Sequential Therapies and the Cost-Effectiveness of Treating Metastatic Colon Cancer Patients

Andinet Woldemichael, PhD; Eberechukwu Onukwugha, MSc, PhD;
Brian Seal, RPh, MBA, PhD; Nader Hanna, MD; and C. Daniel Mullins, PhD

ABSTRACT

BACKGROUND: Technological advances in colon cancer treatment have significantly increased survival outcomes among metastatic patients. With different chemotherapy and biologic regimens administered in first, second, and subsequent lines of treatments, costs and survival outcomes vary considerably. However, there is little evidence on how the type of regime administered in the first line of treatment affects the costs and survival outcomes of the second line of treatment.

OBJECTIVE: To examine how the cost-effectiveness of second-line treatment for elderly metastatic colon cancer patients varies by the type of regimen administered in the first line of treatment.

METHODS: The Surveillance, Epidemiology and End Results (SEER) cancer registry was used, which is linked with the Medicare claims database, to study elderly metastatic patients diagnosed between 2003 and 2009. Average survivals are estimated using the robust nonparametric Kaplan-Meier method. Selection bias was adjusted for using inverse probability weighting and censoring using robust nonparametric methods of estimating the average of total health care costs.

RESULTS: Mean incremental survival was 6.7 months for patients who received second-line treatment (95% CI=5.7-7.7) compared with those receiving only first-line treatment. However, the mean incremental survival varied between 4 months (95% CI=0.0-7.3) and 9 months (95% CI=6.5-11.0) depending on whether fluorouracil with or without leucovorin, irinotecan, oxaliplatin, or other agents were administered in first-line treatment. The mean incremental cost associated with receipt of second-line treatment was \$60,231 (95% CI=52,461-64,198) but ranged between \$55,368 (95% CI=48,294-61,290) and \$71,211 (95% CI=43,168-99,667), depending on the type of regimen administered in the first-line treatment. Combining survival benefits and costs, the incremental cost-effectiveness ratios per life-year gained associated with the receipt of second-line treatment were \$97,368 (95% CI=80,415-117,965); \$110,621 (95% CI=89,560-133,961); \$130,689 (95% CI=101,459-171,918); and \$247,951 (95% CI=112,629-808,976) when irinotecan, fluorouracil/leucovorin, oxaliplatin, and "other" combinations were, respectively, administered in first-line treatment. In addition, the results varied depending on which statistical method was used.

CONCLUSIONS: When therapies are administered in a sequential manner, the cost-effectiveness of the second line of therapy depends on what was administered in the first line of therapy.

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- According to the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, therapies are administered sequentially with important implications for survival and cost outcomes.

What this study adds

- This study examined how the cost-effectiveness of second-line treatment for elderly metastatic colon cancer patients varied by the type of regimen administered in the first line of treatment.
- Population-level data were used from the Surveillance, Epidemiology, and End Results cancer registry linked with Medicare claims (SEER-Medicare) to identify the sequence of therapies administered to metastatic colon cancer patients.
- The results highlighted that cost-effectiveness of the second line of therapy depends on what was administered in the first line of therapy.

Advances in chemotherapies and targeted drugs have significantly increased survival outcomes among metastatic colon cancer patients. Studies show that, without chemotherapy, metastatic patients survive for only a median duration of 8 months.¹ When treated with a combination of chemotherapies such as fluorouracil (5-FU), irinotecan (IRI), and oxaliplatin (OX), survival increases to 21 months.¹ In addition, there is evidence that biologics in combination with chemotherapy further improves survival outcome. For instance, 1 study found that progression-free survival rates in a group who received bevacizumab (BEV) plus IRI and 5-FU/LV (IFL) was 10.6 months compared with 6.2 months in the group administered with IFL plus placebo.² While BEV and ziv-aflibercept (Zaltrap) block the growth of blood vessels to tumors, cetuximab (CET) and panitumumab (PAN) are epidermal growth factor receptor (EGFR) inhibitors, which block effects of hormone-like factors that promote cancer cell growth.

According to the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, chemotherapies alone, or in conjunction with biologics, are sequentially administered in first line, second line, and subsequent lines of treatments depending on a patient's tolerance of toxicity, gene mutation profile, tumor progression, and prognosis. Sequential treatment protocol has important implications for survival and cost outcomes. Studies show that the type of regimen administered in the

What is already known about this subject

- Studies show that when metastatic colon cancer patients are treated with a combination of chemotherapies, survival increases to 21 months; biologics alone or in combination with chemotherapy may further improve progression-free survival.

