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Analysis of capecitabine plus oxaliplatin (xelox) combination in the management of metastatic colorectal cancer compare with fluorouracil and oxaliplatin combination (folfox)

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Review Article

ABSTRACT

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Keyword:
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Background: Combinations of Fluorouracil (FU) and biomodulator Leucovorin (LV) established as a standard regimen for therapy of colorectal cancer with metastases. To give better antitumor activity in colorectal cancer therapy, oxaliplatin is combined with FU/LV and give significant improvement. Fluorouracil can only be given by intravenous administration. This limitation raised effort to find alternative drugs that can be given orally, such as capecitabine. Capecitabine is an oral FU prodrug, with high oral bioavailability, highly accumulated in neoplastic tissue to be converted in FU, and well tolerated. Some clinical studies revealed effectivity of capecitabine plus oxaliplatin (XELOX) compared to FU/LV plus oxaliplatin (FOLFOX).
Objective: This article is aimed to compare non inferiority of XELOX to FOLFOX in colorectal cancer with metastases, viewed form primary outcomes and secondary outcomes.
Results: XELOX was comparable to FOLFOX with some benefitsover FOLFOX.
Conclusion: XELOX could be considered as FOLFOX replacement as a standard therapyfor colorectal cancer with metastases.

Latar Belakang: *Sampai saat ini, terapi untuk kanker kolorektal masih didominasi oleh penggunaan fluorouracil (FU) yang dikombinasi dengan biomodulator leucovorin (LV). Penggunaan FU/LV seringkali dikombinasikan dengan oxaliplatinuntuk meningkatkan aktivitas antitumornya serta mencegah metastasis. Keterbatasan FU adalah hanya bisa diberikan secara intravena sehingga menyebabkan digalinya alternatif obat secara oral, salah satunya capecitabine. Capecitabine adalah prodrug bagi FU yang mempunyai bioavailabilitas oral tinggi, terkonsentrasi dalam jumlah besar dalam jaringan tumor untuk dikonversi menjadi FU, serta dapat ditoleransi dengan baik. Beberapa penelitian klinis telah menguji efektivitas penggunaan capecitabine plus oxaliplatin (XELOX) dibandingkan FU/LV plus oxaliplatin (FOLFOX).*
Tujuan: *Tulisan ini bertujuan untuk membandingkan efek penggunaan kombinasi XELOX dibandingkan FOLFOX dalam terapi kanker kolorektal dengan metastasis yang ditinjau dari beberapa penelitian klinis, dengan melihat outcome primer dan sekundernya.*
Hasil: *Hasil menunjukkan bahwa penggunaan XELOX non inferior dari FOLFOX pada kanker kolorektal dengan metastasis, yang dilihat darioutcome primer dan outcome sekunder, serta memberikan beberapa*

kelebihan dibandingkan dengan FOLFOX
Kesimpulan: *XELOX dapat dipertimbangkan sebagai regimen pengganti FOLFOX untuk terapi kanker kolorektal dengan metastasis.*

BACKGROUND

Colorectal cancer is a malignancy with a high incidence rate, in which there are approximately one million new patients each year, and 33% of them resulted in death.[1] Within the last few decades, the treatment of metastatic colorectal cancer was dominated by fluorouracil (FU), a fluoropyrimidine anti-cancer, which since it was introduced in 1957, is still considered the drug of choice because it has been proven effective and capable of improving patient outcome.[2] This medicine could not be given orally because it would be damaged severely by the hepar,[3] hence it is given as intravenousprolonged infusion combined with leucovorin (LV) biomodulator.[4]

Some randomized control trial showed that the administration of fluoropyrimidine anti-cancer drugs (such as : fluorouracil/FU) combined with pre-operative radiation were able to improve local tumor condition, but were not able to prevent metastases.[5] This becomes the based of oxaliplatin utilization, a platinum anti-cancer analog, in combination with FU. Just as its predecessor, cisplatin, oxaliplatin works by producing covalent bond between platinum with guanine and adenine in cell DNA, altering replication and transcription process of the DNA. Oxaliplatin is more preferred than cisplatin because it is more concentrated in colon cancer cells.[6]

Oxaliplatin works especially by inducing apoptosis, not only p53-independent pathway which would go through ERK signaling, but also p53-dependent pathway which involve the role of p53 up-regulate modulator of apoptosis (PUMA),[7] or by increasing the concentration of phospho-p53 and p53 total protein.[8] Compare to cisplatin and carboplantin, oxaliplatin cause less side effects for the kidneys and bone marrow, while its main side effect is sensoric neuropathy.[9]

Oxaliplatin combined with FU/LV for colorectal cancer has been proven capable of increasing response rates and time to disease progression (TTP) significantly compare to the combination of FU/LV alone. A meta-analysis showed that the addition of weekly oxaliplatin as neoadjuvant to FU/LV in colorectal cancer are able to improve partial complete response (pCR) and reduce intra-abdominal as well as peri-operative. In addition to that, even though this combination cause more G3/4 side effects, but this does not require further operative treatment and reduce mortality- 60 days post-operative.[5]

