ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 11, pp. 14099-14102, November, 2016

International Journal of Recent Scientific Research

Research Article

CAPOX AS FIRST LINE CHEMOTHERAPY IN RECURRENT AND PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER - AN EXPERIENCE FROM SOUTH INDIA

Abdul Majeed K., Palaniappan M., Kishore Kumar., Wesley M Jose., Pavithran K And Ganesan TS

Department of, Cancer Institute, Amrita institute of medical sciences, AIMS Ponekkara post, Edappally, Kochi, Kerala – 682041, India

ARTICLE INFO

Article History:

Received 15th July, 2016
Received in revised form 25th September, 2016
Accepted 23rd October, 2016
Published online 19th November, 2016

Key Words:

Capecitabine, Oxaliplatin, colorectal, metastatic, Hand-Foot Syndrome.

ABSTRACT

Background: Though 5-FU is the mainstay of treatment for colorectal cancer, its prolonged administration is associated with infusion-related complications and patient inconvenience. Capecitabine, an oral drug, has been found to be equally or more effective in many studies.
Aim: To determine the safety and efficacy of combination of Capecitabine and Oxaliplatin (CAPOX) as first line chemotherapy in South Indian patients with recurrent and previously untreated metastatic colorectal cancer.
Methods and material: Thirty one patients from June 2006 to December 2008 of recurrent or previously untreated metastatic colorectal carcinoma who were treated with Capecitabine / Oxaliplatin combination regimen as first line therapy.
Results: Fourteen new patients had disease response (one complete response and 13 partial responses) and eleven had progressive disease. On follow up, five of them have died of disease while one was lost to follow up. The remaining nineteen patients are alive. The median progression-free survival was 17 weeks (range: 4 weeks - 104 weeks).
Conclusions: Chemotherapy with CAPOX regimen has resulted in 45% response rate in patients with recurrent or previously untreated metastatic colorectal cancer. The regimen was well tolerated with minimal toxicity.

INTRODUCTION

5-fluorouracil (FU) has been the mainstay of chemotherapy for patients with metastatic colorectal cancer (MCRC) for many years. As far as administration is concerned, prolonged infusion of FU in combination with bio-modulator leucovorin (LV) has an enhanced safety and efficacy profile when compared with short infusion of both.[1,2] Capecitabine is an oral fluoropyrimidine that generates FU through a three-step enzymatic process.[3] It has been shown that Capecitabine monotherapy achieves significantly higher response rate than FU/LV combination with relatively minimal side effects.[4-6] The side effects such as diarrhea, stomatitis, etc. are less frequent and less severe with Capecitabine.[7] Thereafter, oral Capecitabine offers an edge over FU/LV combination. Addition of Oxaliplatin to FU/LV combination in the first-line treatment of previously untreated advanced colorectal cancer raises significantly the response rate and the time to disease progression as compared with those of FU/LV combination alone. [8,9] Based on the above studies, the combination of Capecitabine and Oxaliplatin (CAPOX) needs to be evaluated as a first line chemotherapy in the clinical setting of previously untreated MCRC. We have administered the same regimen in patients with recurrent colorectal cancer not previously exposed to oxaliplatin.

METHODS

Patients with histologically confirmed disease of recurrent or previously untreated metastatic colorectal cancer treated with CAPOX as first line were extracted from the electronic medical records of our hospital from June 2006 to December 2008 and reviewed. Of the total 31 patients, 27 patients were metastatic on presentation and 4 had recurrent disease. Prior to the start of treatment, all patients were assessed for baseline status with routine investigations. (Complete blood count, renal and liver function tests), carcinoembryonic antigen (CEA) and computed tomograms (CT) of abdomen, pelvis and chest. The CAPOX regimen was Oxaliplatin (130 mg/sqm) in 500ml of 5% dextrose intravenously over 2 hours on day 1 and Capecitabine (2 gm/sqm/day in two divided doses) orally on days 1 - 14. The cycle was repeated every 3 weeks and a maximum of 6 cycles were administered. Appropriate dose reductions were made if

Corresponding author: **Abdul Majeed K*
Department of, Cancer Institute, Amrita institute of medical sciences, AIMS Ponekkara post, Edappally, Kochi, Kerala – 682041, India

clinically indicated. Treatment responses were typically evaluated with CT imaging as per WHO criteria. The toxicity was assessed according to the common toxicity criteria of the National Cancer Institute.

