Research Article

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Effects on hepatic and renal biomarkers in patients of colorectal carcinoma treated with two different schedules of 5FU/LV

Nusrat Bano, Rahila Najam and Ahmed Mateen

Abstract
5 Fluorouracil with leucovorin is the mainstay in the treatment of colorectal carcinoma (CRC), the third leading cause of cancer related deaths. Aims: This study is designed to assess the effects of 5FU and leucovorin chemotherapy (in continuous and intermittent schedules) on the serum biomarkers indicative of hepatic and renal functions.
Methods: Biochemical profiles of patients comprising of age group 61.0 + 4.58, with histologically confirmed colorectal carcinoma, treated either with de Gramont's regimen or Mayo clinic regimen were assessed after each alternate cycle of treatment. The changes in the levels of hepatic enzymes (ALT, AST, bilirubin, $AlkPo_4$, TGS) and renal biomarkers (serum creatinine, BUN) were comparatively assessed with the pretreatment values. Results: Changes in the serum creatinine levels from pretreatment value was significant after fourth cycle of treatment (p=0.035). Changes in AST levels were significant after the second cycle of treatment (p= 0.049) and very significant after fourth cycle of treatment (p=0.008). Conclusion: A gradual rise in mean values is assessed for serum creatinine and BUN levels indicative of progressive decline in renal functional status. Hepatic enzyme elevation is pertinent to cumulative dose intensity.
Keywords: 5Fluorouracil, Colorectal Carcinoma, Creatinine, BUN, Hepatic enzymes

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and women worldwide (1) and a leading cause of cancer related deaths (2). 5FU synthesized in 1957 by Heidelberger (3) is the mainstay in all current standard regimens for CRC (4). Chemotherapy induced hepatic toxicity in 5FU based regimens can be an acute or delayed outcome (5, 6); whereas steatosis is a hallmark of 5FU induced hepatic toxicity (7). Chemotherapy induced nephrotoxicity (8) is also an area of concern for oncologists. The antimetabolite 5FU is often linked with kidney damage (9). Therapeutic outcomes and toxicity of 5FU differs markedly in different doses, combinations, schedules of administration and routes of administration. Leucovorin (LV) incorporated in 5FU based regimen enhances the cytotoxicity of 5FU. In this study we opt to report abnormalities in hepatic enzymes and renal biomarkers biochemically assessed in the serum after alternate cycles of treatment in CRC patients subjected to 5FU/LV based chemotherapy.

Methods

The study was designed in the Department of Pharmacology, University of Karachia and conducted in a leading cancer hospital in Pakistan. Following institutional authorisation, informed consent was obtained from patients being admitted during 2008-2011. The inclusion criterion was maintained on the following grounds:

1. Histologically confirmed advanced colorectal carcinoma
2. Adequate blood count before therapy
3. Age 20-80 years
4. ECOG score of ≤ 3
5. Serum bilirubin $\leq$ 5× normal
6. Serum creatinine $\leq$ 135µmol/liter
7. Serum transaminases $\leq$ ×2.5 normal

Twenty three patients (median age 59 years) who underwent surgery were included in the study. All the patients had measureable disease at CT scan, ultrasonography or clinical examination. Patient's characteristics are shown in Table 1. Seventeen patients were treated with the adjuvant bimonthly regimen of 5FU/LV - high dose Folinic acid (de Gramont Regimen); whereas, six patients were treated with adjuvant monthly regimen of 5FU/LV –low dose Folinic acid(Mayo Clinic Regimen) as follows.

5Fluorouracil/ Leucovorin (*de Gramont's regimen*)
5Fluorouracil: 400mg/m^2 IV followed by 600mg/m^2 CIV for 22 hours on day 1-2.
Leucovorin: 600 mg/m^2 IV as 2 hours infusion before 5FU on day 1-2.
Cycle repeated after 2 weeks.

5Fluorouracil/ Leucovorin (*Mayo clinic regimen*)
5Fluorouracil: 425mg/m^2 IV on day 1-5.
Leucovorin: 20 mg/m^2 IV before 5FU on day 1-5.
Cycle repeated after 4-5 weeks.

