Economic Evaluation Of Cetuximab for Metastatic Colorectal Cancer (mCRC): A Protocol For Evidence Synthesis

Evaluasi Ekonomi Terapi Cetuximab Untuk Pasien Kanker Kolorektal Metastasis: Protokol Untuk Kajian Bukti

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Abstract
Colorectal cancer is fairly common compared to other cancers. The incidence and mortality rates are predicted to increase globally. In some cases, cancer can be potentially spread to another organ or metastatic. One of recent available targeted therapies for metastatic colorectal cancer (mCRC) patient is Cetuximab (Erbitux ®), combined with chemotherapy. Despite clinical effectiveness, there is the importance of the evidence related cost-effectiveness of therapy. This study aims to summary, synthesize, and systematically review the economic evaluation studies of Cetuximab for metastatic colorectal cancer (mCRC). Model based economic evaluation of Cetuximab for metastatic colorectal cancer will be searched and included in the review based on specific eligibility criteria. Several electronic databases that will be used: Medline, Embase, Cochrane, National Institute of Health Research (NIHR) Center for Reviews and Dissemination. Full economic evaluation evidence will be summarized and critically appraised using Drummond as well as (Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. In terms of analysis, we will qualitatively appraise and present the studies that meet our inclusion and exclusion criteria. We are expected to summarize the quality and capture the valuable insights related to health economic evaluation studies of Cetuximab for mCRC patient.
Keyword: economic evaluation, cetuximab, erbitux, colorectal cancer

Abstrak
Kanker kolorektal cukup umum terjadi dibandingkan kanker lainnya, angka kejadian dan angka kematian diprediksi meningkat secara global. Dalam beberapa kasus, kanker berpotensi menyebar ke organ lain atau disebut metastasis. Salah satu terapi yang ditargetkan baru-baru ini untuk pasien kanker kolorektal metastatik (mCRC) adalah Cetuximab (Erbitux®), yang dikombinasikan dengan kemoterapi. Meskipun terdapat bukti klinis, penting untuk mempertimbangkan bukti terkait efektivitas biaya dari terapi tersebut. Penelitian ini bertujuan untuk merangkum, mensintesis, dan meninjau secara sistematis studi evaluasi ekonomi Cetuximab untuk kanker kolorektal metastatik (mCRC). Evaluasi ekonomi berbasis model untuk menilai Cetuximab pada kanker kolorektal metastatik akan ditelusuri sesuai dengan kriteria yang ditetapkan. Beberapa database elektronik yang akan digunakan: Medline, Embase, Cochrane, Pusat Penelitian Kesehatan Nasional (NIHR) untuk Tinjauan dan Diseminasi. Bukti evaluasi ekonomi lengkap akan dirangkum dan dinilai secara kritis dengan menggunakan daftar pertanyaan Drummond dan juga Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Dalam hal analisis, kami akan menilai dan menyajikan secara kualitatif studi yang memenuhi kriteria inklusi dan eksklusi. Kami berekspektasi untuk menyimpulkan kualitas dan menangkap informasi yang berkaitan dengan studi evaluasi ekonomi pada Cetuximab untuk pasien mCRC.
Kata kunci: evaluasi ekonomi, Cetuximab, Erbitux, kanker kolorektal

Introduction

Colorectal cancer (CRC) is one of the most common cancer worldwide, with approximately 1.4 million new cases that were diagnosed in 2012. It is predicted that the disease burden will increase for more than 2.2 million new cases and 1.1 million deaths in 2030 (Ferlay et al, 2012; Arnold et al 2016). The incidence rates have been rising in developing countries, even though colorectal cancer as historical were commonly diagnosed in developed world. The aging population, unhealthy lifestyle and behaviors, gender, geographical variations as well as economic status may become considerably factors that impacted the global burden of this disease (Favoriti et al 2016; Douaiher et al 2017).

Over the past two decades, almost 20% patients with CRC already have metastases in diagnosis. Similar with other types of cancer, CRC can be spread to other parts of patients' body (van der Geest et

al 2015). The most frequent is liver, sometimes it spreads to the lungs, bones, or other organs in the body (Field and Lipton 2007). Most of metastatic colorectal cancer (mCRC) have been not possible to be cured, and palliative care is become the option in the past decades (Ewara, 2012). On the other hand, surgical procedure is also one of the potential options, however in some clinical cases this could not be done. As consequence, chemotherapy may become the most appropriate one. Furthermore, the treatment generally can be undertaken by performing combination intervention such as: surgical, radiotherapy, chemotherapy and another supportive care.

