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Raltitrexed in Patients With Dihydropyrimidine Dehydrogenase Deficiency

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Key Messages

- We found 3 non-randomized studies about the clinical effectiveness of raltitrexed in patients with complete dihydopyrimidine dehydrogenase deficiency.
- We found 4 non-randomized studies about the safety of raltitrexed in patients with complete dihydropyrimidine dehydrogenase deficiency.

Research Questions

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

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, 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 the retrieval by study type. Comments, newspaper articles, editorials, letters, and conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was completed on August 30, 2022, and was limited to English-language documents published since January 1, 2012. Internet links were provided, where available.

Selection Criteria

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed.

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/intolerance.
Intervention	Raltitrexed
Comparator	Q1 and Q2: No comparator, 5-FU, capecitabine

Criteria	Description
Outcomes	Q1: Effectiveness (e.g., progressive 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; Q = question.

Results

Three non-randomized studies[1-3] were identified regarding the clinical effectiveness of raltitrexed in patients with complete dihydropyrimidine dehydrogenase deficiency. Four non-randomized studies[1-4] were identified regarding the safety of raltitrexed in patients with complete dihydropyrimidine dehydrogenase deficiency. No relevant health technology assessments, systematic reviews, or randomized controlled trials were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

References

Health Technology Assessments

No literature identified.

Systematic Reviews

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

1. 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*. 05 2022; 54(5): 684-691. PubMed
2. Batra A, Rigo R, Hannouf MB, Cheung WY. Real-world safety and efficacy of raltitrexed in patients with metastatic colorectal cancer. *Clin Colorectal Cancer*. 06 2021; 20(2): e75-e81. PubMed
3. 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*. 03 2019; 18(1): 64-71.e1. PubMed
4. 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*. Jan 2014; 25(1): 117-21. PubMed

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Appendix 1: References of Potential Interest

Systematic Review

Unclear Methodology

5. 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*. Jul 2013; 49(10): 2303-10. PubMed

Randomized Controlled Trials

Mixed Population- Patients who Were Refractory or Intolerant to Non-Raltitrexed Treatment

6. Ghiringhelli F, Vincent J, Bengrine L, et al. Hepatic arterial chemotherapy with raltitrexed and oxaliplatin versus standard chemotherapy in unresectable liver metastases from colorectal cancer after conventional chemotherapy failure (HEARTO): a randomized phase-II study. *J Cancer Res Clin Oncol*. Sep 2019; 145(9): 2357-2363. PubMed

Non-Randomized Studies

Mixed Population — Patients who Were Refractory or Intolerant to Non-Raltitrexed Treatment

7. 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*. Jun 2022; 13(3): 1112-1120. PubMed

Patients Resistant to 5-FU

8. Chen Y, Wu J, Cheng K, et al. S-1 plus raltitrexed for refractory metastatic colorectal cancer: a phase II trial. *Oncologist*. 05 2019; 24(5): 591-e165. PubMed

Review Articles

9. Vaflard P, Ederhy S, Torregrosa C, Andre T, Cohen R, Lopez-Trabada D. Fluoropyrimidines cardiac toxicity: 5-fluorouracil, capecitabine, compound S-1 and trifluridine/tipiracil. *Bull Cancer*. July - August 2018; 105(7-8): 707-719. PubMed

10. Zhao C, Zhang H, Ye Y, Sun J, Li P. Meta-analysis of TOMOX versus FOLFOX regimens for the treatment of advanced colorectal cancer. *Int J Clin Exp Med*. 30 Mar 2016; 9(3): 5616-5629. Available from: https://e-century.us/files/ijcem/9/3/ijcem0021268.pdf. Accessed 2022 Sep 6.