

Impact case study (REF3b)

Institution: University of Glasgow
Unit of Assessment: Unit 1; Clinical Medicine
Title of case study: Improving tolerability, convenience and cost of bowel cancer chemotherapy
<p>1. Summary of the impact</p> <p>Bowel cancer is the third most frequently diagnosed cancer worldwide. University of Glasgow researchers have established Xeloda (an oral 5-fluorouracil precursor) and XELOX (a chemotherapeutic regimen combining Xeloda with oxaliplatin) as highly effective, targeted therapies for patients with bowel cancer. Since 2008, European regulatory approval of these therapies has been incorporated into major international clinical guidelines. The research has transformed patient care by improving the treatment experience, with more convenient dosing schedules and fewer side effects compared with previous chemotherapy procedures. Xeloda and XELOX have transformed chemotherapy for bowel cancer and decreased therapeutic costs, potentially saving around £4,762 (Xeloda) and £947 (XELOX) per patient for the NHS.</p>
<p>2. Underpinning research</p> <p>Over 40,000 people are diagnosed with bowel cancer in the UK each year. If diagnosed and treated early enough, up to 93% survive for at least 5 years after diagnosis. By contrast, the 5-year survival rate for patients with advanced disease drops to as little as 7%.</p> <p>Until the late 1990s, 5-fluorouracil (5-FU) was the mainstay of post-operative chemotherapy (also known as ‘adjuvant treatment’) for patients with bowel cancer. This fluoropyrimidine targets tumours by inhibiting thymidylate synthase, which is required for cancer-cell growth; the effects of 5-FU can be enhanced by the co-administration of leucovorin (folinic acid). Patients receive 5-FU directly into the bloodstream either by infusion or with an ambulatory in-dwelling pump in repeated lengthy sessions. This treatment schedule requires a costly hospital stay and can cause complications owing to placement of long-term catheters in blood vessels. Thus, the need for a 5-FU-based chemotherapy with improved tolerability, efficacy, patient convenience and cost was identified.</p> <p><i>Roche initiates collaborative research programme with the University of Glasgow</i></p> <p>In the mid-1990s, a major pharmaceutical company Roche — having recognised the University of Glasgow as a world-leader in experimental oncology — established a highly productive collaboration with three of the institution’s medical oncologists, Prof Jim Cassidy, Prof Stan Kaye and Dr Chris Twelves. This collaboration marked the beginning of University of Glasgow-led clinical studies on novel chemotherapeutic options for bowel cancer. In addition to their expertise in both drug development and bowel cancer research, the University of Glasgow had a dedicated pharmacology research programme at that time researching fluoropyrimidines and performing preclinical and early clinical trials, including assessment of pharmacokinetics (bodily absorption, distribution, metabolism and excretion of a drug) and pharmacodynamics (effects of a drug on the body). University of Glasgow researchers identified Roche’s drug development pipeline as an opportunity to take basic research on novel fluoropyrimidines into clinical trials and beyond.</p> <p><i>Xeloda established as a safe and efficient oral targeted therapy for bowel cancer</i></p> <p>The oral fluoropyrimidine Xeloda (generic name, capecitabine) was synthesised by Roche as an alternative to intravenous 5-FU. Once ingested, Xeloda is converted through a three-step process from an inactive precursor to active 5-FU. The final step occurs specifically within the bowel cancer cells owing to the high local expression of the converting enzyme thymidine phosphorylase. This mechanism of activation ensures that 5-FU accumulates within the tumour but much less so in normal surrounding tissues. As such, Xeloda was one of the first targeted therapies for cancer.</p> <p>University of Glasgow researchers were involved in all three key stages of the clinical evaluation of Xeloda (conducted 1995–2006). These trials included assessments of safety, tolerability and recommended dose for use in subsequent clinical trials (phase I, usually fewer than 100 patients); anti-cancer efficacy and safety (phase II, up to several hundred patients); and efficacy compared to</p>

