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Raltitrexed in Patients With Dihydropyrimidine Dehydrogenase Deficiency

Rapid Review

CADTH

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Abbreviations

5-FU	fluorouracil
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
DPD	dihydropyrimidine dehydrogenase
ECOG	Eastern Cooperative Oncology Group
OS	overall survival
PFS	progression-free survival
SR	systematic review

Key Messages

- This review identified limited evidence regarding the clinical effectiveness of raltitrexed for patients who had previously experienced adverse events following treatment with fluoropyrimidines. These studies had several limitations, most notably lacking a separate control group; therefore, the effectiveness of raltitrexed in this population is uncertain.
- Limited evidence was found about the safety of raltitrexed for patients who had previously experienced adverse events with fluoropyrimidine treatment. Reported adverse events included cardiac or vascular adverse events, anemia, and nausea and vomiting. No treatment-associated deaths were reported in the studies included in this review.
- No studies were identified that compared the clinical effectiveness of raltitrexed to other therapies, placebo, or no treatment comparator groups for treatment of patients who had experienced adverse events from fluoropyrimidine therapy.
- This review identified evidence for people who had previously experienced severe adverse events, primarily cardiotoxicity, following treatment with fluoropyrimidines. It is unclear if these findings are appliable to patients with a complete dihydropyrimidine dehydrogenase deficiency.

Context and Policy Issues

Cancer has a significant impact on people and health care systems, and is the leading cause of death worldwide and in Canada.[1,2] While overall cancer rates, including incidence and mortality have declined, as the population ages and grows in Canada, the number of new cancer cases and deaths is likely to increase. A report from the Canadian Cancer Statistics Advisory Committee estimated that in 2022, there would be 233,900 new cancer cases and 85,100 cancer deaths in Canada.[1]

Choices for cancer treatment depend on the type of cancer, and options include surgery, radiotherapy, and/or systemic therapies such as chemotherapy or targeted biological therapies.[2] Fluoropyrimidines, which include 5-fluorouracil (5-FU) and capecitabine, are commonly used in chemotherapy for multiple types of cancer, including colorectal, breast, head and neck, pancreatic, and gastric.[3,4] Fluoropyrimidines are also frequently used with external radiation therapy.[3] Worldwide, an estimated 2 million patients are treated with fluoropyrimidines each year.[4] However, these drugs are also associated with adverse events, including cardiotoxicities (e.g., angina, myocardial infarction, arrhythmias)[3] and non-cardiac adverse events (e.g., mucositis, diarrhea).[5] It is estimated that 10% to 40% of patients who are treated with fluoropyrimidines may experience severe toxicities, and that these toxicities may be fatal in approximately 0.5% to 1% of patients.[4,6]

The risk of cardiotoxicity from fluoropyrimidines may be influenced by numerous factors, including dosing schedule, route of administration, underlying heart disease or other cardiac risk factors, age, type and stage of cancer, and other drugs being used concurrently.[3,6] Genetics may also influence the risk of adverse events from fluoropyrimidines. Fluoropyrimidines are metabolized in the body by the dihydropyrimidine dehydrogenase (DPD) enzyme. Genetic variations, such as in the gene that encodes DPD, can result in reduced DPD enzyme activity.[3,4] It is estimated that 3% to 8% of the population has a partial DPD deficiency (defined as up to approximately 50% lower activity), and that about 0.1% of the population has a complete DPD deficiency (approximately 0% enzyme activity).[4] Studies have estimated that

39% to 61% of patients who experienced severe fluoropyrimidine-associated toxicities had decreased DPD activity.[4]

DPD deficiency may be assessed through strategies such as genotyping or measuring the DPD phenotype, or may be suspected when a patient experiences cardiotoxicity following treatment with fluoropyrimidine.[4] Using a non-fluoropyrimidine treatment may be the preferred strategy, particularly for patients with a complete DPD deficiency.[3] An alternative treatment option is raltitrexed, for which Health Canada issued a Notice of Compliance for the treatment of advanced colorectal cancer.[7]

In September 2022, CADTH published a Reference List on this topic that identified some relevant studies.[8] Thus, the purpose of this report is to summarize and critically appraise evidence regarding the clinical effectiveness and safety of raltitrexed in patients with complete DPD deficiency or who are at risk of severe fluoropyrimidine toxicity or intolerance.

Research Questions

1. What is the clinical effectiveness of raltitrexed in patients with complete DPD deficiency?
2. What is the safety of raltitrexed in patients with complete DPD deficiency?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were raltitrexed and dihydropyrimidine dehydrogenase deficiency. No filters were applied to limit retrieval by study type. Comments, newspaper articles, editorials, letters, and conference abstracts were excluded. When possible, retrieval was limited to the human population. The search was completed on October 4, 2022, and limited to English-language documents published since January 1, 2012.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Patients with complete dihydropyrimidine dehydrogenase deficiency or at risk of severe fluoropyrimidine (including 5-FU and capecitabine) toxicity and/or intolerance
Intervention	Raltitrexed
Comparator	No comparator, 5-FU, capecitabine
Outcomes	Q1: Effectiveness (e.g., progression-free survival, overall survival, objective response rate, duration of response, health-related quality of life) Q2: Safety (e.g., adverse events, serious adverse events, withdrawal due to adverse events, death)
Study designs	Health technology assessments, systematic reviews, randomized-controlled trials, non-randomized studies

5-FU = 5-fluorouracil.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2012.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[9] for the systematic review (SR), and the Downs and Black checklist[10] for the non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 88 citations were identified in the literature search. Following screening of titles and abstracts, 79 citations were excluded and 9 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 4 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. These comprised 1 publication that included both an SR and a non-randomized study, and 4 additional non-randomized studies. Appendix 1 presents the PRISMA[11] flow chart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Five publications were included in this report, with 1 publication that included both an SR and a non-randomized study,[12] and 4 additional non-randomized studies.[13-16] The SR[12] and 3 non-randomized studies[12,13,15] had broader inclusion criteria than the present review, as they were not restricted to patients who had a DPD deficiency or were at severe risk of fluoropyrimidine

toxicity and/or intolerance. Only the characteristics and results of the subset of relevant patients is described in this report.

Additional details regarding the characteristics of the included publications are provided in Appendix 2.

