XELOX ± Bevacizumab compared to FOLFOX4 ± Bevacizumab in First line Metastatic Colorectal Cancer in a Non-reimbursed Health Care System: A Cost Analysis

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ABSTRACT

Introduction. XELOX is non-inferior to FOLFOX-4 as a first-line treatment for metastatic colorectal cancer. This study compares the costs associated with XELOX+/-bevacizumab versus FOLFOX4+/-bevacizumab in a non-reimbursed, out of pocket Philippine health care system.

Methods. This is a cost-minimization analysis using Philippine General Hospital as base case and a typical Filipino patient of 60 kg with BSA 1.66. The outcome data were derived from the NO16966 trial. These included the drugs capecitabine, 5-fluoro-uracil, oxaliplatin, and bevacizumab (BEV); chemotherapy cycles and corresponding hospital admission for each regimen; resources associated with treatment of adverse events such hospital days, ambulatory consultations, concomitant medication, and central venous line insertion/removal, with costs and charges based on the local setting.

Results. Highest cost (direct and/or indirect) was for FOLFOX4+BEV, followed by XELOX+BEV, FOLFOX4, and then XELOX. The use of XELOX resulted in a cost saving of PhP 158,642 per patient compared with FOLFOX4. The use of XELOX+BEV resulted in a cost saving of PhP 186,144 per patient compared with FOLFOX4+BEV.

Conclusion. XELOX+/-BEV is less costly than FOLFOX4+/-BEV in an out-of-pocket Philippine tertiary hospital setting from the patient's perspective.

Key Words: cost analysis, XELOX, FOLFOX, bevacizumab, colorectal carcinoma

Presented and won 3rd Place at the Round Asia Oncology Conference Research Forum, 2009, Cebu, Philippines.

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Introduction

Colorectal cancer is the 6th lead cancer for both sexes in terms of age-world standardized rates [ASR(W)] in the Philippines (incidence of 8.6 per 100,000 population; mortality of 4.7 per 100,000; 5-year prevalence of 19.9 per 100,000). In comparison, colorectal cancer ranks 4th for both sexes globally (incidence of 17.2 per 100,000; mortality of 8.2 per 100,000; 5-year prevalence of 11.3 per 100,000).[1] Established risk factors include age, a high animal fat diet, inflammatory bowel disease, and genetic predisposition, including hereditary polyposis and nonpolyposis syndromes.

If detected early, colorectal cancer is curable by surgery. Adjuvant chemotherapy can prolong survival if there is lymph node involvement. Both systemic and locoregional chemotherapy (e.g., intrahepatic intraarterial chemotherapy for liver metastases) have a role in patients with metastatic colon cancer. Radiotherapy is used in cases of rectal cancer to reduce the risk of local recurrence.

XELOX (capecitabine [Xeloda] plus oxaliplatin) and FOLFOX4 (fluorouracil, leucovorin/folinic acid and oxaliplatin) are internationally considered routine first-line treatment options for patients with metastatic colorectal cancer based on NCCN guidelines version 2013. The NO16966 trial showed that XELOX is similar to FOLFOX4 in terms of efficacy. Subjects with metastatic disease were initially randomly assigned to receive either XELOX or FOLFOLX4. The protocol was later amended such that patients were randomized to receive either bevacizumab (BEV) or placebo in addition to chemotherapy. This amendment was introduced as BEV, an anti-angiogenesis monoclonal antibody, demonstrated improved survival rates when combined with chemotherapy. With an intent-to-treat (ITT) study population of 2,034 patients, median overall survival (OS) was 19.8 months in the pooled XELOX/XELOX+placebo/XELOX+BEV arms versus 19.5 months in the pooled FOLFOX4/FOLFOX4+placebo/FOLFOX4-BEV arms (hazard ratio 0.95 [97.5% CI 0.85–1.06]). Even in the absence of BEV, patients receiving XELOX alone had a median OS of 19.0 versus 18.9 months for patients receiving FOLFOX4 alone (hazard ratio 0.95 [97.5% CI 0.83–1.09]).[2] More grade 3/4 neutropenia/granulocytopenia and febrile neutropenia were

observed in the FOLFOX4 arms than in the XELOX arms. However, XELOX was associated with more grade 3 diarrhea and grade 3 hand-foot syndrome compared with FOLFOX4.

This study compares these two non-inferior effective regimens, XELOX±BEV and FOLFOX-4±BEV, in the metastatic setting, according to their costs in a Philippine tertiary government setting.