Premedication with oral phenothiazines, $5HT_3RA$ and 10-20 mg of dexamethasone was given.

The blood samples were collected before the initiation of the therapy and after each alternate cycle of treatment. The blood was drawn when the patient was rested and comfortable from the antecubital vein under minimal tourniquet pressure. The blood drawn was sampled and collected into vacutainers (BD). The biochemical profile of the pretreatment and subsequent

treatment was comparatively assessed. SGOT, SGPT, bilirubin and alkaline phosphatase levels were measured after each cycle of treatment or on the clinical presentation of any hepatic adverse effect notified by the physician or oncologist and the levels were compared to the pretreatment values. The serum creatinine levels and BUN was measured before the start of chemotherapy and after each alternate cycle of treatment up to six times in each patient.

Table 1 Patient characteristics

Parameters	Arm A de Gramont		Arm B Mayo Clinic	
	No. of Patients	%	No. of Patients	%
Demographic Characteristics				
Male	12	70.58	4	66.6
Female	5	29.41	2	33.3
Total Patients	17		6	
Age: Years				
Median	59			
Range	56-65			
ECOG Performance Status (21)				
0	1	5.88	1	16.6
1	3	17.64	1	16.6
2	13	76.47	4	66.6
3	0	0	0	0
Primary Site				
Colon	11	64.7	3	50
Rectum	5	29.4	2	32.3
Multiple	1	5.88	1	16.6
Metastases				
Synchronous	11	64.7	4	66.6
Metachronous	6	35.2	2	32.3
Metastatic Site				
Liver	8	47.0	1	16.6
Lymph nodes	4	23.5	2	32.3
Other*	5	29.4	3	50
No. of Sites				
1	7	41.1	2	32.3
≥ 2	10	58.8	4	66.6
CEA				
< 10ng/ml	2	11.7	1	16.6
≥10ng/ml	8	47.0	1	16.6
Unknown	7	41.1	4	66.6
* = Peritoneal/ovary				

Results

Table 2shows that the SGOT levels are raised after each cycle of treatment and the difference between the SGOT levels of the patients before treatment and after subsequent cycle of

Table 2 Comparative changes in hepatic biomarkers in patients treated with 5FU/LV regimen

Paired Samples Test						
			Paired Differences		t	p-value
			Mean	Std. Deviation		
Hepatic	TGS	Control - Cycle 2	-1.200	1.643	-1.633	0.178
		Control - Cycle 4	-3.200	3.033	-2.359	0.078
		Control - Cycle 6	-3.400	2.966	-2.563	0.062
		Control - Cycle 8	-10.000	10.198	-2.193	0.093
		Control - Cycle 10	-3.600	8.414	-0.957	0.393
		Control - Cycle 12	-8.800	12.872	-1.529	0.201
	SGOT / AST	Control - Cycle 2	-12.667	5.033	-4.359	0.049
		Control - Cycle 4	-22.000	3.464	-11.000	0.008
		Control - Cycle 6	-22.667	3.055	-12.851	0.006
		Control - Cycle 8	-25.333	3.055	-14.363	0.005
		Control - Cycle 10	-27.000	7.810	-5.988	0.027
		Control - Cycle 12	-28.667	7.024	-7.069	0.019
	SGPT / ALT	Control - Cycle 2	-2.667	3.055	-1.512	0.270
		Control - Cycle 4	-3.667	2.082	-3.051	0.093
		Control - Cycle 6	-9.333	8.505	-1.901	0.198
		Control - Cycle 8	-12.667	8.083	-2.714	0.113
		Control - Cycle 10	-17.667	5.859	-5.222	0.035
		Control - Cycle 12	-22.667	10.214	-3.844	0.062
	Bilirubin	Control - Cycle 2	0.033	0.058	1.000	0.423
		Control - Cycle 4	0.000	0.100	0.000	1.000
		Control - Cycle 6	-0.267	0.058	-8.000	0.015
		Control - Cycle 8	-0.267	0.058	-8.000	0.015
		Control - Cycle 10	-0.267	0.058	-8.000	0.015
		Control - Cycle 12	-0.367	0.115	-5.500	0.032
	$ALKPO_4$	Control - Cycle 2	-6.667	5.774	-2.000	0.184