The impracticality of FU initiates a search of alternative fluoropyrimidine that can be given orally, leading to the invention of capecitabine, which was designed to be able to deposition its active compound in tumor location and not in healthy non-tumor tissues.[4] Capecitabine as an alternative of FU, was developed to improve non-tumor tolerability and toxicity. It is a prodrug of FU, which would be converted into FU both in healthy and tumor tissues by enzyme thymidine phosphorylase (TP), that is contained more in tumor tissues. Hence, drug specificity for tumor becomes higher and reduce systemic side effects.[2]

Capecitabine could be given orally with high predicted bioavailability and could be well-tolerated. A few studies showed that capecitabine was more active than intravenous FU/LV for inducing objective tumor response.[10] Except being used as the first line in the treatment of metastatic colorectal cancer, capecitabine could also be used as adjuvant therapy for late stage colon cancer.[11]

A phase I clinical trial showed that the combination of capecitabine and oxaliplatin (XELOX) with the recommended dose of intravenous oxaliplatin 130 mg/m^2 on day 1, continued with capecitabine 1.000 mg/m^2 twice daily for 14 days in 3 weekly cycles, were not only easy to administer but also has a promising antitumor effect.[12] Currently, XELOX are used for treatment in late stage and metastatic colorectal cancer, both as first and second line treatment, with similar effectivity as FU and oxaliplatin combination (FOLFOX).[11]

Intraoral Fluoropyrimidine would provide

more comfort for patients and medical personnels. If terapeutic outcome of both XELOX and FOLFOX are similar, then orally administered drugs would provide more ease and comfort. Hence, an analysis needs to be done to review some recent Randomised Controlled Trial/RCT regarding the use of XELOX and FOLFOX for the treatment of metastatic colorectal cancer to determine the effectivity of oral fluoropirimidin when compared to intravenous administration by examining terapeutical outcome and side effects.

SEARCHING AND SELECTION METHODS OF ARTICLES

This article review did not use systematic method while searching for medical journals. Instead, it used randomized search by Google® search engine (www.google.co.id). There were 6 (six) randomised controlled trial publication that compare the combination of capecitabine plus oxaliplatin (XELOX) and FU plus oxaliplatin (FOLFOX) in the treatment of metastatic colorectal cancer. In which five studies [12,13,14,15,16] were phase III RCT, while one study[10] was phase II RCT.

Inclusion criteria

This study included randomised controlled trial research that compare the combination of oxaliplatin plus capecitabine and oxaliplatin plus FU/LV or FU in the treatment of metastatic colorectal cancer. Study subjects should be at least 18 years of age, histologically diagnosed with cancer lession that could not be resected, had more than 3 months life expectancy, and had adequate bone, liver, and kidney function. Subjects were excluded if they had history of neuropathy, had been treated with oxaliplatin within less than 6 months before research started, or had severe heart disorder, hypertension, and myocardial infarct, as well as pregnancy.

Evaluation

Every studies did preliminary assessment which included medical record, physical examination, thorax xray, electrocardiography, carcino embryonic antigen (CEA), blood test (haematology and biochemistry) that varies between 1-4 weeks before intervention, but there was one research that did not mention the period of which they did the initial assessment. Response to therapy were evaluated using Response Evaluation Criteria in Solid Tumors Group (RECIST), to define the entire resonse after subjects had been treated for at least 4 weeks. Evaluation was done by the researchers and or independent review committee. Observation of post-research response was done every 12 weeks (3 months), until there was disease progression or death.

The evaluation of toxicity and side effeccts was done during therapy and until 28 days after the last dose, in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 guideline [13,14,15,16]; according to Common Toxicity Criteria v2.0,[10] while one research did not mention which guideline it used.[12] One research[15] also assessed patients quality of life (using the EORTC QLQ-C30 and FACIT Chemotherapy convenience and satisfication questionnaire on therapy guideline) and the utilization of health resources.

Statistical Analysis

Articles contained at least one outcome that was observed, which was overall response rate (ORR), overall survival (OS), progression-free survival (PFS), time to response, median duration of response, time to treatment failure (TTF), safety, and one study[16] assessed one additional parameter which was rate to radical surgery (RRS).

Overall response rate (ORR) was defined as the proportion of patients who experience complete response and partial response. While stable disease was not included into ORR category, eventhough later it could be counted on tumor control rate. The non-inferior margin was when the difference of ORR between XELOX and FOLFOX group less than 15%. Progression-free survival(PFS) was defined as the amount of time between the start of treatment until disease progression, despite the objective response (ORR). It was measured with Kaplan-

Meier method. Median overall survival (OS) was defined as the amount of time between the start of treatment until patient's death of any cause. This was also measured with Kaplan-Meier method.

Median time to failure (TTF) was defined as the amount of time between the start of treatment until drug withdrawal, either due to toxicity, disease progression, or death of any cause. Median duration of response was define as the amount of time between the first recorded response until disease progression or death. Analysis survival (PFS, OS, median duration of response, median TTF) was done using Cox proportional hazards model and Kaplan-Meier estimation[13,14,15] to provide relative Hazard Ratio (HR) with 95%[14,15] and 97,5%[13] CI of XELOX group compare to FOLFOX. Rate to radical surgery was defined as the proportion of patients undergoing surgery to remove primary tumor or its metastases as curative measure after therapy during research period.

