RESEARCH ARTICLE

High and Low Dose Folinic Acid, 5-Fluorouracil Bolus and Continuous Infusion for Poor-Prognosis Patients with Advanced Colorectal Carcinoma

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Abstract

Objective: Evaluation and assessment of response rate, duration and toxicity in patients subjected to 5-FU based chemotherapy. Background: The therapeutic ratio shifts with different 5FU/LV regimens and none yet serve as the internationally accepted Gold Standard . A bimonthly regimen of high dose leucovorin is reported to be less toxic and more effective than monthly low dose regimens. We here compare therapeutic responses and survival benefit of the two regimens in poor prognosis patients with advanced colorectal carcinoma. Patients and Methods: A total of 35 patients with histologically confirmed colorectal carcinoma were subjected to de Gramont and Mayo Clinic regimen. Nineteen patients were treated with high dose folinic acid (200 mg/m^2), glucose 5%, 5-FU (400 mg/m^2) and 22 hr. CIV (600 mg/m^2) for two consecutive days every two weeks. These patients had failed responses to previous chemotherapy and were above sixty years of age with poor general status. Sixteen patients (six below 60 years) with progressive disease were subjected to low dose folinic acid (20 mg/m^2)for five days, 5FU(425 mg/m^2) injection bolus for 5 days, every five weeks. An initial evaluation was made in sixty days and responders were reevaluated at sixty days interval or earlier in case of clinical impairment. Based on positive prognosis, the therapy was continued. Evaluation of treatment response was made on the basis of WHO criteria. Results: The response rate was 44% in thirty four evaluable patients, with 4 complete responses (11.8%) and 11 (32.4%) partial responses. The two schedules were well tolerated, whereas, mild toxicity without WHO Grade ≥2 events was assessed. The response duration was extended (12 months) in a few patients with age above sixty years treated by high dose bimonthly regimen of 5FU/LV. Conclusion: The regimens are safe and effective in advanced colorectal carcinoma patients with poor general status.

Keywords: 5-FU - folinic acid - therapeutic response - colorectal carcinoma

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Introduction

Colorectal carcinoma is the third most common cancer in both men and women worldwide and a leading cause of cancer deaths. The aims of any therapy in patients with advanced colorectal cancer (CRC) are to control symptoms, maintain or improve quality of life and ultimately to prolong survival (Twelves & Cassidy, 2002). 5-FU synthesized in 1957 by Heidelberger, remains to be the most effective drug administered in different schedules, dosages and routes for the treatment of colorectal carcinoma. The clinical oncologists used it earlier as a single treatment agent bearing low response rate and no significant effect on survival (Kemeny, 1987), however, the therapeutic outcome and the toxicity of 5-FU differs markedly in different doses, combinations, schedules of administration and routes of administration. Folinic Acid incorporated in a 5-FU based regimen, enhances the cytotoxicity of 5-FU.Improved tumor response rate and overall survival rate has been demonstrated in many controlled clinical trials when the combination of 5-FU and Folinic Acid was given in different doses and schedules of administration (Petrelli et al., 1989).Mortality rates in patients of colorectal carcinoma have significantly decreased over the last three decades, however hetrogenecity in survival rates is largely governed by patient and tumor characteristics,treatment modalities and host response factors (Chibaudel et al., 2012). Benson et.al reported a 35% decline in mortality rates from colorectal carcinoma from 1990-2007 along with a subjective decline in the incidence rate from 60.5 in 1976 to 46.4 in 2005 (Benson et al., 2011).Today, the standard therapy following resection of high-risk colon cancer is intravenous bolus 5-fluorouracil (5-FU) with Folinic Acid (LV), but there is no consensus on the optimum regimen of these drugs (Patel et al., 2004).

