

Using Pharmacoeconomic Modelling to Determine Value-Based Pricing for New Pharmaceuticals in Malaysia

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Abstract

Background: Decision analysis (DA) is commonly used to perform economic evaluations of new pharmaceuticals. Using multiples of Malaysia's per capita 2010 gross domestic product (GDP) as the threshold for economic value as suggested by the World Health Organization (WHO), DA was used to estimate a price per dose for bevacizumab, a drug that provides a 1.4-month survival benefit in patients with metastatic colorectal cancer (mCRC).

Methods: A decision model was developed to simulate progression-free and overall survival in mCRC patients receiving chemotherapy with and without bevacizumab. Costs for chemotherapy and management of side effects were obtained from public and private hospitals in Malaysia. Utility estimates, measured as quality-adjusted life years (QALYs), were determined by interviewing 24 oncology nurses using the time trade-off technique. The price per dose was then estimated using a target threshold of US\$44 400 per QALY gained, which is 3 times the Malaysian per capita GDP.

Results: A cost-effective price for bevacizumab could not be determined because the survival benefit provided was insufficient. According to the WHO criteria, if the drug was able to improve survival from 1.4 to 3 or 6 months, the price per dose would be \$567 and \$1258, respectively.

Conclusion: The use of decision modelling for estimating drug pricing is a powerful technique to ensure value for money. Such information is of value to drug manufacturers and formulary committees because it facilitates negotiations for value-based pricing in a given jurisdiction.

Keywords: chemotherapy, cost analysis, drug costs, FOLFOX protocol, pharmacoeconomics

Introduction

The rapid growth of healthcare expenditures has led to increased interest in economic evaluations of healthcare programmes (1). This is particularly true for pharmaceuticals, which constitute a substantial portion of the healthcare budget (2). The basic premise of pharmacoeconomic evaluations (PEs) is to compare the costs and consequences of alternative pharmaceutical interventions and determine which treatment offers the best value for money (3). There are several methods available to evaluate economic efficiency (3,4). All of the approaches measure costs in monetary terms, but differ in how consequences are evaluated.

Decision analysis modelling, one of the most commonly used methods for conducting PEs, is a systematic process that assesses appropriate courses of action in the presence of multiple uncertainties (5). Outcomes are typically presented as the incremental cost per quality-adjusted life year (QALY) gained, which is compared against the value threshold set by national formulary committees. For example, the National Institute of Clinical Excellence in the United Kingdom has established the threshold for drug coverage at £30 000 per QALY gained (6). In the Netherlands, the unofficial threshold is €18 000 per QALY (7). However, these thresholds for economic value do not consider the wealth of the nation.

To address this, the World Health Organization (WHO) has proposed using multiples of a country's per capita gross domestic product, GDP (8,9). Based on the WHO criteria, products more than 3 times the GDP are considered cost ineffective (8,9). Using Malaysia as an example (i.e., per capita GDP for 2010 of US\$14 800), the threshold for cost-effectiveness of new drugs would be \$44 400 per QALY (10).

Most PEs are conducted with an established product price to estimate the cost per QALY gained. PEs can also be very informative for determining a drug price based on recommended thresholds for economic value. To illustrate the application of PE, we used decision analysis modelling to estimate a price for a cancer drug in Malaysia using the WHO criteria for cost-effectiveness. The drug selected for the case study was bevacizumab, an agent that provides a 1.4-month survival gain when added to first-line chemotherapy in patients with metastatic colorectal cancer, mCRC (11). Bevacizumab was chosen because it has a high cost of acquisition and its economic value has been questioned in recent PE studies (12,13).

Materials and Methods

Economic model

The mCRC was chosen for this analysis because the sequential use of specific chemotherapy regimens for treatment is well established. In patients with mCRC, randomised trials have demonstrated that irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) in combination with infusional 5-fluorouracil (5-FU) and leucovorin is highly active and superior to the previous standard of 5-FU/leucovorin alone (14,15). Data from a large randomised trial verified that sequential schedules of FOLFOX and FOLFIRI (or in the reverse order) are equally effective and have emerged as the first- and second-line standards of care for patients with mCRC (16). Clinical practice guidelines also recommend the addition of an anti-vascular endothelial growth factor (VEGF) such as bevacizumab at some point during chemotherapy for mCRC (17). FOLFOX, FOLFIRI, and bevacizumab are all available in Malaysia.