RESULTS

There were 6 (six) articles for review. All articles had met inclusion criteria, in which each article's characteristic was described in Attachment 1 Table 1. The resuts of the entire outcome evaluation can be seen in Attachment 2 Table 2, while side effects and toxicity was described in Attachment 3 Table 3.

Patient demography

The basic characteristic of patients on XELOX and FOLFOX group were all proportional in all clinical trial (Table 1). For performance status, several different parameters were used, such as Karnosfky Performance Status (PFS) > 70, or Eastern Cooperative Oncology Group (ECOG) < 2, or WHO performance 0-2. Most subjects had KFS index > 70 (median 90), ECOG score 0 and 1, and WHO score 2. All six studies mentioned exclusion criteria which include pregnant woman, kidney and severe heart disorder, brain metastases; two studies[15,16] exclude patients with history of previous oxiplatin treatment, patients who were a candidate for liver metastasectomy after chemotherapy, and patients with cardiovascular diseases (hypertension, angina pectoris, and myocardial infarct). On one of the studies,[12] patients with previous history of adjuvant cemotherapy were found more in XELOX group (26%) compare to FOLFOX group (16%) (p=0,032). One research classified patients based on their creatinine clearance to analyze the side effects and toxicity of treatment, based on the value of creatinine clearance > 80 mL/minute and 50-80 mL/minute.[16]

One of the studies delayed treatment before completing six cycles, in which treatment delay were found more in FOLFOX group (37,7%) compare to XELOX group (27,8%). Most delay in both groups were caused by disease progression and toxicity, which were 23% of total patients (this would be adressed further in side effects and toxicity section).[10]

Drugs Administration

XELOX combination was administered by giving oxaliplatin 130 mg/m^2 through IV drips for 2 hours on day 1, continued with oral capecitabine 1000 mg/m^2, twice daily for 2 weeks, in 3 weeks cycle. While FOLFOX combination was administered by giving oxaliplatin 85 mg/m^2 IV drips for 2 hours on day 1 continued with LV 200 mg/m2 IV drips for 2 hours, and then continued with FU 400 mg IV injection and FU 600 mg/m2 IV drips for 22 hours for 2 days straight, in 2 weeks cycle.

Outcome

Overall Response Rate (ORR)

The evaluation of ORR was done on all studies, and was made as the primary outcome in one of the studies[10], and as secondary outcome in the other five studies.[12,13,14,15,16] The lowest percentage of ORR was 20% in XELOX group and 18% in FOLFOX group,[14] while the highest was 51% in XELOX group and 57% in FOLFOX group.[16] The ORR value on the other five studies was between 37-48%. In five of the studies,[12,13,14,15,16] it was found that there were no statistically significant difference of ORR value between XELOX dan FOLFOX group.

Overall Survival (OS)

Measurement of OS was done in five studies, where XELOX group had OS between 11,9 – 19,9 months, while FOLFOX group had OS between 12,6 – 20,8 months. On all of the studies, it was found that there was no statistically significant difference of OS between the groups.

Progression-Free Survival (PFS) and Time to Progression (TTP)

PFS values that was found in all five studies varied. In which the PFS value of XELOX group was between 4,7-8,9 months, while in FOLFOX group it was 4,8-9,5 months. There were no statistically significant difference of PFS values between the groups (XELOX and FOLFOX).

Median duration of response

The median value in four of the studies was between 5,6-10,1 months in XELOX group and 6,2-9,4 months in FOLFOX group.[12,13,14,15] Statistically, median duration of response in four of the studies showed no significant difference.

Median time to treatment failure(TTF)

This parameter was found in four of the studies. Results varied between 4,1-6,1 months for XELOX group and 4,0-6,9 months for FOLFOX group.[12,13,14,15,16] Ib line with other outcome parameter, there was no statisticqally significant difference of TTF median between the groups.

Rate to radical surgery (RRS)

There were two research that measured RRS.[15,16] Radical surgery that was done include liver metastasectomy, lung metastasectomy, primary tumor resection, and other part resection. One study showed that the RSS for XELOX group was lower (3,5%) compare to FOLFOX group (6,5%) with OR 1,96 (95% CI 1,18-3,23).[16] While the other research only describe the number of patients who undergo radical surgeries, in which there were 30 patients (19,2%) in XELOX group and 34 patients (22,6%) in FOLFOX group, without further analysis.[15] According to this results, it could be concluded that radical surgery was found more in FOLFOX group compare to XELOX group.

