Original Article

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A Systematic Review on Economic Evaluation of Oxaliplatin Added Regimens as the Adjuvant Chemotherapy in Stage III Colon Cancer

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Abstract

Adjuvant chemotherapy regimens with oxaliplatin added could significantly prolong patient's survival, but are very costly. Therefore, the economic evaluation studies of oxaliplatin added regimens should be explored. The objective of this study was to review the literatures related to economic evaluation of oxaliplatin added regimen as the adjuvant chemotherapy in stage III colon cancer. Studies comparing both costs and outcomes of oxaliplatin added regimens as the adjuvant chemotherapy in state III colon cancer were included. All related literatures until 2009 were searched through the Pubmed and Cochrane databases. All eligible studies were extracted using data extraction forms. The choices of methods used and economic evaluation results were reviewed. The results showed that thirty studies were reviewed and twenty-six studies were excluded. Four eligible studies related to colon cancer were fully reviewed. All four studies were conducted based on the perspective of healthcare payer which considered only direct medical costs. Outcomes were mostly measured as life year gained, disease–free years and quality-adjusted life years. The cost-utility analysis method using Markov model with a lifetime horizon was performed in all studies. Mostly, data used in the model were retrieved from systematic review, published literature and clinical trials. One-way and probabilistic sensitivity analyses were used to handle parameter uncertainty. Based on the systematic review, FOLFOX4 (oxaliplatin plus 5-fluorouracil and leucovorin, 5FU/LV) or capecitapine was more cost-effective in patients with colon cancer in the US and UK compared with 5FU/LV. There has been no cost-effectiveness study of oxaliplatin added regimens as the adjuvant chemotherapy in patients with colon cancer in Asian countries yet. Such study in Thailand would be very useful information for decision making whether oxaliplatin should be included in the National List of Essential Drugs. Therefore, the cost-effectiveness analysis study should be performed to compare the cost and effectiveness oxaliplatin as adjuvant chemotherapy in stage III colon cancer in Thailand.

Key words: Economic evaluation; Cost-effectiveness; Cost-utility; Colonic neoplasms; Adjuvant chemotherapy; Oxaliplatin

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INTRODUCTION

Colorectal cancer is a major public health issue. It is the third most common cancer with one million new cases worldwide and the fourth leading cause of death due to cancer in 2004[1]. In Thailand, colorectal cancer is the third most frequent malignancy in males and the fifth in females with age-standardized incidence rates of 11.3 and 7.9 per 100,000 for males and females during 2001-2003, respectively[2].

Surgical resection is the mainstay initial treatment for stage III colon cancer. However, almost 50% of patients who undergo potentially curative surgery alone can relapse and finally die as microscopic metastases present but are undetected at the time of surgery[3]. The role of chemotherapy for colon cancer after curative resection has been used as adjuvant chemotherapy which has antitumor activity that helps decreasing relapse and death. The benefit of adjuvant chemotherapy (i.e., 5-FU combined with leucovorin) reduces relapse rates and improves overall survival by about 33% in patients with node-positive colon cancer (stage III or Dukes' stage C). These advantages were not observed in stage II or Dukes' stage B[4-5].

At present, 5-Fluorouracil and leucovorin (5-FU/LV) based has been the standard treatment of care which established for six months[6]. Several regimen schedules of 5-FU/LV exist and lead to a difference in toxicity. Besides, the benefits of capecitabine and oxaliplatin (in combination with 5-FU/LV) have been evaluated in the adjuvant treatment of patients with stage III colon cancer. However, oxaliplatin is another drug shown to have synergistic activity with 5-FU in colon cancer[7]. The addition of oxaliplatin to the 5-FU/LV combination has demonstrated significant improvement in disease-free survival and overall survival in the adjuvant setting[8-9].

Currently, oxaliplain has been still expensive and not yet included in National List of Essential Drugs (NLED). The price of oxaliplatin 50 mg per 10 ml is ranged from 9,000 to 14,000 baht[10]. In Thailand, there has been no economic evaluation study of adjuvant chemotherapy for stage III colon cancer patients after resection. Therefore, the NLED committees requested economic evaluation information of adjuvant chemotherapy regimen, particularly oxaliplatin added regimen in stage III colon cancer to consider whether oxaliplatin should be included in the NLED. This study was conducted to review the literatures related to economic evaluation of oxaliplatin added regimen as the adjuvant chemotherapy in stage III colon cancer in order to provide the information for policy decision making.