TABLE 1 Summary Statistics of First- and Second-Line Regimens with Socioeconomic and Clinical Characteristics^a

	Whole Sample (n = 4,513)	Second-Line Treatment	
		Not Received (n = 2,566)	Received (n = 1,947)
First-line regimen			
5-FU/LV	31	35	25
IRI	14	15	14
OX	51	46	59
Other (IROX, biologics)	4	5	2
Second-line regimen			
IRI	NA	NA	57
OX	NA	NA	22
Other (5FU/LV, IROX, biologics)	NA	NA	21
Socioeconomic characteristics			
Age at diagnosis (years), mean (SD)	75.2 (6.2)	76.0 (6.3)	74.1 (5.7)
Married	57	53	62
Male	49	48	51
White	81	80	82
Black	10	10	8
Hispanic	5	5	5
Other race/ethnicity	5	5	5
Urban residence	89	89	90
Received state assistance (buy-ins) following diagnosis	11	10	12
Clinical characteristics			
Charlson Comorbidity Index scores			
0	58	54	62
1	23	24	22
2+	19	22	16
Not available	5	6	4
Tumor size			
Not available	25	28	22
0-39 mm	20	19	22
40-59 mm	29	28	31
60-99 mm	22	21	22
100+ mm	3	4	3
Poorly differentiated tumor	29	30	27
Poor baseline performance	13	15	12

^aAll statistics are percentages unless otherwise noted. Due to rounding, sum of the percentages may exceed 100%.

5-FU/LV=fluorouracil with or without leucovorin; IRI=irinotecan; IROX=irinotecan plus oxaliplatin; OX=oxaliplatin; SD=standard deviation.

first-line treatment significantly affects the likelihood of receiving a second-line treatment.³ Similarly, survival and cost outcomes of second-line treatment could depend on the type of regimen administered in the first-line treatment.

There is little evidence, however, on how the type of first-line regimen affects survival and cost outcomes of second-line treatment. The literature focuses on the cost-effectiveness of second-line treatment without regard to the type of regimen administered as the first line of treatment.⁴⁻⁷ The existing studies compare survival and cost outcomes associated with different regimens in the second-line treatment only. These outcomes are also based on randomized controlled trials (RCTs) conducted in non-U.S. health care systems and study

populations. Furthermore, since elderly individuals are often underrepresented in clinical studies, it can be problematic to generalize the results from RCTs for this high risk-population within the United States.

The purpose of this study was to investigate how the cost-effectiveness of second-line treatment for metastatic colon cancer patients in the U.S. Medicare population varies by the type of first-line regimens.

Methods

Data and Descriptive Analysis

For this investigation, population-level data were used from the Surveillance, Epidemiology, and End Results (SEER)

FIGURE 1 Monthly Average Total Costs

A. Overall: Anchoring Date Is Diagnosis Date

B. Second-Line Treatment Status: Anchoring Date Is Last Date of Receiving First-Line Tx Plus 1 Day

Note: All costs are in January 2009 prices. Green (squared) droplines denote monthly average total costs for patients who received second-line treatment. Red (circle) droplines denote monthly total costs for patients who did not receive second-line treatment.

Dx=diagnosis; NCH=National Claims History records; Tx1=first-line treatment; Tx=treatment.

cancer registries linked with the Medicare claims database from the National Cancer Institute (NCI). The SEER database collects clinical, demographic, and cause of death information; the Medicare data provide claims information from hospital, physician, outpatient, home health care, hospice, and Medicare Part D.⁸ The linked database has clinical, demographic, socioeconomic, and claims information for 1.6 million Medicare beneficiaries diagnosed with various types of cancers. A cohort of 11,010 elderly (aged 66 and above) patients were identified who were diagnosed with metastatic colon cancer between 2003 and 2009. Of the identified cohort members, 4,513 received NCCN-recommended regimens for first-line treatment. While 43.1% (n=1,947) of cohort members received second-line treatment, 56.9% (n=2,566) of cohort members did not.

