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Cost-Effectiveness of Cetuximab, Cetuximab Plus Irinotecan, and Panitumumab for Third and Further Lines of Treatment for KRAS Wild-Type Patients with Metastatic Colorectal Cancer

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ABSTRACT

Objectives: To estimate the cost-effectiveness of cetuximab monotherapy, cetuximab plus irinotecan, and panitumumab monotherapy compared with best supportive care (BSC) for the third and subsequent lines of treatment of patients with Kirsten rat sarcoma wild-type metastatic colorectal cancer from the perspective of the UK National Health Service. **Methods:** An "an area under the curve" cost-effectiveness model was developed. The clinical effectiveness evidence for both cetuximab and panitumumab was taken from a single randomized controlled trial (RCT) in each case and for cetuximab plus irinotecan from several sources. **Results:** Patients are predicted to survive for approximately 6 months on BSC, 8.5 months on panitumumab, 10 months on cetuximab, and 16.5 months on cetuximab plus irinotecan.

Panitumumab is dominated, and cetuximab is extended dominated. An incremental cost-effectiveness ratio (ICER) of £95,000 per quality-adjusted life-year (QALY) was estimated for cetuximab versus BSC and is likely to be relatively accurate, because the relevant clinical evidence is taken from a high-quality RCT. The estimated ICER for panitumumab versus BSC, at £187,000 per QALY, is less certain due to assumptions in the adjustment for the substantial crossing-over of patients in the RCT. The ICER for cetuximab plus irinotecan versus BSC, at £88,000 per QALY, is least certain due to substantial uncertainty about progression-free survival, treatment duration, and overall survival. Nonetheless, when key parameters are varied within plausible ranges, all three treatments always remain poor value for money. **Conclusions:** All three treatments are highly unlikely to be considered cost-effective in this patient population in the United Kingdom. We explain how the reader can adapt the model for other countries.

Keywords: cetuximab, colorectal cancer, cost-effectiveness, cost-utility, decision analytic modeling, Erbitux, irinotecan, panitumumab, Vectibix.

Introduction

Colorectal cancer is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). In the United Kingdom, approximately 41,000 new cases were diagnosed in 2009 [1]. Cancer cells eventually spread to nearby lymph nodes (local metastases), and subsequently to more remote lymph nodes and other organs in the body. The liver and the lungs are common metastatic sites of colorectal cancer. This is described as Stage IV of the American Joint Committee on Cancer tumor node metastases system or Stage D of the modified Dukes' classification. The 5-year survival rate of patients with advanced disease (modified Dukes' D) is less than 7% [2].

Individuals with metastatic disease who are sufficiently fit (World Health Organization performance status ≤ 2) are usually treated with active chemotherapy as first- or second-line therapy. First-line active chemotherapy options include infusional 5-fluorouracil plus folinic acid (5-FU/FA); oxaliplatin plus infusional 5-FU/FA (FOLFOX); and irinotecan plus infusional 5-FU/FA (FOLFIRI); oral analogues of 5-FU (capecitabine and tegafur with uracil) may also be used instead of infusional 5-FU. Current evidence indicates that the use of 5-FU, oxaliplatin, and irinotecan in any sequence within patients' care pathway has survival advantages [3].

More recently, targeted agents have become available including anti–epidermal growth factor receptor (EGFR) agents, for example, cetuximab and panitumumab, and anti–vascular epidermal growth factor receptor agents, for example bevacizumab. The EGFR signaling pathway has been the focus of new drug development for colorectal cancer because it is overexpressed in approximately 80% of colorectal carcinomas. Kirsten rat sarcoma (KRAS) mutation status—wild type or mutant—can explain resistance to anti-EGFR therapy. In colorectal cancer, approximately 65% of the patients are KRAS wild type and the remaining 35% are KRAS mutant [4].

As far as we are aware, there are no fully published studies of the cost-effectiveness of panitumumab or cetuximab plus irinotecan for third and subsequent lines of treatment of patients with

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KRAS wild-type metastatic colorectal cancer. The cost-effectiveness analyses of cetuximab versus best supportive care (BSC) in Canada by Mittmann et al. [5] and in Switzerland by Blank et al. [6] are the only fully published studies of the cost-effectiveness of cetuximab in this setting. The manufacturers of cetuximab (Erbitux, Merck Serono, Geneva, Switzerland) and panitumumab (Vectibix, Amgen, Thousand Oaks, CA) recently made submissions to the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom [7]. Merck Serono submitted cost-effectiveness analyses of cetuximab versus BSC and cetuximab plus irinotecan versus BSC. Here, we estimate the cost-effectiveness of cetuximab, cetuximab plus irinotecan, panitumumab, and BSC for third and further lines of treatment of metastatic colorectal cancer. Our analysis is restricted to KRAS wild-type patients , because post hoc analyses suggest that the clinical benefit of cetuximab and panitumumab is confined to these people [8,9].

Methods

Model Structure

The structure of the model, which was informed by a review of the literature and expert opinion, is simple and has often been used to simulate the progression of metastatic cancers. Three health states are used to represent the progression of metastatic colorectal cancer: progression-free survival (PFS), progressive disease (PD), and death. At the end of each cycle, people either remain in their current health state or move to a more severe state. All people enter the model either receiving a third or subsequent line of treatment or BSC. After treatment discontinuation, no further lines of drug treatment are modeled.