METHODS

A systematic review of the literatures on the cost-effectiveness of oxaliplatin for the treatment of stage III colon cancer patients was searched through Pubmed and Cochrane databases until 2009 using the following keywords: "Colon Neoplasms" [Mesh] AND (cost effectiv* OR cost utilit* OR cost evaluat* OR cost benefit OR economic evaluat*) AND Oxaliplatin "[Substance Name]. Then, the literatures were selected based on the inclusion and exclusion criteria as follows.

Inclusion criteria

1. The studies compared both costs and outcomes in term of incremental cost per quality-adjusted life-year (QALY) gained of oxaliplatin added regimens as the adjuvant chemotherapy in state III colon cancer.
2. The studies were published until 2009.
3. Only English publications were selected.

Exclusion criteria

1. The studies considered only outcome (efficacy, effectiveness) or cost analysis.
2. The studies were editorial article or expert opinion.
3. The studies in which the methodologies were not unclear.

Quality assessment

The relevant studies were critically appraised using the Drummond's checklist for assessing the quality of economic evaluation as shown in Table 1[11].

RESULTS AND DISCUSSIONS

The systematic review resulted in a total of thirty studies for potential inclusion in the review. Twenty-six studies were excluded and four studies were identified as the specified criteria. All eligible studies were extracted using data extraction forms and major key components of economic evaluation for each study were summarized as shown in Table 2.

Four eligible studies (one study in the U.S. and three studies in the U.K.) related to colon cancer were fully reviewed. Target populations in all studies were stage III colon cancer patients after complete resection of primary tumor. All four studies were conducted based on the perspective of healthcare payer which considered only direct medical costs. Outcomes were mostly measured as life year gained, disease–free years and quality-adjusted life years. The cost-utility analysis method was performed in all studies using Markov model with a lifetime horizon but only one study presented the model. Mostly, data used in the model were retrieved from systematic review (1 study), published literature (4 studies) and clinical trials (4 studies). The incremental cost-effectiveness ratio (ICER) was used to interpret the results of cost-effectiveness analysis. One-way and probabilistic sensitivity analyses were used to handle parameter uncertainty (4 studies). All articles compared FOLFOX4 (oxaliplatin in combination with 5-FU/ LV) with 5-fluorouracil and leucovorin (5-FU/LV). Based on the systematic review, FOLFOX4 was more cost-effective in patients with colon cancer in the US and UK compared with 5FU/LV. The summary of each study is presented as follows.

The cost-effectiveness of oxaliplatin in the U.S.

Aballea et al[12] reported the results of cost-effectiveness analysis of FOLFOX4 (oxaliplatin in combination with 5-FU/LV) compared to 5-FU/LV in patients with resected stage III colon cancer based on the perspective of U.S. Medicare. The mean total lifetime disease-related costs were $56,300 with FOLFOX4 and $39,300 with 5-FU/LV. Cost of chemotherapy was the main cost component at approximately $29,000 per patient receiving FOLFOX4 as a treatment and $6,500 per patient receiving 5-FU/LV. In addition, cost associated with relapse due to incidence of relapse and position (i.e., local, lung, liver, and other types of disseminated disease) was the most costly resource use with the average of $16,600 in the FOLFOX4 group and $23,700 in the 5-FU/LV group. The main outcomes were disease-free years (DFYs), life-year (LYs) and quality-adjusted life years (QALYs). DFYs and overall survival (OS) were extrapolated by using data from MOSAIC trial to a lifetime horizon. The predicted life expectancy of stage III colon cancer patients for stage III colon cancer on FOLFOX4 group and 5-FU/LV group was 12.34 and 11.52 years, respectively. In conclusion, FOLFOX4 was likely to be cost-effective compared to 5-FU/LV in adjuvant treatment of stage III colon cancer with an incremental cost of $12,800 per DFY, $20,600 per LY gained, $22,800 per QALY gained with the probability being cost-effective of 91% at the willingness to pay (WTP) of $50,000 per QALY gained.