Different lines of treatments and regimens were identified using a claims-based algorithm.⁹ The algorithm used Current Procedural Terminology (CPT), Health Care Common Procedural Codes (HCPCs), *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, and *International Classification of Diseases, Ninth Revision* (ICD-9) codes along with NCCN-recommended treatment cycles to identify therapies and lines of treatments from claims data. The sample was stratified into 4 groups based on the type of regimens received in first-line treatment: (1) 5-FU with or without leucovorin (5-FU/LV); (2) IRI with or without 5-FU/LV; (3)

OX with or without 5-FU/LV; and (4) “others,” which included combinations such as irinotecan plus oxaliplatin (IROX) or biologics without OX, IRI, or 5-FU/LV. Table 1 presents the percentage of patients who received different types of regimens and descriptive statistics of selected patient-level clinical, demographic, and socioeconomic characteristics for the whole sample and the subsamples stratified by second-line treatment status. OX is the most frequently prescribed first-line regimen, which was administered to more than half of the patients (51%) in the sample, followed by 5-FU/LV (31%) and IRI (14%). Other combinations were administered to only 4% of patients for first-line treatment.

In terms of patient-level characteristics, those who proceeded to second-line treatment were 2 years younger at the time of diagnosis than patients who did not receive second-line treatment. The descriptive statistics show that whites and married patients were more likely to receive second-line treatment. Patients who resided in urban areas and those who received financial assistance in the form of state buy-ins after diagnosis were also more likely to receive second-line treatment. Patients with 1 or more comorbidity, as measured by the Charlson Comorbidity Index (CCI) were less likely to receive second-line treatment than patients with no comorbidities. Similarly, patients who received second-line treatment had better baseline performance status and larger and well-differentiated primary tumors.

FIGURE 2 Distributions of Propensity Scores and Inverse Probability of Treatment Weights

IPTW = inverse-probability-of-treatment weighting.

Estimation Methods

To estimate average total costs, selection bias into and out of receipt of second-line treatment was controlled for using the inverse-probability-of-treatment weighting (IPTW) approach. Censoring was addressed using nonparametric methods proposed by Bang and Tsiatis (2000), referred to here as the B&T method, and Lin et al. (1997), referred to here as Lin's method.^{10,11} Although there are various parametric methods of adjusting survival for covariates in the case of nonproportional hazard rates, unadjusted average survival was estimated using the nonparametric Kaplan-Meier (KM) method.

The study period was restricted to a 5-year follow-up period after the patient's last date of receiving first-line treatment plus 1 day. The event of interest is death from any cause. Patients who were alive at the end of the follow-up period, who were enrolled in health management organizations (HMOs), or who had lost Medicare Part A or Part B coverage were censored. These observations accounted for 17.7% (n=345) of patients who received second-line treatment. Similarly, 20.3% (n=531) of patients who did not receive second-line treatment were censored. The overwhelming majority of patients who were censored were censored because they were alive at the end of the study. The full cost and survival information for the censored individuals not in the dataset were not observed, which could potentially bias the estimation of average total cost, survival, and incremental costs and effects.

Estimation of Costs and Survivals. Costs were measured over a 5-year follow-up period from the anchoring date, which

was set at the last date of receiving first-line treatment plus 1 day. Costs were obtained from Medicare reimbursement for hospital care, physician and clinical services, skilled nursing facility (SNF), home health agency (HHA), and hospice care. Total costs were calculated by summing reimbursements for Medicare Part A and Part B, which represented payments made to inpatient, SNF, HHA, outpatient, hospice, durable medical equipment (DME), and carrier claims, also known as Medicare National Claims History (NCH) records. Payments made for prescription drugs (Part D) were excluded from cost calculations because Part D coverage started in July 2006, whereas this study covers the period between 2003 and 2009. However, excluding Part D from the total costs for metastatic colon cancer patients in both groups had no major impact on the cost-effectiveness analysis, since it represents a small proportion of total cost (Figure 1A). The bulk of total cost comes from Medicare Part A and B reimbursements.

