% CI	P value
Flat-dose	9.5 months	4.8 to 14.2 months	0.254
BSA-adjusted dose	8.8 months	6.2 to 14.1 months	

BSA = body surface area; CI = confidence interval; PFS = progressive free survival.

Table 5: Summary of Findings by Outcome — Overall Survival

Dose of leucovorin	Median OS	95% CI	P value
Flat-dose	28 months	NR	0.923
BSA-adjusted dose	36.2 months	NR	

BSA = body surface area; CI = confidence interval; NR = not reported; OS = overall survival.

Table 6: Summary of Findings by Outcome — Supportive Care for Patients with Different Adverse Events

Adverse events and Supportive care	Flat-dose	BSA-adjusted dose	OR (95% CI)	P value
Thrombocytopenia				
Dose reduction	15.6%	9.7%	1.72 (0.84 to 3.51)	0.13
Delay in treatment > 5 days	9.2%	5.6%	1.73 (0.69 to 4.30)	0.24
Neutropenia				
Dose reduction	10.6%	18.1%	0.54 (0.27 to 1.07)	0.07
Delay in treatment > 5 days	11.3%	8.3%	1.41 (0.64 to 3.09)	0.39
Diarrhea				
Dose reduction	3.5%	1.4%	2.61 (0.50 to 13.68)	0.23
Delay in treatment > 5 days	0.7%	0.7%	1.02 (0.06 to 16.49)	0.99
Mucositis				
Dose reduction	0	1.4%	NR	NR
Delay in treatment > 5 days	0	0.7%	NR	NR
Hospitalized				
Infection	0.7%	2.8%	0.25 (0.03 to 2.26)	0.18

Adverse events and Supportive care	Flat-dose	BSA-adjusted dose	OR (95% CI)	P value
Obstruction	2.1%	0.7%	3.11 (0.32 to 30.25)	0.30
Neutropenic fever	0	2.8%	NR	0.12
Dehydration	0	1.4%	NR	0.50

CI = confidence interval; H = high-dose leucovorin regimen; L = low-dose leucovorin regimen; NR = not reported; NS = not statistically significant; OR = odds ratio; RCT = randomized controlled trial.

Table 7: Summary of Findings by Outcome — Other Adverse Events

Adverse events	Flat-dose	BSA-adjusted dose
Neuropathy	21.3%	13.2%
Nausea	3.5%	8.3%
Constipation	2.1%	0
Confusion	0.7%	0
Fever	0.7%	2.1%
Pulmonary embolism	0	0.7%

Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

Guidelines With Unclear Methodology

Table 8 summarizes the doses of leucovorin used in the fluorouracil-based regimens for treatment of gastrointestinal cancer in guidelines with unclear methodology.

Table 8: Summary of Leucovorin Doses in Different Fluorouracil-Based Regimens

Guidelines	Condition	Fluorouracil-based regimens	Leucovorin dose	Route of administration
NCCN – Colon Cancer, 2023	Advanced or metastatic disease	FOLFOX6 (modified)	400 mg/m^2	IV on day 1
		FOLFOX7 (modified)	400 mg/m^2	IV on day 1
		FOLFIRI	400 mg/m^2	IV on day 1
		FOLFIRINOX	400 mg/m^2	IV on day 1
		Roswell Park regimen (Bolus or infusional 5-fluorouracil/ leucovorin)	500 mg/m^2	IV over 2 hours, days 1, 8, 15, 22, 29, and 36
NCCN – Esophageal and Esophagogastric Junction Cancers, 2023	Unresectable locally advanced, recurrent, or metastatic disease	FOLFOX (for perioperative chemotherapy; for definitive chemoradiation; for postoperative systemic therapy; for first-line therapy of HER2 overexpression positive adenocarcinoma; for MSI-H/dMMR tumours)	400 mg/m^2	IV on day 1
		FOLFIRI	400 mg/m^2	IV on day 1
		FLOT (for perioperative chemoradiation)	200 mg/m^2	IV on day 1
NCCN – Gastric Cancer, 2023	Unresectable locally advanced, recurrent, or metastatic disease	FLOT (for perioperative chemotherapy)	200 mg/m^2	IV on day 1
		FOLFOX (for perioperative chemotherapy; for perioperative chemoradiation; for postoperative chemoradiation;	200 mg/m^2, 400 mg/m^2	IV on day 1

