NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG16: Fluorouracil chemotherapy: The My5‑FU assay for guiding dose adjustment

This guidance was issued in December 2014.

The review date for this guidance is December 2017.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Review decision

Transfer the guidance to the ‘static guidance list’.

At the Guidance Executive meeting of 30 January 2018 the proposal to transfer the guidance to the static list was agreed, without consultation. A list of the options that were considered, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Rationale

No changes to the care pathway or the technology have been identified since the publication of diagnostics guidance 16. Further, no evidence has been found through the updated literature searches that will address the research recommendations or materially impact the recommendations made in diagnostics guidance 16. The guidance will therefore be placed on the static guidance list.

3. Implications for other guidance producing programmes

No overlaps have been identified.

4. Original objective of guidance

To assess the clinical and cost effectiveness of the My5-fluorouracil (My5-FU) assay for guiding dose adjustment in patients undergoing fluorouracil chemotherapy.

5. Current guidance

Adoption recommendations

Recommendation 1.1

The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-FU assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice.

Research recommendations

Research recommendation 7.1

The Committee recommended further research to validate the accuracy and precision of the My5-FU assay for the quantitative determination of 5-fluorouracil (5-FU) at the lower end of its measuring range with analytical reference standard methods, including high-performance liquid chromatography and liquid chromatography-mass spectrometry. Studies should investigate the comparability of the methods and determine the clinical significance of discordant results with reference to their impact on subsequent dose adjustments.

Research recommendation 7.2

The Committee recommended that robust evidence be generated to show the clinical effectiveness of pharmacokinetic dose adjustment of continuous infusion 5-FU in people with colorectal cancer. Where possible, studies should consider the differential impact that pharmacokinetic dose adjustment may have on people with DPD (dihydropyrimidine dehydrogenase) deficiency, people with impaired renal or liver function, people whose body surface area is outside the standard range for dosing 5-FU and people with a less favourable performance status. Future studies might also consider the impact of DPD testing in conjunction with pharmacokinetic dose adjustment.

Research recommendation 7.3

The Committee recommended further research to establish optimal target dose ranges for 5-FU plasma levels in people with head and neck cancer, stomach cancer and pancreatic cancer. Future studies should aim to both establish the optimal target dose range for each cancer and quantify its impact on clinical outcomes, taking into account any variation that may occur between different continuous infusion 5-FU regimens.

Research recommendation 7.4

The Committee recommended further research to explore the impact of having continuous infusion 5-FU on patients. Future studies should investigate the experiences of patients having continuous infusion 5-FU and take into account the impact on quality of life. The potential consequences of introducing pharmacokinetic dose adjustment should also be explored.

6. New evidence

Search strategies from the original diagnostics assessment report for the following objectives were re-run to identify relevant new studies published since the date of the original searches (January 2014):

- Objective A – review evidence on the accuracy of the My5-FU assay
- Objective B – review clinical studies of My5-FU based dose adjustment compared with body surface area based dose estimation
- Objective C – review clinical studies of high performance liquid chromatography (HPLC) and/or liquid chromatography-mass spectrometry (LC-MS) based dose adjustment compared with body surface area based dose estimation
- Objective E – review evidence related to the cost of using My5-FU.

Searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. The company was asked to submit all new literature references relevant to My5-FU along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology, but no response was received to repeated requests. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. Details of ongoing and unpublished studies are presented in Appendix 2.

6.1 Technologies

6.1.1 My5-FU (Saladax Biomedical)

Saladax Biomedical was asked to provide information relating to potential changes in the technology, but did not respond. Information on the company's website suggests that there have been no changes to the technology formulations, quality or pricing. Further internet searches suggest that there have been no changes to the CE marking of the technology. Two of the specialist committee members indicated that

they are not aware of any changes to the technology since the publication of diagnostics guidance 16, but that it remains available to the NHS.

6.1.2 Additional technologies

Two of the specialist committee members indicated that they are not aware of any similar technologies that have been introduced or increased in use since the publication of the original guidance. Studies included in the literature search update did not identify any new technologies to measure 5-FU for therapeutic drug monitoring purposes. A stakeholder highlighted the ODPM Protocol test as an alternative to My5-FU. One published study on this test was identified (Boisdron-Celle et al. 2017), however, it did not meet the inclusion criteria for the literature review because the methods section of the paper suggested that the 5-FU was administered as an intravenous bolus.

Another of the specialist committee members indicated that they are aware of DPYD genotyping for identifying people at risk of 5-FU toxicity being introduced, or increasing in use, since publication of diagnostics guidance 16. DPYD genotyping stratifies patients to a recommended starting dose of 5-FU, or indicates that an alternative drug should be used. DPYD genotyping, therefore, does not fulfil the same purpose as the My5-FU assay.

