OXALIPLATIN RE-INTRODUCTION THERAPY AMONG PATIENTS WITH ADVANCED STAGE COLORECTAL CANCER

Sahaphol Anannamcharoen, Chinnaklit Boonya-Ussadon

Department of Surgery, Phramongkutklao Hospital, Bangkok, Thailand

Abstract

Background: : Retreating with prior chemotherapeutic regimens is a possible option for palliative treatment for patients with advanced stage colorectal cancer (CRC).

Objective: This study aimed to examine the feasibility and clinical outcomes of oxaliplatin re-introduction therapy.

Methods: The present study was a prospective case series of patients with advanced stage colorectal adenocarcinoma who were previously treated and re-treated with oxaliplatin combination therapy at Phramongkutklao Hospital between April 1st, 2011 and March 30th, 2014. Treatment regimens are described below. First, FOLFOX4 (14-day cycles of oxaliplatin 85 mg/ m^2, folinic acid 200 mg/ m^2) was given days 1-2 plus fluorouracil 400 mg/ m^2 (bolus) and 600 mg/ m^2 (continuous 22 hours infusion). Second, modified FOLFOX6 (oxaliplatin 85 mg/ m2) was given day 1 with calcium folinate 400 mg/m^2 as a 2-hour infusion followed by bolus 5-fluorouracil 400 mg/m^2 and a 46-hour infusion of 5-fluorouracil 2,400 mg/m^2). Similarly, XELOX (130 mg/ m^2 intravenous oxaliplatin) was provided for 2 hours day 1 plus oral capecitabine 1,000 mg/ m^2 twice daily for 2 weeks from day 1. Treatment was continued until disease progression (PD), intolerability to therapy, poor performance status, withdrawal of consent or death occurred. Authors evaluated tolerability, feasibility, types and rate of untoward medical occurrences due to adverse reactions of PD.

Results: Thirteen patients with CRC were recruited in the study. The median cycles (range) of receiving oxaliplatin-based chemotherapy before re-introduction therapy was 8 (3-15) cycles. The median age (range) was 50 (27-78) years. Etiologies of treatment cessation were recorded by number of patients as follows: tumor progression (6), lost to follow-up (1), refused to receive further treatment (1), allergic reaction (2) and physical deterioration (2). Efficacy of the treatment was assessed in 10 of 13 patients. Of 10 patients, 2 developed drug allergies and 1 was lost to follow-up. Six patients (60%) had PD while 4 patients (40%) had stabilized disease measured by the Response Evaluation Criteria in Solid Tumors (RECIST).

Conclusion: Reintroducing oxaliplatin combination chemotherapy is one of the treatments in advanced stage CRC. In this study, physical deterioration and tumor progression were the main etiologies of treatment cessation.

Keywords : Oxaliplatin, Reintroduction therapy, Palliative chemotherapy, Advanced colorectal adenocarcinoma, Colorectal cancer

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Correspondence to:

Anannamcharoen S, Department of Surgery, Phramongkutklao Hospital, Bangkok, Thailand
E-mail : sahaphola@yahoo.com

Introduction

Oxaliplatin has been used worldwide to manage colorectal adenocarcinoma (CRC). Oxaliplatin is classified as an "alkylating agent" indicated for adjuvant or palliative chemotherapy for advanced stage CRC. Oxaliplatin is usually given in combination with other chemotherapeutic drugs, i.e., 5-fluoropyrimidine, capecitabine or irinotecan, with or without biologic targeted therapies, i.e., bevacizumab, cetuximab and panitumumab, as first-line or second-line therapy. Although a median survival rate of 11 to 12 months for fluoropyrimidine single-agent in treating advanced stage CRC was reported, the median survival has doubled to 2 years using novel chemotherapeutic regimens.[1] Problems using chemotherapeutic drugs for palliation in advanced stage CRC include that nearly all patients would eventually experience disease progression (PD) after the second- or third-line therapy. Notwithstanding, many patients would still present good performance status and be ready for further later-line chemotherapy. However, later- line chemotherapy is costly, usually provided at an unaffordable price. For this reason, repeating prior chemotherapy is an option for selected cases to delay tumor progression.

Repeating treatment using prior chemotherapy is a practice that may be justified under limited alternatives. However, little clinical evidence is available concerning the efficacy to support this practice. Further studies are needed to examine the feasibility and tolerability of these patients in real practice. This prospective case series was conducted to gain additional evidence concerning the practical application of repeating prior chemotherapy combined with oxaliplatin therapy for patients with advanced stage CRC.

Patients and Methods

Study design

The present study employed a prospective design among patients with advanced stage CRC who had previously received oxaliplatin and were retreated with oxaliplatin- based regimens at Phramongkutklao Hospital between April 1st, 2011 and March 30th, 2014. This study was approved by the Institutional Review Board of the Medical Department, the Royal Thai Army.

Patients

Patients with a diagnosis of advanced stage CRC that was unable to be treated due to distant site metastasis, infiltration, or adherence to adjacent organs/structures were enrolled. The inclusion criteria of the enrolled participants included 1) previously treated with oxaliplatin and planned to retreat with oxaliplatin-based regimens, 2) age <80 years, 3) good health status evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status within the range of 0 to 2 before starting chemotherapy and 4) adequate organ functions. Functions were defined as **renal**: serum creatinine <1.5 x normal, or creatinine clearance GFR >60 ml/min/1.73 m^2 and **liver**: total bilirubin <1.5 x normal, or SGOT (AST) or SGPT (ALT) <3.0 x normal baseline pretreatment patients' characteristics. In addition, disease status was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST)[2], and laboratory results were also recorded.

Chemotherapy regimens

Three treatment regimens are described below. First, **FOLFOX4** (14-day cycles of oxaliplatin 85 mg/ m^2, folinic acid 200 mg/ m^2) was given days 1 to 2 plus fluorouracil 400 mg/m^2 (bolus) and 600 mg/m^2 (continuous 22-hour infusion). Second, modified **FOLFOX6** (oxaliplatin 85 mg/m^2) was given day 1 with calcium folinate 400 mg/m^2 as a 2-hour infusion followed by a bolus of 5-fluorouracil 400 mg/m^2 and a 46-hour infusion of 5-fluorouracil 2,400 mg/ m^2. Similarly, **XELOX** (130 mg/ m^2 intravenous oxaliplatin for 2 hours) was provided day 1 plus oral capecitabine 1,000 mg/m^2 twice daily for 2 weeks from day 1. Treatment was continued until PD, intolerable adverse drug reactions, poor performance status, withdrawal of consent or death occurred. **ELOXATIN**® (Sanofi-Aventis) was used in the present study. Authors evaluated types and rate of unintended medical events, tolerability, feasibility and efficacy.

Tolerability

Combination regimens may cause different types of side effects. All adverse reactions were identified to determine rate and severity based on the Common Terminology Criteria for Adverse Events, Version 4.0. Rate and reasons of treatment cessation were identified to determine feasibility of retreating with oxaliplatin-based regimens.

Evaluation of efficacy

All patients were given regular follow-up using routine physical examination, serum markers, and imaging studies

to assess treatment response. The efficacy of retreatment with oxaliplatin-based regimens was assessed using routine physical examination, blood test for serum markers, and imaging studies (CT scan/MRI/CXR). RECIST criteria[2] were applied to measure tumor response categorized as: 1) complete response (CR) when all target lesions disappeared, 2) partial response (PR) when a 30% decrease was observed in the sum of the longest diameter of target lesions, 3) PD when a 20% increase was observed in the sum of the longest diameter of target lesions and 4) stable disease (SD) when small changes occurred that did not meet the above criteria. Clinical evaluation was used instead of the imaging study in the case of intolerability or when contraindicated for CT scan/MRI with clear clinical evidence of tumor appearance or progression.

Results

A total of 13 patients with advanced CRT who had been previously treated with oxaliplatin were recruited in this study. The median cycles (range) of received oxaliplatin-based chemotherapy before re-introducing therapy comprised 8 (3-15) cycles. The median age (range) was 50 (27 to 78) years. The most common sites of cancer were the rectum (8/13) and sigmoid colon (3/13). Metastases were detected in different parts of the body. The liver (9/13) and lungs (8/13) were the first two most common metastatic sites. Four patients (30.7%) had more than one metastatic site. Two patients had peritoneal metastases detected during primary tumor resection and 2 patients had local recurrence and peritoneal metastases detected after surgery. Four patients presented primary tumors which were unable to be removed and left in situ. XELOX (130 mg/ m^2 intravenous oxaliplatin) provided for 2 hours on day 1 plus oral capecitabine 1,000 mg/ m^2 twice daily for 2 weeks from day 1 was the most commonly prescribed regimen for this retreatment period. Of a total of 13 patients, 9 (69.3%) received oxaliplatin-based reintroduction on a stop and go strategy to avoid possible cumulative toxicities as resistance had not been proved in this group. In addition, 4 (30.7%) patients received oxaliplatin-based re-introduction after exhibiting previous resistance to the oxaliplatin regimens. The planned 4 cycles of Xerox re-introduction were withheld for 2 patients due to allergic reaction at the 3rd cycle of re-challenge treatment. Efficacy was determined in 10 of 13 cases (two cases presented drug allergy and one case was lost to follow-up). Of these, 6 patients (60%) exhibited PD while 4 patients (40%) had SD measured by RECIST criteria. Grade 3/4 adverse events were found among 7 patients (53%) and some events were anticipated, i.e., organ deterioration or consequences of PD including pericardial effusion, neutropenia, anemia, neuropathy, nausea, vomiting, obstructed uropathy and jaundice. The 4 patients (100%) in the tumor resistance group who had received a diagnosis before receiving re-treatment with oxaliplatin combination therapy had grade 3/4 adverse events compared with 33% of the stop and go treatment group. Three patients were excluded because treatments were withheld due to allergic reactions (2), they refused to continue treatment (1) and were lost to follow-up (1). About 77.8% (7/9) of patients successfully received predefine treatment cycles. Etiologies of treatment cessation by numbers of patient were recorded as: tumor progression (6), lost to follow-up (1), refused to receive further treatment (1), allergic reactions (2) and physical deterioration (2). One patient was defined as having SD while three patients died during the treatment period from PD.

Discussion

For advanced stage CRC, a combination of multiple anti-cancer treatments is given that aims to reduce symptoms and prolong patients' survival. Prolonged treatment with chemotherapy until the cancer ceases to respond usually causes drug related toxicities and compromises quality of life. Stop and restart of aggressive anti-cancer drugs or interspersed with periods of maintenance are acceptable practices to ensure a better quality of life as a continuum of care concept. For patients with advanced stage CRC, experiencing tumor progression beyond multiple line chemotherapy, the best supportive care, clinical trial participation and retreating with the previous regimens are possible options. When clinical trial enrollment is unavailable and patients remain in good physical status, oxaliplatin-based re-introduction may be offered.

Physical deterioration due to the PD and accumulative toxicity after exposure to previous multiple lines of chemotherapy were considered the main obstacles of treatment tolerability. For patients with good performance status,

re-introducing therapy comprised a feasible alternative.[1, 3]

Our study found that approximately 78% of patients could complete 4 cycles of re-introduction therapy. This study found 13% of patients developed hypersensitivity reactions that were comparable to 12.7% from a related study.[4] hao et al.[5] revealed that repeated infusion, younger age, being female, extended period and salvage therapy were factors predicting the occurrence of allergic reactions. Based on the present study, re-introducing oxaliplatin-based chemotherapy was a feasible alternative and could provide clinical benefits when no other alternative choices were available. Selecting suitable patients presenting good physical status with close monitoring by physicians is crucial to achieve treatment objectives. We found a better tolerability of patients with no diagnosis of oxaliplatin resistance. Balancing between prolongation of survival and quality of life must be the primary goal of treatment because organ deterioration and PD are anticipated consequences of advanced unresectable metastatic CRC.

Conclusion

Reintroducing oxaliplatin combination chemotherapy is one of treatments used in advanced stage CRC. We concluded that physical deterioration and tumor progression were the main etiologies of treatment cessation.

Table 1. Patient Characteristics

No.	Sex	Age	Site of Metastases	Regimen	Completion of predefine treatment course	Response	Evaluation of treatment response	Reason for Oxaliplatin Cessation	Grade 3/4 adverse events
1	Male	27	Liver, peritoneum	XELOX	no	N/A	-	Drug allergy	-
2	Female	59	Liver, peritoneum	XELOX	no	PD	Clinical	Dead from PD	Anemia, Obstructive uropathy, Peripheral neuropathy
3	Male	62	Lung	XELOX	no	SD	Imaging	Unable to tolerate side effects	Vomiting
4	Male	50	Liver	FOLFOX4	no	PD	Clinical	Dead from PD	Neutropenia, Renal insufficiency
5	Male	60	Lung	XELOX	yes	SD	Imaging	Dead from PD	Heart failure
6	Male	43	Liver	XELOX	yes	PD	Imaging	PD	-
7	Male	42	Liver	mFOLFOX6	yes	PD	Imaging	PD	-
8	Male	53	Lung, Brain	XELOX	yes	N/A	-	Drug allergy	-
9	Male	46	Lung	mFOLFOX6	yes	PD	Imaging	PD	-
10	Female	40	Lung	XELOX	yes	SD	Imaging	PD	Neutropenia, Peripheral neuropathy
11	Male	37	Liver, peritoneum	XELOX	no	PD	Clinical	PD	Jaundice, Neutropenia
12	Male	55	Lung, peritoneum	XELOX	no	N/A	-	Loss to F/U	-
13	Male	78	Lung	XELOX	yes	SD	Imaging	-	Pericardial effusion, Neutropenia, Peripheral neuropathy

PD=disease progression, SD= stable disease

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