Study Design

One SR[12] was identified that was published in 2013 and searched PubMed from January 1, 1991, to August 10, 2011. The authors did not specify if certain study designs were excluded, and encompassed non-randomized studies, including case studies. Their inclusion criteria were broader than this report as they aimed to assess cardiotoxicity following treatment with 5-FU, capecitabine, and raltitrexed. They identified 3 primary studies relevant to this report, which the review authors described as being case studies.

Five non-randomized studies were identified, which were published in 2022,[13] 2021,[13] 2018,[14] 2014,[15] and 2013.[12] All were retrospective cohort studies: 1 was a population-based review,[14] 3 were multicentre studies,[12,13,16] and 1 was a single-centre study.[15]

Country of Origin

The first author of the included SR[12] was from the UK; the review authors did not report the countries in which the relevant primary studies were conducted.

The non-randomized studies were conducted in Canada,[13] Australia,[16] France,[13] and the UK.[12,15]

Patient Population

Systematic Review

The SR[12] included patients who had experienced cardiotoxicity from treatment with 5-FU or capecitabine, with a separate assessment of studies focused on patients who switched to raltitrexed. The study authors did not report the total number of patients, or patients' baseline characteristics.

Non-Randomized Studies

For this report, patients who experienced severe adverse side effects from fluoropyrimidine treatment were considered to fit the population inclusion criteria. Two non-randomized studies specifically enrolled patients who had a history of fluoropyrimidine-induced adverse events: 1 included cardiac and non-cardiac adverse events[14] and the other included cardiac toxicity only.[16] Three non-randomized studies[12,13,15] had broader inclusion criteria than this report, and included patients who experienced fluoropyrimidine-induced cardiotoxicity and patients with pre-existing cardiovascular comorbidities. One study[13] also included patients with confirmed or suspected DPD deficiency, but did not report outcomes specific to this subgroup.

Two studies[13,14] were restricted to patients with metastatic colorectal cancer, 2 studies[12,15] focused on patients with gastrointestinal cancer, and 1 study[16] included multiple types of cancer (primarily colorectal, but also esophageal and ampullary).

For the patients relevant to this report, the sample size ranged from 42 to 155, and, where reported, the mean or median was between 62 and 66.5 years.[13,14,16]

Interventions and Comparators

For all studies, the intervention of interest was raltitrexed. Four non-randomized studies[13-16] included a mix of single-drug and combination regimens, and 3[13,14,16] reported the types of combinations. The reported mean or median number of cycles varied across studies.[13-16] Three studies[13-15] reported the dosages used, with a standard dosage of 3 mg/m^2 (2 studies[13,14] reported every 3 weeks, 1 study[15] did not report the frequency); in some studies, lower dosages[13,15] or higher dosages[15] were used for some patients. The publication that included both an SR[12] and a non-randomized study[12] did not report if they included single-drug and/or combination regimens, the mean or median number of cycles, or the dosage.

The comparators relevant to this report were fluoropyrimidines (e.g., before and after with patients who had been previously treated with fluoropyrimidines, or a historical control), or no comparator.

Outcomes

For clinical effectiveness, the reported outcomes were overall survival (OS) and progression-free survival (PFS).[13,14]

For safety, the reported outcomes were cardiac adverse events (overall[12-15] or attributed to raltitrexed[16]), other adverse events (neutropenia, anemia, nausea and vomiting, diarrhea, and transaminitis),[14] and mortality.[12,14-16] One study[14] also assessed the severity of adverse events retrospectively using the Common Terminology Criteria for Adverse Events, version 5.0.[17]

Summary of Critical Appraisal

An overview of the critical appraisal of the included studies is summarized in the following section. Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3.

Systematic Review

The identified SR[12] stated the aim of the review as well as its population, interventions, and outcomes of interest. Its authors provided their search strategy, and included randomized trials as well as non-randomized studies in their review. They also reported their conflicts of interest and source of financial support.

However, they did not use a comprehensive search strategy, as they did not search multiple databases and or other sources (e.g., grey literature); they also restricted articles to those available in English. Thus, it is possible some relevant studies may have been missed. It was not stated if they had published their methods in advance, or if 2 review authors performed study selection or data extraction. Developing a review protocol in advance and adhering to its methods can help to reduce risk of bias. If study selection and/or data extraction were not conducted in duplicate, there may also be an increased potential for errors. The characteristics of the studies relevant to this report were described in limited detail, which may make it difficult to determine if their findings are potentially applicable to specific groups of patients. In addition, they did not provide a list of excluded studies; thus, it is difficult to determine if potentially relevant studies have been excluded, which may contribute to selection bias. Sources of funding for the included studies were also not reported, so it was also unclear if these results were impacted by their funding source. Quality or risk of bias of the included studies was also not assessed; thus, was not considered during the discussion of the results. Though not formally assessed, the quality of included studies relevant to this

review was expected to be low due to the study design (which the review authors described to be case studies).

Non-Randomized Studies

All included non-randomized study authors[12-16] clearly described their objective, main outcomes, patient inclusion criteria, and interventions. All were retrospective reviews; thus, it is possible that the patients, treatment, and location may have been representative of typical patients and standard of care. Due to the nature of the intervention, it is expected that compliance with the intervention was reliable. Similarly, as the outcomes were objective, it is expected they were accurate and reliable. The main findings were clearly described, with 4 studies[13-16] reporting the 95% confidence interval and/or actual P value for the primary outcomes. All study authors also reported their conflicts of interest.[12-16]

The 2 studies[14,16] that focused on patients who had experienced severe adverse events with fluoropyrimidine treatment described patients' baseline characteristics. From the 3 studies[12,13,15] with broader inclusion criteria, 1[13] described characteristics of the subgroup of interest to this report, while 2 studies[12,15] described their entire sample and not the subgroup of interest. Some studies[13-16] reported that patients varied in the number of cycles of raltitrexed they received, but it was unclear if this could have impacted outcomes or if it was considered in the analysis.

As all the included non-randomized studies[12-16] were single-arm, retrospective studies, they are at risk of several types of bias. As these studies did not have a separate control group, uncontrolled factors may have affected the findings; thus, these results should be interpreted with caution and may not be attributed entirely to raltitrexed. As patients were not randomized to the intervention, the reported results may have been affected by potential confounding factors. For example, physicians may have switched patients they perceived as being more likely to succeed to raltitrexed; therefore, patients who received raltitrexed in these studies may not have been representative of an average patient. None of the studies included a list of confounders, and it was unclear if confounders were considered in the analysis. One study[14] assessed severity of adverse events retrospectively based on electronic medical records; thus, there is a risk of misclassification or underreporting. Specific baseline characteristics and outcomes of interest may also not have been available due to the retrospective design. There was considerable heterogeneity within studies, such as in the type of intervention (e.g., raltitrexed alone versus combination regimens), and it is unclear if this could have influenced the findings.