To make costs comparable over time, all costs were inflated to January 2009 prices using the national U.S. Bureau of Labor Statistics monthly itemized medical care component of the Consumer Price Index. Nursing home services prices were used to adjust hospice, SNF, and HHA claims; inpatient hospital prices were used to adjust inpatient claims; outpatient hospital prices were used to adjust outpatient claims; medical care commodities prices were used to adjust DME claims; and physician services prices were used to adjust NCH claims. Average total monthly cost was mainly driven by inpatient, NCH (physician and suppliers), and outpatient claims (Figure 1A). The average total monthly cost for patients who received

TABLE 2 Estimated Survivals and Costs Associated with Receipt of Second-Line Treatment

		Method	Baseline		IPTW	
			Mean	95% CI	Mean	95% CI
Survival (months)	Received second-line Tx	Kaplan-Meier	16.9	16.3-17.6		
	No second-line Tx	Kaplan-Meier	10.2	9.5-11.0		
	Incremental survival	Kaplan-Meier	6.7	5.7-7.7		
Cost, \$	Received second-line Tx	Simple average	103,711	94,923-107,512	89,322	81,697-92,476
		B&T ^a	117,686	108,998-122,109	100,530	93,064-104,088
		Lin ^b	114,076	105,212-118,487	97,470	89,957-101,020
	No second-line Tx	Simple average	35,068	34,003-36,192	35,877	34,755-37,160
		B&T ^a	41,308	39,936-42,748	41,963	40,561-43,501
		Lin ^b	36,588	35,260-37,920	37,240	35,859-38,721
	Incremental cost	Simple average	68,642	59,764-72,745	53,445	45,946-56,883
		B&T ^a	76,377	67,319-81,288	58,567	50,877-62,558
		Lin ^b	77,488	68,289-82,351	60,231	52,461-64,198

Note: Mean and incremental estimates were based on a bootstrap with 1,000 replications. 95% CIs were calculated using a percentile method from the same bootstrap. Baseline scenario reflects results without accounting for selection bias, and IPTW accounts for selection bias. All values are in January 2009 prices. Anchoring date = last date of receiving first-line Tx plus 1 day. Follow-up period = 5 years (60 months).

^aNonparametric method proposed by Bang and Tsiatis.¹⁰

^bNonparametric method proposed by Lin et al.¹¹

CI = confidence interval; IPTW = inverse-probability-of-treatment weighting; Tx = treatment.

second-line treatment was considerably higher than patients who did not receive second-line treatment (Figure 1B).

The estimated average costs for censoring were adjusted using partitioned B&T and Lin's methods. One-month interval partition over a follow-up period of 60 months was used. This sentence comes from Results section page 7 line 5-6. For comparison, estimates were also reported using unpartitioned methods. While the unpartitioned method used information on total costs only from observations with complete information (uncensored), the partitioned methods used detailed cost history of the censored and uncensored observations. Both methods are nonparametric and do not adjust for the impact of covariates. Partitioned methods are the preferred approaches because the estimates are robust and precise.^{12,13}

Similar to estimating average total costs, censoring poses a challenge for estimating survival times because the entire survival distribution is not observed. The restricted mean survival time (RMST) was estimated for a 5-year follow-up period, which can be written as the following: $\mu(\bar{t}) = E[\min\{T, \bar{t}\}] = \int_0^{\bar{t}} S(t) dt$, where $\mu(\bar{t})$ is the RMST, T is time to death, $\bar{t}$ is the follow-up period, and $S(t)$ is the KM survivor curve.¹⁴ In this case, $\bar{t} = 60$ months. Imposing a time limit on survival and cost also avoids issues of identifiability in the marginal distribution of lifetime medical costs.¹⁵

Selection Bias

Selection bias is one of the major problems that arises when using a nonrandomized observational dataset. The problem of selection bias on observable factors for average total cost estimates was addressed by using the IPTW method. The inverse of predicted probabilities (propensity scores) of

receiving second-line treatment and not receiving second-line treatment were used to adjust for the respective contribution of treated and untreated patients.¹⁶⁻¹⁹ The propensity scores were estimated using a probit model on the probability of receiving second-line treatment. Covariates included age at the time of diagnosis, marital status, sex, race, place of residence, tumor size, tumor grade, composite index of baseline performance measures, and year of diagnosis. Since the IPTW could be extremely high when probabilities are closer to zero, a normalized IPTW was used (Figure 2).

Cost-Effectiveness Analysis: Incremental Costs, Incremental Survivals, and Incremental Cost-Effectiveness Ratios

The average incremental costs associated with the receipt of second-line treatment, denoted by Δ_c , is the difference between the average costs of patients who received second-line treatment (μ_{1c}) and the average costs of patients who did not receive second-line treatment (μ_{0c}), that is, $\Delta_c = \mu_{1c} - \mu_{0c}$. Similarly, the incremental survival associated with the receipt of second-line treatment, denoted by Δ_s , is the difference between the average months survived by patients who received second-line treatment (μ_{1s}) and the average months survived by patients who did not receive second-line treatment (μ_{0s}), that is, $\Delta_s = \mu_{1s} - \mu_{0s}$. Incremental costs and incremental survivals were calculated stratified by the type of regimen received in first-line treatment.

