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The Cost-Effectiveness of Different Chemotherapy Strategies for Patients with Poor Prognosis Advanced Colorectal Cancer (MRC FOCUS)

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A B S T R A C T

Objectives: To assess the value for money of alternative chemotherapy strategies for managing advanced colorectal cancer using irinotecan or oxaliplatin, either in sequence or in combination with fluorouracil. **Methods:** A cost-effectiveness model was developed using data from the UK fluorouracil, oxaliplatin, and CPT11 (irinotecan) – use and sequencing (FOCUS) trial. The analysis adopted the perspective of the UK National Health Service. Input parameters were derived using a system of risk equations (for probabilities), count data regression models (for resource use), and generalized linear models (for utilities). Parameter estimates were obtained using Markov chain Monte Carlo methods, propagating the simulation values through the state-transition model to characterize appropriately the joint distributions of expected cost, survival and quality-adjusted life years for each treatment strategy. An acceptability frontier was used to represent the probability that the optimal option is cost-effective at different values of the cost-effectiveness threshold. **Results:** The base-case analysis used drug unit costs provided by a typical English hospital. First-line doublet therapy combination therapy fluorouracil (5FU) plus irinotecan was the most cost-effective strategy at standard thresholds, with an incremental cost-effectiveness ratio (ICER) of £14,877 (pound sterling) compared with first-line 5FU until treatment failure followed by single agent irinotecan. Other strategies were all subject to extended dominance. A sensitivity analysis using published drug (list) prices found the most cost-effective strategy would be first-line fluorouracil until failure followed by 5FU plus irinotecan (ICER: £19,753). **Conclusions:** The combination of 5FU and irinotecan (whether used first or second line) appears to be more cost-effective than the single agent sequential therapies used in the FOCUS trial, or 5FU plus oxaliplatin.

Keywords: advanced colorectal cancer, cost-effectiveness, FOCUS trial, irinotecan, oxaliplatin.

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Introduction

Colorectal cancer is the third most common cancer in the United Kingdom, with almost 30,000 new cases registered in England and Wales in 2001, representing over 12% of all new cancer cases [1,2]. "Advanced" colorectal cancer (ACRC) is described as a disease that is either metastatic or too locally advanced for complete surgical resection of the primary tumor. Approximately 55% of colorectal cancer patients in England and Wales have ACRC, either at the time of initial presentation or later in the disease course [3,4].

A small but increasing proportion of patients with ACRC are suitable for treatment with curative intent, usually involving major liver and/or lung resections and chemotherapy. For the majority of ACRC patients, however, the treatment objectives are non-curative: to relieve symptoms and improve quality of life, and to modestly increase survival duration. Following trial results [5], palliative chemotherapy became the standard of care in ACRC in patients who were able to tolerate these therapies. Since the mid-1990s the standard treatment for such patients was fluorouracil (FU) with folinic acid, administered in a variety of schedules, the two weekly de Gramont regimen (dG) or a modification of it (MdG) being the most popular in the UK. Subsequently, two cytotoxic drugs, irinotecan (ir) and oxaliplatin (ox), were licensed. These drugs could be given either after or in combination with FU, and had good evidence of efficacy but with some additional toxicity [6–8]. They incurred significant extra cost [9,10], although both have come off patent recently, which reduces their acquisition costs and potentially increases their cost-effectiveness. Since 2004, attention has shifted to newer therapies targeting the epidermal growth factor and vascular endothelial growth factor pathways.

The UK fluorouracil, oxaliplatin, and CPT11 (irinotecan) – use and sequencing (FOCUS) trial was designed to investigate the optimum combination and sequencing for FU and either irinotecan or oxaliplatin in the UK population by comparing five alternative treatment strategies [11]. The published clinical results of this study indicate that sequential single-agent therapy with FU followed by irinotecan produces significantly inferior survival to the same two drugs used as a first-line combination "doublet." In contrast, treatment strategies involving FU alone followed by a second-line doublet were non-inferior to first-line doublet therapy [11].