An "area under the curve"/"partitioned survival" Markov-type model (see, e.g., Hoyle et al. [10]) was developed to model disease progression and treatment effectiveness. The number of patients in PFS and overall survival (OS) at any time is determined directly from the underlying survival curves, and the time in PD is calculated as OS minus PFS. This was preferred to a conventional Markov approach for two reasons. First, it bypasses the need to estimate transition probabilities between health states, and second, it avoids the need for additional assumptions, such as whether death was permitted from both PFS and PD. The model was written in Microsoft Excel (Microsoft Corporation, Redmond, WA).

The model cycle length is 1 month, a half-cycle correction is applied, and the time horizon is 10 years, after which time virtually all people have died. Future costs and benefits are discounted at 3.5% per year, and the perspective is that of the National Health Service (NHS) and Personal Social Services, in accordance with the NICE Reference Case [11].

Clinical Effectiveness Data

The clinical effectiveness of all treatments was informed by a systematic search of the literature [12]. Data for cetuximab were taken from the KRAS wild-type patients in the randomized controlled trial (RCT) of cetuximab versus BSC [8], for panitumumab from the KRAS wild-type patients in the RCT of panitumumab versus BSC [9], and for cetuximab plus irinotecan from several sources: the "BOND" RCT of cetuximab plus irinotecan versus cetuximab [13] and the observational studies by De Roock et al. [14,15] and Lievre et al. [16]. Patient baseline characteristics were similar across the trials: the median age varied from 59 to 63 years, all or almost all patients had previously had two or more prior chemotherapies in the panitumumab versus BSC and cetuximab versus BSC RCTs, and the great majority of patients had had two or more prior chemotherapies in the cetuximab plus irinotecan versus cetuximab RCT. All or almost all patients had previously taken irinotecan and oxaliplatin in the panitumumab verus BSC and cetuximab versus BSC RCTs and in the cetuximab plus irinotecan versus cetuximab RCT. All patients in all trials had previously taken irinotecan, and most had previously taken oxaliplatin.

PFS and OS

Given that there is no single RCT with all treatment groups, it was necessary to perform an indirect comparison. For PFS, OS, and mean time on drug treatment, the baseline treatment for the indirect comparison was BSC taken from the RCT of cetuximab versus BSC [8]. The clinical effectiveness of people on BSC is also available from the RCT of panitumumab versus BSC [9]. This, however, was not considered appropriate for the baseline treatment because the effectiveness of this treatment group was confounded by substantial crossover (76% of the patients receiving BSC crossed treatment arms to receive panitumumab) [9]. The implicit assumption is that the baseline patient characteristics in the two RCTs are reasonably similar, and indeed this is true [12].

The estimated mean PFS and OS for BSC and for cetuximab were all taken from analysis of the individual patient data from the RCT of cetuximab versus BSC by Merck Serono [12]. The mean is the most important summary statistic of survival given that cost-effectiveness is a function of mean survival. In Merck Serono's analysis, almost no extrapolation was necessary for PFS because almost all patients had progressed before the end of the study, but some extrapolation was necessary for OS [8]. Next, Weibull functions were fit to estimate the shape parameters. For estimates of uncertainty for all parameters in the model, see Hoyle et al. [12].

The mean PFS for panitumumab for the indirect comparison was calculated by using the Bucher method [17] as the mean PFS for panitumumab from the RCT of panitumumab versus BSC multiplied by the ratio of the mean PFS for BSC from the RCT of panitumumab versus BSC and the mean PFS for BSC from the RCT of cetuximab versus BSC [12]. The mean OS for panitumumab was calculated in a similar manner as the PFS, with the adjustment for the indirect comparison. In this case, the mean OS for BSC in the panitumumab versus BSC RCT was reduced by 2.7 months to allow for the substantial crossover of patients from the BSC to the panitumumab arm, where the 2.7 months was calculated by Amgen, the manufacturer of panitumumab [12].

The pivotal BOND trial of cetuximab plus irinotecan versus cetuximab [13] did not have KRAS status as a prerequisite for recruitment, and no retrospective KRAS analysis has been systematically undertaken. Given that we do not have direct randomized evidence for PFS, time on treatment, and OS for KRAS wild-type patients on cetuximab plus irinotecan, these quantities were estimated. Details of the methods are given in Hoyle et al. [12].

Treatment Duration

The mean duration of drug treatment is a key determinant of the mean drug acquisition costs, and therefore of cost-effectiveness. Ideally, we would model the mean duration of treatment as experienced in the RCTs. Indeed, this is reported as 10 treatment cycles for patients with KRAS wild-type status on panitumumab [9], which we adjusted for the indirect comparison by multiplying by the ratio of the estimated mean PFS for panitumumab for the indirect comparison and the mean PFS for panitumumab from the RCT, leading to a mean duration of 6 months.

The mean duration of treatment is not reported for patients with KRAS wild-type status on cetuximab or on cetuximab plus irinotecan. Mittmann, however, informs us that the mean duration of cetuximab treatment for KRAS wild-type people was 18.9 weeks in the RCT of cetuximab versus BSC [8] (N. Mittmann, personal communication, May 24, 2011). From this, we estimate a