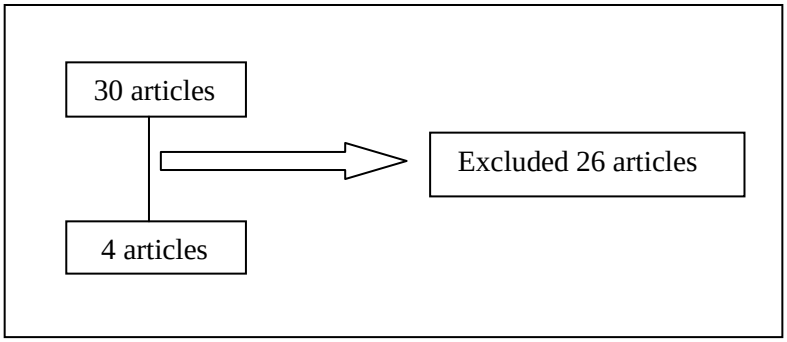

Figure 1. Result of systematic review

The cost-effectiveness of oxaliplatin in U.K.

Eggington et al[13] and Aballea et al[14] conducted the cost-effectiveness analysis of oxaliplatin for the adjuvant treatment of stage III colon cancer. Both studies compared oxaliplatin in combination with 5-FU/LV (FOLFOX4) to 5-FU/LV based on the perspective of the NSH in the UK. The effectiveness data were obtained from MOSAIC trial and extrapolated to DFYs, life-years and overall survival (OS). Eggington et al developed a Markov model to estimate the marginal cost-effectiveness of oxaliplatin. For those who relapsed, the expected survival was modelled using a parametric Weilbull survival model based on the experience of patients in FOCUS trial[15]. Only direct medical cost was £26,000 and £22,000 in FOLFOX4 group and 5-FU/LV group, respectively. FOLFOX4 was estimated to produce 12.15 LY gained while 5-FU/LV produce 10.80 LY gained. The incremental cost-effectiveness ratio (ICER) was equal to £2,970 per QALY gained. Aballea et al found that FOLFOX4 was more cost-effective than 5-FU/LV. The main outcomes measured as DFYs, LYs and QALYs. Cost of FOLFOX4 increased by £3,923 but decreased the cost of relapse by £1,026 compared to that of 5-FU/LV. Total costs of the treatment during four years after resection were higher by £3,407 in patients receiving FOLFOX4 compared with those with 5-FU/LV. The results showed that the incremental cost was £2,600 per DFY, £4,200 per LY and £4,805 per QALY gained with the probability being cost-effective of 94% at the WTP of £20,000 per QALY. In conclusion, the evidences from these two studies showed that FOLFOX4 was more cost-effective at the WTP of £20,000 per QALYs.

Furtheremore, Koperna et al[16] assessed the cost-effectiveness of oxaliplatin in combination with 5-FU/LV compared to 5-FU/LV in patients with resected stage III colon cancer based on the perspective of the Austrian healthcare provider. Cost data in this study included cost of metastatic disease and the efficacy data on disease-free survival and overall survival for oxaliplatin in combination with 5-FU/LV were obtained from clinical trials from stage IV colon cancer. The results were presented as the incremental cost per life-year gained (£24,952) of oxaliplatin in combination to 5-FU/LV. However, Pandor et al conducted a systematic review of clinical effectiveness and economic evaluation of oxaliplatin and capecitabine for the adjuvant treatment of stage III colon cancer and suggested that the study of Koperna et al had many methodological flaws related to cost and effectiveness data collection[17].

CONCLUSIONS

Recently, oxaliplatin has not yet included in the National List of Essential Drug (NLED). This study was conducted to review the literatures related to economic evaluation of oxaliplatin added regimen as the adjuvant chemotherapy in stage III colon cancer in order to provide the background information for policy decision making. Thus, the cost-effectiveness analysis of oxaliplatin added regimen as an adjuvant chemotherapy for stage III colon cancer patients in Thailand should be performed for future research.