other standard treatment (phase III, several hundred to several thousand patients). The first human phase I trial of Xeloda (published in 1998) was led by the University of Glasgow and enrolled 34 patients at two centres.¹ This trial demonstrated that a daily dose of 2,510 mg/m² was well-tolerated in terms of the number and severity of side effects. Subsequent phase II studies established the efficacy of Xeloda and supported its use as a first-line option for advanced bowel cancer. In 2005, a phase III study (X-ACT, also led by the University of Glasgow) demonstrated that Xeloda was effective for adjuvant treatment of bowel cancer to prevent and delay recurrence in cancer that had been removed at operation.² This study of 1,987 patients reported improved relapse-free survival and fewer side effects in patients who received Xeloda compared with those who were given infusions of 5-FU. The X-ACT study also examined the economic benefits of Xeloda (published in 2006).³ Direct annual healthcare costs (chemotherapy drugs, hospital care, managing side effects) and societal costs (time and travel per patient) were both reduced by £3,608 and £4,925, respectively, when Xeloda was prescribed instead of 5-FU.

XELOX established as a combination therapy for bowel cancer

In the late 1990s and early 2000s, the chemotherapy drug oxaliplatin was developed into a combination therapy with 5-FU (known as 'FOLFOX'). Given their considerable clinical evidence that Xeloda is superior to 5-FU, University of Glasgow researchers led clinical investigation of the novel combination of Xeloda plus oxaliplatin (XELOX) and were the first to demonstrate that these two compounds are tolerable in combination and had a co-operative therapeutic effect.

In light of the University of Glasgow's pivotal role in the early clinical trials of Xeloda, the initial phase I trial of XELOX was led by Prof Jeff Evans, in collaboration with Cassidy (at the University of Aberdeen from 1994, returning to Glasgow in 2002), Jose Baselga (Hospital Vall d'Hebron, Barcelona, Spain) and Eduardo Díaz-Rubio (Hospital Clínico Universitario, Madrid, Spain). The findings of this trial helped to determine the optimum doses and administration schedule of XELOX (2002).⁴ A phase II University of Glasgow led trial that was published in 2004 confirmed the clinical activity of XELOX as a well-tolerated first-line option for metastatic bowel cancer: 55% of patients responded to treatment with measurable shrinkage of their tumours.⁵ A subsequent international multicentre phase III trial (NO16966) with leadership from the University of Glasgow showed that XELOX had comparable efficacy and safety profiles to FOLFOX and established XELOX as a credible therapeutic option for patients with bowel cancer (2008).⁶ Cassidy was the joint global lead on this trial (with Prof. Leonard Saltz, Memorial Sloan Kettering Cancer Centre, USA) as well as acting as the UK Chief Investigator and Principal Investigator for the University of Glasgow, which was one of 17 UK study centres. In addition, Cassidy was the Principal Investigator for the University of Glasgow in a second international multicentre phase III study on XELOX (NO16968), which involved 26 UK centres. Cassidy was actively involved in the protocol design, conduct, data interpretation and reporting of these two pivotal trials.

Key University of Glasgow researchers: Jim Cassidy, Senior Lecturer (1986–1994) and Chair of Medical Oncology (2002–2011); Chris Twelves, Senior Lecturer (1994–2003); Stan Kaye, Professor of Medical Oncology (1981–2001); Jeff Evans, Senior Lecturer (1996–2005).