6.2 Clinical practice

Specialist committee members indicated that they are aware of no changes to the management or care pathways relating to guiding dose adjustment of 5-FU or any new or updated guidelines which make reference to the My5‑FU assay. Since diagnostics guidance 16 was published, the NICE guideline on colorectal cancer has been updated and a guideline on cancer of the upper aerodigestive tract has been produced. Neither of these guidelines consider the My5‑FU assay, or any other technology or method, for guiding dose adjustment of 5-FU. No relevant new guidelines were found from any professional societies.

The 2014 update to NICE's guidance on colorectal cancer included new recommendations on surgery and colonic stents in acute large bowel obstruction, and on stage I rectal cancer. These new recommendations are expected to have no effect on the economic model results from the original assessment.

A guideline on the therapeutic drug monitoring of 5-FU is in development by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology.

6.3 New studies

There were 7 studies identified that had been published after the assessment for diagnostics guidance 16 was done. One of these (Patel et al. 2014), was considered

by the committee after consultation on the draft recommendations and therefore is not discussed further. Studies included 2 prospective interventional studies, 2 prospective observational studies, 1 meta-analysis, and 1 cost-effectiveness study.

6.3.1. Diagnostic accuracy of My5-FU (objective A)

None of the studies related to the diagnostic accuracy of My5-FU.

6.3.2. Clinical effectiveness of My5-FU (objective B)

Yang et al. (2016) performed a meta-analysis of individual 5-FU dose adjustment based on pharmacokinetic monitoring compared with the body surface area method in advanced cancers. The authors searched electronic databases up to September 2014 and abstracts presented at the American Society of Clinical Oncology annual meetings held between 2000 and 2014. Five studies were included, 2 of which used OnDose, the former name of the My5-FU assay. In total, there were 654 patients with colorectal cancer or head and neck cancer, of whom 206 were tested using OnDose. Results from the meta-analysis show that pharmacokinetic monitoring of 5-FU therapy was associated with a significant improvement in overall response rate (odds ratio [OR] 2.04, 95% confidence interval [CI] 1.41 to 2.95, p=0.0002) compared with the body surface area dosing. There was no evidence of improved tolerability: grade 3 to 4 diarrhoea, neutropenia, and hand-foot syndrome were not significantly different, but mucositis occurred less often with pharmacokinetic monitored 5-FU dosing (OR 0.16, 95% CI 0.04 to 0.63, p=0.009).

6.3.3. Clinical effectiveness of HPLC and/or LC-MS for monitoring 5-FU (objective C)

None of the studies reported on the clinical effectiveness of HPLC and/or LC-MS for monitoring plasma levels of 5-FU.

6.3.5. Economic evidence (objective E)

Goldstein et al. (2014) developed a Markov model to evaluate the cost effectiveness of 5-FU pharmacokinetic guided FOLFOX (5-FU, leucovorin, and oxaliplatin) compared with body surface area guided FOLFOX in people with metastatic colorectal cancer. Data for the 5-FU pharmacokinetic dosing arm were based on Capitain et al. (2012). Data for the body surface area dosing arm were based on Tournigand et al. (2004). Risk of progression and cause-specific mortality were extrapolated from fitted survival models. Costs were estimated from 2013 Medicare reimbursement rates and mean sale prices. 5-FU pharmacokinetic guided FOLFOX resulted in 2.03 QALYs at a cost of $50,205 compared with body surface area guided FOLFOX, which gave 1.46 QALYs at a cost of $37,173. The incremental cost-effectiveness ratio (ICER) was $22,695 per QALY gained. The ICER stayed below $50,000 per QALY in all univariate and multivariate sensitivity analyses. The authors concluded that at a $50,000 per QALY threshold, 5-FU pharmacokinetic

guided FOLFOX is cost effective in metastatic colorectal cancer. They suggested that it should be evaluated further in comparative effectiveness studies.

6.3.6 Other evidence

The remaining 4 papers met the inclusion criteria, but did not fall under objectives A, B, C or E.

Denda et al. (2016) evaluated the efficacy and safety of pharmacokinetic dose adjustment of 5-FU using the My5-FU assay, in a modified FOLFOX7 plus bevacizumab regimen in 48 people with metastatic colorectal cancer. In the first cycle the target concentration was achieved in 29 people (60%). In the fourth cycle the target concentration was achieved in all 48 people (100%). The overall frequency of grade 3 and 4 adverse effects was 38%, with no significant difference between patients who did and did not require dose adjustments. The overall response rate was 48% (95% CI 34 to 62%). The median progression-free and overall survival rates were 11.3 and 24.1 months, respectively.

Ma et al. (2016) established a 5-FU treatment model based on pharmacokinetic and pharmacodynamic analyses of 5-FU in 122 people with nasopharyngeal carcinoma. Patients had 5-FU plus cisplatin treatment based on body surface area dosing. Pharmacokinetic analyses showed a wide (sevenfold) variability of 5-FU exposure, and that the 5-FU exposure had a significant impact on disease response and adverse events. Patients with low 5-FU exposure had a reduced overall response rate compared with patients with higher 5-FU exposure. In addition, patients with high 5-FU exposure experienced more 5-FU-related toxicities than patients with low 5-FU exposure. The authors concluded that the therapeutic window of 5-FU was 25–35 mg x h/L (milligram hours per litre).