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Credible studies which have been designed to compare the therapeutic ratio of a monthly schedule of low-dose Folinic Acid (LV) and fluorouracil (5-FU) bolus with a bimonthly schedule of high-dose LV and 5-FU bolus plus continuous infusion in patients with advanced colorectal cancer have shown that the bimonthly regimen is more effective and less toxic than the monthly regimen and has increased the therapeutic ratio (De Gramont et al., 1997). A meta-analysis of 22 studies (with 3835 m CRC patients, 629 aged ≥70 years) showed that the response rate in elderly patients to 5FU based chemotherapy is similar to young patients,wheras infusional 5FU had higher response rate as compared to Bolus 5FU (Folprecht et al., 2004). The adjuvant chemotherapeutic modalities for colorectal carcinoma is now well defined, however the therapeutic efficacy for locally advanced rectal carcinoma has room for further investigation (Bachet et al., 2010). A retrospective study by Koca et al. reported the positive effects of modified de Gramont regimen in patients of advanced disease, old age and poor performance status (Koca et al., 2011).The present study reports the therapeutic response and the toxicity ratio of these two regimens (de Gramont and Mayo clinic) in patients of advanced colorectal carcinoma with poor prognosis and poor performance status.

Materials and Methods

The prospective clinical study was designed at University of Karachi and conducted at KIRAN on selected patients admitted during 2006-2011.The study was approved by KIRAN and University of Karachi. Thirty five patients (median age 63 years) who underwent surgery were included in the study. Few patients were treated with oral Fluoropyrimidines earlier and had shown poor prognosis. Histological confirmation of each colorectal tumor was made prior to the treatment according to the grade, degree of lymphatic infiltration, presence of vascular invasion, type of metastases and the growth pattern at the invasive margin. All the patients had measureable disease at CT scan, ultrasonography or clinical examination. Nineteen patients treated with the bimonthly regimen of 5FU/LV - high dose Folinic acid were included in '*Treatment Arm A*' (de Gramont Regimen), whereas, sixteen patients treated with monthly regimen of 5FU/LV –low dose Folinic acid were included in '*Treatment Arm B*' (Mayo Clinic Regimen). An initial evaluation was made in sixty days by clinical examination, colonoscopy, ultrasonography and/or CT scan. Patients who showed response to the treatment were reevaluated after sixty days or earlier in case of any clinical impairment.Response was evaluated according to the criteria of WHO (Therasse et al., 2000).Data was analyzed by SPSS version 19.Unpaired t test was used for statistical analysis. A *p* value less than 0.05 ($p<0.05$) was considered statistically significant.

Treatment Arm A

(Initiate IV: 0.9% sodium chloride, Premedication: Oral phenothiazine or 5-HT3RA and 10–20 mg dexamethasone on indication)

5-Fluorouracil Leucovorin (de Gramont Regimen):

5-Fluorouracil 400 mg/m^2 IV (5 min) and then 600 mg/m^2 IV for 22 hours on days 1 and 2 (Concentration 50 mg/Ml, further diluted with 0.9% sodium chloride or D5W)

Leucovorin: 200 mg/m^2 IV on days 1 and 2 as a 2-hour infusion before 5-Fluorouracil (Powder /Solution reconstituted with sterile water, further diluted with NS or D5W.)

Day 3: Discontinue pump. Chair time 3 hours on day's 1 and 2, and 15 minutes day 3. Repeat cycle every 2 weeks.1, 131

Treatment Arm B

(Initiate IV: 0.9% sodium chloride, Premedication: Oral phenothiazine or 5-HT3RA)

5-Fluorouracil _ Leucovorin (Mayo Clinic Regimen):

5-Fluorouracil: 425 mg/m^2 IV (50 mg/mL,further diluted with 0.9% sodium chloride or D5W.). 1 hour after start of leucovorin, on days 1–5.

Leucovorin: 20 mg/m^2 IV on days 1–5, administered before 5-Fluorouracil. (Powder/Solution reconstituted with sterile water, further diluted with 0.9% sodium

Table 1. Patient Characteristics

Parameters	*Arm A* de Gramont		*Arm B* Mayo Clinic	
	No. of Patients	%	No. of Patients	%
Demographic Characteristics				
Male	12	63.2	13	81.3
Female	7	58.3	3	23.1
Total Patients	19		16	
Age: Years				
Median	64		63	
Range	61–69		42-67	
ECOG / WHO Performance Status				
0	1	5.3	1	6.3
1	4	21.1	2	12.5
2	12	63.2	12	75.0
3	2	10.5	1	6.3
Primary Site				
Colon	12	63.2	11	68.6
Rectum	5	26.3	5	31.3
Multiple	2	10.5	0	0.0
Metastases				
Synchronous	16	84.2	11	68.8
Metachronous	3	15.8	5	31.3
Metastatic Site				
Liver	10	52.6	10	62.5
Lymph nodes	5	26.3	3	18.8
Other*	4	21.1	3	18.8
No. of Sites				
1	15	79.0	11	68.8
>2	4	21.1	5	31.3
CEA				
<10ng/ml	1	5.3	1	6.3
>10ng/ml	11	57.9	10	62.5
Unknown	7	36.8	5	31.3
AlkPO4				
Normal	16	84.2	16	100.0
Increase	3	15.8	0	0.0
Unknown	-			

*Peritoneal/ovar

chloride or D5W). Chair time 1 hour, days 1–5. Nadir at day 14. Repeat cycle every 4-5 weeks for a total six cycles.111 (28 days for 6 cycles).

Results

One of the patient was non evaluable in '*Treatment Arm A*', due to death by generalized sepsis. CR (Complete Response) in *Treatment Arm A* is 15.8% and 6.3% in *Treatment Arm B*. PR (Partial Response) in *Arm A* is 31.6%, and 31.3% in Arm B. SD (Stable Disease) 34.3% and PD (Progressive Disease) 20% is demonstrated in Total number of evaluable patients (n=34). Median value of Response Duration in both the *Arm A* and *Arm B* is 6 months. Mild toxicity ≥2 was seen in the patients of both the treatment arms. Grade 1 head and foot syndrome was seen in 17 (89.5%) patients receiving infusional 5-FU. Grade 1 diarrhea was reported in 12 (75%) patients as the most frequent toxic outcome in the group of patients treated with low dose Folinic acid. Table 1 summarizes the patient's characteristics. Table 2 gives the summary of responses in each treatment arm. Table 3 shows the frequency of adverse effects in each treatment arm.

The total number of reports for Grade 1 toxic events throughout the chemotherapy is 137 in patients of *Treatment Arm A* (n=19) and 80 in *Treatment Arm B* (n=16).The Sig. (2-tailed) value is 0.00 <0.05 , showing that the difference in the frequency of Grade 1 toxic events in *Arm A* and *Arm B* is highly significant. The frequency of toxic events reported is higher in the group of patients treated with de Gramont regimen.

The total number of reports for Grade 2 toxic events throughout the chemotherapy is 35 in patients of *Treatment Arm A* (n=19) and 26 in *Treatment Arm B* (n=16). The Sig. (2-tailed) value is 0.306 >0.05, showing that the difference in the frequency of Grade 2 toxic events in *Arm A* and *Arm B* is not significant. The frequency of toxic events reported is although higher in the group of patients treated with de Gramont regimen.