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IS THE ECONOMIC EVALUATION LIKELY TO BE USABLE?												
Study	**1. Was a well-defined question posed in an answerable form?**	**2. Was a comprehensive description of the competing alternatives given**	**3. Was there evidence that the programme's effectiveness had been established?**	**4. Were all the important and relevant outcomes and costs for each alternative identified?**	**5. Were outcomes and costs measured accurately in appropriate units**	**6. Were the outcomes and costs valued credibly?**	**7. Were outcomes and costs adjusted for different times at which they occurred**	**8. Was an incremental analysis of the outcomes and costs of alternatives performed?**	**9. Was a sensitivity analysis performed?**	**10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?**	**11. Were the conclusions of the evaluation justified by the evidence presented?**	**12. Can the results be applied to the local population?**
Aballea[12] et al (US)	√	√	√	√	√	√	√	√	√	√	√	√
Eggington[13] et al (UK)	√	√	√	√	√	√	√	√	√	√	√	√
Aballea[14] et al(UK)	√	√	√	√	√	√	√	√	√	√	√	√
Pandor A.[17] et al.(UK)	√	√	√	√	√	√	√	√	√	√	√	√

Table 1. Quality of economic evaluation studies according to Drummond checklists

Table 2. Summary on major key components of economic evaluation for each study

Study	Disease and patient group	Objective	Intervention	Perspective	Source of data	Cost	
						Direct	Indirect
1. Aballea S.[12] et al. (2007)(US)	Patients with stage III colon cancer after surgical resection	To confirm the cost-effectiveness of oxaliplatin in combination with infusion 5-FU/LV compared with 5-FU/LV	1. oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. 5-FU/LV	NSH in the UK.	Literature review, MOSAIC trial	Cost of chemotherapy, clinic attendance, Infusion pumps, Premedication adjuvant chemotherapy, Cost of routine follow up, Cost of recurrence, Cost of management serious side effect	N/A
2.Eggington S.[13] et al (2006)(UK)	Patients with stage III colon cancer after surgical resection	To estimate the cost-effectiveness of 1.oxaliplatin plus 5-FU/LV and 2. capecitabine compared to 5-FU/LV	1. oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. Infusion 5-FU/LV (de Gramont) 3. capecitabine 4.bolus 5-FU/LV	NSH in the UK. and personal social service(PSS)	Literature review, MOSAIC trial, X-act trial	Drug acquisition and administration, Pharmacy handling and dispensing infusor pumps, Examinations and tests, Hospitalization resource use for the management of toxicity	
3. Pandor A.[17] et al. (2006)(UK)	Patients with stage III (Duke'C) colon cancer after surgical resection	To assess the clinical and cost-effectiveness of oxaliplatin in combination with infusion 5-FU/LV and capecitabine monotherapy as adjuvant chemotherapy	1. Oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. Infusion 5-FU/LV (de Gramont)	NSH in the UK.	Systematic review	Drug acquisition and administration, Cost of hospitalization from adverse events, Medication cost of associated with the treatment of adverse events, Number of physician consultants(eg. GP visit, hospital outpatient visits, accident and emergency attendences	N/A
4. Aballea S.[14] et al. (2007)(UK)	Patients with stage III colon cancer after surgical resection	To evaluate the long-term cost-effectiveness of oxaliplatin in combination with5-FU/LV	1. oxaliplatin in combination with infusion 5-FU/LV (FOLFOX4) 2. 5-FU/LV	NSH in the UK	Literature review, MOSAIC trial	Cost of chemotherapy, Replacement chemotherapy, Outpatient visit, Laboratory tests, Adverse events and surgery, Treatment for relapse, Treatment for disease monitoring during chemotherapy and afterwards, Treatment associated with non-serious toxicities, serious side effect	N/A

Table 2. Summary on major key components of economic evaluation for each study (cont.)