Recently, there are introduction of several advancements for targeted therapy, including bevacizumab (Avastin®), cetuximab (Erbitux®), and panitumumab (Vectibix®). These targeted therapies have potential benefit in terms of improving the patients' survival-as monotherapy or combination, also depending on treatment patterns (Tappenden et al 2007; Rinaldi et al 2012; Silva et al 2017). In general, most of patients receiving the combination of 5-fluorouracil(FU)/leucovorin (LV) with containing either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) together with monoclonal antibody (MAb) has widely-accepted as standard care. The combination of MAb improves the overall survival, progression-free survival as well as tumor response rate (Chan et al, 2017).

Cetuximab is one of monoclonal antibodies that target the epidermal growth factor receptor (EGFR) and beneficial in order to treat mCRC patients, particularly in patients who had failed with chemotherapy. Epidermal growth factor receptor (EGFR) plays important roles in terms of differentiation, survival, normal or cancerous cells. EGFR is a receptor that can be found in both normal and tumor cells (Martinelli et al 2009; Yarom and Jonker 2011). As EGFR inhibitor, Cetuximab is used to impede the EGFR activity from growing continuously. Moreover, patients with Kirsten rat sarcoma (KRAS) wild-type tumors characteristic can receive this therapy. It means if KRAS is mutated, the EGFR inhibitor unlikely provide favorable respond to patients.

Several studies concluded the additional of cetuximab to chemotherapy has potentially favorable, although not in all expected clinical outcomes. In the Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) study reported that the additional cetuximab to FOLFIRI as first-line treatment potentially increase the response chance and reduce the risk of disease progression in with KRAS wild type patients. Compared to FOLFIRI alone, the overall survival (OS) was (median 23.5 vs 20 months; HR= 0.796; P = .0093), progression free survival (PFS) (median, 9.9 vs 8.4 months; HR, 0.696; P = .0012), and response rate (rate 57.3% vs 39.7%; odds ratio, 2.069; P < .001)(Van Cutsem et al, 2011). Moreover, the Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer (OPUS) study reported that addition of cetuximab to 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX4) as first line therapy in mCRC patients has improved the objective response and PFS. For KRAS wild type tumors, compared to FOLFOX4 alone the chance of response has clinically increased (ORR=61% vs 37%; OR=2.54; P=0.011) and lower risk of disease progression (HR=0.57; P=0.0163). (Bokemeyer et al, 2009) Both of these studies confirmed that the KRAS mutation is impactful predictive marker for the efficacy or outcome when adding the cetuximab with chemotherapy.

The financial burden of colorectal treatment itself are substantial. As the introduction of the new targeted therapy caused the treatment expenditures increasing, and become the challenges in clinical practice and public health policy (Jansman et al, 2007). In terms of resource allocation and to inform coverage decision, as this drug provides clinical improvement but relatively costly, economic evaluation study will be conducted in Indonesia setting (Indonesian Health Technology Assessment). The assessment is intended to assess "value for money" of Cetuximab for mCRC patients in Indonesia. Furthermore, as the initial step for health economic model development, literature review of related studies is required.

The aim of this study is to conduct the review of health economic evaluation studies related Cetuximab as first line therapy for mCRC. We will perform systematic search, summary, narrative and critical review from relevant-available evidence. Several studies previously conducted to assess clinical effectiveness and some cost-effectiveness of this therapy with various comparators and specific population criteria(Tappenden et al, 2007; Gao et al, 2009; Yang et al, 2017). Therefore, we plan to conduct comprehensive review that potentially useful not only to gather the information in order to support our economic model structure, but also to sharpen our critical appraisal skill. As our study assumption,

we specify the review activity to cetuximab plus chemotherapy as first-line treatment compared to chemotherapy alone. The clinical effectiveness review is conducted elsewhere, with similar team member.

Method

Operational Definitions

Colorectal cancer happens when the abnormal cells are growing in colon or rectum. It is often starter with polyp, the overgrowth of the cells and finally turn to cancer. When the cancer spreads or familiarly known as "metastatic", the most often organs that is impacted is liver, sometimes it also spread to the lungs, bones, or other organs in the body(NCCN, version 1.2017).

Cetuximab (Erbitux ®) is "a chimeric monoclonal antibody highly selective for the epidermal growth factor receptor (EGFR), which is over-expressed by 25-80% of colorectal cancer tumors and associated with advanced disease". (Reynolds and Wagstaff, 2004) EGFR is a protein that influence the grow of cancer cell, it appears on the surface of cancer cells, Cetuximab target EGFR, it is given by IV infusion. Several colorectal cancers have mutations in the *KRAS or BRAF gene*, that make Cetuximab ineffective(Laurent-Puig et al, 2009).

Economic evaluation is defined as "comparative analysis of alternative courses of action in terms of both their costs and consequences", it provides evidence whether the health intervention is worth or efficient use of resources, gaining the best value for money. Economic evaluation consists of full economic evaluation and partial economic evaluation (Drummond et al, 2015).

