Fluorouracil plasma monitoring: systematic review and economic evaluation of the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion

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Declared competing interests of authors: Aileen Clarke is a member of the National Institute for Health Research Health Technology Assessment and Efficacy and Mechanism Evaluation Editorial Board and the Warwick Medical School receive payment for this work. Aileen Clarke and Sian Taylor-Phillips are partially supported by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West Midlands at the University Hospitals Birmingham NHS Foundation Trust.

Published November 2015
DOI: 10.3310/hta19910

Scientific summary

The My5-FU assay for guiding dose adjustment

Health Technology Assessment 2015; Vol. 19: No. 91
DOI: 10.3310/hta19910

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Scientific summary

Introduction

5-Fluorouracil (5-FU) is used as a treatment in a variety of cancers including colorectal, head and neck (H&N), pancreatic and stomach cancers. This study investigates a method of pharmacokinetic (PK) adjustment of 5-FU plasma levels – My5-FU. Plasma levels are measured using My5-FU during a cycle of 5-FU chemotherapy and the dose of 5-FU for the subsequent cycle(s) is estimated. My5-FU testing can be performed on automated clinical chemistry analysers present in standard clinical laboratories.

Pharmacokinetic dose adjustment is thought to be needed as wide variations have been found between patients in 5-FU concentrations when treated with standard dosing regimens based on body surface area (BSA). Commonly reported side effects of 5-FU include anaemia, thrombocytopenia, leucopenia, nausea/vomiting, diarrhoea, mucositis and hand and foot syndrome. Estimation of plasma 5-FU using PK dose adjustment with an appropriate algorithm are required three of four times per patient in order to achieve target plasma levels. Dosage changes are more common with PK than with BSA methods.

The assessment of 5-FU with My5-FU is proposed to bring plasma 5-FU more closely into the therapeutic range resulting in fewer side effects and better patient outcomes.

Objectives

(a) Provide a review of studies examining the accuracy of the My5-FU assay when tested against gold standard methods of estimation of 5-FU or which develop a treatment algorithm based on plasma 5-FU measures. [High-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) are considered the gold standard.]
(b) Systematically review the literature on the use of My5-FU to achieve adjusted dose regimen(s) compared with BSA-based dose adjustment for patients receiving 5-FU administered by continuous infusion. Variations in current BSA-based dose regimens are considered where appropriate.
(c) Systematically review the literature on the use of HPLC and/or LC-MS to achieve dose adjustment to compare it with BSA-based dose regimens for patients receiving 5-FU. This is undertaken for the purpose of performing a linked evidence analysis (where clinical outcome evidence is available from PK dose adjustment studies which employ an alternative to My5-FU).
(d) Provide an overview of systematic reviews of clinical outcomes in studies of 5-FU administered by continuous infusion in cancer treatment in order to assess the generalisability of outcomes reported in the control arms of studies included in a and c above.
(e) Identify evidence relevant to the costs of using My5-FU:

- cost of My5-FU testing
- cost of delivering 5-FU
- cost of side effects and 5-FU toxicity and associated treatment or hospitalisation.

Clinical effectiveness summary methods

We investigated the following decision problem:

- *Population* Cancer patients (colorectal, H&N, stomach, pancreatic) receiving 5-FU chemotherapy by continuous venous infusion.
- *Intervention* My5-FU (PK monitoring).
  Including a linked evidence analysis using studies of HPLC and LC-MS to adjust 5-FU dosing.
- *Comparator* BSA.
- *Outcome* Performance of My5-FU [e.g. correlation between My5-FU and 'gold standard' in terms of progression-free survival (PFS), overall survival (OS) and adverse events].
- *Setting* Adjuvant and/or metastatic.

We searched MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; The Cochrane Library; Science Citation Index and Conference Proceedings (Web of Science); National Institute for Health Research Health Technology Assessment programme; PROSPERO (International Prospective Register of Systematic Reviews) between January and April 2014. Current Controlled Trials; ClinicalTrials.gov; UK Clinical Research Network Portfolio Database; World Health Organization International Clinical Trials Registry Platform were also searched.

Two reviewers independently screened titles and abstracts of all records with discrepancies resolved through discussion. Quality assessment was undertaken using the Downs and Black checklist. An adapted quality assessment of diagnostic accuracy studies checklist was used for assessing studies of laboratory measurements of analytic validity. Kaplan–Meier plots were reconstructed for PFS and OS for comparison of BSA and PK dosing in two regimens. Clinical advisors and a relevant laboratory gave us information on clinical pathways and My5-FU assay requirements.

Clinical effectiveness results

A total of 3751 records were identified. Two hundred and three remained after removal of duplicates and exclusions and 35 papers were included in the clinical effectiveness review.