It was not reported whether the studies that used subgroup analyses[12,13,15] were pre-planned. None of the included studies reported blinding the participants or research staff; however, as the outcomes of interest were objective, it is unlikely this introduced bias. Two studies[13,16] had fewer than 50 patients relevant to this report; thus, may be statistically underpowered. Three studies[12,14,15] also did not clearly report their sources of funding.

Summary of Findings

The main findings from the included SR[12] and non-randomized studies[12-16] are summarized in this section. Only the findings from the subset of relevant patients are described. Additional details are provided in in Appendix 4.

Clinical Effectiveness of Raltitrexed

Survival

Two single-arm studies[13,14] reported on the clinical effectiveness of raltitrexed for patients with metastatic colorectal cancer, as measured by OS and PFS. In one study[14] of patients who had experienced cardiac or non-cardiac severe adverse events from fluoropyrimidine treatment, the median OS and PFS were 10.2 months and 8.5 months, respectively. In the other study,[13] which had a subgroup of patients who had experienced fluoropyrimidine-induced cardiotoxicity, the median OS and PFS were 28.3 months and 10.6 months, respectively.

One study[14] also reported on the survival of patients treated with raltitrexed by different types of cancer. No statistically significant difference was found between colon and rectal cancer. In patients treated with raltitrexed, those with left-sided colon cancer experienced longer median OS and PFS (median 18.9 and 17.1 months, respectively) than patients with right-sided colon cancer (median OS and PFS were both 5.4 months); these differences were statistically significant.

Safety of Raltitrexed

Cardiac and Vascular Adverse Events

All included studies assessed cardiac[12-16] or vascular (i.e., cardiovascular or cerebrovascular)[12] adverse events following raltitrexed treatment for patients who had previously experienced fluoropyrimidine-related adverse events. The SR[12] (which reported findings from 3 case studies or series, from an unclear number of patients) and 2 single-arm studies[13,14] reported no cardiac adverse events. One single-arm study[16] reported that 1 patient experienced arrhythmia, but stated this was considered to be unrelated to raltitrexed, and that no cardiac events occurred due to raltitrexed. They also stated that this was statistically significantly lower than the expected rate of cardiotoxicity with rechallenging fluoropyrimidines (20%).[16] From the remaining 2 single-arm studies, 1 study[12] reported that 3 out of 63 patients experienced cardiovascular or cerebrovascular events, and the other[15] reported that 8 out of 155 patients (5.2%) experienced cardiac events.

Other Adverse Events

One single-arm study[14] reported on other adverse events; anemia was the most common (41.7%), followed by nausea and vomiting (27.4%); neutropenia, diarrhea, and transaminitis were also observed. Most observed adverse events were classified as grade 1 or 2 (mild or moderate); 16.7% of patients experienced grade 3 (severe) adverse events, and no grade 4 (life-threatening) events were observed.[14,17]

Mortality

Four single-arm studies[12,14-16] also reported on mortality. Three studies[12,14,15] reported no treatment-related deaths. One study[16] reported that 1 patient died, but stated this was due to sepsis and unrelated to raltitrexed.

Limitations

The identified SR conducted a limited search, and its methodology may have led to exclusion of relevant studies. They identified 3 case studies or series that were described in limited

detail, and did not include a risk of bias assessment. Thus, the quality of evidence identified by this review is unclear, and may be at high risk of bias and uncertainty.

All 5 included primary clinical studies were observational, single-arm retrospective cohort studies. Thus, there is a risk that the findings have been influenced by confounding variables and biases due to their retrospective design, lack of randomization, and lack of a separate control group. Three studies[12,13,15] had broader population inclusion criteria than this review, and reported limited information regarding baseline characteristics and outcomes specific to the patients relevant for this report. There was also clinical heterogeneity within and across studies regarding patients' health status, type of cancer, and treatment protocols, which may have impacted the findings. For example, 1 study[14] conducted a multivariable regression analysis to assess factors that may be associated with survival outcomes, and reported that left-sided colon cancer and a baseline ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1 (a measure of a patient's daily living abilities)[18] were associated with longer PFS. These differences may also impact the generalizability of the reported findings to specific patient groups.

For the studies that reported survival outcomes,[13,14] there was no comparison to a separate control group, so it is unclear how clinically effective raltitrexed is compared to other treatments available to patients. Relevant studies that assessed the impact of raltitrexed on other measures of clinical effectiveness (e.g., quality of life) were also not identified. The non-randomized studies with broader inclusion criteria[12,13,15] reported some outcomes for their full sample but not for the subgroup of interest to this report; as these results included a mixed population, they were not incorporated in this review.

The study findings were specific to patients who had experienced adverse events following treatment with fluoropyrimidines, and it was unclear if these patients had a DPD deficiency. Thus, it is unclear if these findings are generalizable to patients with a complete DPD deficiency.

Where reported, baseline age data also indicates pediatric patients were likely not included in the included studies; thus, the effectiveness and safety of raltitrexed for pediatric patients is unclear.

The generalizability of these findings is also unclear. All studies included data from 2008 or earlier, and it is unknown if older results are applicable to today (e.g., if the quality of treatment has improved). One study[14] was conducted in Canada (Alberta), but it is unclear if the findings from the other studies are applicable to the Canadian context.

Conclusions and Implications for Decision- or Policy-Making

This report included 1 SR[12] and 5 non-randomized studies[12-16] related to the clinical effectiveness and/or safety of raltitrexed for patients who had previously been treated with fluoropyrimidines and experienced adverse events.

Two non-randomized studies[13,14] reported on the clinical effectiveness of raltitrexed. One study[14] reported that the median OS and PFS were 10.2 months and 8.5 months, respectively,

while the other study[13] reported a median OS and PFS of 28.3 months and 10.6 months, respectively. As they did not have a relevant control group, it is unclear how clinically effective raltitrexed is compared to alternative treatments. Subgroup analyses in patients treated with raltitrexed indicated that patients with left-sided colon cancer experienced statistically significantly longer median OS and PFS than patients with right-sided colon cancer, and no significant difference was found between colon and rectal cancer.