Inclusion and Exclusion Criteria

In terms of inclusion criteria, we will include full economic evaluation studies: cost-effectiveness and cost-utility analysis particularly that performing decision analytic or mathematical model. We remain including the evaluation alongside clinical trial. The population are all mCRC patients (age ≥18 years old, with no restriction on metastatic organs, gender characteristics and race) who had received Cetuximab (Erbitux®) as first line treatment, added to chemotherapy. No limitation regarding the dose, administration frequency, and treatment duration. The comparators are standard chemotherapeutic agent including: Folinic acid, 5-fluorouracil (5-FU) and Oxaliplatin (FOLFOX) and Folinic acid, 5-fluorouracil (5-FU) and irinotecan (FOLFIRI) or other standard chemotherapy (i.e: XELOX). The primary outcome of interest must include Incremental Cost Effectiveness Ratio (ICER), the ratio calculation of incremental cost to increase additional unit of outcome/benefit for intervention versus comparators, generally represented by costs per QALY or costs/natural unit.

We exclude the partial economic evaluation studies that only reported cost description, cost analysis or cost of illness. Furthermore, Cetuximab as second or third line therapy for colorectal cancer are excluded for the review.

Electronic Databases and Searching Methods

The search strategy will be performed for Medline/PubMed, Embase and Cochrane Library (see supplementary appendix 1). The searching in database specific headings, vocabulary and terms will follow the Center for Reviews and Dissemination's (CRD) Guidance 2009. The first step of searching process is we will perform several related search terms and synonyms about "cetuximab", "colorectal cancer" and "economic evaluation". Furthermore, we will apply the Boolean connector including "OR" for each similar term/domain and then combine with "AND" to make our searching more specific and close to inclusion criteria. Reference list from main published study also checked to find the relevant literature.

No restriction in terms of year of publication, and only study that reported in English are collected. Grey literature such as conferences abstract, non-full text report/posters are possible to be summarized but not for full review. However, we include the full text of thesis or dissertation if they meet our criteria.

Results

This protocol only provided the information and stages regarding our review plan. The result for narrative review after applying searching strategy will be corresponded with each stage (plan when conducting the review) below:

Study Selection

For this review, we will have four independent reviewers that would be divided into two groups. SP and ES will screen the titles and abstracts, selecting the studies that potentially meet our eligibility criteria. Another reviewers LC and RS, will be working together with SP and ES for re checking the screening stage before critical review process. The disagreements between reviewers will be resolved by discussion. The details of this selection process will be reported using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

diagram (Moher et al, 2009).

Data Extraction

In the stage of data extraction, we will use standardized sheet from in Microsoft Excel. Two reviewers will extract the data (LC and RS). The sheet will be used to summarize the important characteristics of studies that meet our eligibility criteria, there are including: the author and year of publication, type of economic evaluation, modeling method, perspective, result (ICER, QALY, costs), and sensitivity analysis. In order to keep our transparency and consistency, the other reviewers will re-check the completed extraction form (AM and VP).

Quality Assessment

The quality assessment would be assed by two independent authors (SP and ES) and reviewed by a third author (RS). We will use Drummond's Checklist (Drummond et al., 2015) and Consolidated Health Economic Evaluation Reporting Standard (CHEERS) statement (Husereau et al., 2013).

Data Synthesis

As economic evaluation commonly has the substantial heterogeneity between studies such as: study setting, analysis, perspectives, methods and model assumption, we do attempt to synthesize all included studies, narratively. The objective of this narrative presentation is to identify, critically appraise and compare all studies. In addition, we also try to explore the strengths as well as the weaknesses of each study, with expectation to gain insight for our economic model development.

In order to establish the comparison between studies, we will convert the cost to 2017 US dollars (US$) and adjusted international exchange rates based on Purchasing Power Parity (PPP). The data synthesis and level of evidence are presented based on the check list. For this review, there is no scheme for direct-quantifying the risk of bias of each study, as our objective is only focus to exploring and presenting the narrative review of the economic evaluation studies.

Discussion

As this intervention have significant economic burden, not only for the health care providers, but also for patient itself as well as societies. (Jansman et al, 2007; Gerber, 2008; Mittmann et al., 2009) The economic evaluation is needed to provide plausible evidence of health technologies and inform decision maker in decision making process.

Several studies related economic evaluation of targeted therapy with various setting, comparators, and design have been published, such as Bevasizumab (Avastin ®), Panitumumab (Vectibix®) and other therapies (Tappenden et al., 2007; Lange et al., 2014) Currently, we are conducting this review based our need as a part of HTA activity, following our eligibility criteria alongside by discussion with clinicians, practitioners and policy makers. Hence, we provide transparent and systematic way in terms of summarizing the evidence and starting the model construction.

Conclusion

In conclusion, this protocol attempts to provide description as our initial stage for conducting economic evaluation for Cetuximab in mCRC patients. Furthermore, the review of studies also intended to inform and provide description for researchers in our team and respected audience about systematic steps in our HTA studies, particularly to aid model development process. The evidence from health economic evaluation studies is expected to provide us beneficial information, and obtaining more comprehensive input in understanding the method, model development, results and as well as research gap.

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Competing Interests: None declared

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Appendix 1: Sample of search strategy

#1	colorectal neoplasms
#2	colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*
#3	#1 or #2
#4	cancer* or tum$r* or carcinom* or sarcom*
#5	#3 and #4
#6	epidermal growth factor or EGR or EFGR or Cetuximab or Erbitux
#7	#5 and #6
#8	Economic or economic evaluation or cost effectiveness or cost utility or CEA or CUA
#9	#7 and #8

Note: The search strategy would be developed more comprehensive as needed

Appendix 2: Drummond's checklist (Drummond et.,al 2015)

1. Was a well-defined question posed in an answerable form?
   - Were both costs and effects examined?
   - Were alternatives considered?
   - Was the perspective of the analysis stated? Is the analysis embedded in any decision making context?
2. Was a comprehensive description of the competing alternatives given?
   - Were any alternatives that were relevant to evaluation omitted?
   - Was a do-nothing alternative considered or should it be?
3. Was the effectiveness of the programmes or services established?
   - Was this done through a randomised controlled trial? Did the trial reflect what happens in usual care or routine practice?
   - Was this done though a systematic review of evidence from clinical studies? If so, was the search strategy including inclusion and exclusion criteria clearly described?
   - Were observational data or assumptions used when establishing effectiveness? If so, are there any potential biases in the results?
4. Were all the important and relevant costs and consequences for each alternative identified?
   - Was the range wide-enough for the research question at hand?
   - Were all relevant perspectives covered (e.g., community, NHS, patient)?
   - Were capital costs as well as operating costs included? Capital costs are one-time expenses typically incurred to set up a service Operating costs are the recurrent delivery costs of a service, e.g. staff
5. Were costs and effects measured accurately in appropriate physical units (e.g., QALYs)?
   - Were sources of service utilisation described and acceptable?
   - Were any items omitted? If so, what effect does this have on the analysis?
   - Were there any special circumstances that made measurement difficult? Were these difficulties addressed?
6. Were costs and effects valued credibly?
   - Were all sources of the values clearly identified?
   - Were market values employed for changes involving resources gained or depleted?
   - Where market values were absent (e.g. volunteer labour) or market values did not reflect actual values (e.g. equipment given at a reduced rate), were adjustments made to approximate market values?
   - Was the valuation of effects appropriate for the question posed? Was the appropriate type of analysis/analyses (e.g. cost-effectiveness, cost-benefit or cost-utility analysis) undertaken? Market value is the price an asset would fetch in the marketplace
7. Were costs and effects adjusted for differential timing?
   - Were future costs and effects discounted to their present value?
   - What was the discount rate used and was the justification for this rate specified?
8. Was an incremental analysis of costs and effects of alternatives performed?
   - Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?
9. Were allowances made for uncertainty in the estimates of costs and effects?
   - Were appropriate analyses undertaken on patient-level data of costs and effects?
   - If sensitivity analyses were undertaken, were the justification for the ranges and distribution of values chosen (for key parameters)

specified and explained?
- Were conclusions drawn sensitive to uncertainty from the statistical and/or sensitivity analyses?

10. Did the presentation and discussion of study results include all issues of concern to users? - Were conclusions of the analysis based on an index or ratio (e.g. cost-effectiveness or cost-benefit ratio)? Was this ratio interpreted intelligently or in a mechanistic fashion?
    - Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in methodology?
    - Did the study discuss the potential of generalisability of the results to other settings or patient/population groups?
    - Did the study take in account other important factors in the choice or decision under consideration (e.g. ethical issues, limited staff numbers or wider policy context and relevance)?
    - Did the study discuss issues of implementation (e.g. feasibility of adopting recommendations)? Are there any potential issues regarding finance and resources? Could resources be relocated from other areas to assist the implementation?

Appendix 3: CHEERS checklist (Husereau et al., 2013)

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Page/Comment
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Background and objectives	3	Provide an explicit statement of the broader context for the study.	
		Present the study question and its relevance for health policy or practice decisions.	
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	

Section/item	Item No	Recommendation	Page/Comment
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation*:Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	

Section/item	Item No	Recommendation	Page/Comment
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	