The two most common methods used to model the clinical and economic consequences of cancer therapy are decision trees and Markov modelling. The former method is used in situations where uncertainty arises once over a period of time. However, in cases where events occur repeatedly, Markov processes are better

able to capture the uncertainties that are faced iteratively (18). However, one of the disadvantages of Markov modelling is that it requires an extensive amount of detailed data. To construct a Markov model of multiple cycles of FOLFOX and FOLFIRI, disease progression and toxicity data would be required for each cycle of chemotherapy. Unfortunately, such data are not available from published clinical trials. Since only aggregate data were available (i.e., median number of cycles of chemotherapy), a decision tree approach was used for the current study.

A decision model for the sequential treatment of mCRC with FOLFOX (\pm an anti-VEGF) followed by FOLFIRI upon disease progression (Figure 1) was developed with DATA software (Treeage Software Inc., Williamstown, MA). The analytic timeframe was from the first cycle of FOLFOX chemotherapy until death. Perspectives from both the public and private Malaysian health care systems were evaluated. Based on the Response Evaluation Criteria in Solid Tumours, the primary outcome for measuring successful initial therapy was clinical benefit, which was defined as complete tumour response (CR), partial response (PR), or stable disease (SD). Three clinical oncologists, each with experience in treating colorectal cancer, evaluated the face and content validity of the model.

The model (Figure 1) began at the decision node (square) where the first-line treatment choice was either FOLFOX + the "new drug" (bevacizumab) or FOLFOX alone (Figure 1). During the first 2 cycles of chemotherapy, patients were assessed for intolerable toxicity. For patients with severe toxicity, first-line therapy was discontinued in its entirety, and second-line FOLFIRI was offered until disease progression. Upon progression, all patients received best supportive care until death. In contrast, patients not experiencing severe toxicity from first-line FOLFOX (\pm bevacizumab) continued treatment until disease progression. They were offered second-line FOLFIRI alone, and bevacizumab was discontinued. Upon progression, all patients received best supportive care until death. Epidermal growth factor receptor (EGFR) inhibitors such as cetuximab in mCRC patients with KRAS wild-type tumours were not considered because we did not want to overcomplicate the modelling. Furthermore, these agents would be available to both treatment options in the model, so their inclusion would not impact the final results.

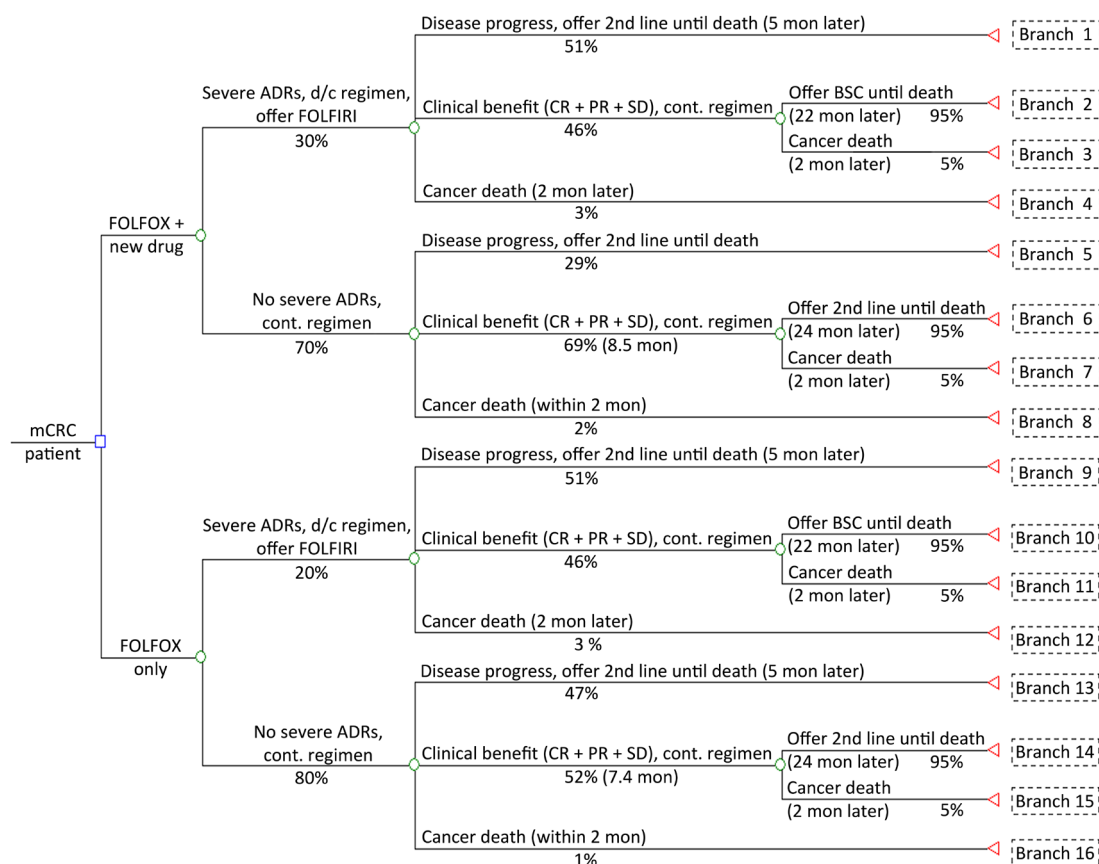


Figure 1: Decision analysis model for the treatment of metastatic colorectal cancer. Abbreviations: mCRC = metastatic colorectal cancer, FOLFOX = oxaliplatin in combination with infusional 5-fluorouracil, FOLFIRI = irinotecan in combination with infusional 5-fluorouracil, ADR = adverse drug reaction, CR = complete response, PR = partial response, SD = stable disease, BSC = best supportive care, mon = month, d/c = discontinued, cont. = continue.

Clinical data

The clinical data required to populate the model consisted of early treatment discontinuations because of toxicity, achievement of clinical benefit (CR, PR, or SD), duration of clinical benefit, risk of cancer-related death during active treatment, and the number of chemotherapy cycles administered. These data were obtained through a literature search of randomised trials evaluating FOLFOX (\pm bevacizumab) and FOLFIRI in first- and second-line settings, respectively, for the treatment of mCRC. Two randomised trials that provided the required data for the decision model were identified (Table 1). The first trial evaluated FOLFOX or a clinically similar regimen of XELOX (capecitabine plus oxaliplatin) \pm bevacizumab in the first-line treatment of mCRC (11). A total of 1401 patients were randomised to receive

FOLFOX/XELOX + bevacizumab ($n = 699$) or FOLFOX/XELOX + placebo ($n = 701$). The interaction between FOLFOX and XELOX on the primary clinical endpoint was not statistically significant ($P = 0.70$), thereby justifying the decision to combine patients who received FOLFOX and XELOX. The median progression-free survival was 9.4 months in the bevacizumab group compared with 8.0 months in the placebo group ($HR = 0.83, P = 0.023$), resulting in a 1.4-month survival benefit (11). Overall, 30% of patients in the bevacizumab group, compared with 20% of the controls, required permanent discontinuation of treatment due to adverse events. Approximately 2% and 1% of patients died during treatment with bevacizumab and placebo, respectively (Table 1).

Data on the safety and efficacy of second-line FOLFIRI following first-line FOLFOX were

Table 1: Published randomised trials providing clinical data to populate the economic model

Reference	Treatment arms	Clinical outcomes	
Saltz et al. (11)	FOLFOX/XELOX + bevacizumab	Disease progression	= 29%
		Median PFS	= 9.40 months
		Median duration of response	= 8.45 months
		Overall survival	= 21.30 months
		Treatment discontinuations	= 30%
		Death during treatment	= 2%
		Serious side effects (grade III/IV)	= 16%
		<i>Specific Grade III/IV Side Effects</i>	
		Deep vein thrombosis	= 8%
		Diarrhoea	= 18%
		Bleeding	= 2%
		Neutropenia	= 50%
		<hr/>	
		FOLFOX/XELOX + placebo	
Median PFS	= 8.0 months		
Median duration of response	= 7.4 months		
Overall survival	= 19.9 months		
Treatment discontinuations	= 20%		
Death during treatment	= 1%		
Serious side effects (grade III/IV)	= 8%		
<i>Specific Grade III/IV Side Effects</i>			
Deep vein thrombosis	= 5%		
Diarrhoea	= 11%		
Bleeding	= 1%		
Neutropenia	= 44%		
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Tournigand et al. (16)	Second-line FOLFIRI		
		Death during treatment	= 3%
		Median PFS	= 10.9 months
		Median number of cycles	= 6

Abbreviations: PFS = progression-free survival, OS = overall survival, FOLFOX = oxaliplatin in combination with infusional 5-fluorouracil, FOLFIRI = irinotecan in combination with infusional 5-fluorouracil.

obtained from a randomised sequential trial reported by Tournigand (16). Patients were randomised to receive sequential FOLFOX followed by FOLFIRI or the reverse sequence upon progression. There was no significant difference in progression-free and overall survival (21.5 months in FOLFOX–FOLFIRI versus 20.6 months in FOLFIRI–FOLFOX, $P = 0.99$) between the 2 sequences (16). Using second-line FOLFIRI, 51% of patients experienced an overall progression-free survival of 2.5 months (16). Approximately 3% of patients died within the first 60 days of second-line FOLFIRI (Table 1).

Estimation of treatment costs

Malaysia's healthcare system is composed of public and private sectors. Physicians are required to complete 3 years of service in public hospitals throughout the nation, ensuring adequate coverage for the general population. With respect to drug access, patients treated under the private system typically have access to a greater selection of therapies than those managed under the public system. However, drug prices and costs for hospital resources tend to be higher in private than in public hospitals. As a result, an analysis was performed for patients treated under the public and private systems.

The duration of the investigation was from the start of first- and second-line sequential chemotherapy until death. Data regarding health care resources and costs for anticancer drugs, materials, patient monitoring, and other related hospital resources (e.g., laboratory, diagnostic tests, and best supportive care) were obtained from 2 private and 2 public health care institutions, using a standardised data collection form. The costs were in Malaysian Ringgit (RM) and converted to US Dollar per currency conversion rates in 2010 (conversion factor \$1.00 = RM3.20, as of September 2010).

Patient preferences for alternative health states

The QALY is a way of measuring the impact of disease on a patient. The QALY includes both the quality and the quantity of life lived by a patient, and it is calculated by multiplying the survival gain by the overall utility benefit of one therapy over another. The health-related quality of life (QOL) values measured in the analysis were patient preferences for alternative health outcomes, as depicted in the decision analysis model. In the current study, quality-adjusted progression-free periods were measured as "healthy month equivalents" for the time spent in each outcome of the decision model using the time trade-off (TTO)

technique (19). The scores, in months, were then converted to utility measures between 0 and 1, where 0 represented death and 1 represented a state of perfect health or optimal QOL.

The TTO technique is a preference-based approach designed to measure the preferences and QOL of respondents for alternative health states (19). After background information on a particular health state (e.g., a cancer that is not responding to treatment) and the duration within that state are presented, respondents are asked to trade length of life in the poorer health state for a lesser duration in a state of optimal health and QOL. For example, a respondent may prefer to live 4 months of optimal health rather than 12 months confined to a wheelchair. Under this scenario, the utility associated with being in a wheelchair for 12 months would be 0.33 (i.e., 4/12) on a scale between 0 and 1, where 0 represents death and 1 is a state of optimal quality of life. In the economic model, all of the possible outcomes were evaluated with this method and used to weigh the time spent in each health state in terms of QOL.

Intuitively, the ideal population for measuring health state utilities and treatment preferences is cancer patients who are in a position to undergo the new treatment. However, the Canadian Guidelines for Economic Evaluations and the Panel on Cost-effectiveness in Health and Medicine in the United States recommend that treatment preferences should be measured by members of the general public who are potential candidates for the new medical intervention (5,20). As a compromise, in this study, a patient surrogate group was used to provide insight from both the perspective of the patient and members of the general public, as the latter group often has difficulty in understanding utility questionnaires. There is evidence in the oncology literature suggesting that nurses are suitable patient surrogates for objective outcomes and that derived utility estimates do not substantially alter the findings of cost-utility studies (21,22). Therefore, a convenience sample consisting of 24 oncology nurses provided utility values for the model. Using a sample of 24 respondents, healthy month equivalents were measured with a precision of approximately 1.0 month and a 95% probability.

After informed consent was obtained, each participant was interviewed for 30 to 45 minutes by trained local field investigators. Respondents were presented with information on FOLFOX, bevacizumab, and FOLFIRI regarding the methods of administration, their efficacy, and their side effects as reported in the literature. Bevacizumab

was not identified by name, but simply referred to as the “new drug”. The interview was continued with a description of 16 health states and the length of time a patient would live in each health state (Figure 1). The respondents were asked how many months of optimal health they considered equivalent to the time spent in each of the less than optimal health states described in the model. These measures were then used to weigh each branch of the model by the QOL experienced by a patient living through that period. An identical process was used for each of the 16 outcomes (Figure 1). The mean healthy month equivalent score for each outcome was then divided by 12 months to estimate the number of QALYs associated with that health state.

A standardised questionnaire supported by printed interview tools and graphical displays was used to facilitate participant understanding of the TTO technique. To minimise the framing effect, all pathways were presented pictorially in a consistent manner. Demographic data were collected from each participant, including years of oncology and colorectal cancer experience, involvement in the development of systemic treatment guidelines for colorectal cancer, familiarity with the cost of anticancer drugs, and family history of colorectal cancer.

Cost-utility analysis

The clinical, economic, and respondents' preference data were combined into a cost-utility analysis of bevacizumab to identify a price per dose that would be considered cost-effective according to the WHO criteria (8,9). The base case analysis assumed that the addition of bevacizumab to standard chemotherapy would provide a survival benefit of 1.4 months. The primary objective of the analysis was to estimate an appropriate price for the bevacizumab with the target benchmark cost of \$44 400 per QALY gained, which is 3 times the 2010 Malaysian per capita GDP. Indirect costs were not included because there was no data available on the association between bevacizumab usage and indirect-cost avoidance. Future costs and benefits were not discounted because of the short period involved. However, the stability of the baseline results was evaluated by a comprehensive sensitivity analysis, consisting of substituting the 95% confidence intervals (CIs) for the health state utilities as well as variations in the overall survival benefit, costs of care, and the target threshold for economic value in Malaysia. Costs of care were varied by approximately 15% to include any potential differences across the country. Individual analyses were conducted for patients treated in public and private hospitals.

Results

Clinical outcomes data and costs used to populate the model are presented in Tables 1 and 2. The economic data revealed that the expenses for chemotherapy, the management of side effects, and the best supportive care were lower in the public health care system compared with the private system in Malaysia. This may be a reflection of a slightly lower level of care offered to patients in public hospitals and the ability of the private sector to mark up the cost of goods and health services.

The second component required for the cost-utility analysis was the health state utilities for the time spent in each of the 16 health states (Figure 1). Utilities for each outcome were estimated from a sample of 24 oncology nurses who consented to participate in the study: 14 from public hospitals and 10 from private institutions. The group had an average of 3.4 years of direct oncology experience (ranged 2–8 years), and all had experience in the treatment of colorectal cancer patients. In addition, all respondents had direct clinical experience in the administration of and the follow-up care associated with FOLFOX (mean experience of 2.2 years), and 92% had experience with FOLFIRI chemotherapy (mean experience of 1.9 years). Furthermore, 22 out of 24 (92%) had experience with the newer targeted therapies bevacizumab and cetuximab. Because lack of knowledge about the cost of drugs could affect treatment preferences, respondents were asked to state their knowledge of costs for modern oncology drugs. The findings revealed that 100% were very or somewhat familiar with the cost of drugs used to treat cancer. The final series of demographic questions focused on the respondents' family history of colorectal cancer. The data revealed that none of the 24 subjects had a family history positive for colorectal cancer.

The health state utilities from the oncology nurses are presented in Table 3. The results suggest that patient utilities were influenced by the severity of drug toxicity, the likelihood of achieving a response to chemotherapy, and the risk of rapid cancer death. The health states with the lowest utilities (i.e., branches 11 and 16 of the model in Figure 1) were those when first-line therapy had to be stopped because of severe toxicity and when the patient had an early progression during second-line treatment followed by rapid death due to cancer. It was interesting to note that, in all of the related scenarios, comparative branches that included treatment with the “new drug” tended to have lower health state utilities (Table 3).

Table 2: Hospital costs for the treatment of metastatic colorectal cancer in Malaysia

Recourse item	Public hospitals	Private hospitals
FOLFOX chemotherapy (\$ per cycle) ^a	998.00	1047.00
FOLFIRI chemotherapy (\$ per cycle) ^a	1395.00	1489.00
Permanent chemotherapy discontinuation because of toxicity (\$) ^b	111.60	241.80
Administration of the “new drug” after FOLFOX chemotherapy (\$)	18.60	40.30
Best supportive care (\$ per month) ^c	156.00	338.00

^a Cost per cycle includes resources for drug administration and routine patient monitoring. In the hospitals that provided data for this study, patients are admitted for 2 days to receive chemotherapy.

^b Patients were admitted for 3 days for the management of side effects and for reassessment.

^c After failing 2 lines of chemotherapy, patients would receive best supportive care on an outpatient basis until death.

Abbreviations: FOLFOX = oxaliplatin in combination with infusional 5-fluorouracil, FOLFIRI = irinotecan in combination with infusional 5-fluorouracil.

This is likely related to the additional side effects that occur with the addition of an anti-VEGF agent such as bevacizumab to chemotherapy (Table 1).

Cost-utility analysis for public and private hospital systems

The outcomes data from the clinical trial, the estimated costs associated with each treatment, and the health state utility estimates were combined into the cost-utility analysis. The price for 1 dose of bevacizumab was varied until the incremental cost-effectiveness ratio reached a threshold of \$44 400 per QALY gained. When using this approach from the public health care system perspective, the base case analysis suggested that a cost per dose that would achieve cost-effectiveness according to the WHO criteria could not be reached because bevacizumab simply did not provide enough of a survival benefit in mCRC patients (Table 4). Similar results were also identified when the analysis was undertaken from the perspective of private hospitals.

A series of one-way sensitivity analyses were conducted using the upper 95% CI for the health state utilities, variations in treatment costs, and the targeted cost per QALY threshold. Identical results in the base-case analysis for both public and private hospitals were achieved. A price per dose that would make bevacizumab cost-effective could not be realised. This was primarily driven by the modest survival benefit offered by bevacizumab in mCRC patients.

The only situation where a cost-effective price per dose was identified occurred when the survival gain was increased to 3 and 6 months. When the survival benefit of bevacizumab was increased from 1.4 to 3 months, the cost per dose for public and private hospitals was estimated to be \$567 and \$490, respectively. When the survival gain was increased to 6 months, the price per dose of bevacizumab increased further to \$1258 and \$1182 for public and private institutions, respectively, and these were considered cost-effective according to the WHO criteria (8,9). Therefore, the single biggest factor controlling the cost-effectiveness of bevacizumab is the ability of the drug to increase overall survival.

Bevacizumab is available in Malaysia for a purchase price of approximately \$1800 per dose (5 mg/kg) for an average 60-kg mCRC patient. A sensitivity analysis was conducted, and the current price of bevacizumab was applied to the model. The results revealed that the incremental cost per QALY gained would be greater than \$200 000 for both public and private institutions. When a \$50 000 cost per QALY threshold was used instead of the WHO criteria, a cost-effective price per dose was still not achievable. In summary, the sensitivity analyses suggested that bevacizumab is not a cost-effective drug in Malaysia according to the WHO criteria. To achieve cost-effectiveness, drug performance in terms of survival gain in mCRC patients would need to improve and the price would have to be reduced to between \$500 and \$1300.

Table 3: Health state utilities derived using the time trade-off technique

Health outcomes evaluated in the decision model	Time in health state (months) ^a	Utility estimate (mean [95% CI]) ^b
<i>FOLFOX ± “new drug” → FOLFIRI → BSC until death</i>		
Branch #1		
FOLFOX + “new drug” were discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10	0.74 (0.65–0.83)
Branch #2		
FOLFOX + “new drug” were discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28	0.80 (0.73–0.87)
Branch #3		
FOLFOX + “new drug” were discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8	0.67 (0.61–0.73)
Branch #4		
FOLFOX + “new drug” were discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4	0.74 (0.65–0.84)
Branch #5		
The patient tolerated side effects but had disease progression after 4 cycles of FOLFOX + the “new drug”. The patient was then treated with FOLFIRI for 4 cycles, but the disease did not respond. The patient received BSC and died 2 months later.	6	0.82 (0.76–0.89)
Branch #6		
The patient tolerated side effects and responded to FOLFOX + “new drug”. The patient went on to receive 17 cycles of first-line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient received BSC and died 21 months later.	29	0.81 (0.77–0.86)
Branch #7		
The patient tolerated side effects and responded to FOLFOX + “new drug”. The patient went on to receive 17 cycles of first-line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11	0.83 (0.79–0.87)
Branch #8		
The patient tolerated side effects but had disease progression after 2 cycles of FOLFOX + “new drug”. The patient died due to cancer 1 month later.	2	0.75 (0.63–0.86)

Health outcomes evaluated in the decision model	Time in health state (months) ^a	Utility estimate (mean [95% CI]) ^b
<i>FOLFOX → FOLFIRI → BSC until death</i>		
Branch #9		
FOLFOX was discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10	0.82 (0.75–0.82)
Branch #10		
FOLFOX was discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28	0.81 (0.76–0.86)
Branch #11		
FOLFOX was discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8	0.72 (0.66–0.79)
Branch #12		
FOLFOX was discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4	0.75 (0.66–0.84)
Branch #13		
The patient tolerated side effects but had disease progression after 4 cycles of FOLFOX. The patient was then treated with FOLFIRI for 4 cycles, but the disease did not respond. The patient received BSC and died 2 months later.	6	0.84 (0.76–0.92)
Branch #14		
The patient tolerated side effects and responded to FOLFOX. The patient went on to receive 15 cycles of first-line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient was offered BSC and died 21 months later.	32	0.91 (0.88–0.94)
Branch #15		
The patient tolerated side effects and responded to FOLFOX. The patient went on to receive 15 cycles of first-line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11	0.84 (0.79–0.90)
Branch #16		
The patient tolerated side effects and but had disease progression after 2 cycles of FOLFOX. The patient died due to cancer progression 1 month later.	2	0.75 (0.63–0.86)

^a As presented in each branch of the decision model.

^b A quality of life score for a health state between 0 and 1, with 0 = death and 1 = optimal health.

Abbreviations: FOLFOX = oxaliplatin in combination with infusional 5-fluorouracil, FOLFIRI = irinotecan in combination with infusional 5-fluorouracil, BSC = best supportive care.

Table 4: Sensitivity analysis on the cost per dose of the “new drug”

Sensitivity analysis ^a	Public hospitals	Private hospitals
Base case	Not reached	Not reached
Upper 95% CI of health state utilities for chemotherapy + “new drug”	Not reached	Not reached
Changing cost of FOLFOX chemotherapy by ± 15%	Not reached	Not reached
Changing cost of FOLFIRI chemotherapy by ± 15%	Not reached	Not reached
Changing cost of BSC cost by ± 15%	Not reached	Not reached
Changing cost of ADR cost by ± 15%	Not reached	Not reached
Changing survival benefit of the “new drug” from 1.4 to 3 months	\$567	\$490
Changing survival benefit of the “new drug” from 1.4 to 6 months	\$1258	\$1182
Using the current cost of bevacizumab (\$1800 per dose) in Malaysia	Not cost-effective	Not cost-effective
Setting the threshold for cost effectiveness at \$50 000 per QALY gained	Not reached	Not reached

^a For a target threshold of US \$44 400 per QALY when the new drug is added to FOLFOX chemotherapy.

Abbreviations: FOLFOX = oxaliplatin in combination with infusional 5-fluorouracil, FOLFIRI = irinotecan in combination with infusional 5-fluorouracil, BSC = best supportive care, ADR = adverse drug reaction costs.

Discussion

Decision analysis modelling is a powerful simulation technique widely used to perform cost-effectiveness evaluations of new drugs. In such studies, the health services researcher develops a decision model comparing the new therapy to the current standard, incorporates the costs and consequences of the two alternatives into the analysis, and estimates the incremental cost per QALY gained using the new intervention. If the cost per QALY is below a pre-determined threshold, the conclusion is that the new treatment is cost-effective and should be added to a hospital or a national formulary.

Decision analysis is a useful tool that can also be used to estimate any unknown in the analysis. The unknown in most published studies has been the incremental cost per QALY gained. However, decision analysis can also be applied in the context of pricing a new drug before it is introduced to the market. In this study, the latter process was used to estimate the cost of bevacizumab, a drug that provides a 1.4-month survival benefit when added to chemotherapy in the first-line treatment of mCRC (11).

The analysis was conducted from the perspective of both the Malaysian public and private health care systems using the WHO criteria for cost-effectiveness. In the base case analysis and in most of the scenarios evaluated, a cost per dose resulting in cost-effectiveness could not be identified because a 1.4-month survival gain

was inadequate. A cost-efficient price was only realised when the survival gain from bevacizumab was artificially increased to at least 3 months. When the current Malaysian price per dose (i.e., \$1800 for bevacizumab) was evaluated, the drug was not considered to be cost-effective according to the WHO criteria.

The findings of this study suggest that the WHO criteria for cost-effectiveness can be applied to a country such as Malaysia for estimating an appropriate price that may be more affordable to the national health care system. Furthermore, our results suggest that bevacizumab is priced excessively high in Malaysia considering the 1.4-month survival benefit that it provides to mCRC patients. For the drug to become cost-effective, the price would have to be reduced and a new treatment algorithm that would increase survival to at least 3 months would need to be identified.

There are a number of limitations in the application of this technique that need to be addressed. Given the lack of data for each cycle of chemotherapy, we constructed a decision tree instead of a Markov model to simulate the clinical and economic consequences of chemotherapy for patients with mCRC; the latter would have been preferable given its ability to incorporate the element of time. For the proposed methodology to be viable, complete data from randomised trials on a drug-by-drug basis is required. This is not always possible. One of the limitations of using the per capita GDP for value-based pricing is

that it represents a national average and does not consider income dispersion. Our study measured health state utilities from a sample of oncology nurses. However, the external validity of our findings would have been enhanced if we had also included patients, family members, and members of the general public. For our modelling strategy to be applied, a new drug must demonstrate either an improvement in QOL over the standard of care or a survival of sufficient magnitude to identify a final price point for cost-effectiveness. In the case of bevacizumab, the drug simply did not provide enough of a survival benefit to identify a price that would be considered cost-effective. Lastly, indirect costs, such as time off work, may be relevant in this setting but were not considered in this analysis because there was a lack of such data in the mCRC literature. Future modelling should consider these elements.

Conclusion

The current paper presents a systematic process to estimate drug costs based on pre-determined thresholds for societal value. The advantages of this technique are that it is relatively straightforward to perform, that it is transparent, and that the decision model can be easily applied to other jurisdictions using local cost data. This information is of value to drug manufacturers and formulary committees because it facilitates negotiations for optimal pricing in a given jurisdiction.

Authors' Contributions

Conception and design, analysis and interpretation of the data: GD, IT, MSL

Provision of study materials: NNS, VMM, SBM

Statistical expertise, drafting of the article: GD

Critical revision and final approval of the article: IT, MSL, NNS, VMM, SBM

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