RESULTS

Of thirty-one patients, the median age was 54.5 years (range of 32 – 78 years) and there were 19 males and 12 females (M/F ratio - 1.58). At diagnosis, 55% of them had primary lesion in colon and 45% had in rectum. The percentages of patients having liver, lung and peritoneal secondaries were 87 %, 16 % and 9.7 % respectively. The CEA level ranged from 3.5 to 8062 (ng/ml) and was elevated in 20 patients. Fourteen patients completed 6 cycles of chemotherapy and eleven received 3 or more. The remaining six patients could only be administered less than 3 cycles for various reasons including financial constraints. Among twenty-five assessable patients (those who have received at least 3 cycles of CAPOX), one patient developed grade IV hematological toxicity (anemia) on receiving chemotherapy. No grade III/IV neurological or gastrointestinal (diarrhea) or skin (Hand-Foot Syndrome) toxicities were encountered. Fourteen cases exhibited disease response (one complete response and 13 partial responses) and eleven had progressive disease.

Table 1 Profile of patients and disease

Factor	Variable	Number of cases (n)	Percentage (%)
Gender	Male	19	61 %
	Female	12	39 %
Disease status	Previously untreated metastatic disease	27	87 %
	Recurrent disease	4	13 %
Site of primary lesion	Colon	17	55 %
	Rectum	14	45 %
Site of metastasis	Liver	27	87 %
	Lung	5	16 %
	Peritoneum	3	9.7 %
Tumor histopathology (assessable patients)	Moderately differentiated adenocarcinoma	12	48 %
	Well differentiated adenocarcinoma	11	44 %
	Mucinous carcinoma	2	8 %
Response	Complete response	1	3.2 %
	Partial response	13	41.9 %
	Progressive disease	11	35.5 %
	Non-assessable	6	19 %

All eleven cases with well-differentiated adenocarcinoma showed response to treatment (100 %), while in moderately differentiated adenocarcinoma subtype; seven out of twelve patients responded (58.33 %). Mucinous carcinoma was found in two patients who showed no response (0 %). During follow-up, five of them have died of disease while one was lost to follow up. The remaining nineteen patients are alive on follow up. The median progression-free survival rate was 17 weeks (range: 4 weeks - 104 weeks).

DISCUSSION

5-fluorouracil (FU) has been the mainstay of chemotherapy for patients with metastatic colorectal cancer (MCRC) for many years. As far as administration is concerned, prolonged infusion of FU in combination with bio-modulator leucovorin (LV) has an enhanced safety and efficacy profile when compared with short infusion of both.[1,2] But the inconvenience and morbidity associated with long-term administration emphasize the need for an alternate patient-friendly regimen that is equally or more effective. Capecitabine is an oral fluoropyrimidine that generates FU through a three-step enzymatic process preferentially and largely at the site of tumor due to the significantly higher availability and activity of thymidine phosphorylase in tumor tissues compared with normal tissue.[3] An integrated analysis of two large, randomized phase III prospective trials in MCRC demonstrated that Capecitabine monotherapy achieves significantly higher response rate than FU/LV combination (tumor response rate 26% *vs.* 17%).[4-6] In addition, the safety profile of oral Capecitabine is also higher than that of FU/LV combination. The side effects such as diarrhea, stomatitis, neutropenia, nausea and alopecia are less frequent and less severe with Capecitabine.[7] However, Capecitabine is frequently associated with the so-called Hand-Foot Syndrome, a form of cutaneous side effect, which can be managed conservatively. Therefore, oral Capecitabine offers an advantage over FU/LV combination by an improved response rate as well as minimal side effects. Addition of Oxaliplatin to FU/LV combination in the first-line treatment of previously untreated advanced colorectal cancer increases significantly the response rate and the time to disease progression as compared with those of FU/LV combination alone. [8,9] According to the above results, the combination of Capecitabine and Oxaliplatin needs to be studied in the clinical setting of previously untreated MCRC as first line therapy. As the management of recurrent colorectal cancer is similar to that of MCRC, the same combination, we believe, will hold good for recurrent lesions also and should be tried in such a setting. Various phase II studies testing the combination of Capecitabine and Oxaliplatin in advanced colorectal cancer have reported response rates ranging from 27 % to 51 %.

Table 2 Statistics of studies of Capecitabine and Oxaliplatin combination in advanced colorectal cancer.

Study	Number of patients	Response rate (CR+PR)	Myelosuppression (Grade III/IV)	Neurotoxicity (Grade III/IV)	Diarrhea (Grade III/IV)	Hand-foot syndrome (Grade III/IV)
Scheithauer W *et al* 2003	45	42 %	15 %	16 %	-	4 %
arm A	44	54 %	7 %	12 %	-	2 %
arm B						
Sumpter K *et al* 2003	15	33 %	Nil	-	-	-
Zeuli M *et al* 2003	43	44 %	9.3 %	7 %	28 %	Nil
Cassidy J *et al* 2004	53	55 %	7 %	17 %	16 %	3 %
Our study 2010	31	45 %	3 %	Nil	Nil	Nil

A study by Gothrey *et al* showed 51 % response rate,[10] while another phase II study by Zeuli M *et al* the response rate was 48 % in untreated patients with advanced colorectal cancer.[11] The AIO study (Association of Medical Oncology of the German Cancer Society) by Arkinau *et al* had a 47 % response rate.[12] A retrospective work by Sumpter K *et al* calculated the overall response rate at 27.6 % in patients with metastatic

colonic cancer treated with Capecitabine and Oxaliplatin.[13] The results of our study show that

CAPOX is effective as first-line regimen for treating patients with recurrent or previously untreated metastatic colorectal cancer. This is based by the fact that the response rate was 45% in our study. A meta-analysis of various related studies suggests that the toxicity profile of CAPOX is much more similar to that of FOLFOX (Leucovorin/5-Fluorouracil/ Oxaliplatin) except for the higher incidence of hand-foot syndrome with the former and grade III/IV neutropenia with the latter.[14,15]

In a randomized phase II (TREE-1) trial,[16] CAPOX had a higher incidence of grade III/IV non-hematologic toxicities viz. nausea, vomiting, diarrhea, dehydration and hand-foot syndrome than FOLFOX (Leucovorin/Fluorouracil infusion/Oxaliplatin) and bFOL (bolus Fluorouracil/Oxaliplatin/Leucovorin) regimens. In German AIO trial, where 476 patients were randomized into two groups for FUFOX regimen (5-Fluorouracil 2,000 mg/sqm over 24-hour infusion, Folinic acid 500 mg/sqm, Oxaliplatin 50 mg/sqm, on days 1, 8, 15, and 22, every 5 weeks) and CapeOx regimen (Capecitabine 1,000 mg/sqm twice a day on days 1–14, Oxaliplatin 70 mg/sqm on days 1 and 8, every 3 weeks), grade III/IV neuropathy were more common with FUFOX arm than with CapeOx arm (25 % vs. 16 %). [12] In Sumpter's study, there were not any grade IV hematological toxicity and treatment related death with CAPOX regimen.[13] The nature and degree of toxicity encountered in our study are similar to those of other studies stated above. One patient had grade IV hematological toxicity in the form of anemia while grade III/IV neurological and skin toxicities were not observed in any patient. There was no grade III/IV Hand-Foot Syndrome. The progression-free survival rate reported across different studies ranges from 5.9 to 8.8 months. In our present study, the median progression-free survival rate is 4 months.

CONCLUSION

From our study, it can be noted that chemotherapy with CAPOX regimen has good efficacy with acceptable toxic profile in the treatment of recurrent and previously untreated metastatic colorectal cancer. It requires only one clinic visit every 3 weeks is a significant advantage over other regimens with long infusion schedules in the form of minimal impact on patients' daily life and convenience for both patients and caregivers. Thus CAPOX regimen, being convenient and well tolerated without any compromise in expected efficacy, might serve as a good platform to which novel targeted agents can be added and tried in the clinical settings of recurrent and previously untreated metastatic colorectal cancer in order to improve on these patients.

References

1. De Gramont A, Bosset JF, Milan C, Rougier P, Bouch O, Etienne PL, *et al*. Randomized trial comparing monthly low dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French intergroup study. *J Clin Oncol* 1997; 15:808-15.
2. Andre T, Colin P, Louvet C, Gamelin E, Bouche O, Achille E, *et al*. Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: Results of a randomized trial. *J Clin Oncol* 2003; 21:2896-903.
3. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, *et al*. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998; 34:1274-81.
4. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, *et al*. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. *J Clin Oncol* 2001; 19:2282-92.
5. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, *et al*. Oral capecitabine compared with intravenous 5-fluorouracil plus leucovorin (Mayo Clinic regimen) in patients with metastatic colorectal cancer: Results of a large phase III study. *J Clin Oncol* 2001; 19:4097-106.
6. VanCutsemE, HoffPM, HarperP, Bukowski RM, Cunningham D, Dufour P, *et al*. Oral capecitabine versus intravenous 5-fluorouracil and leucovorin: Integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 2004; 90:1190-97.
7. Scheithauer W, Kornek GV, Raderer M, Schüll B, Schmid K, Kovats E, *et al*. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2003; 21:1307–12.
8. De Gramont A, Figer M, Seymour M, Homerin M, Hmissi A, Cassidy J, *et al*. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938-47.
9. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, *et al*. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18:136-47.
10. Grothey A, Jordan K, Kellner O *et al*. Randomized phase II trial of capecitabine plus irinotecan (CapIri) vs capecitabine plus oxaliplatin (CapOx) as first-line therapy of advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol 2003; 22:255.
11. Zeuli M, Nardoni C, Pino M. S, Gamucci T, Gabriele A, Ferraresi V *et al*. Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer. Annals of Oncology 2003; 14:1378-82.
12. Arkenau H, Schmoll H, Kubicka S, Kretzschmar A, Freier W, Seufferlein T *et al*. Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first line treatment of metastatic colorectal cancer (MCRC): results of the safety and efficacy analysis. ASCO Annual Meeting 2005; Abstract 3507.

13. Sumpter K, Harper-Wynne C, Cunningham D, Gillbanks A, Norman AR, Hill M. Oxaliplatin and Capecitabine Chemotherapy for Advanced Colorectal cancer: a Single Institution's Experience. Clinical Oncology 2003; 15:221-226.
14. Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, *et al*. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol* 2004; 22:2084–91.
15. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, *et al*. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22:23–30.
16. Hochster HS, Welles L, Hart L, Ramanathan R K, Hainsworth J, Jirau-Lucca G *et al*. Safety and efficacy of bevacizumab (Bev) when added to oxaliplatin/fluoropyrimidine (O/F) regimens as first-line treatment of metastatic colorectal cancer (MCRC): TREE 1 & 2 Studies. ASCO Annual Meeting 2005; Abstract 3515a.

****

How to cite this article:

Abdul Majeed K *et al*., Capox As First Line Chemotherapy In Recurrent And Previously Untreated Metastatic Colorectal Cancer – An Experience From South India. *Int J Recent Sci Res.* 7(10), pp. 14099-14102.