In a fixed budget environment such as the UK National Health Service (NHS), where decision makers are expected to allocate available resources efficiently across a wide range of uses, it is essential to assess the extent to which the benefits of a given

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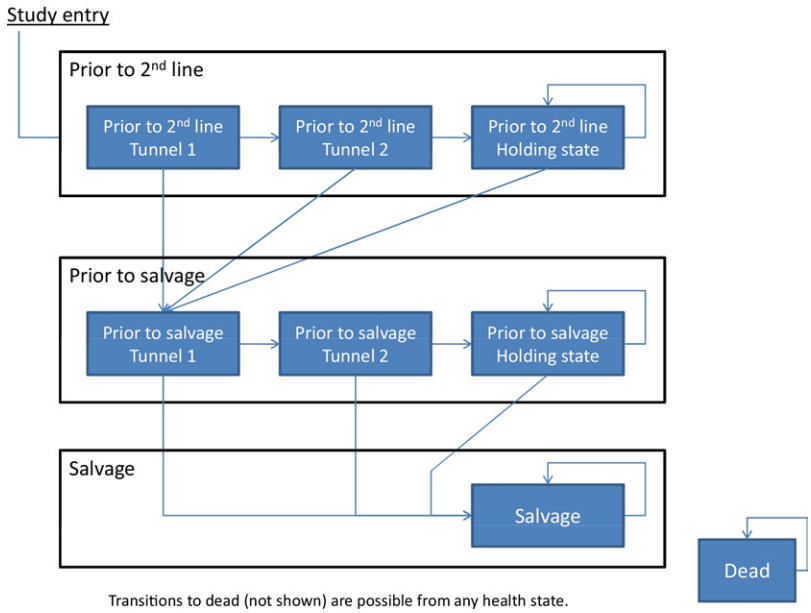

Fig. 1 – State transition diagram.

investment strategy are worth paying for. Cost-effectiveness analysis (CEA) generates the information decision makers need to carry out this task [12]. Using individual patient-level clinical and resource use data from the FOCUS trial, we developed an economic model [13] to estimate the long term cost-effectiveness of the five strategies investigated in the FOCUS trial. Reflecting the trial population in FOCUS, only patients considered fit enough to undergo chemotherapy are relevant to the analysis and, given that palliative chemotherapy is now considered standard of care in such patients, best supportive care was not considered a relevant comparator.

Methods

Overview

Individual patient data (IPD) on the use and sequencing of the study and post-study drugs, non-drug health care resource use as well as patients' health-related quality of life through the EuroQol five-dimension (EQ-5D) questionnaire instrument [14], were collected prospectively at each follow up visit during the trial follow-up.

The median follow-up of the survivors in the FOCUS trial was 26.5 months [11]. Because the differences in benefits and costs between the alternative strategies are expected to extend beyond trial follow-up period, a model to estimate the long-term cost-effectiveness of the five management strategies investigated in the FOCUS trial was developed [15].

The model included costs from the NHS perspective [16] expressed in UK sterling (2009 prices). Health outcomes were assessed in terms of quality-adjusted life years (QALYs) based on mortality and generic health-related quality of life (HRQoL) using the EQ-5D data from FOCUS. Costs and QALYs were discounted using a 3.5% annual discount rate [17].

Treatment strategies

Following the design of FOCUS, five treatment plans involving three different strategies for combining and sequencing FU, irinotecan, and oxaliplatin were modeled. These are described below:

Strategy A: the standard approach of sequential single-agent MdG regimen using FU until evidence of treatment failure, followed by single agent irinotecan;
Strategy B-ir: first-line MdG regimen until treatment failure, followed by doublet therapy with MdG and irinotecan (IrMdG regimen);
Strategy B-ox: first-line MdG regimen until treatment failure, followed by doublet therapy with MdG and oxaliplatin (OxMdG regimen);
Strategy C-ir: first-line doublet therapy with the IrMdG regimen; and
Strategy C-ox: first-line doublet therapy with the OxMdG regimen.

After failing doublet therapy, patients in the C-ir and C-ox arms of the FOCUS trial may have received non-FOCUS chemotherapy and eventually salvage therapy. This was due to a change in crossover policy half way through the conduct of the FOCUS trial [11]. We used salvage to mean any type of chemotherapy initiated after patients failed their trial chemotherapy. The costs of any non-FOCUS chemotherapy were included in the analysis. The management of patients after failing first-line therapy are reported in the main clinical trial publication [11]. All treatment regimens were detailed in the protocol, with guidance on dose reductions and delays for toxicity, and criteria to define treatment failure. For patients fit and willing to receive further chemotherapy after completing the trial strategy, salvage chemotherapy options were offered in the protocol.

Model structure

The structure of the model was designed to reflect the treatment strategies investigated in the FOCUS clinical trial. Briefly, at any point in time, individuals were assumed to be in one of four mutually exclusive states (Fig. 1). Specifically, individuals could be either alive and on a given chemotherapy plan (A to C-ox) and treatment phase (prior to second line, prior to salvage, salvage), or dead (for treatment strategies A, C-ox, and C-ir, the transition is from first line FOCUS to post-FOCUS palliative/salvage treatment). Transitions between these states were modeled over 3 monthly intervals and were governed by probabilities estimated directly from the FOCUS data.

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