Safety and Toxicity

Generally, side effects of all toxicity was found more in FOLFOX group compare to XELOX group, except in one of the studies.[10] Mielotoxicity in the form of anemia and neutropenia was found more in FOLFOX group compare to XELOX group, but thrombocytopenia was found more in XELOX group.[15] The mielotoxicity found in these studies varied from very mild[10] or even death.[12] Neutropenia G4 that was found twice larger in FOLFOX group compare to XELOX group13 presumed to contribute in initiating the occurence of more G4 side effects in FOLFOX group compare to XELOX group which was 25% vs. 12% [13] and 65% vs. 50%.[14]

Non hematology toxicity that was found the most is neurotoxicity, in which G3 neurotoxicity was found more in XELOX group compare to FOLFOX group (24,5% vs. 18,5%), eventhough this number was not statistically different in both groups.[10] Neurological toxicity was also one of the reason of treatment discontinuation[12,13] eventhough it did not cause death.

The incidence of stomatitis between FOLFOX group and XELOX group was also statistically different (25,9% vs. 13,1%).[10] Stomatitis contributed to treatment discontinuation due to toxicity[10] and in one of the pationt of XELOX group was found stomatitis, neutropenia, and thrombocytopenia as the cause of death.[12] Apart of stomatitis, treatment delay and discontinuation happened due to a lot of causes, like: neurological toxicity and oxaliplatin intolerance,[12] diarrhea,[13] in addition to that the presentation of treatment discontinuation was 27% in both groups.[12]

Gastrointestinal symptoms in FOLFOX and XELOX group were quite varied, but hand-foot syndrome was found more in XELOX group.[12,13,14,15,16] One interesting founding was the increase of G3 nausea, diarrhea, and thrombocytopenia in XELOX group in patients with creatinine clearance 50-80 mL/minute compare to patients with creatinine clearance > 80 mL/minutes; likewise, dosage delay was also

found more in patients with lower creatinine clearance. While in FOLFOX group, no side effect difference was found between patients with creatine clearance 50-80 mL/minutes and >80 mL/minute.[16]

Generally, aside from the complications of side effects[10,12] patients cause of death was also due to disease progressivity.[15] The result of treatment-related mortality analysis of both groups showed no significant difference[13,16] while another research found 2,1% (14 patients) for XELOX group and 1,7% (11 patients) for FOLFOX group.[12]All-cause 60-day mortality was 4% in both groups[13] while another research found difference in FOLFOX compare to XELOX group, which was 4,2% vs. 2,1%[15] and 3,4% vs 2,3%.[12]

DISCUSSION

Oxaliplatin and capecitabine combination had been researched a lot and had been approved as anti-cancer treatment in metastatic colorectal cancer. The clinical activity of XELOX combination was based on preclinical datas that found capecitabine and oxaliplatin has supra-additive effect. This combination was able to inhibit in vivo growth of CXF280 colon cancer cells more effectively than othe use of single drug. Oxaliplatin was able to upregulate TP enzyme that was spesific for FU inside CXF280 cancer cells. This TP upregulation by oxaliplatin was the one that produced supra-additive activity in XELOX, that could not be found in FOLFOX intravenous drips combination.[4]

All five phase III RCT research had been able to finish multicenter research for this high epidemiology cancer. Because the objective of the research was to assess the noninferiority of XELOX combination compare to FOLFOX (that has been accepted as first line treatment for metastatic colorectal cancer), hence the non-inferiority of XELOX compare to FOLFOX combination in the treatment of metastatic colorectal cancer was the main concern of the research.

Research outcome

In this article review, one research[10] was not being used to make definitive comparation between researched drugs and standard drugs, because this research was a phase II clinical trial, that aimed to determine the efficacy of the drugs. Nevertheless, this research was able to show that XELOX combination had 43,5% response rate (95% CI 31,0%-56,7%), with 9 months TTP (95% CI 8-10 bulan) as well as symptoms relieved in almost 50% patients with asthenia, anorexia, pain and low KPS index on baseline. This research supported the reccomendation to exchange pviFU with capecitabine, because orally administered medicine was proven to be able to decrease intravenous catheter side effects, such as infection, thrombosis, displacement risk, and personal discomfort.[10]

The results of the other four phase III clinical trial, showed that treatment outcome between XELOX and FOLFOX was relatively comparable, as seen in p value, OR, or HR of each outcome in both groups. ORR or PFS value as primary outcome of the research showed difference in noninferiority margin, hence it could be concluded that XELOX combination was non inferior from FOLFOX combination.

As well as secondary outcome (OS, median duration of response, and median TTF) for all research showed no statistically significant difference. Except for RRS, which showed that FOLFOX group had twice higher rate of radical surgeries compare to XELOX group, however the cause of this was not analyzed. Hence, it could be said that in terms of outcome, XELOX combination was comparable to FOLFOX combination. Even in term of post-therapy radical surgeries, XELOX combination showed more advantages compare to FOLFOX.[15,16]

In terms of side effects and toxicity, XELOX and FOLFOX combination was comparable. The interesting finding was that the occurence of G3/4 neutropenia was found relatively lower in XELOX group compare to FOLFOX, except in one research in which the result of neutropenia was 25% higher in XELOX group. However, this research did not mentioned any possible causes.[10]