The SR[12] and 5 non-randomized studies[12-16] reported outcomes related to safety, and stated that the proportion of patients who experienced cardiac (or cardiovascular or cerebrovascular) adverse events following treatment with raltitrexed ranged between 0% and 5.2%. One non-randomized study[14] also reported other types of adverse events: the most common was anemia (41.7%), followed by nausea and vomiting (27.4%), and most adverse events were grade 1 or 2 in severity on the Common Terminology Criteria for Adverse Events scale. Among the studies that reported mortality, 3 studies[12,14,15] reported no treatment-related deaths, and 1 study[16] reported 1 death considered to be unrelated to raltitrexed.

The limitations of the included publications should be considered when interpreting the findings of this report. Overall, few studies were identified, and comprised 1 SR based on case reports[12] and 5 retrospective, single-arm non-randomized studies.[12-16] The methodological limitations and heterogeneity within and across studies make it difficult to draw definitive conclusions regarding the effectiveness of raltitrexed for patients who have experienced adverse events with fluoropyrimidine treatment, as the results may have been influenced by various sources of bias and uncertainty. Three non-randomized studies[12,13,15] had broader inclusion criteria than this review and did not report all outcomes for the subgroup of interest; thus, these outcomes were not included in this review. It is also unclear if these findings are generalizable to patients with a complete DPD deficiency. It is possible that some or all of the patients from the included studies may have experienced adverse events from fluoropyrimidine treatment for alternate reasons, and it is unclear if these patients may respond differently to raltitrexed compared to patients with a DPD deficiency.

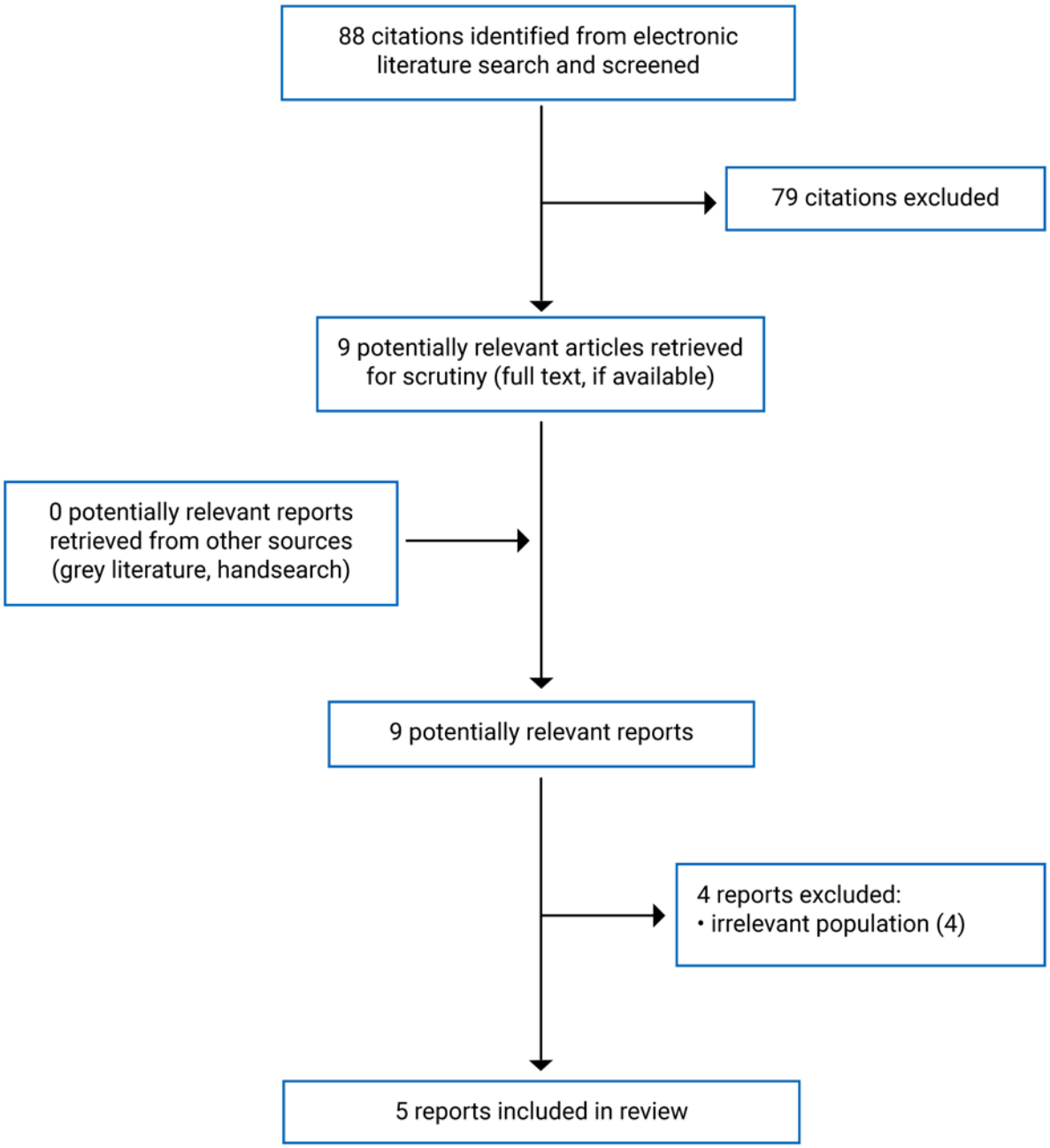
Future high-quality studies that evaluate raltitrexed compared to other treatments (e.g., standard of care) or placebo control groups for patients with a complete DPD deficiency, or for patients who are known to have a high risk of fluoropyrimidine toxicity and/or intolerance, would assist stakeholders with decision-making regarding the use of raltitrexed for these patient groups. Future studies may also consider assessing what variables are associated with greater clinical effectiveness of raltitrexed (e.g., type of cancer) to improve treatment selection. Reporting on other outcomes, such as response rate, quality of life, and other non-cardiac adverse events, may also help further develop an understanding of raltitrexed's clinical effectiveness and safety.