Objective A

There was high apparent correlation between My5-FU, HPLC and LC-MS/mass spectometer (MS) but the Bland–Altman plots show considerable variability. In the comparison of My5-FU with LC-MS/MS even with additional outliers listed as excluded, validation data provided by the manufacturer showed outliers with a range of variation up to –285 ng/ml and 171 ng/ml (approximately –25% and 70%). Only one paper reported upper and lower limits of agreement and these were found to be –18% to 30%. These discrepancies between measurements need to be considered carefully. Clinical advisors suggested that this range of values could be considered clinically equivalent; however, we remain cautious about outliers.

Objectives B and C

Evidence on PK versus BSA dosing in the treatment of colorectal cancer (CRC) patients is weak in both quantity and quality. This holds to an even greater extent for H&N cancer. Evidence on My5-FU is sparse. We found one study of clinical outcomes comparing BSA with PK dose adjustment after application of the My5-FU assay; this study was at risk of selection bias. Of three CRC comparative studies identified, only one was a randomised controlled trial (RCT) but this was of an unrepresentative 8-hour infusion regimen. Single-arm studies were heterogeneous, of poor design and limited in conveying useful data for comparison of PK with BSA dosing. There was no published randomised evidence on the effectiveness of PK dose adjustment for any currently used 5-FU regimen for any cancer type. Limited evidence was available to use for cost-effectiveness modelling.

We combined reconstructed individual patient data of single arms from studies from a variety of sources. Overall PK appeared to confer a benefit over BSA in both regimens for which any comparative data were available [5-FU + folinic acid (FA) and FOLFOX6 regimens] in both PFS and OS. Kaplan–Meier plots resulting from single or combined study arms give approximate median OS for FU + FA of 19.6 [95% confidence interval (CI) 17.0 to 21.0] months for PK and 14.6 (95% CI 14.1 to 15.3) months for BSA, and for FOLFOX6 27.4 (95% CI 23.2 to 38.8) months for PK and 20.6 (95% CI 18.4 to 22.9) months for BSA. However, these apparent benefits should be viewed with extreme caution because of the poor quality of the evidence. For both FOLFOX6 and for 5-FU + FA the PK evidence came from single non-randomised studies which failed to provide full data for the comparator arms.

Differing and selective reporting of toxicity outcomes hampered adverse event comparisons. For H&N cancer, only two studies comparing BSA and PK were identified. Both were more than 15 years old and used out-of-date regimens.

Objective D

We concluded that PK studies with full reporting of OS and PFS were consistent with each other and with comparable BSA studies of CRC.

Cost-effectiveness summary methods

Search strategy

A comprehensive search of the literature for published economic evaluations was performed in March and April 2014. Several search strategies were required.

For metastatic colorectal cancer (mCRC) a de novo model cost-effectiveness was developed which compared dose adjustment using My5-FU with BSA dosing. This adopted a 20-year time horizon with a 2-week cycle to reflect FOLFOX cycle length.

A bottom-up costing of the My5-FU assay was undertaken, with laboratory throughputs and staff timings drawn from expert opinion. Costs of chemotherapy were based on expert opinion coupled with drug costs from the Commercial Medicines Unit electronic market information tool, NHS reference costs and values from the literature including a previous model of mCRC.

Parameterised survival curves were drawn from the main comparative papers. As these did not use My5-FU for dose adjustment, a key assumption was the clinical equivalence between My5-FU and HLPC and LS-MS. FOLFOX and 5-FU + FA regimens were analysed and modelled separately. A range of scenario analyses and sensitivity analyses were undertaken. Quality-of-life (QoL) values for the base case were drawn from the literature using European Quality of Life-5 Dimensions data from Finnish CRC patients and the UK social tariff.

For adverse events, QoL impact was estimated using the Medical Research Council Short Course Oncology Therapy trial coupled with additional values from the literature and expert opinion. Costs of adverse events were based on expert opinion coupled with drug tariff medication costs and NHS reference costs.

For H&N cancer an exploratory analysis was undertaken which examined possible drivers of cost-effectiveness and survival hazard ratios (HRs) required to render dose adjustment using My5-FU cost-effective at a willingness to pay (WTP) of £20,000 per quality-adjusted life-year (QALY). For the BSA dosing arm parameterised OS and PFS curves were drawn from the literature. Adverse event rates for PK dose adjustment and for the BSA dosing arm were drawn from the main comparative paper.

Cost-effectiveness summary results

A total of 4578 records were identified through electronic searches. Fifty-four papers were included.

Metastatic colorectal cancer

The base case estimated a cost per completed My5-FU assay of £61.03 and 3.23 assays per patient.

The FOLFOX Weibull survival curves suggested mean undiscounted OS and PFS estimates of 33.8 and 25.1 months, respectively, in the My5-FU arm, compared with 24.5 and 13.2 months in the BSA arm. These estimates are subject to considerable structural uncertainty.