Table 2. Summary of Response in de Gramont and Mayo Clinic

Age/sex	Disease site	Response	Duration	Evaluation	Survival
de Gramont (n=9)					
62/M	Liver M	CR	9	CT Scan	14
65/M	Peritoneal M	PR	4	Clinical	10
61/M	Lymph Node M	PR	6	Clinical	12
63/F	Lymph Node M	PR	6	Clinical	10
65/F	Ovarian M	PR	12	CT Scan	21+
64/M	Liver M	CR	12	CT Scan	12+
67/M	Liver M	CR	6	CT Scan	9
69/F	Peritoneal M	PR	4	Clinical	4a
64/M	Liver M	PR	6	CT Scan	8
Mayo Clinic (n=6)					
65/M	Peritoneal M	PR	9	Clinical	12
54/F	Ovarian M	PR	6	CT Scan	10
66/M	Liver M	PR	5	CT Scan	8
63/M	Liver M	CR	6	CT Scan	12+
64/M	Lymph M	PR	9	Clinical	10
50/F	Lymph M	PR	6	Clinical	21+

Table 3. Frequency of Adverse Effects

Toxicity	*Arm A* (DeGramomt) n = 19 Grade %				*Arm B* (Mayo Clinic) n = 16 Grade %			
	1	%	2	%	1	%	2	%
Anemia	12	63.2	6	31.6	10	62.5	5	31.3
Thormbocytopenia	9	47.4	7	36.8	8	50.0	2	12.5
Neutopenia	17	89.5	2	10.5	7	43.6	4	25.0
Febrile Neutropenia	3	15.8	0	0.0	4	25.0	1	6.3
Nausea	15	79.0	3	15.8	7	43.8	2	12.5
Vomiting	10	52.6	1	5.3	3	18.8	1	6.3
Diarrhea	11	57.9	2	10.5	12	75.0	4	25.0
Mucositus	5	26.3	1	5.3	10	62.5	2	12.5
Cutaneaus	7	36.8	3	15.8	3	18.8	1	6.3
Alopacia	8	42.1	4	21.1	3	18.8	1	6.3
Neurological	9	47.4	3	15.8	1	6.3	1	6.3
Fatigue	14	73.7	2	10.5	10	62.5	2	12.5
Hand foot	17	89.5	1	5.3	2	12.5	-	

Discussion

Considerable therapeutic response has been measured in both the treatment arms (CR 11.4% and PR 31.4%). The therapeutic outcome is more pronounced in the groupof patients treated with de Gramont's regimen, (CR 15.8% *versus* 6.3%). Partial response is also demonstrated higher in patients treated with de Gramont regimen (PR 31.8% *versus* 31.25%). Progressive Disease has been seen in 4 patients of *Treatment Arm A* and 3 patients of *Treatment Arm B*. The difference in the therapeutic response and the toxicity ratio is seen in the patients of each Treatment Arm. The summary of the overall response in Table 2 shows the difference in effect of the two schedules of administration with high and low doses of drugs. Although it has been reported earlier that the response of 5-FU based chemotherapy is more directly related to the metabolism of the drug and the attained plasma levels (irrespective of the dose) of the patients, and the plasma levels of 5-FU at different time intervals correlate with both the toxicity and efficacy (Gamelin et al., 1996). In contrast to this, a large number of trials, researches and studies in the last three decades have focused on establishing an optimal 5-FU based regimen. It is established in randomized trials and meta-analyses that a higher response, less toxicity and improved Disease Progression free survival with a small difference in overall survival rates is seen in infusional 5-FU regimen as compared to bolus 5-FU regimens, showing that the selection of the route of administration and the mode of administration correlates significantly with the therapeutic and the toxic outcome of chemotherapy (Meta-analysis group in cancer, 1998). It is reported after analysis of 34 randomized trials of chemotherapy for advanced colorectal carcinoma that improvements in Progression free survival(PFS) is strongly correlated with improvements in overall survival(OS) (Petrelli and Barni,2012).

Earlier studies based on these two regimens reported that the bolus dosing have resulted in more hematological toxicity (grade 3 or 4 neutropenia in

7.3% Mayo regimenversus1.9% LV5FU2) as well as nonhaematological toxicities such as diarrhea (7.3% *versus* 1.9%) and mucositis (12.7% *versus* 1.9%) (de Gramont et al., 1997).More cases of Hand and Foot syndrome are reported in de Gramont regimen. The research claimed that the de Gramont regimen, administering a bolus dose of 5FU, followed by a 23 h 5FU infusion delivered on days 1 and 2 every 14 days, and subsequently simplified with the adoption of a 46 h infusion via a central venous line, is widely considered an optimal 5FU regimen (Braun and Seymour, 2011). The toxic profile of the poor prognosis patients of old age diagnosed with advanced carcinoma in our study is different with a deviation in the incidence rates and frequency. The toxicity in both the treatment arms is within the range of Grade 1 and Grade 2.The incidence rate of some adverse effects e.g. Hand and foot syndrome, Nausea and Neutropenia is higher in *Treatment Arm A*. Hand and foot syndrome is a relatively common adverse effect of infusional 5-FU and the rate of incidence is higher in older patients (Scheithauer and Blum, 2004). Severe Neutropenia has been reported before with 5-FU treatment in patients with deficiency of catabolic enzymes (Van Kuilenburg et al., 2002). The most frequently reported toxic event in patients of *Treatment Arm B* is diarrhea and mucositis(Corfu-a study group, 1995). Mild anemia of Grade 1 is frequently seen in patients of both the Treatment Arms(62.83%). It has been reported earlier that bolus 5-FU with leucovorin can induce frequent grade 1 or 2 anemia (27%-53%).There was no reports of Grade 3 or 4 anemia during our study, even though the patients were of advanced disease state, such cases have however been reported in other trials on advanced colorectal carcinoma patients (Hill et al., 1995).

The patients included in this study comprise of a mean age of 61 years. The relative incidence of toxic effects of 5-FU is directly related to the age of the patients which can serve as independent predictor of severe toxicity. It is hence difficult to adjust the therapeutic dose in older patients, keeping in view the organ function status, comorbidities, overall physical status and goals of treatment (Stein et.al 1995). Zalcberg et al. reported that "Grade 3/4 leucopenia and mucositis were significantly correlated with age (especially >70 years) in patients receiving 5-FU + LV" (Zalcberg et al., 1998). A recent retrospective study by Kim et.al reported the safe and effective therapeutic benefit of adjuvant chemotherapy comprising of 5FU (2000 mg/m^2, 46 hrs CIV), Leucovorin(100mg/m^2) with the addition of Irinotecan (150 mg/m^2) in frail and elderly patients of advanced gastric carcinoma of poor performance status, with mild non hematological toxicities and few reports of grade ¾ gastrointestinal toxicity (nausea 12.5%, vomiting 8.3%, diarrhea 4.2% and mucositis 4.2%) (Kim et al., 2012).The difference in the toxicity is attributed to the pharmacokinetic variability implicated by host factors such as age and gender affecting the clearance of 5-FU (Milano et al., 1992). Some of the studies have implied that the toxicity, benefit and survival rate of elderly colorectal patients subjected to chemotherapy is not different from young patients (Sargent et al., 2001). However comorbidities, advanced age and poor general status should be taken in account as these factors may alter the therapeutic response and the frequency of toxic events; whereas, higher mortality rate has also been reported in elderly women diagnosed with colorectal carcinoma as the proportion of cancer related death tends to increase with higher age (Bray et al., 2002).Kohne et.al laid emphasis in the role of the physician in the assessment of 'fitness' of an elderly patient, as considerably fit elderly patient are easily identifiable and can tolerate effectively the same chemotherapeutic protocol as a younger patient, however dose adjustments are essentially required for the seemingly frail and weak elderly patient with a subset of physical and mental deficiency (Kohne et al., 2008).

In conclusion, both the treatment regimens are endured well in poor prognosis patients of advanced colorectal carcinoma with low grade toxicity reports. The overall summary of response depicts considerable efficacy and tolerability even in the elderly patients subjected to both the schedules of high and low dose Folinic acid in infusional and bolus 5-FU regimens.

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