The overall cost-effectiveness of second-line treatment can be represented by the incremental cost-effectiveness ratio (ICER), which is a measure of additional cost per unit of health gained. ICER is the ratio of the incremental cost to the incremental survival ($ICER = \Delta_c / \Delta_s$). ICERs for second-line

FIGURE 3 Kaplan-Meier Estimates of Survival Rates by Second-Line Treatment Status

Tx1 = first-line treatment; Tx2 = second-line treatment.

treatment were estimated stratified by the type of regimen received in first-line treatment. In order to address skewedness in cost distributions, a robust bootstrap method was used with replacement, which does not rely on distributional assumptions.^{20,21} The bootstrapped values were used to then plot cost-effectiveness acceptability curves (CEACs) for a range of willingness-to-pay (WTP) thresholds given the observed data. The CEAC is a graphical tool that summarizes uncertainties surrounding the estimated ICERs with Bayesian spirit of parameter uncertainty. It shows the likelihood that second-line treatment was cost-effective compared with the alternatives for a range of WTP thresholds.

Results

Table 2 presents the KM estimates of RMST and incremental survivals by treatment status. It also presents the estimated average total costs and incremental costs associated with the receipt of second-line treatment for the unadjusted estimate (ignoring selection bias) and results after adjusting for selection using the IPTW method.

Survival Benefits

The estimated mean and median survivals for the entire sample were 13 and 7 months after the last date of receiving first-line

treatment. The 2-year, 3-year, and 5-year survival probabilities for patients who received second-line treatments were 24.3%, 12.2%, and 5%, respectively. For patients who did not receive second-line treatments, the 2-year, 3-year, and 5-year survival probabilities were 13.6%, 10.9%, and 8.1%, respectively. The KM survival estimates for patients who received second-line treatments and patients who did not receive second-line treatments are shown in Figure 3.

Patients who received second-line treatment survived for an average of 16.9 months (95% confidence interval [CI] = 16.3-17.6), whereas those who did not receive second-line treatments survived for an average of 10.2 months (95% CI = 9.5-11). The average incremental survival associated with the receipt of second-line treatment was 6.7 months (95% CI = 5.7-11). However, the gains in survival associated with receipt of second-line treatment vary depending on the type of regimen received in first-line treatment. Patients who started off treatment lines by receiving IRI in first-line treatments gained an average incremental survival of 8.7 months (95% CI = 6.5-11) when they received their second-line treatments. The average incremental survival gained from receipt of second-line treatments for patients who received complex regimens such as IROX or targeted therapies in first-line treatment was only 3.9 months (95% CI = 0.0-7.3).

TABLE 3 Estimated Survivals, Costs, and ICER Per LYG of Second-Line Treatment: Stratified by Type of Regimen Administered in First-Line Treatment

		Method	First-Line Tx = 5FU/LV (n = 1,392)		First-Line Tx = IRI (n = 651)		First-Line Tx = OX (n = 2,339)		First-Line Tx = Others (n = 161)	
			Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Survival (months)	Received second-line Tx	Kaplan-Meier	15.1	13.8-16.3	16.2	14.4-18.1	18.2	17.2-19.3	10.0	7.9-12.3
	No second-line Tx	Kaplan-Meier	8.6	7.6-9.6	7.4	5.9-9.1	13.1	11.8-14.5	6.2	3.7-9.3
	Incremental survival	Kaplan-Meier	6.5	4.8-8.1	8.7	6.5-11.0	5.1	3.5-6.8	3.9	0.0-7.3
Cost, \$	Received Second-line Tx	Simple average	96,226	88,397-103,015	98,766	89,882-107,832	77,470	71,227-82,668	146,170	117,001-174,714
		B&T ^a	102,073	94,081-109,364	110,241	99,344-119,981	91,134	84,349-96,957	146,584	117,302-175,219
		Lin ^b	98,216	90,260-105,424	104,315	93,729-113,671	88,462	81,685-94,276	130,411	103,239-156,705
	No second-line Tx	Simple average	39,821	37,647-42,146	36,065	33,370-38,951	30,020	28,626-31,328	63,753	53,881-73,669
		B&T ^a	44,016	41,562-46,606	40,573	37,487-43,698	37,127	35,270-38,899	71,980	60,541-83,243
		Lin ^b	39,302	36,973-41,649	34,300	31,261-37,220	33,094	31,281-34,815	59,201	49,020-68,949
	Incremental cost	Simple average	56,405	48,090-64,030	62,701	53,509-72,621	47,450	40,927-52,684	82,416	51,644-112,183
		B&T ^a	58,057	49,109-66,058	69,668	58,175-80,804	54,007	46,845-59,892	74,604	43,622-105,644
		Lin ^b	58,914	50,245-66,831	70,015	58,916-80,497	55,368	48,294-61,290	71,211	43,168-99,667
	ICER/LYG	Simple average	105,983	84,634-130,006	87,298	70,628-108,605	112,126	84,367-150,798	289,984	134,810-1,029,969
		B&T ^a	109,026	87,903-132,764	96,912	79,132-118,496	127,493	98,510-168,574	261,485	111,739-867,086
		Lin ^b	110,621	89,560-133,961	97,368	80,415-117,965	130,689	101,459-171,918	247,951	112,629-808,976

