Role of the nutritional support and omega3 in minimizing the side effects of chemotherapy in colorectal cancer patients

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Abstract: Background: Cancer is usually associated with cancer cachexia syndrome, which is one of the factors contributing to deterioration of the results of surgery, chemotherapy or radiotherapy. Fish oil supplementation has been proposed to have anti-inflammatory, anticachectic and antitumoral effects. Aim: The aim of this study was to evaluate the effect of nutritional support and omega3 for minimizing and treatment of chemotherapy toxicity, the performance status and continuity of chemotherapy without dose delay or reduction in patients with colorectal cancer. Patients and methods: Patients were randomly divided into two groups, each group included (30) patients: Group A: patients with CRC received chemotherapy with or without radiotherapy and with nutritional support without omega3. Group B: patients with CRC received chemotherapy with or without radiotherapy and with nutritional support with omega3. The changes of nutritional status, toxicity of chemotherapy and continuity of chemotherapy during six cycles of chemotherapy was investigated. Results: Before the third cycle, NRS was higher (worse) in group A than group B with significance between two groups. BMI was maintained more in group B than group A with significance. Also, the phase angle was higher in group B than group A with significance ($p = 0.004$). level of albumin was maintained in group B more than group B with significance. As regard CRP level, it was higher in group A than group B with significance. Before the 6th cycle (after six months of follow up), NRS was higher (worse) in group A than group B with significance between two groups. Performance status was better in group B than group A with significance. As regard BIA items (BMI, FFM, FFM index and phase angle) were higher in group B than group A with significance. level of albumin was maintained in group B more than group A. As regard CRP level was higher in group A than group B with significance. Before both third and sixth cycles common toxicity of chemotherapy (anemia, febrile neutropenia, diarrhea, nausea, vomiting, fatigue and anorexia) observed more in group A than in group B with significance of all except anemia and febrile neutropenia. Number of patients who need hospitalization was more in group A than group B with significance before the third cycle (4(13.33%) versus 0(0.0%) respectively) and before the 6th cycle (11(6.7%) versus 1(3.33%) respectively). Continuity of chemotherapy was better in group B than group A with less treatment gap in group B than group A with significance before sixth cycle. Time of free of toxicity was longer in group B than group A with significance before third cycle ($p = 0.026$) and before sixth cycle ($p < 0.001$). Conclusion: administration of omega 3 (eicosapentaenoic acid and docosahexaenoic acid) during chemotherapy in colorectal cancer effective in improving the nutritional status (including lean body mass and phase angle) and increase the tolerability of chemotherapy with decrease the need of treatment gap and hospitalization between cycles.

1. Introduction:

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females. The risk of developing CRC is influenced by both environmental and genetic factors (**Marley, A. R., & Nan, H.,2016**).

Prevention and treatment of side effects of anticancer agents is now an important part of cancer treatment (**Beaver, C. C., & Magnan, M. A., 2016**).

In patients with gastrointestinal malignancies progressive malnutrition can be regularly observed. Malnutrition significantly affects the patients' quality of life, morbidity and survival (**Penet, M. F., & Bhujwalla, Z. M., 2015**).

Concurrent individualized dietary counseling and nutritional support are effective in improving nutritional status thereby lessening chemotherapy toxicity. Dietary counseling, including the use of oral nutritional supplements (ONS), should be the first-step towards achieving satisfactory energy intake. Early intervention with nutritional supplementation has been shown to decrease malnutrition, controlling some adverse effects of antitumor therapies and improving quality of life and may improve outcome in some patients (**Gangadharan, A. et al, 2017**).

Dietary omega 3 polyunsaturated fatty acids (PUFA) have been gaining great interest in recent years as possible anti-inflammatory and anticancer agents, especially in areas such as the large bowel. Play a role in several stages of CRC management exhibiting antineoplastic activity against human CRC cells, improving the efficacy of radiation and chemotherapy, ameliorating cancer-associated secondary complications and preventing CRC recurrence (**Miccadei, S. et al, 2016**).

2. Patients and methods:

This study included 60 patients with colorectal cancer received chemotherapy and received nutritional support with or without omega3.

Inclusion criteria:
- Patients with histological confirmed diagnosis of colorectal cancer (CRC) in clinical stage II-IV according to TNM stage II, III and IV treated with chemotherapy with or without radiotherapy.
- Age more than 18 years old.
- Performance status 0 to 2 according to ECOG (Eastern Cooperative Oncology Group) score.
- Absence of contraindications to oral nutrition.