		Control - Cycle 4	-10.000	10.000	-1.732	0.225
		Control - Cycle 6	-26.667	11.547	-4.000	0.057
		Control - Cycle 8	-43.333	40.415	-1.857	0.204
		Control - Cycle 10	-60.000	36.056	-2.882	0.102
		Control - Cycle 12	-63.333	40.415	-2.714	0.113

treatment is significant in the patients treated with 5FU/LV (p value < 0.05). The difference in the SGPT levels of the patients from the pretreatment value is not highly significant (p value >0.05). The difference in the bilirubin levels of the patients after the sixth cycle of chemotherapy with 5FU/LV regimens is highly significant from the pretreatment level (p value < 0.05). The difference in the alkaline phosphatase levels of the patients after chemotherapy with the pretreatment value in the same patients is not significant (p value >0.05).The difference in the triglyceride levels is not significant before and after chemotherapy in the patients treated with 5FU/LV.

Table 3 Comparative changes in renal biomarkers in patients treated with 5FU/LV regimen

Paired Samples Test						
			Paired Differences		t	p-value
			Mean	Std. Deviation		
Renal	Creatinine	Control - Cycle 2	-0.120	0.130	-2.058	0.109
		Control - Cycle 4	-0.160	0.114	-3.138	0.035
		Control - Cycle 6	-0.242	0.204	-2.646	0.057
		Control - Cycle 8	-0.264	0.225	-2.627	0.058
		Control - Cycle 10	-0.546	0.422	-2.893	0.044
		Control - Cycle 12	-0.566	0.463	-2.734	0.052
	BUN	Control - Cycle 2	-1.800	1.924	-2.092	0.105
		Control - Cycle 4	-1.800	1.924	-2.092	0.105
		Control - Cycle 6	-2.000	2.449	-1.826	0.142
		Control - Cycle 8	-3.000	2.550	-2.631	0.058
		Control - Cycle 10	-4.400	4.037	-2.437	0.071
		Control - Cycle 12	-6.400	8.204	-1.744	0.156

Table 3 shows that the creatinine levels are raised in patients following each subsequent cycle of treatment with 5FU/LV regimens. The difference in the serum creatinine levels after the fourth and the tenth cycle of treatment with the pretreatment levels was significant (p<0.05). The difference in the BUN levels measures before and after chemotherapy with 5FU/LV was not significant following alternate cycles of treatment.

Discussion:

The hepatocellular enzyme findings are indicative of deteriorating liver function. The levels of SGOT and SGPT both differ from the control values and point toward 5FU induced hepatic toxicity. Increase in SGOT and SGPT up to grade 2 (CTC of NIC) is reported by Hotta and colleagues (10) in a study based on clinicopathological assessment of 36 patients treated with 5FU/LV. They did not report grade 3 or grade 4 elevations in SGOT and SGPT ratio. In our data there is considerable difference in SGOT levels (mean value) after the second cycle of treatment as compared to the pretreatment levels (mean value). Similarly SGPT levels are perturbed following treatment and the difference in the SGPT levels from the pretreatment control value is statistically significant after the tenth cycle of treatment. The pooled data of all the patients cannot be used for prognostic or diagnostic assessment; however, it shows a pattern of drug induced alterations in hepatic functions. An early effect on SGOT level show mild progressive damages correlated with a prominent rise in SGPT levels. SGOT is found in cytosol whereas SGPT is in mitochondria. Any mild to moderate damage to the hepatic cells will result in a rise in SGOT levels even though SGPT levels may remain normalised. Moderate to Severe hepatic damage will give a rise in both SGOT and SGPT elevation. SGOT is located in red blood cells, kidneys, brain, skeletal muscle and cardiac tissues; hence a prompt rise in SGOT level is indicative of associated damages. SGPT is present in skeletal muscles and cardiac tissues and the serum levels are affected with myocardial and skeletal muscle damages. Cytotoxic chemotherapy is frequently associated with fatty liver disease, chemical hepatitis and reactivation of hepatitis B (11). The elevation in triglyceride levels is indicative of drug induced steatosis (fat globule deposition in hepatocytes) leading to postoperative hepatic insufficiency(8). A significant change in bilirubin from the pretreatment level is observed after the 6th cycle of treatment. Biliary changes are detectable and persistent since the drug is excreted in the bile. Sclerosing cholangitis with elevation in alkaline phosphatase and bilirubin levels secondary to 5FU plus mitomycin therapy is reported by Fukuzumi et al (12). After intravenous administration, 5FU is converted into its active form '5-fluoro-deoxyuridine-monophosphate' by anabolic reactions in the tissues. The drug undergoes catabolism primarily in the liver by reduction of the pyrimidine ring by enzymatic action of dihydrouracil dehydrogenase (13). The compound is then cleaved to urea, ammonia, carbondioxide and α-fluoro-β-alanine. The catabolic process in the liver amounts for 5FU induced hepatic toxicity. Hepatic and renal toxicity associated with 5FU is reported earlier with IV administration of 5FU (14). The risk of 5FU

induced hepatic damages is increased in older patients (15). Older patients included in our study with increased post-treatment transaminase levels were more frequently presented with pruritus and hand and foot syndrome.This complexity of the situation is that altered hepatic function increases the risk of 5FU concentration (since it is catabolized in the liver cells), which in turn adds to the hepatic damage.

Creatinine clearance and blood urea nitrogen (BUN) are conventional biomarkers of renal function for convenient and cost-effective assessment (16). A detectable change in the creatinine levels of the patients ensue after the fourth cycle of treatment. Besides suggesting a decline in the renal function, it also indicates defect in hepatic functional status and progressive cachexia (muscle wasting), both of which are readily assessed in the patients during treatment. BUN levels are also affected by dexamethasone pretreatment, dehydration and azotemia besides renal function. Nephrotoxicity with 5FU chemotherapy is usually reported when it is combined with cisplatin with worsened creatinine levels (17, 18). Tubular damage induced by 5FU plus high dose leucovorin chemotherapy (similar to de Gramont's regimen in our study) is reported by Kintzel, who also reported 50% decline in creatinine clearance in three patients (19). Chemotherapy induced renal damages are detected with abnormal creatinine and BUN levels, but in most cases the renal tubes remain intact and functional as the normal renal blood flow and GFR is reversibly attained (20). Adequate hydration and simultaneous treatment with mesna, which neutralises the toxic metabolites can effectively reduce chemotherapy induced renal damage (8).

Conclusion

SGOT and bilirubin levels are raised after each cycle of treatment and the difference between the SGOT levels of the patients treated with 5FU/LV, before treatment and after subsequent cycle of treatment are highly significant indicative of mild to moderate progressive hepatic toxicity. Risk of clinical and subclinical renal damage is observed by a subsequent rise in serum creatinine and BUN levels. Renal toxicity marked by creatinine elevation is prominent after the fourth cycle of treatment.

Competing Interests
None declared
Author Details
NUSRAT BANO, PhD, University of Karachi, Assistant Professor of Pharmacology, Ziauddin College of Pharmacy, Ziauddin University, Karachi, Pakistan. RAHELA NAJAM, PhD, Professor of Pharmacology, University of Karachi, Karachi, Pakistan. AHMED MATEEN, Doctor of Radiotherapy, MBBS, MCPS, Consultant Clinical Oncologist, Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, Pakistan.
CORRESSPONDENCE: Dr Nusrat Bano, Assistant Professor of Pharmacology,Ziauddin College of Pharmacy, Ziauddin University, 4/B,Block 6,Shara-e-Ghalib, Clifton, Karachi-75600, Pakistan.
Email: nusratbano@hotmail.com

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