Note: Mean and incremental estimates were based on a bootstrap with 1,000 replications. 95% CIs were calculated using a percentile method from the same bootstrap. Results account for selection bias and IPTW accounts for selection bias. All values are in January 2009 prices. Anchoring date = last date of receiving first-line Tx plus 1 day. Follow-up period = 5 years (60 months).

^aNonparametric method proposed by Bang and Tsiatis.¹⁰

^bNonparametric method proposed by Lin et al.¹¹

5-FU/LV = fluorouracil with or without leucovorin; CI = confidence interval; ICER = incremental cost-effectiveness ratio; IPTW = inverse-probability-of-treatment weighting; IRI = irinotecan; LYG = life-year gain; OX = oxaliplatin; Tx = treatment.

Estimated Average Total Costs

The estimated average costs associated with receipt of second-line treatment are shown in Table 2. For the sake of brevity, results are reported from partitioned methods that used detailed cost histories: simple average (naïve), B&T method, and Lin's method. The estimated average total costs varied depending on the methods used to account for censoring and to address selection bias.

While censoring underestimated the average total cost for the treated group and the untreated group, selection bias overestimated the average total cost for the treated group and slightly underestimated the average total cost for the untreated group. When costs were not adjusted for using IPTW, the estimated average 5-year total cost for patients who received second-line treatment was \$103,711, \$117,686, and \$114,076 using simple average (naïve), B&T method, and Lin's method, respectively. When selection bias using IPTW was accounted for, the estimated average 5-year total cost for second-line treatment recipients was \$89,322, \$97,470, and \$100,530, respectively, when simple average, Lin's method, and B&T method were used to adjust for censoring.

For patients who did not receive second-line treatment, the 5-year average total cost was \$35,068, \$36,588, and \$41,308 when simple average (naïve), Lin's method, and B&T method, respectively, were used to adjust for censoring. After selection bias on observable factors was addressed, the estimated average total cost was \$35,877, \$37,240, and \$41,963 when simple average (naïve), Lin's method, and B&T method, respectively, were used to adjust for censoring. The incremental cost associated with receiving a second-line treatment after adjusting selection bias was \$58,567 and \$60,231, using B&T method and Lin's method, respectively. Without adjustment for selection bias, the estimated mean ICERs per life-year gained (LYG) were \$137,384 and \$139,378, when censoring was addressed using B&T method and Lin's method, respectively. When selection bias was controlled for using IPTW, the estimated mean ICERs per LYG became \$105,406 and \$108,394, using B&T method and Lin's method, respectively, for addressing censoring.

FIGURE 4 Scatter Plots of Incremental Costs and Effects of Second-Line Treatment Stratified by Type of Regimen Administered in First-Line Treatment

Note: Scatter points are based on 1,000 bootstrap replications for each strata. Results in (a) baseline do not account for selection bias whereas results in (b) accounts for selection bias. In both cases, censoring is dealt with using Lin et al.'s portioned method.¹¹ All values are in January 2009 prices. Anchoring date = last date of receiving first-line treatment plus 1 day. Follow-up period = 5 years (60 months).

5-FU/LV = fluorouracil with or without leucovorin; BIO = biologic; IPTW = inverse-probability-of-treatment weighting; IRI = irinotecan; IROX = irinotecan plus oxaliplatin; LYG = life-year gain; OX = oxaliplatin; Tx1 = first-line treatment; WTP = willingness to pay.