3. References to the research

1. Mackean M. *et al.* [Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer.](#) *J Clin Oncol* 1998; **16**: 2977–2985. [pay per view – PDF available on request]
2. Twelves C. *et al.* [Capecitabine as adjuvant treatment for stage III colon cancer.](#) *N Engl J Med* 2005; **352**: 2696–2704 doi:10.1056/NEJMoa043116.
3. Cassidy J. *et al.* [Pharmacoeconomic analysis of adjuvant oral capecitabine vs intravenous 5-FU/LV in Dukes' C colon cancer: the X-ACT trial.](#) *Br J Cancer* 2006; **94**: 1122–1129 doi:10.1038/sj.bjc.6603059.
4. Díaz-Rubio E. *et al.* [Capecitabine \(Xeloda®\) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumours.](#) *Ann Oncol* 2002; **13**: 558–565 doi:10.1093/annonc/mdf065.
5. Cassidy J. *et al.* [XELOX \(capecitabine plus oxaliplatin\): active first-line therapy for patients with](#)

- [metastatic colorectal cancer](#). *J Clin Oncol* 2004; **22**: 2084–2091 doi:10.1200/JCO.2004.11.069.
6. Cassidy J. *et al.* [Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer](#). *J Clin Oncol* 2008; **26**: 2006–2012 doi:10.1200/JCO.2007.14.9898.

4. Details of the impact

University of Glasgow researchers led pivotal clinical trials in collaboration with Roche to show that Xeloda and XELOX were safe and effective novel treatments for patients with bowel cancer.^a This research has enhanced patient care by increasing the therapeutic options available and by improving the treatment experience, with more convenient dosing schedules and fewer side effects compared with previous chemotherapy regimens. This was achieved by substituting oral for intravenous chemotherapy, and removing the requirement for either in-patient administration or long-term indwelling venous catheters. Xeloda and XELOX have been approved by drug regulatory bodies and adopted in US and European clinical guidelines for bowel cancer. In the UK, the reduced costs offered by these novel treatments have benefitted the NHS, both economically and in terms of saving time for patients and healthcare staff.

European licensing extensions granted for Xeloda

Xeloda was approved as a first-line therapy for metastatic bowel cancer in 2001 and as an adjuvant therapy for advanced bowel cancer in 2005 (USA and Europe). The European Medicines Agency (EMA) subsequently broadened the use of Xeloda to the first-line and second-line treatment of metastatic bowel cancer in combination with any other chemotherapy drug (February 2008).^b The NO16966 phase III clinical trial of XELOX⁶ was one of two studies cited as the pivotal clinical evidence to support this licence extension.^a The phase I study of XELOX⁴ was cited to support the safety of combining Xeloda with oxaliplatin, whereas the X-ACT phase III trial of Xeloda² was cited as evidence for the beneficial effects of Xeloda on survival and quality of life among patients with metastatic bowel cancer. The specific combination therapy of XELOX was approved in by the EMA in March 2010.^c This update cited the NO16968 phase III clinical trial of XELOX as the sole evidence.^a Both of these EMA approvals were highlighted by PharmaTimes, a leading online forum for the pharmaceutical industry and healthcare systems (94,280 unique visitors to the website, January–February 2013).^d

The Scottish Medicines Consortium (SMC) is responsible for advising NHS Scotland on treatment efficacy and costs. In September 2008, the SMC stated in their assessment of Xeloda (SMC No. 507/08^e) that it was accepted for use alone or as a combination therapy for metastatic bowel cancer and directly referenced the 2008 *J Clin Oncol* paper.⁶ This statement was followed by another SMC assessment in July 2011 that accepted the use of XELOX as an adjuvant treatment, citing data from clinical trial NO16968 (SMC No. 716/11).^f

Xeloda is currently marketed in over 100 countries. Worldwide sales of Xeloda were approximately £1,057 million in 2012, an increase of 9% on the previous year, and it ranked fifth in Roche's top 10 best-selling drug list.⁹ Xeloda showed sustained growth in sales between 2008 and 2013 as XELOX gained regulatory approval. For example, Roche saw its biggest rise in sales of Xeloda (17%) following EMA approval in 2010, demonstrating a substantial economic impact of the research.⁹