The undiscounted survival gain of 0.77 years coupled with the differences in adverse event rates suggested a gain of 0.599 QALYs from My5-FU dose adjustment. Incremental cost was estimated as £2482, mainly due to the increased survival resulting in higher ongoing costs of monitoring and treatment. The base-case cost-effectiveness estimate was £4148 per QALY. Probabilistic modelling resulted in a similar central estimate with a 100% likelihood of My5-FU being cost-effective at a WTP threshold of £20,000 per QALY.

Cost-effectiveness estimates were reasonably stable as the source of parameterised survival curves was varied. Sensitivity analyses demonstrated that cost-effectiveness estimates were relatively insensitive to laboratory throughputs. Incremental cost-effectiveness ratios (ICERs) varied in the following sensitivity analyses as follows:

- 20% of patients receiving a second 12-week course of chemotherapy after a treatment holiday (£5272 per QALY)
- a dedicated outpatient visit for the blood sample (£4506 per QALY)
- using QoL from a previous National Institute for Health and Care Excellence (NICE) CRC clinical guideline (CG) (£6016 per QALY)
- removing all survival and PFS gains (£435,819 per QALY).

For the 5-FU + FA analyses, Weibull survival curves suggested a mean undiscounted OS of 22.6 and 19.7 months in the My5-FU arm and BSA arms respectively. For the base case a Weibull PFS curve from the literature gave a mean of 7.71 months. Scenario analyses resulted in PFS estimates of 7.46 months for My5-FU and 6.00 months for BSA for one set of assumptions and 12.49 months and 8.27 months for another.

The base case additional undiscounted survival of 0.25 years coupled with the impacts on adverse events resulted in an estimated gain of 0.151 QALYs from My5-FU dose adjustment. Net additional costs of £883 resulted in a cost-effectiveness estimate of £5853 per QALY. Scenario analyses which estimated PFS curves from the limited data reported in the main comparative paper worsened the cost-effectiveness estimates to £6965 and £8615 per QALY depending on assumptions.

The 5-FU + FA analyses gave similar sensitivity analysis results to the FOLFOX analyses. When applying the QoL estimates used in the NICE CRC CG the ICER increased to £17,485 per QALY.

Locally advanced head and neck cancer

There was minimal clinical information to inform the cost-effectiveness modelling for locally advanced H&N cancer.

Hazard ratios of around 0.95 were modelled as justifying the additional cost; however, owing to the lack of evidence this result is extremely speculative.

Discussion and conclusions

A cost-effective testing method for 5-FU levels has been considered for some time to be likely to help in replacing BSA for 5-FU dose management. Although the clinical effectiveness and cost-effectiveness evidence is limited and of poor quality, it seems appropriate to conclude that there may be benefits to PK dose adjustment, including benefits in OS and PFS, and reduction in some adverse events (such as diarrhoea). Although there is apparently good correlation between different assays measuring 5-FU we have some concerns about the clinical significance of the discrepancies found, which may affect the validity of a linked evidence approach.

Our deterministic base-case ICER for use of My5-FU for a 12-cycle FOLFOX regimen for mCRC was £4148 per QALY compared with the standard BSA-based approach. Likewise, exploratory threshold analyses of the cost-effectiveness of My5-FU dose adjustment suggest that HRs of around 0.95 would be sufficient for My5-FU to be cost-effective at a WTP threshold of £20,000 per QALY.

All the cost-effectiveness analyses are based on poor-quality evidence, are inferred from limited data, and as a consequence are subject to considerable uncertainty. This structural uncertainty cannot be reflected in the probabilistic sensitivity analyses, and there are no obvious means of quantifying it. All the cost-effectiveness results require an assumption that My5-FU dose adjustment is clinically equivalent to PK dose adjustment using HPLC and LC-MS and rely on parameterised survival curves. There is therefore considerable uncertainty about their reliability.

Given the finding of cost-effectiveness using a linked evidence approach, practical implementation of My5-FU is a consideration. It will require attention to:

- accurate estimation of plasma 5-FU
- an appropriate algorithm for dose adaptation
- identification of an appropriate target plasma 5-FU level (target range).

Research recommendations

In order to compare PK (My5-FU or other) 5-FU dose adjustment with BSA-based dosing, a trial is required (ideally randomised) which compares intervention and control patients receiving a current relevant 5-FU regimen. Improved data are becoming available (e.g. from the COIN trial) which will help in assessing cost-effectiveness of interventions to improve treatment and survival in CRC. However, given the poor quality of the clinical effectiveness and cost-effectiveness evidence available, there are a number of research needs including:

- well-conducted RCTs of PK versus BSA dosing in:
  - metastatic and adjuvant CRC
  - H&N cancer
  - other cancers where a 5-FU regimen is used
- further in depth assessment of the comparability of different methods of current and any newly-introduced PK dose adjustment
- randomised assessment of different algorithms for adjusting 5-FU dosing
- research on the QALY impact of adverse events of 5-FU which would be of benefit in any further economic assessments.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 13/111/01. The protocol was agreed in December 2013. The assessment report began editorial review in July 2014 and was accepted for publication in December 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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