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ORIGINAL ARTICLE

Pharmaco-economic analysis of direct medical costs of metastatic colorectal cancer therapy with XELOX or modified FOLFOX-6 regimens: Implications for health-care utilization in Australia

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Abstract

***Aim*:** The objective of this economic evaluation, which was based on patients from two randomized controlled clinical trials (NO16966 and NO16967), was to compare direct medical costs to the Australian health-care system of capecitabine plus oxaliplatin (XELOX) and bolus and/or infusional 5-fluorouracil (5-FU) plus folinic acid combined with oxaliplatin (modified [m] FOLFOX-6) in first-line and second-line treatment of advanced or metastatic colorectal cancer (mCRC).

***Methods*:** Direct medical costs were estimated for five treatment settings from a public and private hospital. The costs included in evaluation were for drug acquisition, preparation (oxaliplatin, bolus and infusional 5-FU), administration and wastage. The cost of drug acquisition was calculated based on dosage data and the mean number of treatment cycles from the pivotal studies NO16966 and NO16967. There were no costs associated with preparing capecitabine and leucovorin. An oncology grouping and costing study was performed to determine the relevant administration costs associated with central venous access devices, their placement, maintenance and removal (for oxaliplatin administration) and the continuous infusion of 5-FU via a continuous ambulatory delivery device pump or infuser.

***Results*:** This economic evaluation has shown that treating mCRC patients with XELOX in the first and second-line settings results in average cost savings of $9110 and $7113, respectively, compared with mFOLFOX-6. A multi-way sensitivity analysis demonstrated that the use of XELOX remained cost-saving from an Australian government health budget perspective.

***Conclusion*:** The use of XELOX, compared with mFOLFOX-6, for the treatment of mCRC is cost-saving in the Australian government health budget.

Key words: FOLFOX-6, metastatic colorectal cancer, pharmaco-economic, XELOX.

INTRODUCTION

Colorectal cancer (CRC) is the second most commonly occurring cancer in Australia, accounting for 14 234 (13%) of all cancer registrations (excluding basal and squamous cell carcinomas of the skin) and 4047 deaths

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in 2007.[1] The primary treatment for colorectal cancer is surgical resection. However, despite effective surgery, up to 25 percent of patients have advanced disease at presentation and another 25 percent will relapse post-operatively.[2] Chemotherapy is offered to an increasing proportion of metastatic (m) CRC patients with the aim of improving both the duration and quality of their life.[3] Standard treatments for mCRC include infusional fluorouracil (5-FU) plus leucovorin in combination with oxaliplatin (the FOLFOX regimen), capecitabine monotherapy, the infusional 5-FU plus leucovorin in combination with irinotecan (FOLFIRI) regimen and capecitabine plus oxaliplatin (XELOX). The choice of second-line treatment is largely determined by the treatment administered in the first-line setting.

Where feasible, chemotherapy is administered on an outpatient basis, either at home or in a day procedure center.[4] In Australia access to medicines for outpatients is subsidized by the national pharmaceutical benefits scheme (PBS), a key component of Australia's public health system. During the 1990s the Pharmaceutical Benefits Advisory Committee (PBAC) introduced the need for a pharmaco-economic evaluation to accompany major submissions requesting reimbursement of a medicine on the PBS.[5] Such rigorous cost-effectiveness evaluations, against an already PBS-listed alternative and utilizing Australian health-care costs, aim to ensure that optimal health outcomes and economic objectives are achieved.[5,6]

Capecitabine, an oral prodrug that mimics continuous infusion 5-FU, was first registered with the Therapeutic Goods Administration (TGA) in Australia for the treatment of mCRC in 2000.[7,8] In 2001 monotherapy for this indication was reimbursed on the PBS. XELOX for the treatment of mCRC was TGA-registered in 2008.[8]

FOLFOX was identified, through a clinical survey of Australian oncologists, as the regimen that most prescribers would replace with XELOX in Australian clinical practice in both first-line and second-line mCRC.[3] In particular, modified FOLFOX-6 (mFOLFOX-6) was considered the most commonly used chemotherapy regimen in these settings. The PBAC had previously accepted that in terms of comparative effectiveness and safety, XELOX was non-inferior to mFOLFOX-6 in both the first-line and second-line settings.[3] Our objective was to compare the direct medical costs associated with XELOX and mFOLFOX-6 regimens in first-line and second-line mCRC treatment from an Australia government (both state and federal) health-care perspective. The economic analyses described here were pivotal in gaining a positive PBAC recommendation for the reimbursement of XELOX for the treatment of first-line and second-line mCRC in 2010. The PBS listing was effective from 1 August 2010.