Changes in clinical guidelines

The National Comprehensive Cancer Network (NCCN) is a consortium of 23 US centres of clinical excellence in cancer care. In 2013, the NCCN published clinical guidelines that recommended XELOX (referred to as 'CapeOX' by this organisation) for use in bowel cancer.^h The guidelines on colon cancer provide detailed treatment protocols for advanced and metastatic cancer that directly cite research by University of Glasgow on the basis of evidence and consensus classified as 'category 2A' (uniform NCCN consensus). In the 'Principles of adjuvant therapy (COL-E)' chapter it is stated that "*capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer,*" citing the 2005 *NEJM* publication.² The 2008 *J Clin Oncol* publication⁶ is cited in the chapter 'Chemotherapy for advanced or metastatic disease (COL-C)'.

In 2010, the European Society for Medical Oncology (ESMO) published clinical guidelines on primary and advanced bowel cancer.^{i,j} These guidelines advocated the use of Xeloda in the adjuvant treatment of patients with primary colon cancer (class of recommendation A), citing the phase III clinical trial X-ACT² (level of evidence I). XELOX (referred to as 'CAPOX' by this organisation) was recommended as an alternative to FOLFOX for patients with advanced bowel cancer (level of evidence I, class of recommendation A). The 2008 *J Clin Oncol* paper⁶ informed the evidence base for this recommendation.

Benefits for patients and the NHS

The XELOX regimen requires only one clinic visit every 3 weeks for the 2-hour infusion of oxaliplatin, demonstrating a marked advantage over treatment with 5-FU. Information on XELOX has been disseminated to patients via support groups, including Macmillan Cancer Support.^k This UK organisation describes what patients with bowel cancer should expect in terms of treatment schedule, tumour response and side effects if they are prescribed XELOX, citing the 2008 *J Clin Oncol* paper⁶ as the only clinical trial evidence. Similarly, Genentech provides online material for US patients.^l This resource directly references X-ACT² as the sole evidence base supporting the efficacy of XELOX as an adjuvant therapy for bowel cancer.

The use of Xeloda and XELOX has reduced treatment costs for the NHS. A 2011 National Institute for Health and Care Excellence (NICE) costing report determined that adjuvant treatment with Xeloda cost £3974 per patient versus £8736 for 5-FU.^m The cost of XELOX was £10,514 per patient versus £11,461 for FOLFOX. Costs to the NHS will drop further when Xeloda comes off patent in December 2013, enabling generic formulations to enter clinical practice.

5. Sources to corroborate the impact

- a. Statement from Global Head Oncology/Immuno-Oncology Partnering, F.Hoffmann-La Roche Ltd (available on request)
- b. [EMA assessment report](#) for Xeloda, February 2008 (sections 1.1 and 1.2, pg 2–16)
- c. [EMA procedural update](#) for Xeloda, March 2010 (No. II/0044, pg 5)
- d. *PharmaTimes* coverage of EMA approval, [February 2008](#) and [March 2010](#)
- e. Scottish Medicines Consortium [No. 507/08](#), September 2008 (pg 2–4 and 8)
- f. Scottish Medicines Consortium [No. 716/11](#), July 2011 (pg 2–4)
- g. Roche 2012 [financial summary](#) (pg 5 and 7 of "Full Media Release" PDF) and 2010 [annual report](#) (pg 34–36, 42, 47)
- h. [NCCN guidelines](#) version 3.2013 colon cancer, 2013 (Col-E, pg 1–2; Col-C, pg 1–9) (log-in required; PDF available on request)
- i. ESMO clinical guidelines for [primary colon cancer](#), 2010, doi:10.1093/annonc/mdq168 (pg V74)
- j. ESMO clinical guidelines for [advanced colorectal cancer](#), 2010, doi:10.1093/annonc/mdq222 (pg V94)
- k. Macmillan Cancer Support, [cancer treatment information for patients](#)
- l. Genentech, Xeloda product [information for patients](#)
- m. NICE, CG131 colorectal cancer [costing report](#), November 2011 (Table 1, pg 16)