References

1. Brenner DR, Poirier A, Woods RR, et al. Projected estimates of cancer in Canada in 2022. *Can Med Assoc J.* 2022;194(17):E601-E607. PubMed
2. Cancer. Geneva (CH): World Health Organization; 2022: https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed 2022 Oct 6.
3. Saif WM, Banchs J, Kohne C-H. Fluoropyrimidine-associated cardiotoxicity: incidence, clinical manifestations, mechanisms, and management. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2022: https://www.uptodate.com. Accessed 2022 Oct 20.
4. Henricks LM, Opdam FL, Beijnen JH, Cats A, Schellens JHM. DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update. *Ann Oncol.* 2017;28(12):2915-2922. PubMed
5. Padegimas A, Carver JR. How to diagnose and manage patients with fluoropyrimidine-induced chest pain. *JACC CardioOncol.* 2020;2(4):650-654. PubMed
6. DPYD genotyping in patients who have planned cancer treatment with fluoropyrimidines: a health technology assessment. *Ont Health Technol Assess Ser.* 2021;21(14):1-186. PubMed
7. Tomudex® (raltitrexed): lyophilized powder, 2 mg raltitrexed per vial, intravenous injection [product monograph]. Kirkland (QC): Pfizer Canada; 2021 Dec 7: https://pdf.hres.ca/dpd_pm/00063865.PDF. Accessed 2022 Oct 31.
8. Madakadze C, Premji Z, Bailey S. Raltitrexed in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. *(CADTH reference list)*. Ottawa (ON): CADTH; 2022: https://www.cadth.ca/raltitrexed-patients-dihydropyrimidine-dehydrogenase-dpd-deficiency. Accessed 2022 Oct 20.
9. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. PubMed
10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. PubMed
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34. PubMed
12. Kelly C, Bhuva N, Harrison M, Buckley A, Saunders M. Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. *Eur J Cancer.* 2013;49(10):2303-2310. PubMed
13. Gallois C, Hafliger E, Auclin E, et al. First-line chemotherapy with raltitrexed in metastatic colorectal cancer: an Association des Gastro-enterologues Oncologues (AGEO) multicentre study. *Dig Liver Dis.* 2022;54(5):684-691. PubMed
14. Batra A, Rigo R, Hannouf MB, Cheung WY. Real-world safety and efficacy of raltitrexed in patients with metastatic colorectal cancer. *Clin Colorectal Cancer.* 2021;20(2):e75-e81. PubMed
15. Khan K, Rane JK, Cunningham D, et al. Efficacy and cardiotoxic safety profile of raltitrexed in fluoropyrimidines-pretreated or high-risk cardiac patients with GI malignancies: large single-center experience. *Clin Colorectal Cancer.* 2019;18(1):64-71.e61. PubMed
16. Ransom D, Wilson K, Fournier M, et al. Final results of Australasian Gastrointestinal Trials Group ARCTIC study: an audit of raltitrexed for patients with cardiac toxicity induced by fluoropyrimidines. *Ann Oncol.* 2014;25(1):117-121. PubMed
17. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. Bethesda (MD): U.S. Department of Health and Human Sciences; 2017: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 2022 Oct 21.
18. ECOG Performance Status Scale. Philadelphia (PA): ECOG-ACRIN cancer research group; 2022: https://ecog-acrin.org/resources/ecog-performance-status/. Accessed 2022 Oct 19.

Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Kelly et al. (2013)[12] UK **Funding source:** Hospira UK Ltd	**Study designs:** Unclear; appears to include randomized trials and non-randomized studies **Number of included studies:** 23 in total; 3 relevant to the present review (reported by review authors to be case studies)	NR	**Eligible interventions:** 5-FU, capecitabine, raltitrexed **Relevant intervention:** Raltitrexed **Comparators**: 5-FU or capecitabine **Relevant comparator:** 5-FU (alone, with leucovorin, or with oxaliplatin)	**Outcome:** Cardiac adverse events **Follow-up:** NR

5-FU = 5-fluorouracil; NR = not reported.

Table 3: Characteristics of Included Non-Randomized Studies

Study citation, country, funding source	Study design	Population characteristics	Relevant intervention and comparator(s)	Relevant clinical outcomes, length of follow-up

Gallois et al. (2022)[13]
France
Funding source: No specific funding received for this report
	Retrospective multicentre study with data since 2006	Patients with metastatic colorectal cancer (N = 75)
		• Subgroup relevant for this report: patients with a history of fluoropyrimidine-induced cardiotoxicity (n = 36)
		Characteristics of relevant subgroup (N = 36):
		• Mean age, years: 65.4
		• WHO-PS 0 to 1 rate: 94%
		Characteristics of full sample (N = 75):
		• Male, n (%): 51 (68)
		• Location of primary tumour, n (%):
		  ◦ Right colon: 20 (27)
		  ◦ Right + left colon: 3 (4)
		  ◦ Transverse colon: 2 (3)
		  ◦ Left colon: 48 (66)
		• Median serum CEA, ng/mL (range): 15 (0 to 2,169)
			Intervention: Raltitrexed, single-agent or combination chemotherapy; combinations were raltitrexed with:
			• oxaliplatin
			• irinotecan
			• bevacizumab
			• oxaliplatin and bevacizumab
			• irinotecan and bevacizumab
			<u>From entire sample:</u>
			• Mean number of cycles (SD): 7.9 (5.1)
			• Dosage: 3 mg/m^2 every 3 weeks or 2.5 mg/m^2 every 2 weeks
			Comparators:
			• Fluoropyrimidines (before-after)
			• No comparator
				Outcomes:
				• Overall survival
				• Progression-free survival
				• Cardiac adverse events
				Median follow-up from full sample, months (95% CI): 51.3 months (41.9 to not reached); until death or last follow-up

Study citation, country, funding source	Study design	Population characteristics	Relevant intervention and comparator(s)	Relevant clinical outcomes, length of follow-up
Batra et al. (2021)[14] Canada **Funding source:** NR	Retrospective, population-based review of provincial administrative data from 2004 to 2018	Patients with metastatic colorectal cancer, initially treated with fluoropyrimidine-based systemic therapy and developed serious cardiac and/or non-cardiac adverse events (N = 86) • Cardiac events (n = 32, 37.6%) • Non-cardiac events (n = 64, 63.4%) Median age, years (IQR): 66.5 (42 to 86) Male patients, n (%): 50 (58.1%) Primary cancer site, n (%): • Left colon: 33 (38.4) • Transverse colon: 5 (5.8) • Right colon: 24 (27.9) • Rectum: 21 (24.4) Previous lines of systemic therapy, n (%): • 1 or 2: 49 (57.0) • > 2: 37 (43.0) ECOG performance status (N = 84), n (%): • 0 or 1: 68 (81.0) • 2 or 3: 16 (19.0) Median serum CEA (N = 26), ug/L (IQR): 35.5 (5.4 to 470)	**Intervention:** Raltitrexed (single-agent or combination with irinotecan) • 1 patient received combination; all other patients received raltitrexed alone • Median number of cycles (range): 3 (1 to 23) • Dose: 3 mg/m^2 every 3 weeks (except 1 patient who received raltitrexed and irinotecan) **Comparators:** • Fluoropyrimidines (before-after) • No comparator	**Outcomes:** • Overall survival • Progression-free survival • Adverse events (cardiac and non-cardiac) • Treatment-related deaths **Median follow-up, months:** 46.7