Drug Administration Technique and Treatment Cycle

The administration of XELOX combination is mainly via oral for capecitabine and intravenous drips for oxaliplatin given in 2 hours with 3 weeks cycle; while FOLFOX combination needed 48 hours of intravenous catether (2 days straight) because the administration of FU or FU/LV and oxaliplatin should be given intravenously in 2 weeks cycle. From the perspective of patients comfort and visit frequencies, XELOX combination is more advantegous because the time needed for one dosage administration is shorter and the frequencies of hospital visits is less often (rest period of every cycle is longer). In addition to that, capecitabine could be given orally, hence it reduced the risk of complication in intravenous catheter administration compare to FU or FU/LV. It could be seen from the frequencies of hospital visits, central venous access, and the time needed for drugs administration is shorter in XELOX combination compare to FOLFOX combination. From this perspective, XELOX combination is more superior than FOLFOX combination. Nevertheless, further statistical analysis is needed.

In terms of comfort, XELOX combination provides more comfort for both patients and care giver. XELOX combination allows patients to only come to health facilities every 3 weeks for only 2 hours during oxaliplatin intravenous drips. Colorectal cancer patients who were given paliative care with FU/LV, would have uncomfortable treatment schedule that would severely reduce their resting period. In addition to that, patients are at larger risk of infection due to intravenous catheter insertion.[4] Another factor that affect patients comfort is that the 3 weeks cycle in the administration of oxaliplatin in XELOX combination (compare to 2 weeks cycle in FOLFOX combination), and the fact that capecitabine could be given orally.[11] Hence, XELOX combination contibutes heavily in terms of patients condition and autonomy.[4]

All six published research did not analyze the financial effectivity of XELOX combination compare to FOLFOX combination. However, there are two studies which found that XELOX combination were more financially effective compare to FOLFOX combination. This financial advantages could happen due to direct or indirect causes, for instance : social cost that patients and their families would suffer while they were hospitalized for longer period.[17,18]

CONCLUSSION

The utilization of XELOX combination is non-inferior compare to FOLFOX combination that can be concluded from primary outcome (according to the value of Odds Ratio, Hazard Ratio, and Progression Free Survival) and secondary outcome (Overall Survival, median duration of response, and median Progression Free Survival), even in terms of Response Rate to Surgery, XELOX combination is better than FOLFOX combination. XELOX combination is also better in terms of patients comfort especially regarding drugs administration technique because it could be given orally, hence it could avoid intravenous administration complication. Also in terms of treatment cycle, in which the period for drugs administration is shorter in XELOX combination with longer resting period, hence reducing the frequencies of hospital visits. Financially speaking, XELOX combination is more cost-effective compare to FOLFOX combination.

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Table 1. Characteristics of reviewed literatures

Research	(10)	(12)	(13)	(14)	(15)	(16)
Publication Year	2006	2007	2008	2008	2011	2012
Research periods	2001-2005	2002-2007	2003-2004	2003-2005	2003-2004	2005-2008
Total patient involved	118	342	634	627	306	2397
Regimen	FOLFOX: oxaliplatin 130 mg/m2 infusion for 2 hour on first day and FU protracted venous infusion 250 mg/m2/day for 1-21 days	XELOX: Capecitabine 1.000 mg/m2, 2 times per day , 14 days plus oxaliplatin i.v 130 mg/m2, on first day every 3 weeks cycles	XELOX: oxaliplatin 130 mg/m2 for 2 hours on first day one continued with capecitabine oral 1000 mg/m2, 2 times per day , 2 weeks every 3 weeks	XELOX: oxaliplatin infusion 130 mg/m2 for 2 hours on 1st day and capecitabine 1000 mg/m2, two times perday, 2 weeks, every 3 weeks	XELOX: oxaliplatin infusion 130 mg/m2 for 2 hours on first day, continued with capecitabine oral 100 mg/m2 2 times perday, 2 weeks, every 3 weeks	XELOX : Oxaliplatin 130 mg/m2 i.v for 2 hours on first day, continued with capecitabine 1000 mg/m2, 2 times perday, 2 weeks, every 3 weeks
	XELOX: xaliplatin 130 mg/m2 for 2hours in day 1 continued with capecitabine oral 1000 mg/m2, 2x daily, 2 weeks every 3 weeks	FOLFOX: FU 2.250 mg/m2 for 48 hours in day 1, 8, 15, 22, 29, and 36, plus oxaliplatin 85 mg/m2 in day 1, 15, and 29, every 6 weeks	FOLFOX: LV 200 mg/m2 IV infusion for 2 hours continued with FU 400 mg/m2 IV and FU 600 mg/m2 infusion for 22 hours, two days straight every 2 weeeks, in addition to oxaliplatin 85 mg/m2 infusion for 2 hours in day 1	FOLFOX: LV 200 mg/m2 IV infusion for 2 hours continued with FU 400 mg/m2 IV and FU 600 mg/m2 infusion for 22 hours, two days straight every 2 weeeks, in addition to oxaliplatin 85 mg/m2 infusion for 2 hours in day 1	FOLFOX: oxaliplatin 100 mg/m2infusion for 2 hours continued with LV 400 mg/m2 infusion then i.v injection of FU 400 mg/m2 and FU 2.400-3000 mg/m2 continous infusion for 46 hours every 2 weeks	FOLFOX: LV 175 or 350 mg i.v every 2 weeks in addition to oxaliplatin 85 mg/m2 for 2 hours in day 1 continued with FU 400 mg/m2 i.v and FU 2400 mg/m2 infusion for 46 hours