Methods

In this cost-minimization analysis from the Filipino patient's (payer's) perspective, a Philippine General Hospital patient of 60 kg with BSA 1.66 was used as a base case. The outcome data were derived from the NO16966 study of Cassidy et al.[2]

Chemotherapy regimens (given until disease progression or death) were as follows:

1. FOLFOX4: oxaliplatin 85mg/m^2 as a 2-hr intravenous (IV) infusion for day 1; leucovorin 200mg/m^2 as a 2-hr IV infusion then fluorouracil (FU) 400mg/m^2 IV bolus followed by FU 600mg/m^2 continuous 22-hr infusion for days 1-2; cycles repeated every 2 weeks.
2. XELOX: oxaliplatin 130mg/m^2 as a 2-hr intravenous (IV) infusion for day 1; capecitabine given at 1000mg/m^2 twice daily per orem from days 1 to 14; cycles repeated every 3 weeks
3. FOLFOX4 + BEV: FOLFOX4 as above, with BEV at 5mg/m^2 IV given on day 1 every 2 weeks
4. XELOX + BEV: XELOX as above, with BEV at 7.5mg/m^2 IV given on day 1 every 3 weeks

The median number of cycles administered were 11 (range 1–24) for FOLFOX4, 12.3 (range 1–25) for FOLFOX4+BEV, 7.6 (range 1–18) for XELOX, and 8.6 (range 1–17) for XELOX+BEV. XELOX required fewer planned office visits than the FOLFOX regimens since XELOX was administered every 3 weeks while FOLFOX was every 2 weeks. Capecitabine in the XELOX ams were taken orally for 14 days at home while FU and leucovorin were given intravenously for 2 days in the hospital.

The cost of central venous line insertion and maintenance were also considered. The mean number of IV-based treatment per patient, which corresponded to the mean number of treatment cycles given, were 7.40 (XELOX), 10.9 (FOLFOX4), 7.4 (XELOX+BEV), and 12.6 (FOLFOX+BEV). The mean number of times the IV line was maintained per patient (i.e., flushing of the port or instillation of heparin into central lines during or outside chemotherapy schedule) were 3.5 (XELOX), 13.35 (FOLFOX4), 4.09 (XELOX+BEV), and 14.37 (FOLFOX+BEV). These maintenance procedures added to the cost of treatment.

Adverse Events

Based on the NO16966 trial, XELOX and FOLFOX4 had similar adverse events (AEs), which were mostly gastrointestinal (i.e., diarrhea, nausea, vomiting and stomatitis) and neurosensory (i.e., paraesthesia and peripheral neuropathy) toxicities. Cardiac disorders were also seen in both treatment arms but with less frequency. Differences in the rates of occurrence of neutropenia/granulocytopenia, febrile neutropenia, diarrhea and hand-foot syndrome were observed. Neutropenia, mostly grade 3 or 4, was encountered more frequently with FOLFOX4 than with XELOX. More hand-foot syndrome and diarrhea were seen with XELOX than with FOLFOX4. The mean hospital days due to AEs per patient with the addition of bevacizumab did not alter the similarities and differences in safety profiles between XELOX and FOLFOX4.[3] 25.94 (XELOX), 21.28 (FOLFOX4), 25.49 (XELOX+BEV), and 24.35 (FOLFOX+BEV).

Cost

The value of the Philippine peso (PhP) in 2011 was used when considering direct costs (costs of chemotherapeutic agents, drug administration per regimen, treatment of adverse event in terms of hospitalization and concomitant medication use, and central venous line insertion and maintenance) and indirect costs (time costs of ambulatory visits including travel time to the hospital and waiting time). The cost estimates were from the Philippine General Hospital (PGH) pay ward setting. Costing of drugs was based on PGH Pharmacy prices. The charges for administration of the different chemotherapy regimens were derived from the standard professional fees used for the different regimens by the PGH medical oncology consultants.

Chemotherapy drug costs were expressed on a per milligram basis: oxaliplatin = PhP 219.84; FU = PhP 0.23; capecitabine = PhP 0.36; BEV = PhP 259.68; and leucovorin = PhP 12.00. The cost of drugs per administration cycle were as follows: oxaliplatin = PhP 3,000; FU (continuous infusion) = PhP 1,000; FU (bolus) = PhP 1,000; leucovorin = PhP 1,000; capecitabine = PhP 2,000; bevacizumab PhP 3,000. The cost of the initial central line placement and port maintenance was computed as follows: placement = PhP 65,000; removal = PhP 0.00; maintenance = PhP 2,250).