Exclusion criteria:
- Performance status more than 2.
- Inadequate cardiac, renal and hepatic functions.
- diagnosis of infectious disease.
- pregnancy or lactation.
- inability to take capsules orally.
- Disqualification from oncologic treatment.

Study design:

This is a prospective study that evaluates the role of entral and parental nutritional support and omega 3 in minimizing and treatment of chemotherapy and radiotherapy side effects in colorectal cancer patients.

Staging of the patients:

All patients are subjected to accurate diagnosis and proper staging through:
1- Complete history.
2- General and Local clinical examination.
3-Investigations:

a) Pathological examination confirm colorectal cancer (endoscopic or surgical).

b) Laboratory: complete blood picture, Renal function tests, Liver function tests, Serum alkaline phosphatase, Tumor markers, electrolytes (Na, K, Mg, Ph and Calcium) and C-reactive protein (CRP).

c) Imaging Studies: CT abdomen & pelvis with contrast or MRI abdomen & pelvis with contrast, chest x-rays or CT chest, triphasic CT, bone scan & PET-CT in some cases.

Patients grouping:

As regard study groups, Patients were randomly divided into two groups using closed envelop, each group included (30) patients:
- **Group A**: patients with CRC received chemotherapy with or without radiotherapy and with nutritional support without omega3.
- **Group B**: patients with CRC received chemotherapy with or without radiotherapy and with nutritional support with omega3.

Assessment (Data collection):

Basically and during each visit assessment of:

1) **Assessment of the nutritional status:** was done by use of

a) Nutritional Risk Score 2002(NRS 2002).

b) Bioelectrical impedance analysis (BIA).

2) **Performance status**: based on the Eastern Cooperative Oncology Group (ECOG) scale.

3) **Toxicity of anticancer treatment**: anemia, febrile neutropenia, diarrhea, nausea, vomiting, fatigue and anorexia by Common Terminology Criteria for Adverse Events (CTCAE) version 5.

4) **Need to hospitalization** due to treatment toxicity.

5) **Treatment gap** between cycles was recorded.

6) **Also** at each visit all participants were measured in serum concentration of albumin, complete blood count (CBC) [WBC (white blood cells), PLT (platelets), NEUT (neutrophiles), Hb (hemoglobin)] and C-reactive protein (CRP).

7) **Imaging studies and tumor markers** were assessed every three cycles of chemotherapy and after finish concurrent chemoradiotherapy.

Nutritional intervention:

Nutritional intervention was done at Nutritional clinic in Tanta University Hospital. According to ESPEN guidelines (**Arends, J et al, 2017**) we calculated the nutritional requirements for all patients, total daily energy intake ranged 30-35 kcal,70% obtained from carbohydrates and 30% from fats and plenty protein intake (1.5 gm. /kg / day). By nutritional assessment of every patient we sewed own nutritional needs.

Also, for all patients diet counseling was done in the form of printed instructions by ESPEN guidelines

(**Arends, J et al, 2017**) and all of them follow the following: eating frequent times daily (6-8 times), increase consumption of food contain antioxidants, drinking 2-3 liter fluids daily, fruits and vegetables daily intake, mixing food if difficult to swallow it, avoid processed foods and making physical activity in the form of daily walk or home training three sessions/ week for 10-60 minutes. Any patient suffered from vomiting, fungal mouth infection or mucositis we gave proper treatment to increase oral intake.

For patients who could not met daily nutritional requirements oral nutritional supplements was given in form of high-energy (400kcal/ 200ml), high-protein (20 gm. / 200ml), contained carbohydrates (45 gm. / 200 ml), lipids (15.6 gm. / 200 ml), minerals, trace elements and vitamins oral liquid nutritional supplements.

Some patients were received intravenous infusion three chamber bag system of amino acid solution with electrolytes (315 ml (37.1 gm. of proteins) /1000ml), glucose solution (544 ml (71 gm.) / 1000 ml), lipid emulsion (141 ml (28 gm.) / 1000 ml) and 700 kcal / 1000ml) only during cycle due to loss of appetite during this time.

For group-B consumption of the supplements containing omega 3 started in the same day of the first cycle of chemotherapy and continued during the whole treatment period with nutritional counseling. All the patients of the group B received oral nutritional supplements contain 2gm omega 3 fatty acids comprising of Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA). For the assessment of patients' compliance, we provided patients with a fixed number of supplement tablets or bottles.