Subjects selection criteria	Pasient age >18 years old, confirmed histologicaly of colorectal cancer, Karnofsky status > 70, life expectancy > 3 months, finished previous adjuvant treatment for at leats 6 months, Hb > 10 g/dL, neutrophil > 2000/mm3, platelet count > 100.000/mm3, serum creatinine < 1,2 mg/dL, creatinine clearance > 55mL/ minutes, bilirubin and serum transaminase < 3x normal	Outpatient, age >18 years old, confirmed histologicaly of colorectal cancer, Karnofsky status > 70, life expectancy > 3 months , had minimum one lession according to Response Evaluation Criteria in Solid Tumors Group Criteria, if had previous history of FU chemotherapy should at least > 1 year before research period	Outpatient, age >18 years old , Eastern Cooperative Oncology Group (ECOG) status < 2 life expectancy > 3 months, without history of chemotherapy for advance diseases, radiotherapy or surgical terapy for metastases had been finished for at least 4 months before research period, adequate hematological, liver, and kidney function, not currently pregnant	Outpatient, age >18 years old , Eastern Cooperative Oncology Group (ECOG)status < 2, life expectancy > 3 months, had minimum one lession with diameter > 20 mm measured by CT scan or > 10 mm by MRI adequate hematological, liver, and kidney function, not currently pregnant	Pasient age >18 years old, confirmed histologicaly of colorectal cancer (RECIST criteria > 1), ECOG score < 2, life expectancy > 3 months adequate hematological, liver, and kidney function, not currently pregnant l, no heart disorder or neuropathy	Pasient age >18 years old , had metastatic or advanced adenocarsinoma colorectal, tno history of chemotherapy for advance diseases, WHO performance status(PS) 0-2, adequate bone marrow, liver and kidney function
Number of subjects in each group	FOLFOX: 56 XELOX: 62	XELOX : 171 FOLFOX: 171	XELOX: 1017 FOLFOX: 1017	XELOX: 313 FOLFOX: 314	XELOX: 156 FOLFOX: 150	XELOX: 1575 FOLFOX: 822
Male subjects	FOLFOX : 28 (50%) XELOX : 33 (543,2%)	XELOX : 107 (63%) FOLFOX: 100 (58%)	XELOX: 612 (60,2%) FOLFOX: 595 (58,5%)	XELOX: 194 (62%) FOLFOX:191 (61%)	XELOX: 100 (64%) FOLFOX: 90 (60%)	XELOX: 1039 (66%) FOLFOX: 537 (64%)
Median of age (range)	FOLFOX : 64 (41-79) XELOX : 67 (25-79)	XELOX : 64 (32-80) FOLFOX: 65 (35-81)	XELOX: 61 (24-84) FOLFOX: 62 (24-83)	XELOX: 60,7 (26-81) FOLFOX: 59,7 (26-83)	XELOX: 66 (32-83) FOLFOX: 64 (42-84)	XELOX: 64 (57-70) FOLFOX: 63 (57-69)
Location of primary tumor						
• Colon	FOLFOX : 51 (82,3%) XELOX : 46 (82,1%)	XELOX : 110 (64%) FOLFOX: 116 (68%)	XELOX: 673 (66,2%) FOLFOX: 655 (64,4%)	XELOX: 185 (59%) FOLFOX: 201 (64%)	XELOX: 94 (60%) FOLFOX: 95 (63%)	XELOX: 843 (53%) FOLFOX: 465 (57%)
• Rectum	FOLFOX : 11 (17,7%) XELOX: 10 (17,9%)	XELOX : 49 (29%) FOLFOX: 49 (29%)	XELOX: 252 (24,8%) FOLFOX: 292 (28,8%)	XELOX: 102 (32%) FOLFOX: 89 (28%)	XELOX: 37 (24%) FOLFOX: 38 (25%)	XELOX: 497 (32%) FOLFOX: 247 (30%)
• Both	NA	XELOX : 12 (7%) FOLFOX: 6 (3%)	XELOX: 92 (9%) FOLFOX: 70 (6,8%)	XELOX: 26 (8%) FOLFOX: 24 (8%)	XELOX: 25 (16%) FOLFOX: 17 (11)	NA

