Oncology Research, Vol. 22, pp. 311–319
Printed in the USA.

0965-0407/15 $90.00 + .00
DOI: http://dx.doi.org/10.3727/096504015X14424348426152
E-ISSN 1555-3906
www.cognizantcommunication.com

Cost-Effectiveness Analysis of Adjuvant Stage III Colon Cancer Treatment at Veterans Affairs Medical Centers

Amy Soni,* Sherrie L. Aspinall,†‡§ Xinhua Zhao,‡ Chester B. Good,†‡§¶ Francesca E. Cunningham,† Gurkamal Chatta,# Vida Passero,** and Kenneth J. Smith††

*University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA
†VA Pharmacy Benefits Management Services, Hines, IL, USA
‡VA Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA
§University of Pittsburgh, School of Pharmacy, Pittsburgh, PA, USA
¶University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA
#Virginia Mason Medical Center, Seattle, WA, USA
**VA Pittsburgh Healthcare System, Pittsburgh, PA, USA
††University of Pittsburgh, Division of Clinical Modeling and Decision Sciences, Pittsburgh, PA, USA

The objective of this study was to evaluate the real-world cost effectiveness of adjuvant stage III colon cancer chemotherapy regimens, given that previous analyses have been based on data from clinical trials. The study was designed using integrated decision tree and Markov model, which was developed to evaluate the cost effectiveness of 5-fluorouracil/leucovorin (5-FU/LV), capecitabine, and the combination of each with oxaliplatin. The analysis was performed from a US Veterans Affairs perspective via retrospectively collected data, over a 5-year model time horizon. Outcome and cost data were used to calculate cost per quality adjusted life year (QALY), and one-way and probabilistic sensitivity analyses were performed. In the base case analysis, capecitabine and capecitabine plus oxaliplatin both cost more and were less effective than other regimens, and 5-FU/LV plus oxaliplatin, compared to 5-FU/LV alone, resulted in a cost of $25,997 per QALY gained. Model results were generally robust to parameter variation. Capecitabine plus oxaliplatin could be economically reasonable if full dosing occurred ≥76% of the time (base case 42%). In a real-world setting, the addition of oxaliplatin to 5-FU/LV is more effective but also more costly than 5-FU/LV alone. If full dosing of capecitabine-containing regimens can be assured, they may also be cost-effective strategies.

Key words: Colon cancer; 5-Fluorouracil (5-FU); Capecitabine; Oxaliplatin; Cost-effectiveness

INTRODUCTION

Colorectal cancer is projected to be the second leading cause of cancer-related death in the US in 2014, leading to an estimated 50,310 deaths (1). Outcomes improve when the disease is diagnosed and treated at localized or regionally advanced stages compared with distant spread. New adjuvant chemotherapy options for stage III colon cancer were established starting in 2004 (2–4), and several chemotherapy regimens may now be used to improve survival.

Chemotherapy choice for stage III disease may depend on tumor characteristics, patient performance status and comorbidities, patient preference/ability to comply with an oral regimen, and overall clinician assessment. There are also real, although somewhat subtle, differences in disease-free survival (DFS) and overall survival (OS) between regimens that should be balanced with differences in the cost of treatment.

Previous cost-effectiveness analyses (CEAs) based on seminal clinical trials have generally shown an acceptable incremental cost-effectiveness ratio with adding oxaliplatin to a 5-fluorouracil (5-FU)/leucovorin (LV)-containing regime (5–7) and also the dominance (i.e., decreased cost and improved health outcomes) of capecitabine monotherapy compared to 5-FU/LV without oxaliplatin (8). To our knowledge, there have been no published clinical trials directly comparing 5-FU plus oxaliplatin to capecitabine plus oxaliplatin in the adjuvant setting, but one Greek CEA (unpublished clinical data) demonstrated that capecitabine plus oxaliplatin was less expensive (9).

Address correspondence to Amy Soni, M.D., Palo Alto Medical Foundation, Sunnyvale Center, 301 Old San Francisco Road, Level 1, Sunnyvale, CA 94086, USA. E-mail: soniac@sutterhealth.org

However, real-world outcomes may differ from clinical trial outcomes. For example, patients may be older and have a poorer performance status in clinical practice, and adherence may be less than optimal. These differences may affect the improvements in DFS and OS that adjuvant chemotherapy regimens provide and, in turn, affect cost-effectiveness analysis results.

The MOSAIC (2), X-ACT (3), and XELOXA (4) trials were published several years ago, and widespread use of the adjuvant regimens described has now produced real-world outcome data. In this study, we evaluated the cost-effectiveness of adjuvant chemotherapy regimens for Veterans with stage III colon cancer diagnosed between 2003 and 2008, using data from a retrospective, cohort study (10).

MATERIALS AND METHODS

Overview

An integrated decision tree and Markov model was developed to compare the 5-year benefits and medical costs for the four most commonly used adjuvant colon cancer regimens: 5-FU/LV, capecitabine, 5-FU/LV plus oxaliplatin, and capecitabine plus oxaliplatin. Costs and benefits were combined into an incremental cost-effectiveness ratio (ICER): the difference in cost per patient divided by the difference in benefits. In this study, the ICER is the cost after start of adjuvant chemotherapy per quality adjusted life year gained.

The Markov model was developed to track outcomes in 6-month cycles for 5 years; chemotherapy was completed in 6 months and outcome data were available for approximately 5 years. The model has four health states (following surgical resection): no complications, acute complications, chronic complications, and death (Fig. 1). Patients began the model in either the no complications or acute complications (during chemotherapy) states and then transitioned to other states based on specified probabilities. Only patients with an acute complication could develop chronic complications.

The cost-effectiveness analysis was performed from a Veterans Affairs (VA) perspective with a discount rate of 3%. The decision model was implemented in TreeAge Pro 2013 (www.treeage.com; TreeAge Software Inc., Williamstown, MA, USA).

Study Setting

Model data were based on a retrospective cohort study of 356 patients diagnosed with stage III colon cancer from 2003 to 2008 and treated with adjuvant chemotherapy at one of 19 VAs nationally (10). Patients were followed through June 30, 2011, and chemotherapy was typically administered on an outpatient basis (infusional 5-FU started in clinic and continued at home). Tumor stage and characteristics, performance status, adverse drug events, and chemotherapy data were recorded at each site using the VA electronic medical record. Patient demographic information was obtained from VA administrative databases. Baseline characteristics are outlined in Table 1.

The four most commonly used regimens were 5-FU/LV, capecitabine, 5-FU/LV plus oxaliplatin, and capecitabine

Table 1. Baseline Characteristics of the Study Population (Patients Starting Treatment With Adjuvant Chemotherapy at VA Medical Centers, 2003–2008)

Characteristic	5-FU/LV (*N*=126) [*N*(%)]	Capecitabine (*N*=48) [*N*(%)]	5-FU/LV Plus Oxaliplatin (*N*=152) *N*(%)	Capecitabine Plus Oxaliplatin (*N*=30) [*N*(%)]
Age (mean, in years)	67.2	73.1	63.7	65.6
Age (years)				
<55	11 (8.7)	0 (0.0)	23 (15.1)	3 (10.0)
55–64	41 (32.5)	8 (16.7)	66 (43.4)	13 (43.3)
65–74	45 (35.7)	17 (35.4)	38 (25.0)	7 (23.3)
75+	29 (23.0)	23 (47.9)	25 (16.4)	7 (23.3)
Male	124 (98.4)	47 (97.9)	148 (97.4)	30 (100.0)
Charlson Comorbidity Index [mean (SD)]	1.3 (1.8)	1.2 (1.2)	1.1 (1.9)	0.8 (1.4)
ECOG performance status				
0	26 (20.6)	6 (12.5)	52 (34.2)	7 (23.3)
1	19 (15.1)	8 (16.7)	14 (9.2)	2 (6.7)
2-4	8 (6.3)	7 (14.6)	3 (2.0)	1 (3.3)
Missing or unknown	73 (57.9)	27 (56.3)	83 (54.6)	20 (66.7)

5-FU/LV, 5-fluorouracil/leucovorin; ECOG, Eastern Cooperative Oncology Group.

plus oxaliplatin (Table 1). Because this was a retrospective study, different versions of these regimens were administered by clinicians. For example, FOLFOX4 or modified FOLFOX6 could have been used as a 5-FU/LV plus oxaliplatin regimen. For the CEA, the most commonly prescribed version was used in cost and dose intensity calculations. The standard versions were: 5-FU/LV—Roswell Park (5-FU 500 mg/m^2 IV and LV 500 mg/m^2 IV, weekly for 6 weeks with 2 weeks off, for three cycles) (11,12), capecitabine – X-ACT study (1,250 mg/m^2 orally twice daily, 14 days on/7 days off, for eight cycles) (3), 5-FU with oxaliplatin—mFOLFOX6 (5-FU 400 mg/m^2 bolus followed by 2,400 mg/m^2 46 h continuous infusion IV, LV 400 mg/m^2 IV, and oxaliplatin 85 mg/m^2 IV, every 2 weeks, for 12 cycles) (13,14), and capecitabine plus oxaliplatin—XELOXA study (capecitabine 1,000 mg/m^2 orally twice daily for 14 days on/7 days off and oxaliplatin 130 mg/m^2 IV, every 3 weeks, for eight cycles) (4).

The proportion of patients receiving each regimen varied over time, reflecting the more recent publication of studies involving oxaliplatin (2) and capecitabine (3,4). 5-FU/LV was most commonly administered in 2003–2004, and 5-FU/LV plus oxaliplatin rose to prominence starting in 2005. Both capecitabine-containing regimens gradually increased in use throughout the study period, but were used less often than the 5-FU-based regimens. Additionally, patients receiving capecitabine monotherapy were older and had a worse ECOG performance status compared to those receiving other regimens (Table 1).

The study specifically examined outcomes in patients who received greater than 70% relative dose intensity (RDI) compared to those who did not. RDI is the proportion of the standard regimen (considering both number of cycles and dose with each cycle) actually received. Study patients who received >70% RDI had an improved 5-year OS (10); thus, this is the RDI cutoff used to define full-dose chemotherapy in our analysis.

Cost Calculations

Cost data were derived from the national VA databases in 2008. Four cost categories were created: chemotherapy, acute complications, chronic complications, and surveillance costs.

Chemotherapy cost was comprised of medications, medication administration, antiemetic prophylaxis, central line placement, and laboratory tests. Medication cost took into account the mean body surface area of study subjects, cost per milligram of drug, and RDI. Medication administration cost was derived from the hourly wages of VA nurses, pharmacists, and pharmacy technicians multiplied by hours worked by each in preparing and administering chemotherapy. For 5-FU/LV and capecitabine, it was assumed that all patients took prochlorperazine orally for antiemetic prophylaxis, whereas ondansetron and dexamethasone intravenously were given for oxaliplatin-containing regimens. It was assumed that a central intravenous line was required for 5-FU/LV, 5-FU/LV plus oxaliplatin, and capecitabine plus oxaliplatin but not capecitabine monotherapy. Laboratory studies consisted of a complete blood count with differential and comprehensive metabolic panel, drawn prior to each chemotherapy dose.

The six most common study acute adverse drug events (ADEs) resulting in changes or delays in chemotherapy were diarrhea/GI toxicity, hand–foot syndrome, mucositis, neuropathy, neutropenia, and thrombocytopenia. For each chemotherapy regimen, the average cost of an emergency department (ED) visit or hospitalization for each ADE was multiplied by the observed probability of each occurring. Inpatient stays and ED visits contributed most to the cost of ADEs, but extra outpatient clinic visit costs for ADEs were also estimated by multiplying clinic visit cost by the probability of having any ADE. Neutropenia cost included growth factor use (filgastrim or pegfilgastrim) given as an outpatient. The only chronic complication was assumed to be prolonged neuropathy from oxaliplatin-containing regimens (15). Gabapentin 300 mg per day was given for this complication.

Surveillance over the 5-year period consisted of two screening colonoscopies, office visits every 3 months, carcinoembryonic acid levels every 3 months, and CT chest, abdomen, and pelvis every 6 months. This schema is based on current National Comprehensive Cancer Network guidelines (16), except that CT scans were assumed to be ordered twice yearly instead of yearly, based on expert opinion.

Probability and Utility Values

Chemotherapy benefit was expressed as 5-year OS, estimated by unadjusted Kaplan–Meier curves. Two 5-year OS probabilities were used for each adjuvant regimen: one for patients who received full-dose (>70% RDI) chemotherapy and one for patients who did not. Additionally, the probability of a patient on a given regimen completing full-dose treatment was incorporated in the model. Acute complication probabilities were available from study data, but the rate of developing chronic neuropathy was derived from the literature (in MOSAIC, 5.9% of patients had grades 2–3 neuropathy at 12 months) (2).

All quality of life utility values were derived from the medical literature (17–20) and were used to calculate quality adjusted life years gained. Distinct utility values were not found for specific regimens (e.g., 5-FU/LV vs. capecitabine); thus the same value was used for each regimen. Utility values for each state were 0.8 for receiving chemotherapy without complications (8,17), 0.63 for acute complications (18), 0.60 for chronic complications (only applies for oxaliplatin regimens) (6,19,20), and 0.92 for posttreatment/remission (17).

Sensitivity Analyses

Model parameter uncertainty was evaluated with one-way and probabilistic sensitivity analyses. Parameters were varied based on model assumptions and by comparison with medical literature values. One-way sensitivity analyses were first performed, and the most influential parameters are reported.

Then probabilistic sensitivity analysis was performed using nonparametric Monte Carlo simulations with 5,000 iterations for all variables. Gamma distributions were used for cost variables, and beta distributions were used for probability and utility values. A willingness-to-pay threshold of $100,000/QALY was used. These results are displayed as a cost-effectiveness acceptability curve. Given demographic differences between chemotherapy groups, we also attempted an analysis adjusting for age and comorbidities.

RESULTS

Base Case Parameters

Chemotherapy and acute complication costs were incurred during the first 6-month interval. As expected, medication costs for capecitabine-containing regimens were greater than 5-FU-containing regimens (Table 2). Administration and central line costs increased the total chemotherapy costs for all regimens except capecitabine monotherapy. Acute complication costs were higher for 5-FU-containing regimens than the capecitabine-containing regimens, and this was primarily driven by neutropenia

Table 2. Model Inputs: Per Patient Costs of Treatment, Complications, and Surveillance Over 6-Month Time Periods and Probability Values

	5-FU/LV	Capecitabine	5-FU/LV Plus Oxaliplatin	Capecitabine Plus Oxaliplatin
Chemotherapy cost				
Medication itself	$247.67	$4,488.54	$1,271.10	$5,140.04
Administration	$2,337.96	$0	$3,996.78	$1,349.33
Anti-emetics	$2.82	$35.15	$33.93	$57.77
Central line	$819.08	$0	$819.08	$819.08
Labs	$460.08	$204.48	$306.72	$204.48
Total	**$3,867.61**	**$4,728.17**	**$6,427.61**	**$7,799.14**
Acute complication cost				
Diarrhea, n/v	$589.70	$533.22	$206.57	$632.26
Hand–foot syndrome	$31.61	$91.83	N/A	N/A
Mucositis	$184.98	N/A	$42.11	N/A
Neuropathy	N/A	N/A	$2.25	N/A
Neutropenia	$1,155.87	N/A	$3452.25	N/A
Thrombocytopenia	$39.26	N/A	$73.88	N/A
Clinic visit	$127.87	$163.29	$222.30	$173.65
Total	**$2,129.29**	**$788.34**	**$3,998.86**	**$805.91**
Chronic complication (neuropathy) cost	**$0**	**$0**	**$4.97**	**$4.97**
Surveillance cost*	**$1,522.17**	**$1,522.17**	**$1,522.17**	**$1,522.17**
Probability values				
Acute complications	40.5%	51.7%	70.4%	55.0%
Chronic complications	0%	0%	5.9%	5.9%
Receiving full dose (>70% RDI)†	66.7%	31.3%	78.3%	42.1%
5 year OS, full dose	55.9%	61.2%	77.7%	77.6%‡
5 year OS, if NOT full dose	54.0%	50.9%	44.3%	45.5%

Note: Chemotherapy and acute complication costs occur over the first 6-month interval only. Chronic complication and surveillance costs are incurred over the remaining 4.5 years; average cost of these values over a 6-month interval is listed. 5-FU/LV, 5-fluorouracil/leucovorin; n/v, nausea/vomiting; CEA, carcinoembryonic acid; CT c/a/p, computed tomography of chest, abdomen, pelvis; RDI, relative dose intensity; OS, overall survival.

*Over the 4.5-year surveillance interval, assumed that two colonoscopies, 18 office visits, 18 CEA levels, and 9 CT c/a/p would be required. Value reported is total cost of these tests divided by 6 months.

†Patients with missing values for RDI (4.3–8.7% of patients, depending on regimen) were excluded.

‡All patients who received full-dose capecitabine plus oxaliplatin survived to 5 years. Given that this represented only eight patients, 5-year OS probability for this group was assumed to be 77.6% (instead of 100%), based on the XELOXA trial (4).

and subsequent growth factor administration. Over the model's 5-year time horizon, surveillance costs contributed most to total cost for each regimen.

The probability of having at least one acute complication (i.e., one of the six ADEs that led to a change or delay in chemotherapy) was highest for 5-FU/LV plus oxaliplatin, but patients receiving this regimen were also more likely to actually receive full-dose chemotherapy (Table 2). Five-year OS was improved for patients on each regimen receiving full-dose chemotherapy.

Base Case Results

Over the model's 5-year time period, total costs (including all chemotherapy, treatment of complications, and continuing management costs) by regimen were 5-FU/LV $14,361.88, capecitabine $14,670.49, 5-FU/LV plus oxaliplatin $19,905.87, and capecitabine plus oxaliplatin $18,022.08. Benefits, in terms of QALYs gained, were 5-FU/LV 3.25, capecitabine 3.20, 5-FU/LV plus oxaliplatin 3.46, and capecitabine plus oxaliplatin 3.24.

In the cost-effectiveness analysis, both capecitabine monotherapy and capecitabine plus oxaliplatin were strictly dominated, meaning that they were both more expensive and less effective than other regimens. When compared to 5-FU/LV alone, 5-FU/LV plus oxaliplatin cost an additional $25,977 to gain one QALY.

Sensitivity Analyses

Parameters leading to a regimen other than 5-FU/LV plus oxaliplatin being favored in one-way sensitivity analyses were probability of 5-year OS if full-dose 5-FU/LV was received; probability of receiving full-dose capecitabine plus oxaliplatin, and the utility value for 5-FU/LV plus oxaliplatin posttreatment/remission (Table 3). The probability of receiving full-dose capecitabine plus oxaliplatin was low in the base case at 42%; at values over 76%, it was the favored strategy. Neither increasing the chemotherapy costs for capecitabine-containing regimens (accounting for higher medication costs) nor greatly increasing chemotherapy costs for 5-FU-containing regimens (accounting for higher administration costs) changed the favored strategy.

Probabilistic sensitivity analyses revealed that 5-FU/LV plus oxaliplatin is likely to be cost-effective at willingness-to-pay thresholds greater than $28,000/QALY (Fig. 2). Overall, sensitivity analyses supported both model result robustness to variation and that 5-FU/LV plus oxaliplatin was the most effective regimen with an acceptable ICER.

We attempted to perform an analysis adjusting for age and comorbidities and found that 5-year OS improved for capecitabine monotherapy (older, sicker patients) and worsened for capecitabine plus oxaliplatin (fewer comorbidities). However, this analysis is not reliable because the linear regression model assumes a constant age gradient (21), and patients in the capecitabine group were much older.

DISCUSSION

Previous CEAs using data from stage III colon cancer adjuvant chemotherapy clinical trials have generally demonstrated that capecitabine is less expensive and more effective than 5-FU/LV (8,22)-containing regimens and that adding oxaliplatin to 5-FU/LV has an acceptable ICER compared to 5-FU/LV alone (5–7). We used real-world VA data to compare 5-FU/LV and capecitabine, both alone and in combination with oxaliplatin. In contrast to previous CEAs, we show that capecitabine and capecitabine plus oxaliplatin were more expensive and less effective than 5-FU/LV-containing regimens. Also, 5-FU/LV plus oxaliplatin had an acceptable ICER compared to 5-FU/LV alone, at $25,997 per QALY gained. The results were robust in one-way and probabilistic sensitivity analyses.

Table 3. Key One-Way Sensitivity Analysis Results: Parameters Whose Variation Changed the Preferred Strategy

Parameter	Base Case	Range [Reference(s)]	5-FU/LV Plus Oxaliplatin Not Favored if Value
Probability 5-year OS, full dose 5-FU/LV	55.9%	50% to 80% (3,4,26,27)	≥71%*
Probability receiving full-dose capecitabine plus oxaliplatin	42.1%	40% to 85% (4)	≥76%†
Utility: patients completing 5-FU/LV plus oxaliplatin	0.92	0.75 to 0.95 (17)	≤0.85‡

5-FU/LV, 5-fluorouracil/leucovorin; OS, overall survival.
*5-FU/LV (without oxaliplatin) favored if value ≥71%. Also, for values between 68% and 70%, 5-FU/LV plus oxaliplatin favored but is >$100,000/QALY.
†Capecitabine plus oxaliplatin favored if value ≥76%.
‡5-FU/LV (without oxaliplatin) favored if value ≤0.85. Also, for values between 0.86 and 0.87, 5-FU/LV plus oxaliplatin favored but is >$100,000/QALY.

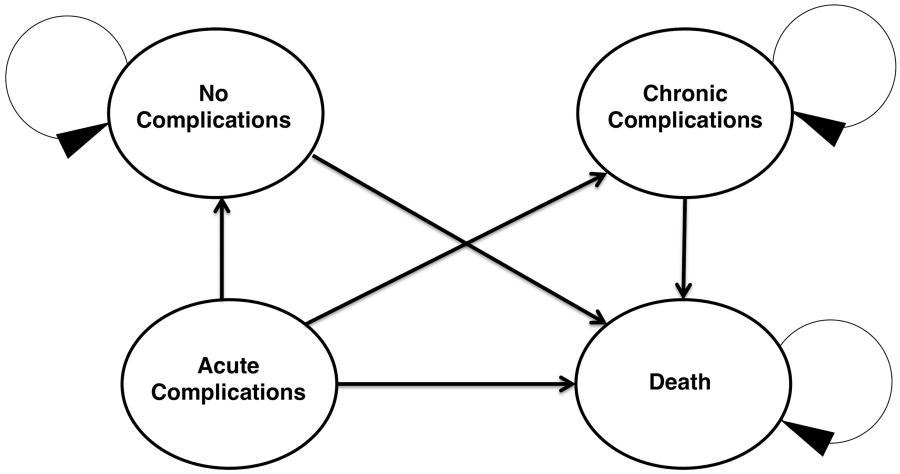

Figure 1. Simplified Markov model, representing transitions between states after the start of adjuvant chemotherapy. Note: All patients start in either the No Complications or Acute Complications states. Cycle length was 6 months, and the model was run for 5 years.

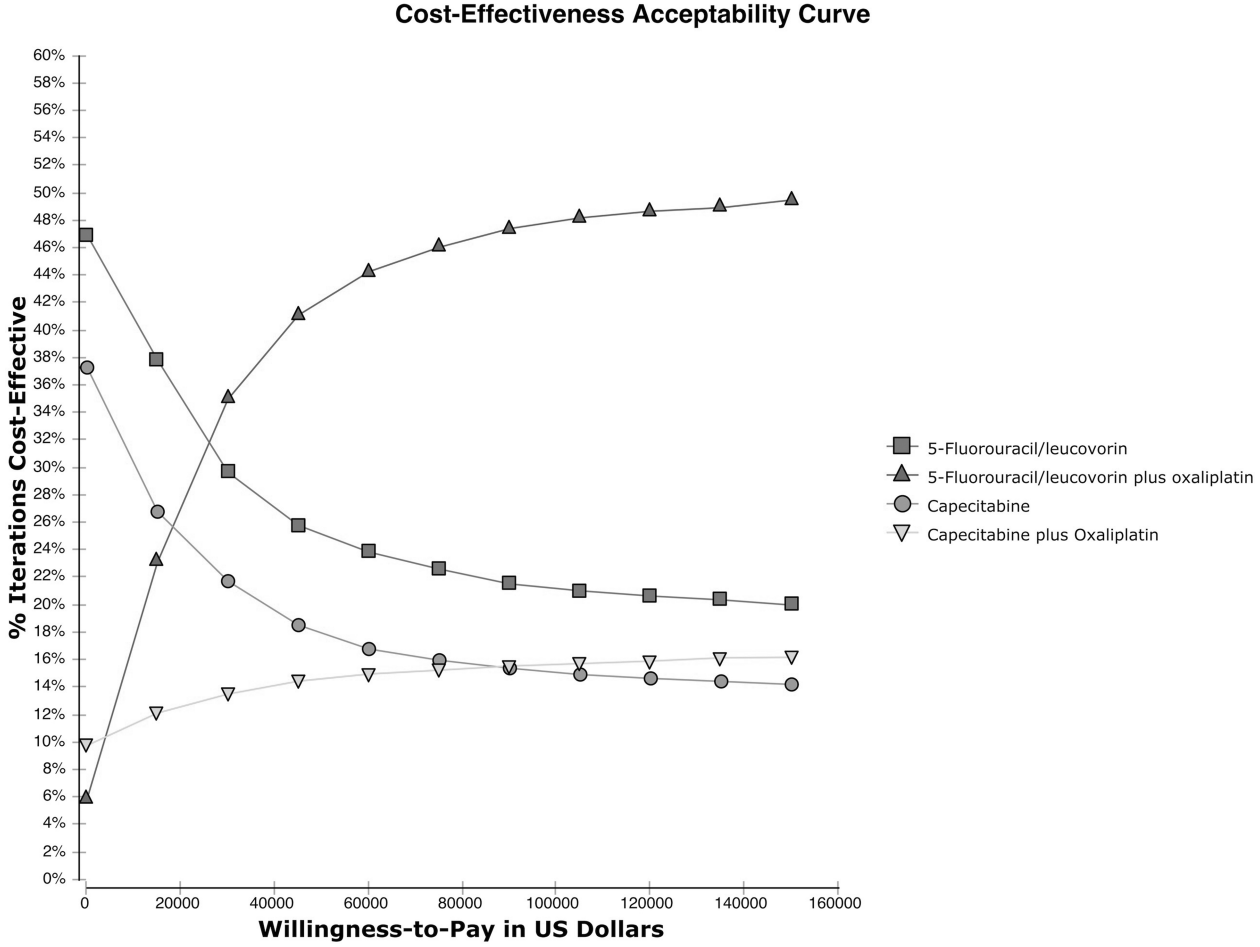

Figure 2. Cost-effectiveness acceptability curves for the four adjuvant chemotherapy regimens.

Comparison to Previous Studies

The dominance (i.e., decreased cost and increased effectiveness) of 5-FU/LV-containing regimens over capecitabine-containing regimens in this study may be accounted for by a few key differences in model inputs compared to previous CEAs. First, clinical outcome data were based on real-world VA patients. Suboptimal compliance with capecitabine in the nontrial setting may have decreased effectiveness (23,24), and capecitabine dose reductions may have been greater than in trials. Indeed, in this study, those patients who received >70% RDI for all regimens had improved OS. With the oxaliplatin-containing regimens in particular, increasing the probability of receiving >70% RDI for capecitabine plus oxaliplatin to 76% (base case 42.1%) made it favored over 5-FU/LV plus oxaliplatin.

Furthermore, survival in some previous CEA studies was defined differently. One study used relapse-free survival (RFS) (22), and several others extrapolated OS from DFS data (5–8). While 3-year DFS has been shown to correlate with OS in the adjuvant setting (25), we argue that actual OS remains the best effectiveness measure. OS from clinical trials has been somewhat less impressive than DFS results (26–28). Our study used OS values from real-world clinical practice.

Many previous CEAs were performed in Europe, where 5-FU infusions are administered in the hospital (in day care wards/observation units) (5,8,9,22,29). The costs of 5-FU-containing regimens are, in turn, largely driven by the inpatient administration costs. In the US, the 5-FU infusion is typically started in clinic and continued at home, diminishing administration costs.

Additionally, a few cost assumptions in our analysis deserve mention. Central intravenous line placement was assumed for all patients receiving capecitabine plus oxaliplatin; but, this may not always be done in clinical practice. However, no change in the favored strategy was seen when this cost was eliminated. Also, the 5-FU infusion pump costs were not included because they are typically VA owned and are a fixed cost not relevant for CEAs per the Panel on Cost-Effectiveness in Health and Medicine (30). Similar to one previous study (8), we assumed that scheduled office visit frequency would be similar for the four regimens.

Limitations

Although we followed the recommendations from the Panel on Cost-Effectiveness in Health and Medicine as closely as possible (30), and we strove for a "real-world" rather than a clinical trial-based analysis, the limitations of our data led to some limitations in our results. A key limitation contributing to 5-FU regimens being less expensive and more effective in our analysis is that there were fewer patients in both the capecitabine monotherapy and capecitabine plus oxaliplatin groups, compared to 5-FU-containing groups. Study patients were diagnosed from 2003 to 2008, and capecitabine use became more prevalent only toward the study's end (10). Furthermore, patients receiving capecitabine monotherapy were older and had more comorbidities than those in other groups. Adjusting our analysis for age/comorbidities was not reliable given that the capecitabine group was so different. The observational nature of the real-world outcome data used led to these limitations.

Using VA data and conducting the analyses from the VA perspective enabled use of multicenter US data and transparent cost data. However, non-VA costs are often higher than at the VA (31). Despite this, we expect that practice patterns (e.g., how to manage chemotherapy complications) are similar to non-VA settings. Also, most patients were male, perhaps making the current study less generalizable, but we are not aware of data suggesting different clinical outcomes between men and women. Using the VA perspective and not a societal perspective also meant that patient-related costs, travel cost, and cost of missed work were not included. This could be relevant for patients taking oral capecitabine instead of IV 5-FU/LV.

We chose a 5-year time horizon for the analyses because OS study data were available for this length of time. Some other CEAs in this setting have used a lifetime horizon by making assumptions about relapse and its treatment (5–7). This makes our analysis more difficult to compare to those studies, but treatment at relapse would be similar regardless of what adjuvant chemotherapy regimen was chosen, particularly after more time had passed.

Neuropathy is a key oxaliplatin complication. Cost attributed to acute neuropathy, which accounted for the rate of neuropathy, were minimal for both oxaliplatin regimens. Acute complication costs were based on ED visits and hospitalizations, and thus neuropathy managed in clinic was not directly evaluated in our analysis. It was indirectly evaluated in that dose reductions may have occurred due to neuropathy, and RDI was a key part of the analysis. Occurrence of chronic neuropathy was not available, and thus its frequency and cost were based on the medical literature and our clinical experience. Similarly, other assumptions regarding antiemetic prophylaxis regimens used were based on clinical experience.

Finally, utility values were obtained from the medical literature, and the same values were used for each chemotherapy regimen. However, differential quality-of-life decrements may occur; for example, acute complications for 5-FU/LV may be less than capecitabine plus oxaliplatin. Such potential differences in utility values were evaluated in sensitivity analyses, and only a decreased utility post-treatment for 5-FU/LV plus oxaliplatin affected the model result, with 5-FU/LV becoming the favored strategy.

Thus, our analysis, like any model-based cost-effectiveness analysis, is an attempt to depict reality and not reality itself. We used real-world data, supplemented by other data as necessary and varied all model parameters within clinically plausible ranges to test the robustness of our results.

CONCLUSION

In this cost-effectiveness analysis of adjuvant stage III colon cancer chemotherapy regimens, performed from a real-world VA perspective over a 5-year time horizon, we found that 5-FU/LV and 5-FU/LV plus oxaliplatin were less expensive and more effective than capecitabine monotherapy and capecitabine plus oxaliplatin. Also, 5-FU/LV plus oxaliplatin was more effective than 5-FU/LV alone and had an acceptable ICER. If compliance with capecitabine can be assured, leading to full-dose administration of capecitabine plus oxaliplatin, then this regimen may also be an acceptable alternative to 5-FU plus oxaliplatin. Future CEA studies could evaluate treatment of stage IIB disease and 3 versus 6 months of adjuvant treatment.

ACKNOWLEDGMENTS: The views expressed in this article are those of the authors, and no official endorsement by the Department of Veteran Affairs or the United States Government is intended or should be inferred. There was no funding support for the work. These findings are the result of work supported in kind by VA Pharmacy Benefits Management Services, Hines, IL, USA, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA, and the other VA medical centers that participated in the study. None of the authors has a relevant financial interest in this manuscript. The VA Oncology Pharmacotherapy Research Group includes Bernadette B. Heron, Pharm.D. (VA Pharmacy Benefits Management Services, Hines, IL, USA); Mark Geraci, Pharm.D. (VA Pharmacy Benefits Management Services, Hines, IL, USA); Roslyn A. Stone, Ph.D. (VA Pittsburgh Healthcare System, Pittsburgh, PA, USA; University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA); Renee Rogers, Pharm.D. (VA Pittsburgh Healthcare System, Pittsburgh, PA, USA); Jenna Shields, Pharm.D. (VA Pittsburgh Healthcare System, Pittsburgh, PA, USA); Megan Sartore, Pharm.D. (VA Pittsburgh Healthcare System, Pittsburgh, PA, USA); D. Patrick Boyle, RPh (VA Maine Health Care System, Augusta, ME, USA); Sherry Giberti, CTR (VA Maine Health Care System, Augusta, ME, USA); John Szymanski, Pharm.D. (VA Connecticut Healthcare System, West Haven, CT, USA); Doug Smith, Pharm.D. (Martinsburg VA Medical Center, Martinsburg, WV, USA); Allen Ha, Pharm.D. (Richmond VA Medical Center, Richmond, VA, USA); Jolynn Sessions, Pharm.D. (Asheville VA Medical Center, Asheville, NC, USA); Shawn Depcinski, Pharm.D. (James A. Haley Veterans Hospital, Tampa, FL, USA); Shane Fishco, Pharm.D. (James A. Haley Veterans Hospital, Tampa, FL, USA); Irvin Molina, Pharm.D. (Miami VA Medical Center, Miami, FL, USA); Tanja Lepir, Pharm.D. (Miami VA Medical Center, Miami, FL, USA); Carmela Jean, Pharm.D. (Miami VA Medical Center, Miami, FL, USA); Lymaris Cruz-Diaz, Pharm.D. (VA Caribbean Healthcare System, San Juan, PR, USA); Jessica Motta, Pharm.D. (VA Caribbean Healthcare System, San Juan, PR, USA); Rebeca Calderon-Vargas, Pharm.D. (VA Caribbean Healthcare System, San Juan, PR, USA); Janelle Maland, Pharm.D. (Harry S. Truman VA Hospital, Columbia, MO, USA); Sean Keefe, Pharm.D. (Kansas City VA Medical Center, Kansas City, MO, USA); Marshall Tague, Pharm.D. (Iowa City VA Medical Center, Iowa City, IA, USA); Alice Leone, R.Ph. (Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA); Brian Glovack, Pharm.D. (Jesse Brown VA Medical Center, Chicago, IL, USA); Blair Kaplan, Pharm.D. (Jesse Brown VA Medical Center, Chicago, IL, USA); Sean Cosgriff, Pharm.D. (Portland VA Medical Center, Portland, OR, USA); Lindsay Kaster, Pharm.D. (Boise VA Medical Center, Boise, ID, USA); Ivy Tonnu-Mihara, Pharm.D. Long Beach VA Medical Center, Long Beach, CA, USA); Kimmai Nguyen, Pharm.D. (Long Beach VA Medical Center, Long Beach, CA, USA); Jenna Carmichael, Pharm.D. (VA Sierra Nevada Health Care System, Reno, NV, USA); and Kan Lu, Pharm.D. (Sacramento VA Medical Center, Mather, CA, USA).

REFERENCES

1. Cancer of the Colon and Rectum - SEER Stat Fact Sheets. Surveillance, Epidemiology, and End Results (SEER) Program Research Data (1973-2011), National Cancer Institute. http://seer.cancer.gov/statfacts/html/colorect.html. Accessed June 30, 2014.
2. André, T.; Boni, C.; Mounedji-Boudiaf, L.; Navarro, M.; Tabernero, J.; Hickish, T.; Topham, C.; Zaninelli, M.; Clingan, P.; Bridgewater, J.; Tabah-Fisch, I.; de Gramont, A.; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N. Engl. J. Med. 350(23):2343–2351; 2004.
3. Twelves, C.; Wong, A.; Nowacki, M. P.; Abt, M.; Burris, H. 3rd; Carrato, A.; Cassidy, J.; Cervantes, A.; Fagerberg, J.; Georgoulias, V.; Husseini, F.; Jodrell, D.; Koralewski, P.; Kröning, H.; Maroun, J.; Marschner, N.; McKendrick, J.; Pawlicki, M.; Rosso, R.; Schüller, J.; Seitz, J. F.; Stabuc, B.; Tujakowski, J.; Van Hazel, G.; Zaluski, J.; Scheithauer, W. Capecitabine as adjuvant treatment for stage III colon cancer. N. Engl. J. Med. 352(26):2696–2704; 2005.
4. Haller, D. G.; Tabernero, J.; Maroun, J.; de Braud, F.; Price, T.; Van Cutsem, E.; Hill, M.; Gilberg, F.; Rittweger, K.; Schmoll, H. J. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J. Clin. Oncol. 29(11):1465–1471; 2011.
5. Eggington, S.; Tappenden, P.; Pandor, A.; Paisley, S.; Saunders, M.; Seymour, M.; Sutcliffe, P.; Chilcott, J. Cost-effectiveness of oxaliplatin and capecitabine in the adjuvant treatment of stage III colon cancer. Br. J. Cancer 95(9):1195–1201; 2006.
6. Aballéa, S.; Chancellor, J. V.; Raikou, M.; Drummond, M. F.; Weinstein, M. C.; Jourdan, S.; Bridgewater, J. Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/leucovorin in adjuvant treatment of stage III colon cancer in the US. Cancer 109(6):1082–1089; 2007.
7. Attard, C. L.; Maroun, J. A.; Alloul, K.; Grima, D. T.; Bernard, L. M. Cost-effectiveness of oxaliplatin in the adjuvant treatment of colon cancer in Canada. Curr. Oncol. 17(1):17–24; 2010.
8. Cassidy, J.; Douillard, J. Y.; Twelves, C.; McKendrick, J. J.; Scheithauer, W.; Bustová, I.; Johnston, P. G.; Lesniewski-Kmak, K.; Jelic, S.; Fountzilas, G.; Coxon, F.; Díaz-Rubio, E.; Maughan, T. S.; Malzyner, A.; Bertetto, O.; Beham, A.; Figer, A.; Dufour, P.; Patel, K. K.; Cowell, W.; Garrison, L. P. Pharmacoeconomic analysis of adjuvant oral capecitabine vs intravenous 5-FU/LV in Dukes' C colon cancer: The X-ACT trial. Br. J. Cancer 94(8):1122–1129; 2006.

9. Maniadakis, N.; Fragoulakis, V.; Pectasides, D.; Fountzilas, G. XELOX versus FOLFOX6 as an adjuvant treatment in colorectal cancer: An economic analysis. Curr. Med. Res. Opin. 25(3):797; 2009.
10. Aspinall, S. L.; Good, C. B.; Zhao, X.; Cunningham, F. E.; Heron, B. B.; Geraci, M.; Passero, V.; Stone, R. A.; Smith, K. J.; Rogers, R.; Shields, J.; Sartore, M.; Boyle, D. P.; Giberti, S.; Szymanski, J.; Smith, D.; Ha, A.; Sessions, J.; Depcinski, S.; Fishco, S.; Molina, I.; Lepir, T.; Jean, C.; Cruz-Diaz, L.; Motta, J.; Calderon-Vargas, R.; Maland, J.; Keefe, S.; Tague, M.; Leone, A.; Glovack, B.; Kaplan, B.; Cosgriff, S.; Kaster, L.; Tonnu-Mihara, I.; Nguyen, K.; Carmichael, J.; Clifford, L.; Lu, K.; Chatta, G. Adjuvant chemotherapy for stage III colon cancer: Relative dose intensity and survival among veterans. BMC Cancer 15:62; 2015.
11. Petrelli, N.; Herrera, L.; Rustum, Y.; Burke, P.; Creaven, P.; Stulc, J.; Emrich, L. J.; Mittelman, A. A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J. Clin. Oncol. 5(10):1559–1565; 1987.
12. Haller, D. G.; Catalano, P. J.; Macdonald, J. S.; O'Rourke, M. A.; Frontiera, M. S.; Jackson, D. V.; Mayer, R. J. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: Final report of Intergroup 0089. J. Clin. Oncol. 23(34):8671–8678; 2005.
13. Cheeseman, S. L.; Joel, S. P.; Chester, J. D.; Wilson, G.; Dent, J. T.; Richards, F. J.; Seymour, M. T. A "modified de Gramont" regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br. J. Cancer 87(4):393–399; 2002.
14. Hochster, H. S.; Hart, L. L.; Ramanathan, R. K.; Childs, B. H.; Hainsworth, J. D.; Cohn, A. L.; Wong, L.; Fehrenbacher, L.; Abubakr, Y.; Saif, M. W.; Schwartzberg, L.; Hedrick, E. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: Results of the TREE Study. J. Clin. Oncol. 26(21):3523–3529; 2008.
15. Land, S. R.; Kopec, J. A.; Cecchini, R. S.; Ganz, P. A.; Wieand, H. S.; Colangelo, L. H.; Murphy, K.; Kuebler, J. P.; Seay, T. E.; Needles, B. M.; Bearden, J. D. 3rd; Colman, L. K.; Lanier, K. S.; Pajon, E. R. Jr.; Cella, D.; Smith, R. E.; O'Connell, M. J.; Costantino, J. P.; Wolmark, N. Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. J. Clin. Oncol. 25(16):2205–2211; 2007.
16. Benson, A. B.; Venook, A. P.; Bekaii-Saab, T.; Chan, E. Colon cancer version 3.2014. J. Natl. Compr. Canc. Netw. 2014.
17. Ramsey, S. D.; Andersen, M. R.; Etzioni, R.; Moinpour, C.; Peacock, S.; Potosky, A.; Urban, N. Quality of life in survivors of colorectal carcinoma. Cancer 88(6):1294–1303; 2000.
18. Ness, R. M.; Holmes, A. M.; Klein, R.; Dittus, R. Utility valuations for outcome states of colorectal cancer. Am. J. Gastroenterol. 94(6):1650–1657; 1999.
19. Launois, R.; Reboul-Marty, J.; Henry, B.; Bonneterre, J. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Pharmacoeconomics 10(5):504–521; 1996.
20. Shiroiwa, T.; Fukuda, T.; Tsutani, K. Health utility scores of colorectal cancer based on societal preference in Japan. Qual. Life Res. 18(8):1095–1103; 2009.
21. McNamee, R. Regression modelling and other methods to control confounding. Occup. Environ. Med. 62(7):500–606; 2005.
22. Douillard, J-Y.; Tilleul, P.; Ychou, M.; Dufour, P.; Perrocheau, G.; Seitz, J. F.; Maes, P.; Lafuma, A.; Husseini, F. Cost consequences of adjuvant capecitabine, Mayo Clinic and de Gramont regimens for stage III colon cancer in the French setting. Oncology 72(3–4):248–254; 2007.
23. Simons, S.; Ringsdorf, S.; Braun, M.; Mey, U. J.; Schwindt, P. F.; Ko, Y. D.; Schmidt-Wolf, I.; Kuhn, W.; Jaehde, U. Enhancing adherence to capecitabine chemotherapy by means of multidisciplinary pharmaceutical care. Support. Care Cancer 19(7):1009–1018; 2011.
24. Hohneker, J.; Shah-Mehta, S.; Brandt, P. S. Perspectives on adherence and persistence with oral medications for cancer treatment. J. Oncol. Pract. 7(1):65–67; 2011.
25. Sargent, D. J. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: Individual patient data from 20,898 patients on 18 randomized trials. J. Clin. Oncol. 23(34):8664–8670; 2005.
26. André, T.; Boni, C.; Navarro, M.; Tabernero, J.; Hickish, T.; Topham, C.; Bonetti, A.; Clingan, P.; Bridgewater, J.; Rivera, F.; de Gramont, A. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J. Clin. Oncol. 27(19):3109–3116; 2009.
27. Yothers, G.; O'Connell, M. J.; Allegra, C. J.; Kuebler, J. P.; Colangelo, L. H.; Petrelli, N. J.; Wolmark, N. Oxaliplatin as adjuvant therapy for colon cancer: Updated results of NSABP C-07 trial, including survival and subset analyses. J. Clin. Oncol. 29(28):3768–3774; 2011.
28. Twelves, C.; Scheithauer, W.; McKendrick, J.; Seitz, J. F.; Van Hazel, G.; Wong, A.; Díaz-Rubio, E.; Gilberg, F.; Cassidy, J. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: Final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann. Oncol. 23(5):1190–1197; 2012.
29. Jansman, F. G. A.; Postma, M. J.; van Hartskamp, D.; Willemse, P. H. B.; Brouwers, J. R. B. J. Cost-benefit analysis of capecitabine versus 5-fluorouracil/leucovorin in the treatment of colorectal cancer in the Netherlands. Clin. Ther. 26(4):579–589; 2004.
30. Weinstein, M. C.; Siegel, J. E.; Gold, M. R.; Kamlet, M. S.; Russell, L. B. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 276(15):1253–1258; 1996.
31. Piette, J. D.; Wagner, T. H.; Potter, M. B.; Schillinger, D. Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. Med. Care. 42(2):102–109; 2004.