METHODS

Patients and treatments

A literature review of available clinical data, comparing XELOX and FOLFOX in mCRC, identified five randomized controlled trials (RCT) in the first-line setting[9–14] and one RCT in the second-line setting.[15] The largest trial in each treatment line (Study NO16966 first-line[14] and Study NO16967 second-line[15]) was selected to provide an input into the relevant economic evaluation. Australian oncologists were surveyed to determine local treatment practices and to refine the potential clinical scenarios in use at the time of this evaluation; and mFOLFOX-6 was identified as the appropriate comparator. Although both studies used FOLFOX-4 as the comparator arm, the PBAC accepted that FOLFOX-4 and mFOLFOX-6 were equivalent in clinical terms.[3]

Study NO16966 was a multi-center, randomized, controlled trial in patients receiving first-line therapy for mCRC.[14] The initial two-arm portion of the study involved 634 patients randomized to either XELOX or FOLFOX-4. The study was subsequently amended to a two by two factorial design with an additional 1400 patients further randomized to receive bevacizumab or placebo.[9,16] The consistency of the patients' baseline and disease characteristics across the XELOX and FOLFOX-4 treatment arms, with and without placebo, permitted the pooling of the results for the analyses (Table 1). Study NO16967 was a multi-center, randomized, controlled trial in which 627 patients with mCRC, who had received prior treatment with irinotecan in combination with a 5-FU/leucovorin (LV) regimen as first-line therapy, were randomized to treatment with either XELOX or FOLFOX-4.[15] The baseline characteristics of patients treated in study NO16967 were well balanced between the treatment groups (Table 1).

Economic evaluation

Economic evaluations were performed retrospectively based on patient-level data from the two pivotal studies comparing XELOX and FOLFOX (NO16966 and NO16967).[14,15] Analyses were conducted from an Australian government (both state and federal costs were included) health-care perspective with the economic

Table 1 Baseline patients' and disease characteristics of intent-to-treat (ITT) patients in studies NO16966 and NO16967[14,15]

	First-line study NO16966 (ITT)				Second-line study NO16967 (ITT)	
Characteristics	FOLFOX-4 (n = 317)	FOLFOX-4 + placebo (n = 351)	XELOX (n = 317)	XELOX + placebo (n = 350)	FOLFOX-4 (n = 314)	XELOX (n = 313)
Mean age years (SD)	60.6 (10.9)	58.8 (10.9)	60.3 (10.8)	59.1(12.1)	59.7 (10.5)	60.7 (9.9)
Sex (% male)	64	53	61	59	61	62
Mean weight kg (±SD)	73.6 (16.2)	71.8 (15.4)	72.61 (16.2)	72.8 (14.9)	77.3 (17.21)	75.4 (15.90)
Caucasian%	74	89	75	89	82	82
Mean body surface area m^2 (SD)	1.83 (0.22)	1.80 (0.21)	1.81 (0.23)	1.82 (0.21)	1.86 (0.23)	1.85 (0.22)
ECOG performance status (% of patients)						
0	51	60	50	59	46	48
≥1	49	40	50	41	54	52
Normal alkaline phosphatase, baseline (%)	57	58	58	57	54	53
Cancer type at 1st-diagnosis (% of patients)						
Colon and rectal	5	7	9	9	8	8
Colon	63	66	64	67	64	59
Rectal	32	27	26	25	28	33
Number of organ sites with metastases (n, % of patients)						
1	37.2	40.5	40.1	44.3	34.4	31.6
2					35.7	35.8
≥2	62.5	59.2	59.9	55.7		
>2					28.5	32.6
Prior cancer treatment (% of patients)						
Any	87	85	87	85	100	100
Surgery	84	83	85	84	89	91
Radiotherapy	<1	<1	<1	0	22	27
Adjuvant chemotherapy	26	24	28	26	31	34
Irinotecan/fluorouracil for mCRC %/%					100/99	100/100

