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Original Article

OXALIPLATIN AND CAPECITABINE IN THE TREATMENT OF METASTATIC COLORECTAL CARCINOMA (PHASE-11 STUDY)

Mohammad Hassan[1], Hussein Omar[2], Ehab Alnakory[3], Ehab Esmat[4], and Ehab Hassan[5]

[1]Erfan Hospital,[2]King Abdulaziz Hospital,[3]Saudi German Hospital,[4]King Faisal Hospital,[5]King Fahd Hospital, Saudi Arabia

ABSTRACT

Background: Capecitabine and oxaliplatin are two new chemotheraputic agents with potential synergistic activity, both have demonstrated promising antitumor efficacy in advanced and metastatic colorectal cancer. Capecitabine plus oxaliplatin, established in a previous dose-finding study, have the same efficacy like oxaliplatin with infused FU and leucovorin (FOLFOX) regimens. The present studies further characterize efficacy and safety of capecitabine and oxaliplatin regimen.

Objectives: To evaluate the objective tumor response rate and safety profile of oxaliplatin and capcitabine when administered to patients with previously untreated metastatic colorectal carcinoma (MCRC).

Patients and Methods: A total of 23 patients with MCRC received first-line oxaliplatin plus Capecitabine in three weeks.

Treatment cycles: Intravenous oxaliplatin 130mg/m² (day one) followed by oral capecitabine 1,250mg/m² twice daily (day one, to day 14).

Results: Twelve patients (52%) achieved an objective response and 6 patients (26%) had stable disease for three or more months following treatment. After a minimum follow-up of 21 months, the median time to disease progression (TTP) was7.5months and median overall survival was 18 months. Capecitabine plus oxaliplatin safety was predictable; the most common grade three to four toxicities were hand and foot syndrome (17%), diarrhea (13%), neutropenia and neurotoxcities 8.6%and 4%, respectively.

Conclusion: This phase II study provides clear evidence of the efficacy and safety of oxaliplatin and capcitabine as a convenient first-line treatment for patients with previously untreated metastatic colorectal carcinoma.

Key Words: Colorectal carcinoma, oxaliplatin, capecitabine.

Corresponding Author: Ehab Alnakory, German-Saudia Hospital, Sudia Arabia, Tel.: 00966561541037,

INTRODUCTION

Colorectal carcinoma is a leading cause of cancer death worldwide, with nearly 150,000 new cases and 60,000 attributed deaths annually in the United States. Despite these sobering statistics, the 21 century heralds a new era in colorectal cancer treatment. From the late 1950s until very recently, fluorouracil (FU) was the only drug approved for the treatment of colorectal cancer with response rates ranged from 10% to 15% and median survival of 10 months, affording treated patients minimal improvement in survival over supportive care.[1, 2]

This response rate was improved to nearly 25% when leucovorin (LV) was used to modulate FU[3]. A modest survival benefit came at the cost of a small increase in toxicity, and subsequently FU/LV became standard first-line therapy for metastatic colorectal cancer from the late 1980s to 2002[4,5]. The recent availability of new active chemotherapeutic agents has doubled the median overall survival for metastatic colorectal cancer from 10 to 20 months, and though the optimal strategy for incorporation of all drugs is still unclear, current data support the use of chemotherapy doublets in first-line rather than sequential single-agent therapy. Multidrug regimens increase both response rate and the proportion of patients able to undergo potentially curative resection[6]. In addition, as many as 20% to 30% of patients never receive second-line chemotherapy. When used as single agents, bolus and infusional FU/LV and capecitabine are similarly effective but have differing toxicity.[7]

Chemotherapy combinations that incorporate infusion of FU are less toxic and more effective than those using bolus FU dosing[8]. Capecitabine is under study as an alternative dosing method for use in combination regimens; however, the optimal dose has not been defined and final safety and efficacy outcomes are being addressed in ongoing phase II and III investigations[9,10]. Three combinations have shown excellent first-line efficacy in phase III trials—IFL (Iri notecan, 5FU, and Leucovorine) with bevacizumab, FOLFOX (5FU, Leucovorine and

Oxaliplatin) and FOLFIRI (5FU, Leucovorine and Irinotecan), but neither of these combinations is clearly superior.[11-13]

Despite the increased efficacy associated with infused FU/LV plus oxaliplatin, the administration schedules for the FU component are inconvenient for both patients and healthcare professionals. These require two bolus injections plus two 22-hour infusions every two weeks[14] or five days of continuous infusion with chronomodulation equipment every three weeks[15] or weekly 24-hour infusion[10]. Because capecitabine has already demonstrated its ability to replace FU/LV as a highly effective and more convenient treatment for colorectal cancer, there is a strong rationale for investigating the efficacy and safety of capecitabine in combination with oxaliplatin.

The current, phase II study was conducted to evaluate further the efficacy and safety of oxaliplatin and capcitabine regimen as first-line therapy for patients with MCRC.

PATIENTS AND METHODS

This was a multicenter phase II study, conducted at Saudi Arabia. The primary end point was overall response rate. Secondary end points included time to disease progression (TTP), one year survival, overall survival, and safety. All patients provided written informed consent.

Patients aged 18 to 75 years with measurable, histologically confirmed metastatic colorectal cancer were eligible for the study. Patients were required to be ambulatory and have a WHO performance status of <2. No prior chemotherapy for advanced disease, but adjuvant or neoadjuvant chemotherapy was allowed, providing it was completed at least 6 months before start of study treatment.

Exclusion criteria included prior therapy with capecitabine, oxaliplatin, or irinotecan, clinically significant cardiac disease, radiotherapy or surgery within four weeks before treatment, neutropenia (<1.5 / µL), thrombocytopenia (<100/µL), severe renal function impairment (creatinine clearance <30mL/min), or abnormal liver function and pregnant women.

A full medical history and physical examination, hematological and blood chemistry tests were necessary. Tumor assessments were performed by computed tomography scan, and/or magnetic resonance imaging during first assessment, after the first three cycles of treatment, then after every three cycles of treatment until disease progression or withdrawal from the study medication.

In patients whose disease had not progressed when stopping treatment, tumor assessments were performed every three months until progression. Tumor response was assessed according to WHO criteria[16]. TTP was defined as the interval between the first dose of study treatment and the first recording of disease progression or death. Adverse events, including neurosensory toxicity and hand and foot syndrome (HFS), were classified by National Cancer Institute Common Toxicity Criteria version 2.

Treatment protocol:

Oxaliplatin 130mg/m^2 (diluted in a 5% glucose solution) IV day one then oral capecitabine 1,250mg/m^2 twice daily from day one to day 14, followed by a 7-days treatment-free interval, in a three weeks cycle. The capecitabine starting dose was reduced to 75% of the standard dose in patients with moderate renal impairment (with creatinine clearance between 30 and 50 mL/min) or grad three hand and foot syndrome (HFS)[17]. The dose of oxaliplatin was also reduced to 75% for grade three vomiting, grade three or four thrombocytopenia, or grade four neutropenia, and for paresthesia with pain or functional impairment >7 days, or paresthesia with pain persistent between cycles. For paresthesiae with functional impairment persistent between cycles, oxaliplatin was discontinued.

The planned number of treatment cycles was 6, but patients maintaining a response or stable disease after this time could continue treatment at the same protocol. Patients could also continue capecitabine monotherapy after discontinuation of oxaliplatin irrespective of the number of cycles already received. The primary end point was overall confirmed response rate, TTP and survival were estimated by Kaplan-Meier analysis version 10. Safety was analyzed in all patients who received at least one dose of study medication.

RESULTS

A total of 23 patients were recruited between July 2002 and June 2004. Approximately half of the patients had multiple metastases, with liver, lung, and bone being the most frequent sites of metastases (Table 1). fourteen patients had received prior adjuvant chemotherapy with IV 5FU, and four patients had received prior radiotherapy.

An objective response was observed in 12 patients (52%) with complete response in one patient (4%). All objective responses were confirmed at least four weeks after first observation (Table 2). Disease stabilization was achieved in a further 6% (26%). Notably, disease stabilization lasted longer than three months from start of treatment in all of these patients; one patient of them had increase in the CEA tumor marker but clinically and radiologically had stable disease.

Table 1: Patients chractarstics.

Patients character (23 patients)	No.
Age- year	
Range	29- 72
Median	59
Sex M/F	14/9
WHO performance	
0	13
1	8
2	2
Primary tumor site	
Colon	16
Rectum	7
First presentation with mets	4
Mets site	
Liver	14
Lung	4
Bone	2
Others	6
Prior adjuvant treatment:	
Chemotherapy	14
Radiotherapy	4

Table 2: Treatment Response.

Response	No.	%
Objective response (PR+CR)	12	52
Partial response (PR)	11	48
Complete response (CR)	1	4
Stable disease	6	26
Progressive disease	5	22

After a minimum follow-up of 21 months, the median TTP in the intent-to-treat population was 7.5 months. Median overall survival was 18 months. The estimated survival rate was 68% at one year and 27% at two years.

A total of 14 patients (60%) received second-line and 7 (30%) received third-line chemotherapy. The most common second-line chemotherapy was irinotecan (10 patients), either as monotherapy or in combination with 5FU. two patients received bevacizumab. One patient had received cetuximab, three patients (13%) received palliative radiotherapy, and two patients underwent surgery, and one patient underwent radiofrequency for small hepatic metastases.

Toxcities

The most common treatment-related adverse events are shown in table 3. Hand and foot syndrome (HFS), a frequent side effect of capcitabine, was the most common treatment-related adverse event, occurring in 14 patients (60%). The majority of hand and foot syndrome was mild to moderate, with only four patients (17%) experienced grade three or four. Other grade three or four treatment-related adverse events were diarrhea (13%), and nausea or vomiting (8.6%). Neurotoxicity was experienced by fourpatients (17%), only one was grade three (4%). Grade three neutropenia (8.6%), thrombocytopenia (4%), and anemia (4%).

Table 3: Treatment toxicity.

Toxicities	Grade 1-2		Grade 3-4		Total	
	NO.	%	NO.	%	NO.	%
H FS	10	43	4	17	14	60
Neurotoxcities	3	13	1	4	4	17
Diarrhea	4	17	3	13	7	30
Stomatitis	13	39	0	0	13	39
Fatigue	7	30	0	0	7	30
Neusea&vomiting	4	17	2	8.6	6	25.6
Neutropenia	5	21	2	8.6	7	29.6
thrombocytopenia	2	8.6	1	4	3	12.6
Anemia	4	17	1	4	5	21

Capecitabine and oxaliplatin demonstrated a similar favorable safety profile among the subgroups of patients aged ≥ 60years or younger than 60 years. Stomatitis was the only treatment-related adverse event more common in patients ≥ 60years old than those younger than 60years (26% v 13%, respectively), but no patients in either age groups experienced grade three or four stomatitis. Overall, there was a similar incidence of grade three or four treatment-related adverse events in the two age groups (15 patients younger than 60years and 8 patients 60 years or older) with no significant differences in the incidences of any grade three or four treatment-related adverse events.

Seventeen patients received full doses of capecitabine and oxaliplatin throughout the study. Dose reduction was required for capecitabine in 6 patients (26%), for oxaliplatin in two patients (8.6%). Myelosuppression and hand and foot syndrome were the most common adverse events leading to dose reduction. The incidence of dose reduction was similar in the subgroups of male and female patients but more in those age group ≥ 60 years.

DISCUSSION

Until a few years ago, treatment options for patients with advanced colorectal cancer (ACC) were limited to fluorouracil (FU) a therapy plagued by poor response rates and dismal median survival. The introduction of biochemical modulators such as leucovorin (LV) or methotrexate has led to improvements in response rates with minimal effect on survival. Similarly, various modifications of the original FU bolus administration schedule, such as continuous infusion or chemomodulation, have yielded only marginal improvement[18]. Within the

last five years, a number of new, promising anticancer agents with unique and different mechanisms of action, synergism with FU, or reduced toxicity have been introduced[19,20]. Oral FU prodrugs, specifically capecitabine, characterized by high and predictable oral bioavailability, as well as a preferential conversion to FU in neoplastic tissues, are notable examples[20,21]. In two recently published randomized trials, each comprising about 600 patients, a superior therapeutic index was reported for capecitabine compared with bolus FU/LV. Another promising agent, the third-generation one, 2-diaminocyclohexane-platinum derivate oxaliplatin, was approved for the treatment of ACC in Europe in 1999.[22,23]

Oxaliplatin and capcitabine combination regimen is a rational combination treatment. The addition of oxaliplatin to infused FU/LV chemotherapy results in higher response rates and TTP in both first- and second-line treatment of advanced colorectal cancer[24]. Oral capecitabine monotherapy has previously shown superior antitumor activity to bolus FU/LV (Mayo Clinic regimen) in this setting, with higher response rates (26% v 17%, P < .0002) and at least equivalent TTP and overall survival in two large randomized studies.[23,25]

This phase II study was undertaken to further evaluate the combination of oxaliplatin and capcitabine as first-line therapy for MCRC. oxaliplatin and capcitabine achieved a high response rate of 52%, with an additional 26% of patients maintaining stable disease for at least three months. These results were comparable to the results achieved in recent published study by Jim et al.[26] Also, subgroup analysis showed that the response rate remained high irrespective of patient and disease characteristics. These efficacy results compare favorably with the randomized studies of FU/LV with oxaliplatin[14] which demonstrated significant improvements for the combination (FOLFOX) compared with FU/LV alone. Oxaliplatin and capcitabine achieved similar response rates and progression-free and overall survival to most of the regimens combining protracted FU/LV infusion with oxaliplatin.

Capecitabine and oxaliplatin have no overlapping toxicities, and the combination was well tolerated even with long treatment duration. The safety profile of oxaliplatin and capcitabine was similar to that of FU/LV plus oxaliplatin, with a lower incidence of grade three or four neutropenia. In this study 17% showed grade three hand and foot syndrome which was higher comparable to other study[26]. However in this study the incidence of grade three neurotoxcities was low (4%). The low incidence of grade three neurotoxcities with oxaliplatin and capcitabine regimen may be due to the hot whether in Saudi Arabia in comparison to the higher neurotoxcities in western studies[23]. It is also possible that oxaliplatin-induced neurotoxicity may be masked by the symptoms of HFS. In addition, oxaliplatin and capcitapine demonstrated a similar safety profile in patients younger than or at least 60 years.

The data therefore indicate that three weekly cycles of capecitabine and oxaliplatin is a highly effective regimen as a first-line treatment for metastatic colorectal cancer and that capecitabine has strong potential to replace FU/LV as the optimal combination partner for oxaliplatin. The Capecitabine and oxaliplatin dose schedule of capecitabine 1,250mg/m² twice daily with oxaliplatin 130mg/m² had been previously identified in another phase II trial evaluated the same dose of capecitabine in combination with oxaliplatin in patients with pretreated and previously untreated MCRC[25] While a response rate of 49% was obtained in patients receiving the combination as first-line therapy, the incidence of grade three or four diarrhea was 33% in treatment-naïve patients and 50% in pretreated patients. Although the authors recommend the full dose of both agents for treatment of patients with advanced CRC, more than 25% of the chemotherapy-naïve population required a capecitabine dose reduction after the first cycle. A similar incidence of capcitabine dose reduction was noted in our study 26% (6 patients).

A randomized phase II trial has evaluated two schedules of capecitabine plus oxaliplatin as first-line therapy in 89 patients with MCRC[27]. Patients were randomly assigned to receive a dose-intensified regimen (capecitabine 1,750mg/m² twice daily on days one to 7 and 14 to 21 plus oxaliplatin 85mg/m² on days one and 14, every 28 days) or XELOX (capecitabine 1,000mg/m² twice daily days one to 14 plus oxaliplatin 130mg/m² on day one, every 21 days). No formal prospective comparison of efficacy in the two treatment groups was planned and the study was not powered statistically for such a comparison. Both regimens were active, achieving response rates of 55% and 42%, with median progression-free survival of 10.5 and 6.0 months, respectively. However, in the absence of data from a prospective, randomized, phase III comparison, no conclusions about the efficacy and safety of the dose-intensified regimen relative to XELOX can be drawn. Another phase II study has evaluated a lower dose of capecitabine (750mg/m² twice daily) than used in our study[28]. This regimen achieved a response rate of only 34% in 35 treated patients which is much lower than our achievement (52%). In summary, the dose of 1,250mg/m² capecitabine twice daily in combination with oxaliplatin, as used in this regimen, achieves high efficacy while maintaining a good safety profile.

The capecitabine and oxaliplatin regimen has demonstrated similar efficacy and safety to FOLFOX. Interestingly, the incidence of grade three or three neutropenia is lower with the capecitabine and oxaliplatin regimen than with the FOLFOX regimen, as is the incidence of febrile neutropenia[14]. In addition, Capecitabine and oxaliplatin requires only one clinic

visit per three weeks cycle for a two hours infusion of oxaliplatin. This constitutes a marked advantage over regimens combining infused FU/LV and oxaliplatin in terms of the impact on patients' convenience and the cost. In summary, this study shows that Capecitabine and oxaliplatin is a highly effective therapy for patients with MCRC. Response rates, time to disease progression, and overall survival compare favorably with previous studies of FU/LV/oxaliplatin, and the Capecitabine and oxaliplatin combination offers substantially improved convenience and is less disruptive for patients. In addition, the Capecitabine and oxaliplatin regimen offers a novel, well-tolerated, and active backbone for incorporation of innovative targeted agents such as the EGFR-directed drugs (cetuximab), and the antiangiogenic monoclonal antibody (bevacizumab).

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