The cost associated with AEs was estimated in three separate components: hospitalizations, consultations, and drug treatment. The average length of stay and average number of hospital admissions considered in this analysis were based on the most common (incidence) hospitalizations due to AEs (>1). The cost of a hospital stay per day was derived from the mean cost per day of cancer patients in the pay ward. The standard room rate of PhP 2,000/day, and laboratory fees of PhP 3,000 per confinement were considered. Concomitant drug costs per patient were

calculated by multiplying the mean total number of days of each drug treatment per patient and the daily drug cost of each drug. Main drugs used for AEs were aminoglycosides (e.g., gentamicin), quinolones (e.g., ciprofloxacin, levofloxacin), cephalosporins (e.g., cephalexin, cefuroxime, ceftriaxone, cloxacillin), drugs for gastro-intestinal AEs (ondansetron, metoclopramide, domperidone, loperamide), filgrastim, anti-fungal (amphotericin B, nystatin, fluconazole), emollient, and lorazepam.

Time costs consisted of the sum of ambulatory visits and routine drug administration. Adverse event encounters were also included in the ambulatory visits. The travel time was computed for hospital admissions, drug administration visits and adverse event related ambulatory visits, using assumptions on travel distance and Land Transportation Office cost per mile. The average number of visits per patient was calculated and the patient's time valued at the average hourly wage rate based on data derived from the Department of Labor and Employment to produce total time costs per patient.

Results

Cost of Chemotherapy Drugs

Total cost per complete treatment regimen was computed as follows: XELOX = PhP 569,760; FOLFOX4 = PhP 629,088; XELOX+BEV = PhP 1,639,968; and FOLFOX4+BEV = PhP 1,744,560.

Cost of Central Venous Access

Table 1 shows XELOX with the least cost of central venous access.

Table 1. Central Venous Access (CVA) Cost in PhP.

	Chemotherapy Regimen			
	XELOX	FOLFOX4	XELOX +BEV	FOLFOX4 +BEV
Mean CVA placement cost per patient	30,768	79,632	35,904	74,160
Mean CVA maintenance cost per patient	7,824	29,904	9,168	32,208
Total CVA cost per patient	38,592	109,536	45,072	106,368

Costs Associated with Adverse Events (AE)

Table 2 shows XELOX with the least AE hospital and AE treatment cost per patient.

Table 2. AE Hospital Days and Cost in PhP

	Chemotherapy Regimen			
	XELOX	FOLFOX4	XELOX +BEV	FOLFOX4 +BEV
Mean AE hospital cost per patient	5,712	3,888	6,816	4,320
Mean AE treatment costs per patient	9,840	12,336	8,640	13,824
TOTAL	14,552	16,224	15,456	18,144

Time and Travel Costs

Table 3 shows XELOX with the least patient time and travel cost for hospital/ clinic visits.

Table 3. Patient Time and Travel Costs (PhP) for Hospital/ Clinic Visits

	Chemotherapy Regimen			
	XELOX	FOLFOX4	XELOX +BEV	FOLFOX4 +BEV
Patient Time Costs	2,256	9,648	2,832	11,232
Patient Travel Costs	7,104	16,320	9,936	19,104
Total Indirect Costs	9,360	25,968	12,768	30,336

Overall Cost Summary

FOLFOX4+BEV had the highest overall cost. The other chemotherapy regimens that follow in order of descending cost are: XELOX+BEV, FOLFOX4, and then XELOX (Table 4).

Table 4. Overall Cost Summary (PhP)

	Chemotherapy Regimen			
	XELOX	FOLFOX4	XELOX +BEV	FOLFOX4 + BEV
Total Direct Medical Costs	612,814	754,848	1,700,496	1,869,072
Total Indirect Costs	9,360	25,968	12,768	30,336
Total Costs	622,174	780,816	1,713,264	1,899,408

Discussion

The use of XELOX regimen resulted in a direct medical cost saving of PhP142,034 per patient compared with FOLFOX4. A cost saving of PhP168,566 per patient was made when XELOX+BEV was used compared with FOLFOX4+BEV. XELOX+/-BEV was least costly since these involved an average of 8.6 and 7.6 cycles of parenteral administration, respectively, in an out-patient setting. For FOLFOX4+/-BEV, parenteral administration involved a mean of 12.3 and 11 cycles, respectively, with two days of parenteral chemotherapeutic drugs per cycle in an in-patient setting. More cycles also required more instances for medical oncologist professional fee payment.