Khan et al. (2018)[15]
UK
Funding source: Unclear; reported support and research funding received by authors, but unclear which funding sources supported this study.
	Retrospective single-centre cohort study with data from 1998 to 2011	Patients with gastrointestinal cancer (N = 247)
		• Subgroup relevant for this report: patients who had cardiac side effects following 5-FU or capecitabine (n = 155)
		Characteristics of full sample (N = 247):
		• Female, n (%): 179 (72.5)
		• Mean age (range), years: 65.5 (31 to 88)
		• Type of cancer, n (%):
		  ◦ Upper GI: 75 (30.4)
		  ◦ Lower GI: 162 (65.6)
		  ◦ Miscellaneous: 10 (4.0)
		  ◦ Early-stage: 140 (56.7)
		  ◦ Advanced metastatic: 107 (43.3)
			Intervention: Raltitrexed (single-agent or combination chemotherapy; combinations not reported)
			• Median number of cycles (range) from subgroup: 5 (1 to 8)
			<u>From entire sample:</u>
			• Approximately 31% and 68% received single-agent and combination respectively
			• Standard dose: 3 mg/m^2 as a 15-minute infusion; 22% received reduced doses (1.3 to 2.8 mg/m^2); 44% received higher doses (3.10 to 6.60 mg/m^2)
				Outcome: Cardiac adverse events
				Median follow-up (IQR), months from full sample: 47.1 (32.4 to 65.7)

Study citation, country, funding source	Study design	Population characteristics	Relevant intervention and comparator(s)	Relevant clinical outcomes, length of follow-up
			Comparator: Fluoropyrimidines (5-FU- or capecitabine-containing chemotherapy; before-after)	
Ransom et al. (2014)[16] Australia **Funding source:** Astra Zeneca	Retrospective multicentre review of pharmacy and medical records from 2004 to 2012	Patients with cancer who had cardiac toxicity with 5-FU or capecitabine (N = 42) Median age (range), years: 62 (36 to 81) Patients by type and stage of cancer at time of initiating raltitrexed, n: • Colorectal (stage II or III): 14 • Colorectal (stage IV): 25 • Esophageal (stage II or IV): 2 • Ampullary (stage IV): 1	**Intervention:** Raltitrexed (single agent [N = 11] or combination [N = 31]) • Combination was usually with irinotecan or oxaliplatin • Median number of cycles (range): 6 (1 to 21). **Comparator**: Fluoropyrimidines (5-FU or capecitabine, alone or combination; historical control)	**Outcome:** Rate of further cardiac events attributed to chemotherapy **Follow-up:** up to 30 days after last dose of raltitrexed

Kelly et al. (2013)[12]
UK
Funding source: Unclear; mentions financial support from Hospira UK Ltd., but unclear if this was for conducting the study or for editorial assistance
	Retrospective review of medical records at 2 treatment centres from 2008 to 2011	Patients with gastrointestinal tumours (N = 111):
		• Subgroup relevant for this report: patients who experienced vascular complications associated with 5-FU or capecitabine (n = 63)
		  ◦ Cardiovascular complications: n = 60
		  ◦ Cerebrovascular complications: n = 3
		Characteristics from full sample (N = 111):
		• Male, n (%): 82 (74%)
		• Median age (range), years: 68 (33 to 85)
		• Type of cancer, n:
		  ◦ Metastatic colorectal: 67
		  ◦ Colorectal, no distant metastases: 40
		  ◦ Anal: 2
		  ◦ Mucinous appendicular: 1
		  ◦ Lower esophageal: 1
			Intervention: Raltitrexed (unclear if single-agent and/or combination)
			Comparator: Fluoropyrimidines (5-FU or capecitabine; before-after)
				Reported outcomes: Cardiovascular or cerebrovascular complications
				Follow-up: NR

5-FU = 5-fluorouracil; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; NR = not reported; WHO-PS: WHO Performance Status.
Note: For serum CEA measurements: ng/mL and ug/L are equivalent.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitations of Systematic Review Using AMSTAR 2[9]

Strengths	Limitations
Kelly et al. (2013)[12]	
• Stated the aim of the review, as well as the population, interventions, and outcomes of interest • Does not appear to have restricted to randomized-controlled trials, as non-randomized studies and case reports have been included • Searched the previous 20 years, and the report was published approximately 2 years after the last search date • Provided their search terms and strategy • Reported authors' conflicts of interest and financial support	• Did not explicitly state that the review methods were published before the conduct of the review • Assessed 1 database, and does not report if they checked published reviews specialized registrars, or grey literature, or if they contacted experts in the field • Search was restricted to articles in English, and authors did not provide a justification for this restriction • Unclear if 2 review authors performed screening, study selection, and/or data extraction; no statement that these were done in duplicate • A list of excluded studies and reasons for exclusion were not provided • Included studies were not described in detail • Risk of bias was not assessed • Sources of funding for the studies was not reported, which may have influenced the studies' reporting • Potential causes of heterogeneity across the studies were not discussed, though this may have been because no adverse events were reported for any identified studies

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[10]

Strengths	Limitations
Gallois et al. (2022)[13]	
• Objective, main outcomes, patient inclusion criteria, patient characteristics, and interventions were clearly described • Main findings were clearly described including the 95% confidence interval and actual p-values where reported • As this is a retrospective review, it is possible that patients were representative of the population of interest and the treatment received was representative of typical treatment • All patients were recruited from the same locations • Statistical tests appear to have been appropriate, including use of survival analysis for survival outcomes • Compliance with the intervention was likely reliable • Main outcome measures were likely accurate and reliable • Reported conflicts of interest and funding	• List of confounders not provided • Unclear if all important adverse events were reported • Unclear if patients who participated in this study were representative of the entire population • Comparisons were within-group (before-after) or no comparator; without between-group comparisons (i.e., without a separate control group that received a different treatment, placebo, or no treatment), the results are susceptible to several types of bias, which may impact internal and external validity; overall, all findings should be interpreted with caution, as uncontrolled factors may have influenced the findings • Unlikely that participants or research staff were blinded to treatment; however, the outcome was objective, so it is

Strengths	Limitations
	unlikely this caused bias • Unclear if subgroup analyses were pre-planned • Patients varied in the number of cycles they received; it is unclear if this could have impacted outcomes, or if this was considered in the analysis • Patients were not randomized to intervention • Unclear if a sample size was calculated
Batra et al. (2021)[14]	
• Objective, main outcomes, patient inclusion criteria, patient characteristics, and interventions were clearly described • Main findings were clearly described including the 95% confidence interval and actual p-values where reported • As this is a retrospective review, it is possible that patients were representative of the population of interest and the treatment received was representative of typical treatment • All patients were recruited from the same locations • Discussed potential causes of heterogeneity in their results • Statistical tests appear to have been appropriate • Compliance with the intervention was likely reliable • Main outcome measures were likely accurate and reliable • Reported no conflicts of interest	• List of confounders not provided • Unclear if all important adverse events were reported • Unclear if patients who participated in this study were representative of the entire population • Unlikely that participants or research staff were blinded to treatment; however, the outcome was objective, so it is unlikely this caused bias • Comparisons were within-group (before-after) or no comparator; without between-group comparisons (i.e., without a separate control group that received a different treatment, placebo, or no treatment), the results are susceptible to several types of bias, which may impact internal and external validity; overall, all findings should be interpreted with caution, as uncontrolled factors may have influenced the findings • Unclear if subgroup analyses were pre-planned • Patients varied in the number of cycles they received; it is unclear if this could have impacted outcomes, or if this was considered in the analysis • Patients were not randomized to intervention • Unclear if a sample size was calculated, though this was a population-based study • Did not report funding
Khan et al. (2019)[15]	
• Objective, main outcomes, patient inclusion criteria, patient characteristics, and interventions were clearly described • Main results were clearly described including the 95% confidence interval and actual p-values where reported • As this is a retrospective review, it is possible that patients were representative of the population of interest and the treatment received was representative of typical treatment • All patients were recruited from the same locations • Statistical tests appear to have been appropriate, including use of survival analysis for survival outcomes • Compliance with the intervention was likely reliable • Main outcome measures were likely accurate and reliable • Reported conflicts of interest	• Subgroup comparisons did not report the 95% confidence interval • List of confounders not provided • Unclear if all important adverse events were reported • Unclear if patients who participated in this study were representative of the entire population • Unlikely that participants or research staff were blinded to treatment; however, the outcome was objective, so it is unlikely this caused bias • Comparisons were within-group (before-after); without between-group comparisons (i.e., without a separate control group that received a different treatment, placebo, or no treatment), the results are susceptible to several types

Strengths	Limitations
	of bias, which may impact internal and external validity; overall, all findings should be interpreted with caution, as uncontrolled factors may have influenced the findings • Unclear if subgroup analyses were pre-planned • Patients varied in the number of cycles they received; it is unclear if this could have impacted outcomes, or if this was considered in the analysis • Patients were not randomized to intervention • Unclear if a sample size was calculated • Unclear reporting of funding
Ransom et al. (2014)[16]	
• Objective, main outcome, patient inclusion criteria, and interventions were clearly described • Main findings were clearly described including the 95% confidence interval and actual P value • As this is a retrospective review, it is possible that patients included in this study were representative of the population of interest and that the treatment received was representative of typical treatment • All patients appear to have been recruited from the same locations (participating centres) • No retrospective unplanned subgroup analyses were reported • Compliance with the intervention was likely reliable • Main outcome measure was likely accurate and reliable • Reported source of funding and no conflicts of interest	• Patient characteristics not well-described other than type of cancer and risk of cardiac event; missing age, sex, and so forth • List of confounders not provided • Unclear if all important adverse events were reported • Unclear if patients who participated in this study were representative of the entire population • Unlikely that participants or research staff were blinded to treatment; however, the outcome was objective, so it is unlikely this caused bias • Comparisons were within-group (before-after); without between-group comparisons (i.e., without a separate control group that received a different treatment, placebo, or no treatment), the results are susceptible to several types of bias, which may impact internal and external validity; overall, all findings should be interpreted with caution, as uncontrolled factors may have influenced the findings • Follow-up was up to 30 days after the last dose of raltitrexed, but patients varied in the number of cycles they received; it is unclear if this could have impacted outcomes, or if this was considered in the analysis • Statistical test used was not described • Analysis did not appear to adjust for confounding • Patients were not randomized to intervention • Unclear if a sample size was calculated
Kelly et al. (2013)[12]	
• Objective, main outcomes, patient inclusion criteria, patient characteristics, and interventions were clearly described • As this is a retrospective review, it is possible that patients were representative of the population of interest and the treatment received was representative of typical treatment • All patients were recruited from the same locations • Compliance with the intervention was likely reliable	• Main findings were not reported in detail, and did not present 95% confidence intervals or p-values as no statistical analyses were conducted • List of confounders not provided; unclear if these results may be biased due to confounding • Unclear if all important adverse events were reported • Unclear if patients who participated in this study were representative of the entire population

Strengths	Limitations
• Main outcome measures were likely accurate and reliable • Reported conflicts of interest	• Unlikely that participants or research staff were blinded to treatment; however, the outcome was objective, so it is unlikely this caused bias • Comparisons were within-group (before-after); without between-group comparisons (i.e., without a separate control group that received a different treatment, placebo, or no treatment), the results are susceptible to several types of bias, which may impact internal and external validity; overall, all findings should be interpreted with caution, as uncontrolled factors may have influenced the findings • Number of cycles and follow-up length were not reported • Patients were not randomized to intervention • Unclear if a sample size was calculated • Unclear reporting of funding

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 6: Summary of Findings by Outcome — Survival

Outcome	Gallois et al. (2022),[13] NRS	Batra et al. (2021),[14] NRS				
		All patients	By type of cancer		By side of colon cancer	
			Colon	Rectal	Right-sided	Left-sided
Overall survival						
Overall survival (months), median	28.3 (95% CI, 22.7 to 48.8)	10.2 (95% CI, 7.5 to 12.6)	9.4	10.6	5.4	18.9
p-value	—	—	0.369		0.001	
Progression-free survival						
Progression-free survival (months), median	10.6 (95% CI, 7.9 to 18.8)	8.5 (95% CI, 6.6 to 11.3)	8.3	7.5	5.4	17.1
P value	—	—	0.784		0.001	

CI = confidence interval; NRS = non-randomized study; OS = overall survival; PFS = progression-free survival.

