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# OXALIPLATIN/5-FLUOROURACIL/LEUCOVORIN IN THE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

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**SUMMARY:**

**Objective:** Oxaliplatin/ 5- Fluorouracil/ Leucovorin is an effective therapy for patients with metastatic colorectal cancer. The aim of this study was to explore the efficacy and safety of this chemotherapy regimen in the treatment of patient with advanced colorectal cancer.

**Methods:** From January 2008 to May 2010 twenty six consecutive patients with advanced colorectal cancer entered the study. Treatment schedule consist of intravenous Oxaliplatin 80 mg/m$^2$ on day 1, Leucovorin 200 mg/ m$^2$ administered as intravenous infusion on day 1 and 2 and 5- Fluorouracil 400 mg/m$^2$ bolus followed by 5- Fluorouracil 600 mg/m$^2$ as 22- hours infusion with repetition every two weeks.

**Results:** Overall response rate was 34,6% with one complete response and eight partial responses achieved. The overall survival time was 12,6 months. The main toxicity observed were leukopenia and diarrhea.

**Conclusions:** That data suggest that chemotherapy with Oxaliplatin/ 5- Fluorouracil/ Leucovorin remain reasonable chemotherapy regimen for the treatment of patients with advanced or metastatic colorectal cancer.

**Key words:** Chemotherapy, Metastatic colorectal cancer, Survival;

## INTRODUCTION

The colorectal cancer (CRC) is the third most common cancer after lung and breast and the third cause of cancer death in western countries [1]. Although surgery is potentially curative, about 50% of patients with stage III cancer and 20% of patients with stage II cancer are destined to develop liver metastases [2]. Prognosis in these patients is poor although palliative chemotherapy is more effective than the best supportive care in improving survival as well as the quality of life. Combined chemotherapy is the first treatment option when tumor lesions are frequently not fully resectable at presentation [3]. 5- Fluorouracil (5-FU) is the most commonly used agent for treatment of metastatic CRC in last 45 years [4]. A fluorinated pyrymidine, 5-FU acts by inhibiting thymidylate synthase, an enzyme necessary for the production of thymidine nucleotides required for DNA synthesis. 5-FU is usually given in combination with leucovorin (LV), a biomodulating agent that increases the binding of FU with to thymydilate synthase, thereby increasing the inhibition of DNA synthesis and enhancing the antitumor effect of 5-FU. This approach has increased response rate from 11% for 5-FU alone to 23% with FU/LV but has provided no meaningful survival benefit- median survival 11,0 months with 5-FU alone versus 11,5 months with 5-FU/LV [5].

Oxaliplatin is a new, third generation cytotoxic agent from the diaminocyclohexane platinum family. Similarly to other platinum derivates, its main mechanism of action is mediated by the formation of DNA adducts. Its spectrum of antitumor activity against tumor models differs from those of Cisplatin and Carboplatin. Activity against Cisplatin- resistant colon carcinoma cell lines has been demonstrated. In addition, experimental data showed synergistic activity of the Oxaliplatin/ 5-FU combination [6]. Oxaliplatin clinical toxicity is also distinct from other platinum drugs: it has no renal toxicity and minimal hematotoxicity; it causes both a reversible acute, cold-related dysesthesia and a dose- limiting cumulative peripheral sensory neuropathy that usually rapidly regresses after treatment withdrawal. Activity as a single agent in metastatic colorectal cancer patients either previously untreated or treated with 5-FU was demonstrated in phase II trials with response rates (RR) ranging between 10% and 24% [7-10]. Consistent with laboratory evidence of Oxaliplatin/ 5-FU synergy, there is evidence for the clinical activity of 5-FU /LV/ Oxaliplatin combinations, with RRs of 20% to more than 50% reported for the three- drug combination in phase II trials [11-13].

The aim of this study was to investigate the efficacy and safety of the combination Oxaliplatin, 5- Fluorouracil and Leucovorin in patients with advanced or metastatic colorectal cancer.

## PATIENTS AND METHODS

Participants in this study needed to be between 18 and 75 years of age. Eligibility criteria included histolo-

gically confirmed adenocarcinoma of the colon or rectum and relapsed or progressive disease. Other eligibility criteria were measurable or evaluable metastatic lesions of tumor, World Health Organisation /WHO/ performance status 0 to 2, life expectancy of minimum three months, no prior chemotherapy for metastatic disease, adequate bone marrow function /absolute granulocyte count >1,5x$10^9$/L, platelet count > 140x$10^9$/L/ as well as normal renal /serum creatinine level < 1,5 cmol/L/ and hepatic function /serum bilirubin level < 21 cmol/L/, absence of active infections. If prior adjuvant chemotherapy with 5-FU/ LV had been given, it had to be completed for at least one year. Patients with central nervous system metastases, bowel obstruction or ileus and these patients with prior chemotherapy or radiotherapy for metastatic disease were excluded from the study.

Pretreatment evaluation included: a complete medical history and physical examination, complete blood cell counts, chemistry profile, urine analysis, chest x- ray, CT scans of the abdomen, and/ or chest, if necessary. A complete blood cell count was obtained before the start of each treatment cycle, together with a serum chemistry profile, physical examination, body weight, performance status, subjective symptoms and toxicity assessment. Patients had radiological tumor parameter assessment every three cycles. The tumor response classification was evaluated according to standard WHO response criteria [14]. Response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). A CR was defined by the disappearance of all known disease, confirmed by two observations not less than 4 weeks apart. PR was defined as a decrease in tumour size of 50% or more (either measured or estimated in the case of measurable or assessable disease). In addition, there could be no appearance of any new lesions or progression of any known lesion(s). Objective tumor response (ORR) included both confirmed CR and PR. Stable disease was defined as no appearance of new areas of disease or less than 25% increase in the described measurements. Tumor control included CR, PR and SD. Progressive disease was defined as increase with more than 25% of the measurements or appearance of new lesions.

The toxicities of each course were recorded prior to the commencement of the subsequent course, and were graded according to the WHO toxicity criteria [15].

The duration of response was calculated from the day of the start of treatment to disease progression; overall survival was measured from study entry to death. The time to disease progression was calculated from study entry until the day of the first evidence of disease progression. The actuarial survival was estimated by the method of Kaplan and Meier [16].

Oxaliplatin, 5-FU and LV were obtained from commercial sources. Oxaliplatin was supplied as a freeze- dried powder in 50- and 100-mg vials. Oxaliplatin was reconstituted by adding 10 mL (for the 50-mg vials) or 20 mL (for the 100-mg vials) of water for injection or Dextrose in 5% water and then by diluting it in an infusion solution of 250 to 500 mL of Dextrose in 5% water. The treatment schedule consisted of Oxaliplatin 85 mg/$m^2$ as a 2- hour intravenous infusion on day 1, LV 200 mg/$m^2$ as a day as a 2-hour intravenous infusion on day 1 and 2 and 5-FU 400 mg/$m^2$ a 3- minute bolus injection on days 1 and 2 followed by 5-FU 600 mg/$m^2$ intravenous infusion for 22 hours on day 1 and 2. This regimen was repeated every two weeks for six courses or until disease progression. Treatment was delayed if neutrophils were less than 1,5x$10^9$/L, if platelets were less than 100x$10^9$/L, and if there were any persisting mucositis, diarrhea, or any grade 2 toxicity. The dose of 5-FU was reduced by 20% in subsequent cycles for the following toxicities: febrile neutropenia, grade 4 thrombocytopenia, grade 3 to 4 gastrointestinal toxicity, and failure of hematologic recovery to neutrophils more than 1,5x$10^9$/L and platelets more than 100x$10^9$/L within 2 weeks of the scheduled start of the next treatment. A second 20% dose reduction of 5-FU was made if the above toxicities recurred. If the toxicities then recurred, the patients continued treatment with the same regimen. No dose reductions were performed for FA. The Oxaliplatin dose was only modified for neurologic toxicity. In case of persisting paresthesias between cycles, the next Oxaliplatin dose was reduced by 25%. A second 25% dose reduction was possible if no improvement took place. If, after that, no improvement took place, the patients continued treatment on 5-FU as monotherapy. Oxaliplatin was also discontinued if paresthesia was associated with functional impairment. No dose modifications were made for cold dysesthesias. Neither 5-FU nor Oxaliplatin doses were escalated during cycles subsequent to dose reduction. All patients were given intravenous antiemetics prior chemotherapy, 5-hydroxytryptamine-3- antagonist Ondasetron 8 mg and/ or Dexamethasone 4 mg.

## RESULTS

From January 2008 to May 2010 twenty six consecutive patients with advanced or metastatic colorectal cancer entered the study. Table 1 lists demographic data, baseline disease and pretreatment characteristics for all patients. The median age of patients was 65 years, ranging from 42 to 78 years. There were 19 male and 7 female patients. Twelve patients had a WHO performance status of 0, 9 had a WHO status of 1 and only five had a WHO performance status of 2. Eleven and fifteen patients had rectal and colon cancers, respectively. The most common disease sites were the liver, lung and peritoneum. Fourteen of patients had received adjuvant chemotherapy with 5-FU/ FA. A total of 143 treatment courses were provided. The median follow- up period for the entire group was 11,5 months.

Tumor response

The resulting antitumor effects are presented in Table 2. All 26 patients were evaluable for response. The overall response rate was 34,6% including one CR and eight PR (30,8%) achieved. Nine patients (34,6%) showed SD, and ten patients (38,5%) had PD. The tumor control rate were 61,5% (16 patients). The median time to response was 4,1 months and the median duration of response was 4,2 months. The median PFS was 5,6 months. At the median follow- up period we observed 15 events (57,7%). Median survival time was 12,6 months. Twenty patients (46,1%) were alive at one year. Prognostic factors for improved overall survival were WHO good performance status and absence of liver metastases.

Toxicity

All twenty six patients and all 143 treatment chemotherapy courses were evaluated for toxicity. Hematologic toxicity (grade 3 or 4) is summarized in Table 3. The most common adverse event was leukopenia without fever and febrile neutropenia, which were experienced by four and two patients, respectively. The incidence of this side effect was reduced after 5-FU dose reduction in these patients. Thrombocytopenia was rare and a platelet count below $25x10^9$/L was observed in only one patient (3,8% of all treated). Anemia grade 3- 4 was not observed.

Non- hematologic toxicity is displayed in Table 4. Six and one patients experienced grade 3 or 4 diarrhea (23,1% and 3,8%) respectively . Dose reduction of 5- FU or the administration of the supportive care allowed the incidence of grade 3 and 4 diarrhea to be limited. Dose adaptation or modification of antiemetic prophylactic therapy allowed adequate control of grade 3 or 4 nausea or vomiting, observed in three and two patients (11,5% and 7,7%) respectively. Dysesthesias or transient paresthesias were observed in eleven patients (42,3%) and functional impairment from peripheral sensory neuropathy occurred in six patients (23,1%), but grade 3 or 4 of this side effects were only in two and one patients (7,7% and 3,8%). For all 12 patients with neuropathy, it was estimated that 58,3% occurred during the first course of chemotherapy (seven patients). Reversibility of neurotoxicity was observed in the entire cohort of patients. No treatment- related deaths were observed.

**DISCUSSION**

Historically, 5-FU has been the mainstay of chemotherapy in advanced or metastatic CRC, and different 5-FU regimens have been developed to improve the efficacy and safety ratio in these patients. This had led to a variety of therapy approaches, including bolus and continuous- infusion regimens or hybrid regimens [17]. Oxaliplatin has been demonstrated to be effective when used with combination with different 5-FU regimens for first line treatment in patients with advanced or metastatic CRC. Most phase III data have been obtained using combinations with infusional 5-FU regimens [18, 19]. These trials have consistently demonstrates a doubling in response rate, a significant increase in PFS, and overall survival durations of 16 and 20 months. In the de Gramont et al phase III study, more than 400 patients were randomized to receive a 2- hour infusion of LV followed by a 5- FU bolus and 22- hour infusion for 2 consecutive days every 2 weeks, either alone or together with oxaliplatin as a 2- hour infusion on day 1 (18). Patients allocated to Oxaliplatin plus 5-FU/LV had significantly longer PFS (median, 9.0 versus 6,2 months, $p<0,0003$) and a better response rate (50,7% versus 22,3%, $p<0,0001$) compared with the control arm. Overall survival reached 16,2 months in the Oxaliplatin- containing arm. Results of another phase III trial were reported at the Thirty- seventh annual meeting of the American Society of Clinical Oncology and demonstrated in 252 patients with advanced CRC patients that a weekly regimen of a 2- hour infusion of Oxaliplatin 50 mg/m$^2$ plus a 24- hour infusion of 5-FU 2,000 mg/m2/LV 500 mg/m$^2$ had superior efficacy to the standard Mayo regimen [19].

The aim of our study was to explore the efficacy and safety of addition of Oxaliplatin to the 5-FU/ LV chemotherapy regimen. The result we obtained were consistent with those observed in prior studies: the median PFS of 5,6 months and ORR of 38,5% in the present study are comparable to the median PFS of 6,4 months and ORR of 32,6% in the previous French Intergroup study [20] and the ORR of 27% in the study conducted by the Medical Research Council (21). The toxicity of this regimen was tolerable. There was 15,4 % grade 3-4 leukopenia and 26,9% grade 3-4 diarrhea. No treatment- related deaths were observed.

In conclusion, the results of the present study indicate that the treatment with Oxaliplatin, 5- Fluorouracil and Leucovorin in patients with advanced or metastatic colorectal cancer appears promising with of survival rate of 12,6 months and low hematological and non- hematological toxicity.

**Table 1.** Patient characteristics

| Patient characteristics | Number of patients - 26 |
|---|---|
| Age (years) | 41 - 78 |
| Sex | |
| Males | 19 (73,1%) |
| Females | 7 (26,9%) |
| Primary tumor site | |
| Colon | 11 (42,3%) |
| Rectum | 15 (57,7%) |
| Dominant site of metastasis | |
| Liver | 11 (42,3%) |
| Lung | 4 (15,4%) |
| Lymph nodes | 2 ( 7,7%) |
| Peritoneum | 4 (15,4%) |
| Local relaps | 3 (11,5%) |
| Others | 2 ( 7,7%) |
| Performance status WHO | |
| 0 | 12 (46,1%) |
| 1 | 9 (34,6%) |
| 2 | 5 (19,3%) |
| Previous treatment | |
| Surgery | 10 (38,5%) |
| Surgery+ radiotherapy | 2 (7,7%) |
| Surgery+ adjuvant chemotherapy | 14 (53,8%) |

**Table 2.** Objective responses

| Patients/ Response | CR | PR | NC | PD | ORR % |
|---|---|---|---|---|---|
| 26 | 1 | 8 | 7 | 10 | 34,6 % |

CR - Complete response; PR - Partial response; NC - No change; PD - Progressive disease; ORR - Overall response rates (ORR= CR + PR)

**Table 3.** Hematological toxicity- Grade 3- 4

| Adverse drug reactions | Number of patients |
|---|---|
| Leukopenia | 4 (15,4%) |
| Febrile neutropenia | 2 ( 7,7%) |
| Thrombocytopenia | 1 ( 3,8%) |

**Table 4.** Non-hematologic toxicity- Grade 3- 4

| Adverse drug reactions | Number of patients |
|---|---|
| Diarrhea | 7 (26,9%) |
| Neurotoxicity | 3 (11,5%) |
| Nausea | 2 ( 7,7%) |
| Vomitus | 2 ( 7,7%) |

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