INAHTA Briefs

Issue 2010/089

Title **The Use of Irinotecan, Oxaliplatin and Raltitrexed for the Treatment of Advanced Colorectal Cancer: Systematic Review and Economic Evaluation (Review of NICE Guidance No. 33)**

Agency **NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre**
Alpha House, University of Southampton Science Park, Southampton, SO16 7NS, United Kingdom;
Tel: +44 2380 595 586, Fax: +44 2380 595 639; hta@soton.ac.uk, www.hta.ac.uk

Reference Volume 12.15. ISSN 1366-5278. www.hta.ac.uk/project/1432.asp

Aim

To evaluate 3 technologies for managing advanced colorectal cancer: 1) first-line irinotecan combination (with 5-fluorouracil [5-FU]) or second-line monotherapy; 2) first- or second-line oxaliplatin combination (again, with 5-FU); and 3) raltitrexed, where 5-FU is inappropriate.

To examine the role of irinotecan and oxaliplatin in reducing the extent of incurable disease before curative surgery (downstaging).

Conclusions and results

Treatment with 3 active therapies appears most clinically effective and cost effective. NHS routine data could be used to validate downstaging findings, and a meta-analysis using individual patient-level data is suggested to validate the optimal treatment sequence. We found 17 trials of varying methodological quality. Compared to 5-FU, first-line irinotecan improved overall survival (OS) by 2 to 4 months ($p = 0.0007$), progression-free survival (PFS) by 2 to 3 months ($p < 0.00001$), and response rates ($p = 0.001$). It offered a different toxicity profile and no quality of life (QoL) advantage. However, second-line irinotecan compared with 5-FU improved OS by 2 months ($p = 0.035$) and PFS by 1 month ($p = 0.03$), and provided a better partial response rate, but with more toxicities and no QoL advantage. Compared to second-line best supportive care, irinotecan improved OS by 2 months ($p = 0.0001$), had a different toxicity profile, and maintained baseline QoL longer, but with no overall difference. Adding oxaliplatin to second-line 5-FU is associated with a borderline significant improvement in overall survival ($p = 0.07$), a significantly higher response rate (<0.0001), and more serious toxicities. There is no evidence of a significant difference in QoL. Schedules with treatment breaks may not reduce clinical effectiveness, but reduce toxicity. The addition of oxaliplatin to second-line 5-FU also saw no improvement in OS ($p = 0.07$), better PFS (by 2.1 months, $p = 0.0001$), an 8.9% higher response rate ($p = 0.0001$), more toxicities, and no QoL advantage. There was no significant difference in OS or PFS between first-line irinotecan and oxaliplatin combinations except when 5-FU was delivered by bolus injection, when oxaliplatin provided better OS ($p = 0.032$) and response rates ($p = 0.032$), but not PFS ($p = 0.169$). The regimens had different toxicity profiles and neither conferred a QoL advantage. When compared to 5-FU, raltitrexed is associated with no significant difference in overall or progression-free survival; no significant difference in response rates; more vomiting and nausea, but less diarrhea and mucositis; no significant difference in, or worse, QoL. Raltitrexed treatment was cut short in 2 of 4 trials due to excess toxic deaths. 5-FU followed by irinotecan was inferior to any other sequence. First-line irinotecan/5-FU combination improved OS and PFS, although further unplanned therapy exaggerated the OS effect size. See Executive Summary link at www.hta.ac.uk/project/1432.asp.

Recommendations

Treatment with 3 active therapies appears to be most clinically effective and cost effective.

Methods

Searches in 10 electronic bibliographic databases identified studies of the effectiveness and economics of the methods. Studies that evaluated any of the indications outlined above were included. Two reviewers independently extracted data and assessed generic components of methodological quality. Survival outcomes were meta-analyzed.

Further research/reviews required

Collection of routine data from within the NHS would help validate the downstaging of people with liver metastasis. A meta-analysis using individual patient-level data is suggested to validate the optimal treatment sequence and to provide a baseline against which future treatment sequences could be compared.

Written by Mr Paul Tappenden, NETSCC, United Kingdom

ISSN 1654-501X