ECOG, Eastern Cooperative Oncology Group; FOLFOX, 5-fluorouracil plus folinic acid combined with oxaliplatin; XELOX, capecitabine plus oxaliplatin; SD, standard deviation; mCRC, metastatic colorectal cancer

Table 2 Summary of treatment regimens used in the economic evaluation

Chemotherapy component	XELOX[†14,15]	Modified (m)FOLFOX-6[‡]
Oxaliplatin	130 mg/m^2 by i.v. infusion on day 1	100 mg/m^2 by i.v. infusion on day 1
5-fluorouracil	–	400 mg/m^2 by i.v. push on day 1
	–	2400 mg/m^2 by continuous i.v. infusion over 46 h starting on day 1
Leucovorin	–	50 mg by i.v. push on day 1
Capecitabine	1000 mg/m^2 orally twice daily for 14 days	–
Frequency	Every 3 weeks	Every 2 weeks
Number of cycles	Until disease progression	Until maximal improvement, progression or unacceptable toxicity

[†]Based on data from the in NO16966 and NO16967[14,15] and the recommendations of the *Chemotherapy Drug Protocol for XELOX*, Cancer Institute of NSW. [‡]Based on the recommendations from the *Chemotherapy Drug Protocol for Modified FOLFOX-6*, Cancer Institute of NSW (Australia). 5-FU, 5-fluorouracil; FOLFOX-6, bolus and/or infusional 5-fluorouracil plus folinic acid combined with oxaliplatin; XELOX, capecitabine plus oxaliplatin.

outcome of Australian dollar costs (savings) per average chemotherapy course. The results are a trial-based estimation of average patient cost, with some translations to improve applicability.

Both economic evaluations included direct medical costs of drug acquisition, drug preparation and drug administration. Costs of hospitalization for treatment-related adverse events, laboratory tests, health-care professional visits and concomitant treatments were excluded as these were either not likely to impact significantly on the economic evaluation, were comparable between the treatment arms, or were lower in the XELOX arm. Discounting was not applied to any of the cost components since these were incurred within the first 12 months following the start of treatment.

As per PBAC guidelines for major submissions, pre-modeling studies were undertaken to translate the characteristics of the trials used for the clinical evaluation into a decision analysis appropriate for the intended clinical use of the proposed drug regimens in the PBS in Australia.[5] Differences in the trial doses of capecitabine and oxaliplatin compared with local clinical practice at the time of the evaluations were identified (Table 2). For XELOX, the capecitabine and oxaliplatin trial dosage data were used in the base case economic evaluation and no truncation of the oxaliplatin dose was applied. However, for the FOLFOX regimen, the estimated mean number of oxaliplatin cycles was adjusted for an increase in oxaliplatin dose from the FOLFOX-4 regimen used in the clinical trials to the mFOLFOX-6 regimen used in clinical practice (85 to 100 mg/m^2), based on an assumption of constant cumulative oxaliplatin toxicity. A dose of 100 mg/m^2 was used based on the recommendations, at the time of the evaluations, by the *Chemotherapy Drug Protocol for Modified FOLFOX-6*,[17] Cancer Institute of NSW (Australia).

Accepting that XELOX is non-inferior to mFOLFOX-6 in both the first and second-line settings on the basis of the XELOX versus FOLFOX-4 results from studies NO16966 and NO16967,[14,15] it was appropriate to use dosage data from the studies to determine the equi-effective doses of XELOX versus mFOLFOX-6. In the cost-minimization economic evaluations, equi-effective doses were based on the mean cumulative dose of each drug, calculated as the average dose used by the remaining participants after excluding those who discontinued the drug.

The time horizon used in each economic evaluation was the average duration of the course of chemotherapy. The mean number of treatment cycles, on a drug-by-drug basis, was calculated from studies NO16966 and NO16967,[14,15] with cycles of zero doses excluded (Table 3). XELOX was assumed to be prescribed until disease progression or toxicity as per the trial data as this was consistent with Australian clinical practice. Key parameters and assumptions used in the base case were explored in sensitivity analyses to determine the impact on results.

Direct medical costs

Drug acquisition

PBS dispensed prices per pack from the *Schedule of Pharmaceutical Benefits*[6] September 2009 were used to calculate the cost of drug acquisition. In the first-line setting, the cost of each drug component of XELOX and mFOLFOX-6 was calculated by multiplying the cost per pack of the drug by the mean number of packs per patient derived from individual patient dosage data

Table 3 Mean number of cycles calculated from the clinical trials NO16966 and NO16967 (zero dose cycles excluded)

	First-line setting (NO16966)[14]			Second-line (NO16967)[15]		
Drug component	XELOX	FOLFOX-4 (as per trial)	mFOLFOX-6	XELOX	FOLFOX-4 (as per trial)	mFOLFOX-6
Capecitabine	7.45	–	–	5.09	–	–
5-FU	–	11.01	As per trial-based estimate	–	7.49	As per trial-based estimate
Leucovorin	–	11.02	As per trial-based estimate	–	7.49	As per trial-based estimate
Oxaliplatin	6.93	10.16	8.64†	4.98	7.43	6.32†

†Calculated by dividing the mean number of oxaliplatin cycles for FOLFOX-4 in NO16966 (10.16 cycles) and NO16967 (7.43 cycles) by the ratio of the oxaliplatin dose in mFOLFOX-6 to FOLFOX-4 (100 mg/m^2 ÷ 85 mg/m^2); FOLFOX, bolus and/or infusional 5-fluorouracil (5-FU) plus folinic acid combined with oxaliplatin; XELOX, capecitabine plus oxaliplatin.

from study NO16966. A similar approach was used to calculate the cost of XELOX and mFOLFOX-6 in the second-line setting using individual patient dosage data from study NO16967. Dose adjustments between cycles were made through use of individual patient dosage data. Drug wastage was included in the calculations.

Drug preparation

For XELOX, the cost of drug preparation was calculated by multiplying the reconstitution fee ($40, intravenous chemotherapy supply program)[18] by the mean number of doses of oxaliplatin administered to a patient treated with the regimen during studies NO16966 and NO16967.[14,15] The mean number of doses of oxaliplatin was calculated as the mean number of cycles of oxaliplatin received by a XELOX patient multiplied by the number of administrations of the drug per cycle. There was no cost of drug preparation associated with orally administered capecitabine. A similar approach was used to calculate the cost of drug preparation for mFOLFOX-6 (bolus 5-FU, infusional 5-FU and oxaliplatin); drug preparation costs were not applicable to ready-prepared leucovorin.

Drug administration

In the Australian health-care system, i.v. chemotherapy administration can take place in five possible treatment settings: public in-patient in a public hospital; private in-patient in a public hospital; public hospital outpatient; private in-patient in a private hospital and private hospital outpatient. In-patient costs were limited to same day patients.[19]

The costs of the various clinical scenarios associated with the administration of XELOX and mFOLFOX-6 chemotherapy regimens were determined using Australian refined diagnosis related group Medicare benefits scheme (MBS) items (including pathology, radiology, and anesthesia), the prostheses list and other medical resources costs for i.v. administration in the different treatment settings. In addition, central venous access device (CVAD) placement, maintenance and removal costs associated with the administration were calculated.

For XELOX, where a port catheter or a peripherally inserted central catheter [PICC]) was required for drug administration, the costs associated with CVAD placement, chemotherapy administration and CVAD removal were included. The cost of chemotherapy administration was also included where a CVAD was not required for the administration of XELOX. A drug delivery device (such as a CADD pump/cassette or infuser) was not required for the administration of XELOX as neither capecitabine nor oxaliplatin were administered by continuous infusion.

For mFOLFOX-6 the costs associated with CVAD placement and connection of a drug delivery device (a CADD pump/cassette or infuser), changeover and flushing of drug delivery device during the course of treatment and CVAD removal were included. A drug delivery device was required to administer 5-FU as a continuous i.v. infusion over 46 h starting on day 1 of each cycle. The cost of disconnecting a drug delivery device at the end of treatment was also included where a CVAD was not removed.

Drug administration algorithms were developed for each chemotherapy administration setting to illustrate the approach used to calculate the costs of drug administration (see example in Fig. 1). A treatment pattern survey of medical oncologists specializing in CRC treatment ($n = 11$) and oncology nurse practitioners ($n = 8$) was conducted to determine probabilities of the clinical scenarios and resource use associated with the administration of each regimen. Of the survey respondents, 63 percent (eight oncologists and four nurse practitioners), were from three Australian states (New South Wales, South Australia and Victoria) and represented both the

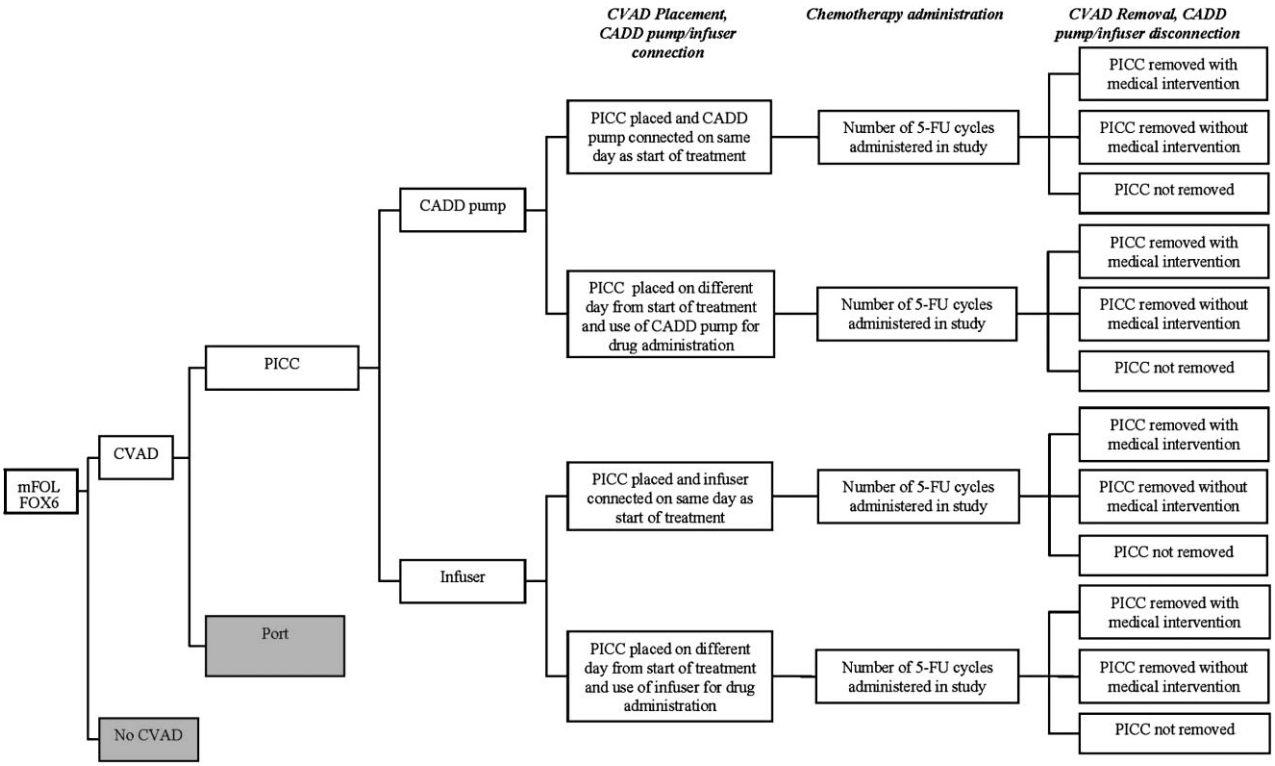

Figure 1 Drug administration algorithm for modified fluorouracil (5-FU) plus leucovorin in combination with oxaliplatin mFOLFOX-6 central venous access device (CVAD) via a peripherally inserted central catheter (PICC). 5-FU, 5-fluorouracil.

private and public hospital sectors. The results were combined with costs of the clinical scenarios to calculate an average cost of drug administration for a patient treated with XELOX versus that for a patient treated with mFOLFOX-6 for each treatment setting.

The costs, estimated probabilities and resource use associated with each identified clinical scenario were combined to calculate the average cost of drug administration for a patient receiving XELOX or mFOLFOX-6 in each chemotherapy treatment setting. These calculated costs were multiplied by the number of cycles of each drug and weighted by the estimated proportion of patients treated in the five treatment settings to give a weighted average drug administration cost per chemotherapy course for the XELOX and mFOLFOX regimens.

RESULTS

The most common treatment setting for mCRC patients in Australia (for the period 2006–2007) was private in-patients in a private hospital, which accounted for 30 percent of chemotherapy episodes. Private hospital outpatients (25%), public in-patients in a public hospital (22%) and public hospital outpatients (21%) were also well represented. Private in-patients in a public hospital represented only 3 percent of episodes.

Results from the survey administered to Australian clinicians showed that for patients treated with XELOX, in the base case analysis, an average of 49 percent required a CVAD; of these patients 63 percent required a port catheter and 38 percent required a PICC line. In the mFOLFOX-6 base case analysis, an average of 99 percent of patients required a CVAD; 49 percent of whom required a port catheter and 51 percent required a PICC line. Of the patients requiring a PICC line, 72 percent required an infuser and 28 percent a CADD pump.

The administration costs for a first-line course of XELOX ranged from $1618 in the private outpatient treatment setting to $4847 for a private in-patient in a public hospital. Administration costs for mFOLFOX-6 were $9419 (private outpatient) and $19 607 (private in-patient in a public hospital). The weighted (by treatment setting) total administration costs per first-line

Table 4 Summary of weighted total treatment costs for an average patient treated with XELOX versus mFOLFOX-6 (base case analysis) in Australian dollars

	Average use of resources per patient over total chemotherapy course					
	First-line			Second-line		
Type of resource item (unit/pack cost)	XELOX	mFOLFOX-6	Difference	XELOX	mFOLFOX-6	Difference
Drug acquisition costs†						
Capecitabine	4 468			3 848		
Fluorouracil		575			475	
Leucovorin		351			278	
Oxaliplatin	11 849	12 035		10 411	10 649	
Total acquisition cost per average patient	16 317	12 961	3 356	14 259	11 402	2857
Drug preparation costs†						
Total preparation cost per average patient	277	1 226	–949	199	852	–653
Drug administration costs						
Weighted total administration cost per average patient	3 523	15 040	–11 517	2 728	12 046	–9318
Weighted total treatment cost per average chemotherapy patient	20 117	29 227	–9 110	17 186	24 300	–7114

†Drug acquisition and drug preparation costs are applicable to all chemotherapy treatment settings and are not weighted in final calculations. FOLFOX, 5-fluorouracil plus folinic acid combined with oxaliplatin; XELOX, capecitabine plus oxaliplatin.

chemotherapy course were $3523 for XELOX and $15 040 for mFOLFOX-6.

In second-line treatment, the administration costs for a XELOX course ranged from $1339 in the private outpatient treatment setting to $3753 for a private in-patient in a public hospital, while mFOLFOX-6 administration costs for the same settings were $8304 and $15 374, respectively. The weighted total administration costs per second-line chemotherapy course were $2728 for XELOX and $12 046 for mFOLFOX-6.

The costs of drug acquisition, preparation and administration for the base case economic evaluation in both first-line and second-line treatment of mCRC are summarized in Table 4).

Economic evaluation

The total average cost of a first-line chemotherapy course for treatment of a mCRC patient with XELOX was $20 117 compared to an mFOXFOX6 regimen cost of $29 227 per course. In second-line treatment, these costs were XELOX $17 186 and mFOLFOX-6, $24 300 (Table 4). The economic evaluation demonstrated that the first-line treatment of a mCRC patient using the XELOX regimen resulted in an average cost saving of $9110 per course (Fig. 2) to the Australian government health-care budget, compared with mFOLFOX-6. In second-line, the average cost saving was $7113 per course (Fig. 2).

Sensitivity analyses conducted at extreme scenarios for XELOX and mFOLFOX-6 demonstrated that these results were robust. All (100%) patients receiving XELOX were assumed to require a CVAD and a port catheter for drug administration (i.e. a worst-case scenario for XELOX, as the cost associated with use of a port catheter is generally higher than that of a PICC) and conversely, all patients receiving mFOLFOX-6 were assumed to require a CVAD, PICC and an infuser for drug administration (i.e. the best-case scenario for mFOLFOX-6, as costs associated with use of a PICC and an infuser are generally lower than that for a port catheter and CADD pump/cassette). In the first-line setting, using XELOX resulted in an average cost saving of $4297 per patient, compared with mFOLFOX-6. In the second-line setting the same assumptions resulted in an average cost saving of $3009 per patient, compared with mFOLFOX-6.

Other sensitivity analyses conducted around changes to various cost estimates, probabilities for the use of different drug administration components and treatment setting weights also supported the base case results.

DISCUSSION

The presented economic evaluations show that treating a mCRC patient in Australia with XELOX results in cost savings, compared with mFOLFOX-6, in both the

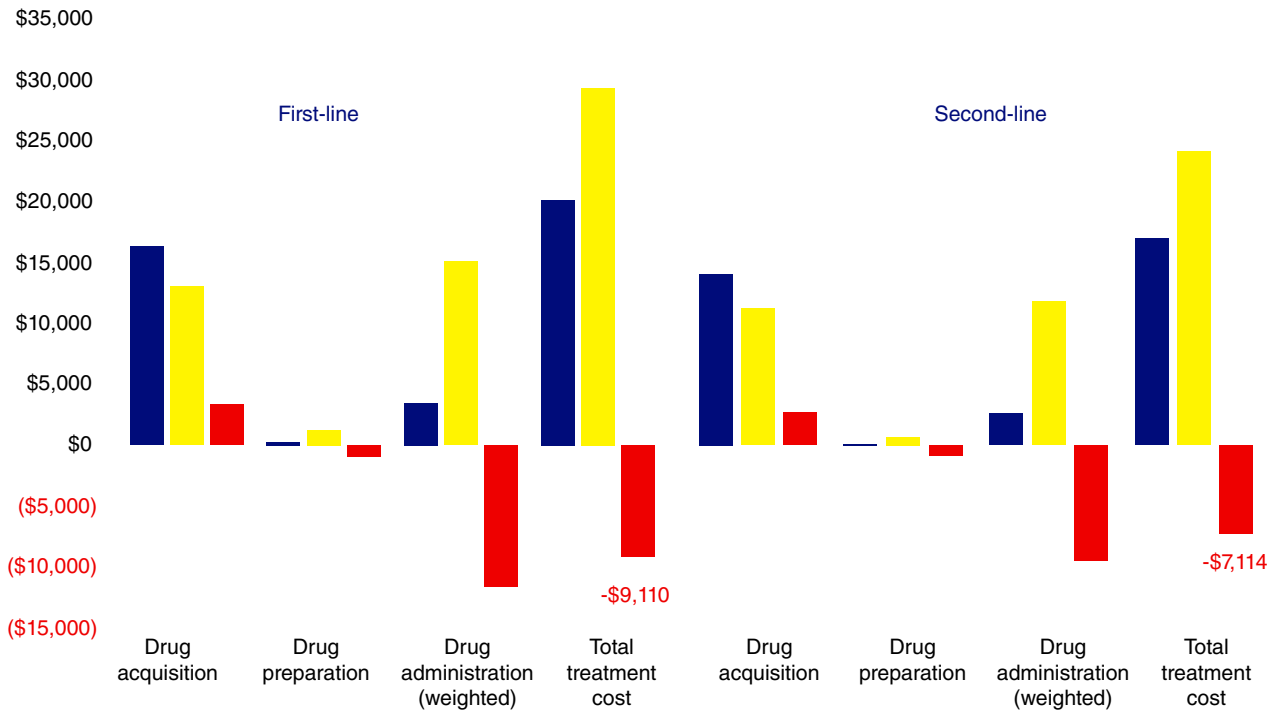

Figure 2 Average first and second-line cost of metastatic colorectal cancer mCRC treatment course per patient (Australian dollars) for ■ fluorouracil plus leucovorin in combination with oxaliplatin and ■ capecitabine plus oxaliplatin, and ■ difference.

first-line ($9110 per average chemotherapy patient) and second-line ($7113) settings. The sensitivity analyses verified the robustness of these results. Differences in pharmaceutical acquisition costs between the capecitabine and 5-FU-containing arms were offset by differences in the costs of drug preparation and drug administration. Most significantly, capecitabine avoids the additional procedures and visits required by patients receiving 5-FU via continuous infusion in the mFOLFOX-6 regimen.

In the base case, drug acquisition costs for a course of XELOX (first-line $16 317, second-line $14 259) were approximately 25 percent higher than mFOLFOX-6 (first-line $12 961; second-line $11 402). Preparation costs for XELOX (first-line $277; second-line $199) were lower than those for mFOLFOX-6 (first-line $1226; second-line $852). Calculated administration costs for mFOLFOX-6 were up to 84 percent higher than those of XELOX in the different possible chemotherapy settings for both first-line and second-line treatment. This difference was principally due to the administration of i.v. 5-FU by continuous infusion over 46 h each cycle, the connection of a CADD pump/cassette or an infuser and disconnection every 2 weeks. The costs associated with CADD pump/cassette or infuser connection and disconnection did not apply to XELOX, as neither capecitabine nor oxaliplatin were administered by continuous infusion.

The cost savings that accrue as a result of using XELOX in preference to mFOLFOX-6 are not in terms of PBS expenditure, but rather from an Australian government health-care perspective at both the state and federal government levels. These savings were derived through the cost of drug administration (MBS item numbers), prostheses costs and the cost of drug administration in public and private hospitals. In practical terms, these savings would be generated at an individual hospital/clinic level; for example, a switch to XELOX in suitable patients is likely to result in a reduced demand on physician and nursing resources at the individual oncology units.

If half the approximately 3500 Australian patients newly diagnosed with mCRC annually were administered XELOX instead of mFOLFOX-6, and assuming that first-line XELOX decreases direct medical costs by approximately $9000 per patient, estimated annual savings of $3500 \times \$9000 = \$31.5$ million would accrue to the Australian government health-care budget.

The observed savings are consistent with the findings of Best and Garrison (2010) who conducted a systematic review of the literature from January 2003 to December 2009 on the economics of capecitabine for the treatment of colon cancer.[20] Six economic studies of capecitabine in mCRC were identified, of which two included capecitabine in combination therapy with oxaliplatin.[21,22] Since this review, Perrocheau *et al*. (2010) have conducted a cost-minimization analysis of XELOX versus FOLFOX-6 in the first-line treatment of French mCRC patients and reported that treatment with XELOX decreased the cost per patient and reduced the mean overall hospitalization length of stay in comparison to FOLFOX-6.[23]

Other direct medical costs were not included in these analyses for reasons that can be justified. The safety profile of XELOX and FOLFOX has been well documented in the literature.[9–14] An analysis of the co-administered agents used to treat adverse events in the pivotal trials NO16966 and NO16967 showed that the use of these treatments was either balanced or lower in the XELOX arm, compared with the comparator arm. Excluding these concomitant treatments from the economic evaluation was a conservative assumption and in fact is biased against XELOX (data not presented; the clinical study reports for both trials were assessed for concomitant medications).[14,15] Furthermore, costs of hospitalization for treatment-related adverse events, laboratory tests and professional health-care visits (primary care, specialist and nursing visits) were excluded because they did not have a significant impact on the economic evaluation. Indirect costs, such as days of work lost due to chemotherapy, and direct non-medical costs, such as costs of transportation of patients to clinics, were neither calculated nor included as these are not considered by the PBAC in their deliberations.

Although first-line chemotherapy in Australia is now mainly given with the anti-angiogenic inhibitor bevacizumab, the costs associated with bevacizumab, which were not factored into this evaluation, will not impact on the outcome, considering that the treatment will apply to both regimens equally. We also note that despite reductions in the cost of oxaliplatin in recent times due to the expiry of the patent; it will not have an impact on the relative cost comparisons between the two regimens. The cost-minimization analyses presented here demonstrated that XELOX is cost saving as compared with mFOLFOX-6 in both the first-line and second-line treatment of mCRC from an Australian government health-care budget perspective.

During the evaluation of the PBAC submission, the analyses were revised based on changes suggested by the pharmaceutical evaluation section of the Australian Department of Health and Ageing. Key changes made included modifying the assumptions around the mode of administration of XELOX and mFOLFOX-6, changing the unit costs associated with the administration of XELOX and mFOLFOX-6 and changing the percentage of patients who would receive i.v. chemotherapy in each treatment setting (i.e., public in-patient in a public hospital, private in-patient in a public hospital, private in-patient in a private hospital, private hospital outpatient and public hospital outpatient). When all changes were incorporated in the cost-minimization analysis, XELOX remained cost saving from an Australian government health budget perspective.

Based on the analyses discussed in this article, XELOX received a positive recommendation from the PBAC for the treatment of first-line and second-line mCRC in March 2010. XELOX was listed on the PBS on 1 August 2010.

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