Table 3 presents the estimated survivals, incremental survivals, average total costs, incremental costs, and ICERs associated with receipt of second-line treatment stratified by the type of regimen administered in first-line treatment. For the sake of brevity, only results obtained after adjusting for selection bias in average total cost using IPTW are presented. For patients who received OX in first-line treatment, the incremental cost associated with receipt of a second-line treatment ranged between \$47,450 and \$55,368, and for patients who received IROX or biologic agents alone in first-line treatment, the incremental cost ranges between \$71,211 and \$82,416, depending on the method used to address censoring.

With the exception of patients who received other combinations in first-line treatment, the estimated mean ICERs associated with second-line treatment ranged between \$96,912 and \$130,689 per LYG. The conservative estimate (i.e., the higher average total costs estimate) showed that patients who received IRI, 5FU/LV, and OX in first-line treatment incurred costs of about \$97,368, \$110,621, and \$130,689, respectively, for a LYG from receiving second-line treatment. However, patients who received other chemotherapy regimens and biologics in

first-line treatment on average incurred costs between \$71,211 and \$74,604 for only a 4-month gain in survival from receiving second-line treatment, which implies a mean ICER of above \$250,000 for an additional LYG.

Discussion

This study compared costs and survival outcomes of patients who received second-line treatment with patients who did not receive second-line treatment. Incremental survivals, incremental costs, and ICERs associated with second-line treatment were estimated stratified by the type of regimen administered in first-line treatment. Because costs were obtained from Medicare claims, this analysis is from the payer's perspective.

This study showed that receiving second-line treatment significantly increased survival outcome by 6.7 months. However, survival benefits of second-line treatment varied by the type of regimen administered in the first line of treatment. Similarly, costs associated with second-line treatment varied by the type of regimen administered in first-line treatment. For instance, patients who were given OX as first-line treatment incurred lower average total costs in second-line treatment, whereas

FIGURE 5 Cost-Effectiveness Acceptability Curve by Type of Regimen Administered in First-Line Treatment

Note: CEACs were based on 1,000 bootstrap replications for each strata. Results are from specification that account for selection bias using IPTW and censoring using Lin et al.'s partitioned method.¹¹ All values are in January 2009 prices. Anchoring date = last date of receiving first-line Tx plus 1 day. Follow-up period = 5 years (60 months). 5-FU/LV = fluorouracil with or without leucovorin; BIO = biologic; CEAC = cost-effectiveness acceptability curve; IPTW = inverse-probability-of-treatment weighting; IRI = irinotecan; IROX = irinotecan plus oxaliplatin; LYG = life-year gain; OX = oxaliplatin; Tx1 = first-line treatment; WTP = willingness to pay.

patients who were given IROX or a biologic agent alone as first-line treatment incurred higher average total cost in second-line treatment. Furthermore, the results showed variation in the ICER for second-line treatment, depending on the type of regimen administered in first-line treatment. For instance, for all but patients who received other (IROX or biologics) regimens in first-line treatment, bootstrap values of ICERs associated with receipt of second-line treatment were scattered in the northeast region of the cost-effectiveness plane. This result is shown in Figure 4A for the baseline scenario without adjusting for selection bias and in Figure 4B after adjusting for selection bias using IPTW. This result underscores the finding that receiving second-line treatment increases survival outcomes at additional cost, which vary by the type of therapeutic agent received in the first-line of treatment. The scatter plots for 5FU/LV, IRI, and OX are tighter compared with other combinations. The same pattern is also reflected in the CIs, perhaps because of the small sample size of patients who received other regimens in first-line treatment.

Finally, the assessment of uncertainty associated with estimated mean ICERs using CEAC (Figure 5) shows that,

for second-line treatment to be cost-effective 50% of the time, the required WTP per LYG should be about \$108,000 for all patients who received second-line treatment. However, if patients received IRI, 5FU/LV, OX, and other regimens in their previous lines of treatment, the WTP for an additional LYG should be \$97,000, \$110,000, \$128,000, and \$230,000, respectively. The CEACs also indicate that there is substantial heterogeneity in the cost-effectiveness and uncertainty surrounding the effectiveness of second-line treatment. Among other factors, it is important to note that the level of uncertainty surrounding estimated incremental costs and ICERs vary considerably depending on statistical method used to address bias and censoring (Figure 6).

Limitations

Some limitations to this study need to be considered. First, the SEER-Medicare dataset is nonrandomized. Problems associated with a typical observational dataset such as selection bias and censoring in measurement of costs are critical issues that could undermine the validity of estimated parameters. However, SEER-Medicare data are commonly used to conduct economic

FIGURE 6 Cost-Effectiveness Acceptability Curves Associated with Receipt of Second-Line Treatment

^aNonparametric method proposed by Bang and Tsiatis.¹⁰

^bNonparametric method proposed by Lin et al.¹¹

IPW=inverse probability weighting; LYG=life-year gain; WTP=willingness to pay.

evaluations and national cost projections.²²⁻²⁴ Unlike most RCT studies, the SEER-Medicare database has detailed clinical and claims information on millions of patients, making it one of the most comprehensive datasets available to conduct population-level comparative effectiveness studies for the elderly population in the United States.

Second, this analysis does not account for selection on an unobservable dimension. The estimated incremental costs, incremental benefits, and ICERs associated with second-line treatment could be sensitive to unmeasured confounders at patient, provider, and geographic levels. Third, the results are not generalizable to the population outside this sample of elderly patients in the Medicare population diagnosed with metastatic colon cancer between 2003 and 2009. Fourth, the cost estimation did not account for generic versus brand price variations. Such variations could impact the cost-effectiveness analysis, since generic drugs are cheaper than brand names.²⁵ Although the drugs considered in this study were brand name during the study period, OX briefly went generic in 2009 until it was reverted back to brand. Also, providers could combine generic with brand-name drugs. Such unaccounted price varia-

tions could underestimate incremental costs and ICERs associated with OX, as well as impact the degree of uncertainty.

Last, immortal time bias (survivorship bias) serves as a problem for this study. Patients who survived long enough after first-line treatment were more likely to receive second-line treatment (survivors). Patients whose conditions were deteriorating could discontinue intensive therapy after first-line treatment in favor of supportive/palliative care. As a result, the estimated second-line survival benefits could be overstated.

Conclusions

Among elderly metastatic colon cancer patients, costs and survival benefits associated with the receipt of second-line treatment depend on the type of regimen administered in the first-line treatment. The estimated incremental survivals, incremental costs, and ICERs vary by the type of regimen administered in the first-line treatment. Patients who received second-line treatment lived for an additional 6.7 months compared with patients who did not receive second-line treatment. However, the gain in survival varies between 4 and 9 months, depending on the type of regimen received in the first-line treatment.

The incremental cost associated with the receipt of second-line treatment was \$60,231 but ranged between \$47,450 and \$82,416, depending on the type of regimen administered in the first-line treatment. Combining unadjusted survival benefits and costs, the ICER per LYG associated with receipt of second-line treatment ranged between \$96,912 and \$247,951, depending on the type of regimen administered in the first-line treatment. This study's results were robust to different statistical models. However, unmeasured confounders were not accounted for, and interpretation of results should be limited to the SEER-Medicare population. The ultimate conclusion, however, is that when therapies are administered in a sequential manner, the cost-effectiveness of the second line of therapy depends on what was administered in the first line of therapy.

Authors

ANDINET WOLDEMICHAEAL, PhD, Department of Pharmaceutical Health Services, University of Maryland School of Pharmacy, Baltimore. EBERECHUKWU ONUKWUGHA, MSc, PhD, and C. DANIEL MULLINS, PhD, Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore. BRIAN SEAL, RPh, MBA, PhD, Bayer Healthcare Pharmaceuticals, Wayne, New Jersey, and NADER HANNA, MD, Department of Surgery, Division of General and Oncologic Surgery, University of Maryland School of Medicine, Baltimore.

AUTHOR CORRESPONDENCE: Andinet Woldemichael, PhD, Department of Pharmaceutical Health Services, University of Maryland School of Pharmacy, 220 Arch St., Baltimore, MD 21201. Tel.: 410.706.6627; Fax: 410.706.5394; E-mail: andinet.michael@gmail.com.

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All authors contributed to the concept and design of this study. Onukwugha, Seal, and Mullins collected the data, with assistance from Woldemichael and Hanna, while Woldemichael interpreted the data, assisted by the other authors. The manuscript was written primarily by Woldemichael, with assistance from the other authors, and revised by Seal, Hanna, and Mullins, with assistance from Woldemichael and Onukwugha.

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