The costs of central venous line placement and maintenance fee were cheaper with XELOX+/-BEV, compared to that of FOLFOX4+/-BEV, if the number of placements was based on the trial of Cassidy et al.[1] More patients on FOLFOX4+/-BEV were being treated with the aid of central line: 3 times the number of patients on the FOLFOX4 regimen compared to that of XELOX was placed on central venous line for convenience; FOLFOX4 had an average of 4 more cycles compared to XELOX; an average of six times more patients on FOLFOX4 had central lines replaced during treatment. The cost of central venous line removal was omitted in our study since majority of our patients at PGH did not have their central line removed during the course of their treatment. In actual practice, an average of one fifth of our metastatic colorectal cancer

patients had central venous lines in place mainly due to economic reasons. If ever the central venous line cost was omitted from the total direct medical costs then FOLFOX would be cheaper by PhP11,616 compared to XELOX; however, if the patient was on bevacizumab it would favor XELOX by PhP43,296.

Hospitalization costs for treatment of adverse events were noted to be cheaper for FOLFOX4 compared to XELOX; for the patient on bevacizumab, hospitalization cost favored the FOLFOX4 arm. Based on the incidence of adverse events,[1] patients on XELOX had grade 3/4 diarrhea necessitating hospitalization as compared to patients on FOLFOX4, where more patients had grade 3/4 neutropenia and febrile neutropenia who were mostly treated on an outpatient basis thus lowering their hospitalization expenses.

Costs of concomitant medications used for treatment of adverse events were cheaper for XELOX and XELOX+BEV compared to FOLFOX4 since more patients on the FOLFOX4 arm had febrile neutropenia requiring G-CSF, anti-microbials and antifungals; patients on XELOX had diarrhoea requiring anti-diarrheal medications, which were cheaper than G-CSF and anti-microbials.

For total indirect costs, XELOX was cheaper than FOLFOX4. For patients on bevacizumab, XELOX was still cheaper. The indirect costs consisted of the patient time costs and travel costs. Patient time costs were cheaper for XELOX+/-BEV compared to FOLFOX4 because patients on FOLFOX4 had more time lost from work due to more frequent hospital visits for drug administration. Time lost in queuing to receive the treatment was also considered. Patients on XELOX had lower travel costs since they had fewer treatment cycles compared to those on FOLFOX.

From the patient's perspective in a Philippine tertiary government setting, the highest cost (direct and/or indirect) was seen in FOLFOX4+BEV, followed by XELOX+BEV, FOLFOX4, and then XELOX. The use of XELOX resulted in a cost saving of PhP158,642 per patient compared with FOLFOX4; the use of XELOX+BEV resulted in a cost saving of PhP186,144 per patient compared with FOLFOX4+BEV.

Other pharmaeconomic studies[4-8] show similar results. In these studies, from both the healthcare provider and societal perspectives, the treatment of metastatic colorectal cancer with XELOX costs less than FOLFOX4.

References

1. IARC. Incidence, mortality, 6-year prevalence of colorectal cancer in Philippines and the world. Globocan [Online]. 2008 [cited 2013 June]. Available from http://globocan.iarc.fr/factsheet.asp.
2. Cassidy J, Clarke S, Diaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer. 2011; 105(1):58–64.
3. Garrison L, Cassidy J, Saleh M, et al: Cost comparison of XELOX compared to FOLFOX-4 with or without bevacizumab (bev) in metastatic colorectal cancer. J Clin Oncol. 2007; 25:182s (suppl; abstr 4074).
4. Tse VC, Ng WT, Lee V, et al. Cost-analysis of XELOX and FOLFOX4 for treatment of colorectal cancer to assist decision making on reimbursement. BMC Cancer. 2011; 11:288-94.
5. Shiroiwa T, Fukuda T, Tsutani K. Cost-effectiveness analysis of XELOX for metastatic colorectal cancer based on the NO16966 and NO16967 trials. Br J Cancer. 2009; 101(1):12–8.
6. Scheithauer W, Cassidy J, Figer A, et al. A comparison of medical resource use for 4 chemotherapy regimens as first-line treatment for metastatic colorectal cancer (MCRC): XELOX vs. FOLFOX-4 bevacizumab (A). J Clin Oncol. 2007; 25:188s, (suppl; abstr 4098).
7. Perrocheau G, Bennouna J, Ducreux M, et al: Cost-minimization analysis of a phase III study of capecitabine _ oxaliplatin (XELOX) vs. infusional 5-FU/LV _ oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer (MCRC) in the French setting. J Clin Oncol. 2007; 25:184s (suppl; abstr 4083).
8. Chu E, Zelt S, Song X. A claims database cost-comparison analysis of capecitabine in the treatment of patients with colon or rectal cancer (CRC). Gastrointestinal Cancer Symposium. January 26-28, 2008 (abstr 364).