Wilhelm et al. (2016) used the My5-FU assay to adjust 5-FU dosing in 75 people with metastatic colorectal cancer. Initial 5-FU dosing was based on body surface area. Subsequent 5-FU doses were adjusted according to the previous cycle's 5-FU exposure. At the first administration, 64%, 33%, and 3% of the patients were below, in, or above the target 5-FU exposure range, respectively. By the fourth administration, 54% of patients were in the target 5-FU exposure range. The incidence of 5-FU related grade 3 and 4 diarrhoea (4.6%), nausea (3.4%), fatigue (0.0%), and mucositis (0.2%) was reduced compared with historical data, despite 55% of patients receiving increased doses.

Levi et al. (2017) studied the pharmacokinetics of irinotecan, oxaliplatin and 5-FU, using HPLC, during a hepatic artery chronomodulated infusion chemotherapy schedule in 11 patients. The HPLC results were not used to change the chemotherapy drug administration. Plasma concentrations of 5-FU were determined at five timepoints, including baseline. Trends were found between levels of irinotecan, SN38 (a bioactive metabolite), total oxaliplatin and platinum ultrafiltrate

and leukopenia severity. Levels of platinum ultrafiltrate were predictive of diarrhoea and anaemia.

6.3.7. Ongoing trials

Appendix 2 lists potentially relevant ongoing trials that have an objective of monitoring the pharmacokinetics of 5-FU and adjusting doses to optimise exposure. Other ongoing studies were identified that listed the pharmacokinetic profile of 5-FU as an outcome, but they focused on dose finding or safety of new cancer treatments rather than optimisation of 5-FU treatment, and therefore these studies were not included.

7. Summary of new evidence and implications for review

No evidence was found which could have a material impact on the guidance recommendations. Seven studies have been published since the original assessment was done, but they do not relate to any of the research recommendations made in diagnostics guidance 16. In particular, no studies have validated the accuracy and precision of the My5-FU assay for the quantitative determination of 5-FU at the lower end of its measuring range and it is therefore unlikely that this uncertainty can be addressed at present. There do not appear to have been any changes to the technology or its acquisition cost since diagnostics guidance 16 was published.

8. Implementation

Clinical experts indicated that they are not aware of any NHS use of the My5-FU assay since the publication of diagnostics guidance 16.

9. Equality issues

No new equality issues have been identified since the publication of the guidance.

Paper sign off by: Mark Campbell, Acting Programme Director – Devices and Diagnostics, February 2018

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to when data from	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

Suspected cancer: recognition and referral (2017) NICE guideline NG12

Colorectal cancer: diagnosis and management (2011) NICE guideline CG131 (updated 2014)

Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (2016) NICE guideline NG36

In progress

Oesophago-gastric cancer. NICE guideline. Publication expected January 2018.

Pancreatic cancer: diagnosis and management in adults. NICE guideline. Publication expected January 2018.

End of life care for adults in the last year of life: service delivery. NICE guideline. Publication expected July 2018.

Colorectal cancer: diagnosis and management (update). NICE guideline. Publication expected October 2019

Cancer of the upper aerodigestive tract (update NG36) NICE guideline. Publication date to be confirmed.

Referred - QSs and CGs

None identified

Suspended/terminated

None identified

Registered and unpublished trials

Trial name and registration number	Details
Evaluation of chemotherapy efficacy and toxicity of 5-Fluoruracil by conventional dosage and pharmacokinetic dosing for Chinese gastrointestinal patients Chinese Clinical Trial Registry identifier: ChiCTR-TRC-14004328	Observation of pharmacological parameters by monitoring blood 5-FU dosing in Chinese people with late or advanced gastrointestinal tumours (gastric, colorectal cancer). Validation of the correlation with 5-FU toxicity and efficacy of pharmacological parameters, in order to establish the therapeutic window of 5-FU for Chinese people. Identification of gene polymorphisms of key enzymes for 5-FU activity. Administration of individualized chemotherapy based on therapeutic drug monitoring and gene polymorphisms. Estimated completion date: October 2017
Retrospective Evaluation of 5-FU Exposure Optimization in CRC Patients Clinicaltrials.gov identifier: NCT02055560	Sponsored by Saladax Biomedical. The primary objective of this study is to evaluate whether the management of colorectal cancer with 5-FU exposure optimisation testing reduces 5-FU related toxicities and improves outcomes compared to the current standard of care. Secondary objectives are: to characterize the variability of 5-FU levels in people with colorectal cancer who have dose adjustment based on 5-FU exposure optimization testing; to record the impact of such management on 5-FU plasma levels and drug doses during the course of chemotherapy. Estimated completion date: December 2017

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