Study	Outcome	Method	Discounting	Sensitivity analysis	Results
1. Aballea S.[12] et al. (2007)(US)	1. Disease-free years (DFY) 2. Life years gained (LYs)	CUA (No model presented)	3% per year	Bootstrap method	1. The predicted life expectancy of stage III on FOLFOX4 and 5-FU/LV was 17.6 and 16.26 years 2. Mean total life time disease-related costs on FOLFOX4 and 5-FU/LV were $56,300 and $393,000 3. oxaliplatin/5FU/LU is cost effectiveness compared with 5-FU/LU (ICER=$12,900 per DFY gained, $20,600 per LY gained,$22,800 per QALY 4. FOLFOX4 is cost effective 91-96% probability (willingness to pay of $50,000 to $1000,000 per QALY gained)
2. Eggington S.[13] et al (2006)(UK)	1.Life years gained (LYs) 2.Quality of life adjusted year	CUA (model presented)	6% per year	One way and Probabilistic sensitivity analysis	1. The incremental cost per QALY gain of capecitabine is dominant to 5-FU/LU (MAYO clinic) 2. FOLFOX4 is estimated to cost £2970 per additional QALY gained compared with 5FU/LU(de gramont)
3. Pandor A.[17] et al. (2006)(UK)	1.Life years gained(LYs) 2.Quality of life adjusted year gained	CUA (No model presented)	6% for cost and 1.5% for QALY per year	Probabilistic sensitivity analysis	1. capecitabine and FOLFOX4 are clinically effective and cost-effective in comparison with 5-FU/LV regimens (Mayo Clinic and de Gramont schedules) 2. capecitabine was a dominating and cost-saving of £3320 per patient in comparison with the Mayo Clinic 3. FOLFOX4 in comparison with de Gramont 5-FU/LV regimens is to cost an additional £2970 per QALY gained
4. Aballea S.[14] et al. (2007)(UK)	1. Disease-free years(DFY) 2. Life years gained(LYs)	CUA (No model presented)	3.5% per year	Bootstrap method	1. Folfox4 (oxaliplatin/5FU/LV) is cost effectiveness compared with 5-FU/LV (ICER = £4805 per QALY) 2. The probability of oxaliplatin/5-FU/LV from The cost - effectiveness acceptability curve is 94.7% for a threshold of £20,000 and 96.7% for a threshold of £30,000

REFERENCES

1. World Health Organization. The global burden of disease: 2004 update. WHO 2004.
2. Khuhaprema T. MD, F.I.C.S., Srivatanakul P. PD, Sriplung H. MD, Wiangnon S. MD, Sumitsawan Y. MD, Attasara P. MD, et al. *Cancer in Thailand* 2001-2003 Vol.V. 2001-2003; 5.
3. Obrand DI, PH G. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. *Dis Colon Rectum* 1997; 40:15-24.
4. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. *J Clin Oncol* 1993; 11:1879-1887.
5. O'Connell M, Mailliard J, Kahn M, et al. Controlled trial of fl uorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997; 15:246-250.
6. Cristina Gra'valos, Ignacio Garci'a-Escobar, Pilar Garci'a-Alfonso, Javier Cassinello, Diego Mal'on, Alfredo Carrato. Adjuvant chemotherapy for stage II,III and IV of colon cancer. *Clin Transl Oncol* 2009; 11:526-533.
7. Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity *Semin Oncol* 1998;25((suppl5)):4-12.
8. Thierry André MD, Corrado Boni MD, Lamia Mounedji-Boudiaf MD, Matilde Navarro MD, Josep Tabernero MD, Tamas Hickish MD, et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. *New Engl J Med* 2004; 350(23):2343-2351.
9. Kueble J, Samuel Wieand H, Michael J, O'Connell, Smith R, Colangelo L, et al. Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for Stage II and III Colon Cancer: Results From NSABP C-07. *J Clin Oncol* 2007; 25:2198-2204.
10. http://dmsic. moph.go.th/download/rp_4-6_52.pdf. (accessed 2010)
11. Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford Medical Publications. 1987.
12. Aballea S, Jeremy V.M, Raikou M, Drummond M., Weinstein M, Bridgewater J. Cost-Effectiveness Analysis of Oxaliplatin Compared With 5-Fluorouracil/ Leucovorin in Adjuvant Treatment of Stage III Colon Cancer in the US. *cancer* 2007; 109 (6):1082-1089.
13. Eggington S, Tappenden P, Pandor A, Paisley S, Saunders M, Seymour M, et al. Cost-effectiveness of oxaliplatin and capecitabine in the adjuvant treatment of stage III colon cancer *British J Cancer* 2006; 95:1195-1201.
14. Aballea S, Boler A, Craigc A, Wasan H. An economic evaluation of oxaliplatin for the adjuvant treatment of colon cancer in the United Kingdom (UK). *Eur J Cancer* 2007; 43:1687-1693.
15. Maughan T. obotNcg, Fluorouracil(FU), Oxaliplatin (Ox), CPT-11 (irinotecan, Ir), Use and Sequencing, in advanced colorectal cancer (ACRC): the UK MRC FOCUS (CR08) Trial. ASCO Gastrointestinal Cancers Symposium
16. Koperna T, Semmler D. Innovative chemotherapies for stage III colon cancer: A cost-effectiveness study. *Hepatogastroenterol* 2003; 50:1903-1909.
17. Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P. The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer:systematic review and economic evaluation. *Health Technol Assess* 2006; 10(41)