Primary outcome	ORR	TTP (PFS)	PFS	PFS	ORR	PFS
Secondary outcome	TTP (PFS), toxicity	ORR, Safety, response rate, TTF, OS, duration of response	OS, ORR, duration of response, TTF, safety	OS, ORR, time to response, duration of response, TTF, safety	PFS, OS, time to response, duration of response,safety	OS, ORR, rate of radical surgeries (RRS), safety
Statistical power	To detect at least 35% remission rate difference with power 80% and alpha 0,05, need 56 patients for every group	Sample size estimation was 165 patients for every group, to obtain power 80% and alpha 0,05	Power 90%, non inferiority if upper limit was 97,5% CI from Hazard Ratio (HR) < 1,23. Final analysis if 1.200 event found in EPP	Noninferiorority margin XELOX vs FOLFOX if upper limit 95% CI HR < 1,30, power 80%, 610 patients were needed	Noninferiority margin was 15%, with power 80% and alpha 0.05, 152 patients were needed for each group (total 304 patients)	NA
Treatment history						
• Surgery	FOLFOX : 52 (83,9%) XELOX : 45 (80,4%)	XELOX : 138 (81%) FOLFOX: 142 (83%)	XELOX: NA FOLFOX: NA	XELOX: 286 (91%) FOLFOX: 279 (89%)	NA	XELOX: NA FOLFOX: NA
• Radiotherapy	NA	XELOX : 16 (9%) FOLFOX: 27 (16%)	XELOX: NA FOLFOX: NA	XELOX: 84 (27%) FOLFOX: 70 (22%)	NA	XELOX: NA FOLFOX: NA
• Chemotherapy	FOLFOX : 18 (29,9%) XELOX : 13 (23,2%)	XELOX : 44 (26%) FOLFOX: 27 (26%)	XELOX: NA FOLFOX: NA	XELOX: NA FOLFOX: NA	XELOX: 30 (19%) FOLFOX: 29 (19%)	XELOX: NA FOLFOX: NA
Metastases						
• Liver	FOLFOX : 46 (74,2%) XELOX : 46 (82,1%)	XELOX : 128 (75%) FOLFOX: 141 (83%)	XELOX: NA FOLFOX: NA	XELOX: NA FOLFOX: NA	NA	XELOX: 1167 (74%) FOLFOX: 634 (77%)
• Lung	FOLFOX : 16 (25,8%) XELOX : 22 (39,2%)	XELOX : 54 (32%) FOLFOX: 50 (29%)	XELOX: NA FOLFOX: NA	XELOX: NA FOLFOX: NA	NA	XELOX: 643 (41%) FOLFOX: 333 (41%)
• Others	FOLFOX : 19 (30,6%) XELOX: 14 (25%)	XELOX : 71 (41%) FOLFOX: 46 (26%)	XELOX: NA FOLFOX: NA	XELOX: NA FOLFOX: NA	NA	XELOX: 955 (61%) FOLFOX: 464 (56%)

Notes :
NA = not available = no data/not mentioned; FU = fluorouracyl; OS = Overall survival; TTF = time to treatment failure; PFS = progression-free survivalatau TTP = Time to progression;; RRS = rate of radical surgeries; ORR = overall response rate; the eligible patient population (EPP)

Table 2. Efficacy Outcome from reviewed literatures

Outcome	(10)	(12)	(13)	(14)	(15)	(16)
Overall Response Rate (ORR)	FOLFOX: 27 (48,2%) XELOX: 27 (43,5%)	XELOX: 64 (37%) FOLFOX: 78 (46%) p=0,154	XELOX: 48% FOLFOX: 47% OR=0,94 (97,5% CI = 0,77 – 1,15)	XELOX: 20% FOLFOX: 18% OR=1,19 (95% CI 0,79-1,77)	XELOX: 39% FOLFOX: 46% Difference between group=4,7% (less than 15%)	XELOX: 50-51% FOLFOX: 54-57% p value> 0,05
Overall survival (OS)	NA	XELOX: 18,1 months FOLFOX: 20,8 months p=0,145	XELOX: 19,8 months FOLFOX: 19,6 months HR=0,99 (97,5% CI 0,97-1,20)	XELOX: 11,9 months FOLFOX: 12,6 months HR=1,03 (95% CI 0,87-1,23)	XELOX: 19,9 months FOLFOX: 20,5 months HR=1.,02 (90% CI 0,81-1,30)	XELOX: 13,8-16,0 months FOLFOX: 13,8-15,8 months p value> 0,05
Progression-free survival (PFS) or time to tumor progression (TTP)	NA FOLFOX: 7 months XELOX 9 months	XELOX: 8,9 months FOLFOX: 9,5 months p=0,153	XELOX: 8,0 months FOLFOX: 8,5 months HR=1,04 (97,5% CI 0,93-1,16)	XELOX: 4,7 months FOLFOX: 4,8 months HR=0,97 (0,83-1,14)	XELOX: 8,8 months FOLFOX: 9,3 months HR=1,00 (90% CI 0,82-1,22)	XELOX: 7,4 months FOLFOX: 8,8 months p value> 0,05
Median duration of response	NA	XELOX: 9,2 months FOLFOX: 9,4 months p=0,430	XELOX: 7,5 months FOLFOX: 7,6 months HR=1,00 (97,5% CI 0,85-1,18)	XELOX: 5,6 months FOLFOX: 6,2 months HR=1,15 (95% CI 0,79-1,68)	XELOX: 10,1 months FOLFOX: 8,8 months HR=0,88 (90% CI 0,64-1,21)	NA
Median time to treatment failure (TTF)	NA	XELOX: 6,0 months FOLFOX: 6,9 months p=0,204	XELOX: 5,9 months FOLFOX: 6,3 months HR=1,08 (97,5% CI 0,97-1,20)	XELOX: 4,1 months FOLFOX: 4,0 months HR=0,96 (95% CI 0,81-1,12)	XELOX: 6,1 months FOLFOX: 6,8 months HR=1,32 (90% CI 0,97-1,78)	NA
Response rate to surgery	NA	NA	NA	NA	XELOX: 30 (19,2%) FOLFOX: 34 (22,6%) Nnot analyzed	XELOX: 3,5% FOLFOX: 6,5% OR=1,96 (95% CI 1,18-3,23)