Note: Reported outcomes are based on the patients relevant to this report: i.e., patients who experienced serious adverse events (cardiac or non-cardiac) from fluoropyrimidine treatment.

Table 7: Summary of Findings by Outcome — Cardiac and Vascular Adverse Events

Outcome	Gallois et al. (2022),[13] NRS	Batra et al. (2021),[14] NRS	Khan et al. (2018),[15] NRS	Ransom et al. (2014),[16] NRS		Kelly et al. (2013),[12] SR	Kelly et al. (2013),[12] NRS
				Treated	Control [a]		
Number of patients	36	84 [b]	155	42	NA	NR	63
Patients who experienced cardiac events during raltitrexed therapy, n (%)	0	0	8 (5.2)	—	—	0	—
Angina	—	—	3 (1.9)	—	—	—	—
Arrhythmia	—	—	3 (1.9)	1 (2.4) [c]	—	—	—
Palpitations	—	—	1 (< 0.1)	—	—	—	—
Myocardial infarction	—	—	1 (< 0.1)	—	—	—	—
Rate of cardiac events attributed to raltitrexed, % (95% CI)	—	—	—	0 (0 to 8.4)	20% (NA)	—	—
Patients who experienced cardiovascular or cerebrovascular events, n (%)	—	—	—	—	—	—	3 (4.8)

CI = confidence interval; NA = not applicable; NR = not reported; NRS = non-randomized study; SR = systematic review.

Note: Reported number of patients and outcomes are based on the patient relevant to this report: i.e., patients who experienced serious adverse events (cardiac or

non-cardiac) from fluoropyrimidine treatment.

[a]The authors assumed a true rate of cardiac toxicity of 20%: "Current evidence suggests that the rate of cardiac events due to continuing FU [fluoropyrimidines] after initial cardiac event is at least 20%" (p.118).[16]

[b]This study[14] included 86 patients, but adverse outcomes were measured out of 84; it was not clearly reported why 2 patients were excluded from this analysis.

[c]The reported outcome was cardiac toxicity specific to the raltitrexed treatment. One patient experienced arrhythmia; however, the arrhythmia was considered to be unrelated to the raltitrexed (with oxaliplatin) treatment.

Table 8: Summary of Findings by Outcome — Other Adverse Events

Outcome	Severity [b]	Batra et al. (2021),[14] NRS n = 84 [a]				
		Neutropenia	Anemia	Nausea and vomiting	Diarrhea	Transaminitis
Patients who experienced an adverse event, n (%)	All	10 (11.9)	35 (41.7)	23 (27.4)	10 (11.9)	8 (9.5)
	Grade 1	2 (2.4)	19 (22.6)	14 (16.7)	4 (4.8)	2 (2.4)
	Grade 2	6 (7.1)	12 (14.3)	7 (8.3)	3 (3.6)	3 (3.6)
	Grade 3	2 (2.4)	4 (4.8)	2 (2.4)	3 (3.6)	3 (3.6)
	Grade 4	0	0	0	0	0

Notes: Reported number of patients and outcomes are based on the patient relevant to this report: i.e., patients who experienced serious adverse events (cardiac or non-cardiac) from fluoropyrimidine treatment.

[a]This study[14] included 86 patients, but adverse outcomes were measured out of 84; it was not clearly reported why 2 patients were excluded from this analysis.

[b]Severity was graded retrospectively based on the Common Terminology Criteria for Adverse Events, version 5.0.[17] In brief, grade 1 = mild; grade 2 = moderate; grade 3 = severe but not immediately life-threatening; grade 4 = life-threatening and indicates urgent intervention.

Table 9: Summary of Findings by Outcome — Mortality

Outcome	Batra et al. (2021),[14] NRS	Khan et al. (2018),[15] NRS	Ransom et al. (2014),[16] NRS	Kelly et al. (2013),[12] NRS
Number of patients	84 [a]	155	42	63
Treatment-related deaths, n (%)	0	0 [b]	NR	0
Deaths considered to be unrelated to treatment, n	—	—	1 [c]	Unclear [d]

NA = not applicable; NR = not reported; NRS = non-randomized study.

Note: Reported outcomes are based on the patient relevant to this report: i.e., patients who experienced serious adverse events (cardiac or non-cardiac) from fluoropyrimidine treatment.

[a]This study[14] included 86 patients, but adverse outcomes were measured out of 84; it was not clearly reported why 2 patients were excluded from this analysis.

[b]Reported outcome was fatal myocardial infarction: while 1 patient experienced a myocardial infarction associated with raltitrexed, it was not fatal.

[c]One patient experienced arrhythmia and died due to peritonitis; however, the arrhythmia was considered to be due to sepsis, and unrelated to the raltitrexed (with oxaliplatin) treatment.

[d]From the entire sample, 4 patients died, though it is unclear how many were from the subgroup of interest. All 4 patients were noted to have had progressive disease and death was likely disease-related.

Appendix 5: References of Potential Interest

Previous CADTH Reports

Madakadze C, Premji Z, Bailey S. Raltitrexed in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. (CADTH reference list). Ottawa (ON): CADTH; 2022: https://www.cadth.ca/raltitrexed-patients-dihydropyrimidine-dehydrogenase-dpd-deficiency. Accessed 2022 Oct 5.

Non-Randomized Studies

Mixed Population – Patients Refractory or Intolerant to Fluoropyrimidine

Li X, Shen J, Xia F, Zhu J. Efficacy and safety of radiotherapy combined with raltitrexed and irinotecan for treating unresectable recurrent colorectal cancer: a single-arm phase II trial. *J Gastrointest Oncol*. 2022 Jun;13(3):1112-1120. PubMed

Case Series and Reports

Cucciniello L, Bidoli E, Viel E, Canale ML, Gerratana L, Lestuzzi C. The puzzling clinical presentation of fluoropyrimidines cardiotoxicity. *Front*. 2022;9:960240. PubMed

Winquist LE, Sanatani M, Kim RB, Winquist E. Near miss or standard of care? DPYD screening for cancer patients receiving fluorouracil. *Curr Oncol*. 2021 February;28(1):94-97. PubMed