Guidelines	Condition	Fluorouracil-based regimens	Leucovorin dose	Route of administration
		for postoperative chemotherapy; for chemoradiation for unresectable disease; for first-line therapy of HER2 overexpression positive adenocarcinoma; for MSI-H/dMMR tumours)		
		FOLFIRI (for second-line and subsequent therapy)	400 mg/m^2	IV on day 1
NCCN – Anal Carcinoma, 2023	Metastatic cancer	FOLFCIS	400 mg/m^2	IV on day 1
		FOLFOX6 (modified)	400 mg/m^2	IV on day 1
NCCN – Rectal Cancer, 2023	Unresectable locally advanced, recurrent, or metastatic disease	FOLFOX6 (modified) (for perioperative chemotherapy;	400 mg/m^2	IV on day 1
		FOLFOX7 (modified)	400 mg/m^2	IV on day 1
		FOLFIRI	400 mg/m^2	IV on day 1
		FOLFIRINOX	400 mg/m^2	IV on day 1
		Roswell Park regimen (Bolus or infusional 5-fluorouracil/ leucovorin)	500 mg/m^2	IV over 2 hours, days 1, 8, 15, 22, 29, and 36
NCCN – Small Bowel Carcinoma, 2023	Unresectable locally advanced, recurrent, or metastatic disease	FOLFOX6 (modified)	400 mg/m^2	IV on day 1
		5-FU/LV	400 mg/m^2	IV on day 1
		FOLFOX7 (modified)	400 mg/m^2	IV on day 1
		FOLFIRI	400 mg/m^2	IV on day 1
		FOLFIRINOX (modified)	400 mg/m^2	IV on day 1
		Roswell Park regimen 5-FU/LV	500 mg/m^2	IV over 2 hours, days 1, 8, 15, 22, 29, and 36
		Simplified biweekly infusional 5-FU/LV	500 mg/m^2	IV over 2 hours on day 1
		Weekly infusional 5-FU/ LV	20 mg/m^2	IV over 2 hours on day 1
eviQ – Colorectal cancer, 2023 eviQ – Colorectal cancer, 2022	Colon cancer	FOLFOX6 (modified)	50 mg flat dose	IV bolus

Guidelines	Condition	Fluorouracil-based regimens	Leucovorin dose	Route of administration
		QUASAR (modified) – Weekly infusional 5-FU/LV	50 mg flat dose	IV bolus
Saskatchewan guidelines – Esophageal Cancer and Gastro-esophageal Junction Cancer, 2018	Gastro-esophageal junction adenocarcinoma	5-FU/LV	20 mg/m^2	IV day 1 to 5
Saskatchewan guidelines – Colorectal Cancer, 2019	Localized cancer, unresectable advanced, or metastatic disease	Biweekly infusional 5-FU/LV	400 mg/m^2	IV on day 1
		Roswell Park regimen 5-FU/LV	500 mg/m^2	IV over 2 hours
		Mayo clinic regimen 5-FU/LV	20 mg/m^2 to 25 mg/m^2 per day	IV bolus day 1 to 5
		FOLFOX6 (modified)	400 mg/m^2	IV on day 1
Alberta guidelines – Colon cancer, 2023	Metastatic colon cancer	FOLFIRI	400 mg/m^2	IV on day 1
		FOLFOX6 (modified)	400 mg/m^2	IV on day 1
		FOLFIRINOX	400 mg/m^2	IV on day 1
		Simplified biweekly infusional 5-FU/LV	500 mg/m^2	IV over 2 hours on day 1
Alberta guidelines – Gastric Cancer, 2021	Gastric cancer	FLOT (for perioperative chemotherapy)	200 mg/m^2	IV over 2 hours on day 1
		5-FU/LV + radiotherapy	20 mg/m^2	IV
		5-FU/LV (de Gramont)	100 mg/m^2	IV over 2 hours
		FOLFOX	400 mg/m^2	IV
		FOLFIRI	400 mg/m^2	IV
Alberta guidelines - Esophageal Cancer, 2021	Esophageal cancer	FLOT (for perioperative chemotherapy)	200 mg/m^2	IV over 2 hours on day 1
	Unresectable esophageal cancer	FOLFOX	200 mg/m^2	IV

dMMR = MSI-H or mismatch repair deficient; 5-FU = 5-fluorouracil; FLOT = fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFIRI = fluorouracil, leucovorin, irinotecan; FOLFIRINOX = fluorouracil, leucovorin, irinotecan, oxaliplatin; FOLFCIS = fluorouracil, leucovorin, cisplatin; FOLFOX = fluorouracil, leucovorin, oxaliplatin; IV = IV; LV = leucovorin; MSI-H = microsatellite instability-high; NCCN = National Comprehensive Cancer Network.

Note: eviQ is an Australian Government, freely available online resource of cancer treatment protocols developed by multidisciplinary teams of cancer specialists.

Systematic Review

Hsu CY, Chen CY, Lin YM, Tam KW. Efficacy and safety of high-dose vs low-dose leucovorin in patients with colorectal cancer: systematic review and meta-analysis. *Colorectal Dis.* 2020;22(1):6-17. PubMed

Randomized Controlled Trial

Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. *Lancet.* 2000;355(9215):1588-1596. PubMed

Authors: Khai Tran, Melissa Walter

Contributors: Elizabeth Carson, Camille Santos

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Questions or requests for information about this report can be directed to **Requests@CADTH.ca**