OR = Odds Ratio, HR = Hazard Ratio

Table 3. Side effects and toxicitys G3/4 reported in reviewed literatures

Research	(10)		(12)		(13)		(14)		(15)		(16)	
	XELOX	FOLFOX	XELOX	FOLFOX	XELOX	FOLFOX	XELOX	FOLFOX	XELOX	FOLFOX	XELOX	FOLFOX
Hematology												
Anemia	0	1 (1,9%)	5 (3%)	3 (2%)	NA	NA	NA	NA	3 (2%)	6 (4%)	NA	NA
Trombocytopenia	2 (3,3%)	1 (1,9%)	6 (4%)	6 (4%)	46 (7,0%)	20 (3,1%)	10 (3,2%)	7 (2,3%)	18 (12%)	8 (5%)	25 (2%)	12 (2%)
Neutropenia	6 (9,8%)	4 (7,4%)	12 (7%)	18 (11%)	45 (6,9%)	279 (43%)	14 (4,5%)	108 (35,1%)	8 (5%)	70 (47%)	32 (3%)	152 (28%)
Non hematology												
Nausea	NA	NA	5 (3%)	9 (5%)	30 (4,6%)	33 (5,1%)	62 (19,9%)	8 (2,6%)	4 (3%)	9 (6%)	87 (8%)	27 (5%)
Vomiting	NA	NA	9 (5%)	13 (8%)	34 (5,2%)	29 (4,5%)	10 (3,2%)	10 (3,2%)	3 (2%)	7 (5%)	61 (6%)	24 (4%)
Diarrhea	5 (8,2%)	7 (13%)	24 (14%)	41 (24%)	134 (21%)	73 (11%)	62 (19,9%)	15 (4,9%)	22 (14%)	10 (7%)	165 (16%)	55 (10%)
Constipation	NA	NA	1 (<1%)	3 (2%)	9 (1,4%)	15 (2,3%)	6 (1,9%)	8 (2,6%)	NA	NA	NA	NA
Anorexia	NA	NA	5 (3%)	4 (2%)	16 (2,4%)	17 (2,6%)	11 (3,5%)	6 (1,9%)	NA	NA	NA	NA
Mucositis/stomatitis	0 (0%)	2 (3,7%)	4 (2%)	7 (4%)	8 (1,2%)	13 (2%)	1 (0,3%)	10 (3,2%)	0 (0%)	1 (<1%)	11 (1%)	22 (4%)
Letargia (fatigue)	NA	NA	NA	NA	34 (5,2%)	51 (7,9%)	22 (7,1%)	27 (8,8%)	NA	NA	212 (20%)	95 (18%)
Palmar-plantar erythem (PPE)/hand-foot syndrome	0 (0%)	1 (1,9%)	4 (2%)	2 (1%)	40 (6,1%)	8 (1,2%)	11 (3,5%)	2 (0,6%)	5 (3%)	1 (<1%)	41 (4%)	3 (1%)
Neuropathy/ paraesthesia	15 (24,6%)	10 (18,5%)	31 (18%)	28 (16%)	55 (8,4%)	48 (7,4%)	1 (0,3%)	9 (2,9%)	17 (11%)	38 (26%)	107 (10%)	72 (13%)
Abdominal pain	1 (1,6%)	0	1 (<1%)	4 (2%)	36 (5,5%)	25 (3,9%)	14 (4,5%)	14 (4,5%)	NA	NA	NA	NA
Asthenia	NA	NA	21 (12%)	29 (17%)	26 (4,0%)	22 (3,4%)	10 (3,2%0	14 (4,5%)	13 (8%)	14 (9%)	NA	NA
Hyperbilirubinemia	NA	NA	5 (3%)	6 (4%)	NA	NA	NA	NA	NA	NA	NA	NA
IncreasedTransaminase	NA	NA	3 (2%)	4 (2%)	NA	NA	NA	NA	NA	NA	NA	NA
Fever	NA	NA	0	1 (<1%)	6 (0,9%)	9 (1,4%)	0	2 (0,6%)	3 (2%)	4 (3%)	NA	NA
Rash	NA	NA	3 (2%)	1 (<1%)	NA	NA	NA	NA	NA	NA	NA	NA
Epistaxis	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA