Cost-effectiveness of Treatment Sequences for Elderly Metastatic Colorectal Cancer Patients: A SEER-Medicare–Based Modeling Analyses

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BACKGROUND

- Colorectal cancer (CRC) is one of the most expensive cancers to treat and manage among the elderly in the United States (US).[1] In 2010, the cost for CRC was $14.1 billion; with an assumed 2% increase in medical costs each year, it has been projected to cost $17.7 billion by 2020.[2]
- Metastatic colorectal cancer (mCRC) has poor prognosis with an overall survival rate of 5% to 13% at 5 years.[3] Treatments for mCRC have changed considerably over the last decade with the approval of oxaliplatin, irinotecan, bevacizumab, cetuximab, and panitumumab.[4]
- Notably, the cost to treat patients with mCRC is twice the cost to treat patients with CRC ($121,800 vs. $61,800 per patient per year), and patients with mCRC are likely to receive more regimens, resulting in increased costs.[5] A study by Song et al. (2011)[6] found that mCRC costs $14,565 more per patient per month compared with noncancer patients, and systemic treatment accounts for 17.5% of this incremental cost.
- To our knowledge, no study has characterized the treatment sequences commonly administered specifically to elderly patients with mCRC and evaluated the cost-effectiveness of treatment sequences using real-world data.

OBJECTIVE

- This study aimed to identify the commonly administered treatment sequences using the Surveillance, Epidemiology, and End Results (SEER)–Medicare linked dataset and to conduct a decision-analytic pharmacoeconomic evaluation of treatment sequences based on parameters derived from the SEER-Medicare dataset, thereby increasing the generalizability of the findings.

METHODS

Data Source

- The SEER-Medicare linked dataset, which provides health care utilization and cost information for inpatient, outpatient, professional (provider), skilled nursing facility, hospice, devices, and medical equipment for elderly (65 years and older) patients, was used for the study.

Patient Selection Criteria

- Patients 65 years and older diagnosed from January 2004 to December 2009 with American Joint Cancer Committee stage IV colorectal cancer (i.e., mCRC) were included.
- The study was restricted to patients diagnosed after 2004, as drugs like oxaliplatin, bevacizumab, and cetuximab were approved by the Food and Drug Administration in 2004 for treating mCRC.
- For the completeness of the health care utilization data, patients who were enrolled in both Medicare Part A and Part B without any health maintenance organization enrollment from the time of diagnosis to death or the end of the study (December 31, 2010) were included.
- A total of 9,819 patients with mCRC met the inclusion/exclusion criteria and were eligible for further analyses.

Treatment Sequences

- The treatment sequences most commonly received by patients with mCRC[7] were compared and are listed as follows:
  1. First-line oxaliplatin/irinotecan followed by second-line oxaliplatin/irinotecan + bevacizumab (OI-OIB)
  2. First-line oxaliplatin/irinotecan + bevacizumab followed by second-line oxaliplatin/irinotecan + bevacizumab (OIB-OIB)
  3. First-line oxaliplatin/irinotecan followed by second-line oxaliplatin/irinotecan + bevacizumab followed by a third-line targeted biologic (OI-OIB-TB)
  4. First-line oxaliplatin/irinotecan + bevacizumab followed by second-line oxaliplatin/irinotecan + bevacizumab followed by a third-line targeted biologic (OIB-OIB-TB)

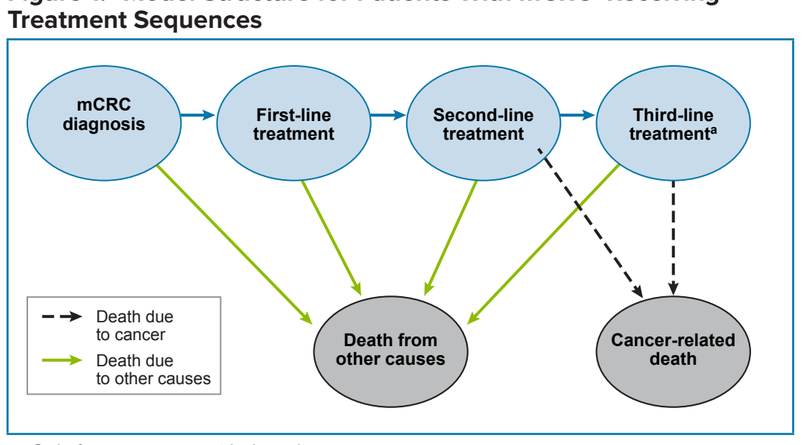
Discrete-Event Simulation Model

- A probabilistic discrete-event simulation (DES) model (also referred to as a time-to-event model) was developed to estimate the cost-effectiveness of treatment sequences, assuming a US national payer (Medicare) perspective using the TreeAge Pro 2015 software.
- At the decision node, the model branched into four sequence alternatives: (1) OI-OIB, (2) OIB-OIB, (3) OI-OIB-TB, and (4) OIB-OIB-TB.
- The model structure is shown in Figure 1, where microsimulation depicts individual patients traveling through the treatment pathway (i.e., events in DES model).
- Treatment line transitions were modeled using parametric survival distributions and rewards aggregated were total health care costs and quality-adjusted life-years (QALYs).
- Costs and effectiveness were discounted at an annual rate of 3%.

Model Parameters

- Treatment line transition time and time to death (Figure 1) were individually estimated for each treatment sequence by conducting inverse probability treatment-weighted parametric survival analysis using the SEER-Medicare data.
- Parametric survival regressions were modeled using Weibull distribution. For each treatment sequence, the regressions computed were as follows:
  1. Diagnosis to first-line treatment (all sequences)
  2. First-line to second-line treatment (all sequences)
  3. Second-line treatment to cancer-related death (sequences OI-OIB and OIB-OIB)
  4. Second-line treatment to end of second-line treatment (sequences OI-OIB-TB and OIB-OIB-TB)
  5. Third-line treatment to cancer-related death (sequences OI-OIB-TB and OIB-OIB-TB)
- Death due to causes other than cancer was modeled using the US vital statistics for 75- to 80-year-old individuals (mean age of mCRC diagnosis), assuming an exponential distribution.
- Total health care costs (2014 US dollars) were estimated from diagnosis until death or the end of the study (December 31, 2010) using claims for inpatient, outpatient, physician, skilled nursing facility, hospice, and durable medical equipment, as cancer treatment may affect overall morbidity.
- Total health care costs for each treatment sequence were divided into average monthly costs for each line of treatment.
- Health state utility for newly diagnosed mCRC was obtained from the study by Ramsey et al. (2000),[8] while utilities specific to treatment line were obtained from the recent study by Stein et al. (2014).[9] The mean (standard deviation) utility was assumed to be 0.841 (0.120) at diagnosis, 0.741 (0.230) at first-line and second-line treatments, and 0.731 (0.292) at third line.

Figure 1. Model Structure for Patients With mCRC Receiving Treatment Sequences



[a] Only for sequences with three lines.

Cost-effectiveness Analysis

- Cost-effectiveness of treatment sequences was assessed by conducting microsimulated DES analyses for 100,000 patients with mCRC in each treatment sequence.
- Cost-effectiveness was evaluated as incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB).
- Probabilistic sensitivity analysis for 10,000 iterations with 100,000 patients sampled in each iteration (i.e., 1 billion patients) was conducted and results were presented as cost-effectiveness acceptability curves (CEACs).

Model Assumptions

- For sequences OI-OIB-TB and OIB-OIB-TB, after the end of second-line treatment, patients were assumed to start the third-line treatment without a treatment gap.
- Cancer-related death in the time-to-event parametric survival analysis was characterized if the cause of death was reported either as any type of cancer or unknown.

DISCUSSION

- To our knowledge, this is the first study to conduct a probabilistic DES cost-effectiveness evaluation of commonly administered treatment sequences among elderly patients with mCRC using parameters derived from real-world data. Use of real-world data renders the findings more generalizable and informs decision makers regarding the cost-effectiveness of commonly used sequences in day-to-day clinical practice.
- This analysis found that as more treatments and lines were administered, survival was prolonged marginally but with considerable increase in costs.
- Addition of bevacizumab to first line may not be cost-effective at the WTP threshold of $100,000 per QALY gained. Similarly, addition of a third-line targeted biologic (OIB-OIB-TB) was not cost-effective. Notably, we found that a sequence with a third-line targeted biologic without bevacizumab at first line (OI-OIB-TB) was dominated by a second-line sequence (OIB-OIB).
- Threshold analyses conducted to estimate the cost at which OIB-OIB (vs. OI-OIB) and OIB-OIB-TB (vs. OIB-OIB) may become cost-effective at a WTP of $100,000 per QALY found OIB-OIB to be cost-effective if the first-line cost would be reduced by $286 per month.

RESULTS

- Table 1 shows the DES-estimated total health care costs, total QALYs, ICER per QALY, and NMB for each patient with mCRC using the Weibull distribution. The total health care costs were lowest for OI-OIB ($305,868) and highest for OIB-OIB-TB ($402,228).
- The lowest QALYs were estimated for OI-OIB, followed by OI-OIB-TB, OIB-OIB, and OIB-OIB-TB.
- In our base-case analysis assuming a Weibull distribution, the ICER for OIB-OIB as compared with OI-OIB was $119,636 per QALY gained.
- Similar ICER results were obtained for OIB-OIB versus OI-OIB ($119,007 per QALY gained) and OIB-OIB-TB versus OIB-OIB ($370,444 per QALY gained) in our sensitivity analysis using a log-normal distribution (Table 1).
- The cost-effectiveness frontiers using both Weibull and log-normal distributions (Figure 2) showed treatment sequence OI-OIB-TB either being dominated (i.e., more costly and less effective) or extended dominated (i.e., higher ICER than the next more effective alternative).
- Probabilistic sensitivity analyses results presented as CEACs are shown in Figure 3, with willingness to pay (WTP) varying from $0 to $1,000,000.

Table 1. ICERs and NMB Using Weibull and Log-Normal Distributions

Treatment Sequence[a]	Total Health Care Cost (US $)	Incremental Health Care Cost (US $)	Total QALY	Incremental QALY	ICER per QALY (US $)	NMB[b] (US $)
Weibull distribution						
OI-OIB	305,868	–	1.42	–	–	–
OIB-OIB	333,981	28,113	1.65	0.23	119,636	–5,113
OI-OIB-TB	355,690	21,709	1.65	Dominated	Dominated	Dominated
OIB-OIB-TB	402,228	68,247	1.82	0.17	405,857	–51,247
Log-normal distribution						
OI-OIB	308,548	–	1.43	–	–	–
OIB-OIB	336,875	28,327	1.67	0.24	119,007	–4,327
OI-OIB-TB	361,025	24,150	1.68	0.01	Extended dominance	Extended dominance
OIB-OIB-TB	415,102	78,227	1.88	0.21	370,444	–57,227

[a] Arranged in the order of increasing costs.

[b] At WTP of $100,000.

Figure 2. Cost-effectiveness Frontiers With Weibull and Log-Normal Distributions

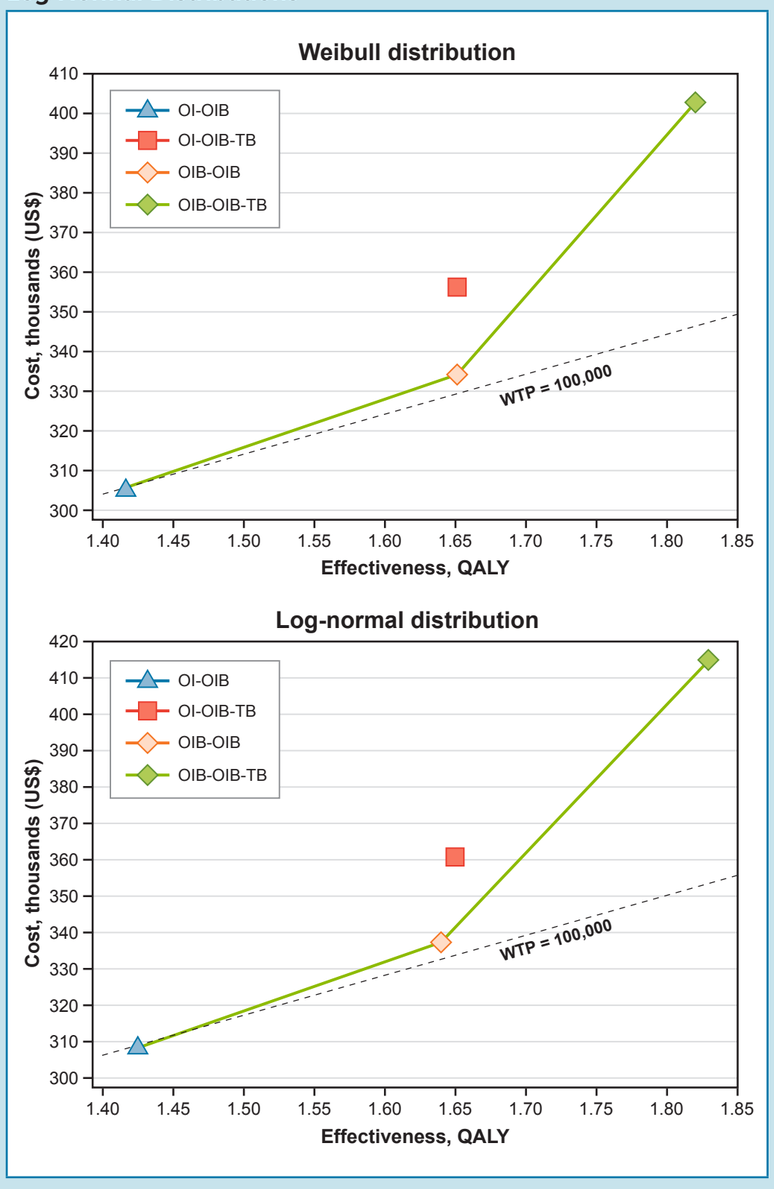
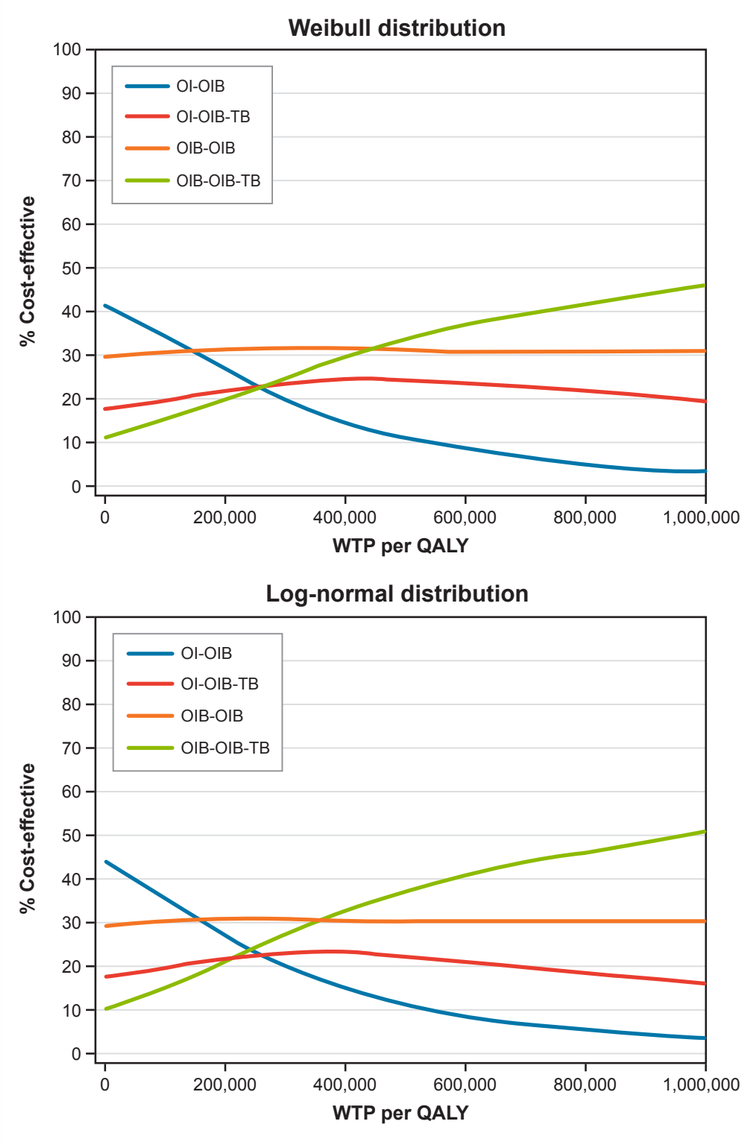


Figure 3. CEACs Based on Probabilistic Sensitivity Analysis



CONCLUSIONS

- Treatment sequences with bevacizumab at first-line treatment and targeted biologics at third-line treatment may not be cost-effective at the commonly used threshold of $100,000 per QALY gained, but a marginal decrease in the cost of bevacizumab may make treatment sequences with first-line bevacizumab cost-effective.

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