2. Results:

Patients characteristics:

As regard the patients characteristics in our study, the mean age was 49.60±14.00 years and 49.47±13.53 years in group A and B respectively, ranged from (30-68) and (22-67) years in group A and B respectively, with non-significant p value. Fifty three percent of our patients were female in group A, while in group B was 33.3%. Most of our patients in both groups were non smokers. Most of our patients were stage II and III. All the patients in both groups underwent nutritional counseling in the form of printed instructions. All patients received chemotherapy. All the patients' characteristics are shown in table (1).

1. Nutritional assessments:

There were no significance difference between both groups as regard NRS, BIA, and laboratory investigations in the visit before start chemotherapy table (2).

As regard the comparison between both groups before the 3rd cycle table (3), patients with NRS score less than 3 were higher in group B than that in group A, with 63%vs 93% in group A and B respectively with significant p value, While the patients with NRS score more than or equal 3 were higher in group A than that in B with 36.3% vs 6.7% respectively with significant p value. The mean BMI were 22.19 ±3.8 and 25.56±4.09 in group A and B respectively with significant (sig.) p value.

Also the mean phase angle was higher in group B than A before 3rd cycle with sig. p value. CRP and albumin were sig. higher in group B with omega than that in group A without omega 3.

The patients with NRS score less than 3 were higher in group B than that in group, with 53.3 % vs 96.7% in group A and B respectively with sig p value.

Table (1): Shows the patients' characteristics in both groups

Demographic data	Group A	Group B	Tests t/X²	P-value
Age	49.60± 14.00	49.47± 13.53	0.027	0.979
Sex				
Female	16 (53.3%)	10(33.3%)	2.443	0.118
Male	14 (46.7%)	20(66.7%)		
Smoking				
No	24 (80.0%)	22(73.3%)	0.373	0.542
Yes	6(20.0%)	8(26.7%)		
tumor stage				
II	12 (40.0%)	10(33.3%)	1.364	0.506
III	12	10(33.3%)		

Demographic data	Group A (40.0%)	Group B	Tests t/X^2	P-value
IV	6(20.0%)	10(33.3%)		
Other diseases				
DM	6(20.0%)	4(13.3%)	0.480	0.488
HTN	4(13.3%)	6(20.0%)	0.480	0.488
surgical resection				
Rt hemicolectomy	7 (23.33%)	9(30%)	0.509	0.973
Lt hemicolectomy	9(30%)	8(26.7%)		
Sigmidectomy	3(10%)	2(6.67%)		
Anterior lower resection	1(3.33%)	1(3.33%)		
Colostomy	10 (33.3%)	10(33.3%)		
Chemotherapy regimen				
FOLFOX	18 (60.0%)	16(53.3%)	2.340	0.310
FOLFIRI	10 (33.3%)	8(26.7%)		
Cabe Ox	2(6.7%)	6(20%)		
concomitant chemoradiotherapy	6(20.0%)	6(20.0%)	0.000	1.000
monoclonal antibodies	2(6.7%)	2(6.7%)	0.000	1.000

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

The BMI, phase angle and FFM were higher in patients in group B who received omega3 than those in group A who did not received omega3 with sig p value. As regard the comparison between the two groups in lab investigations before the 6th cycle, the mean albumin and CRP value were higher in group B than that of group A, with sig p value table (4).

2. Toxicity assessments:

As regard the comparison between the both groups, treatment toxicity was less in patients who received omega3 (group B) than those in group A who did not received omega3. Diarrhea, nausea, anorexia and wt loss were higher in group A than group B with sig. p value table (5).

Table (2): Shows comparison between both groups in NRS, BIA, and laboratory investigations before start in chemotherapy

Assessment before chemotherapy	Group A (without omega3)		Group B (with omega3)		Tests t / X^2	P-value
NRS	3.67	± 0.82	4.15	± 1.14	1.310	0.202
<3	26(86.7%)		28(93.3%)		0.741	0.389
≥3	4(13.3%)		2(6.7%)			
ECOG	1.13	± 0.83	1.31	± 0.85	0.545	0.590
BIA						
wt. (kg)	63.84	± 12.95	59.31	± 12.66	0.933	0.359
BMI (wt/m2)	25.52	± 3.85	22.91	± 3.98	1.758	0.090
Fat mass (kg)	17.32	± 8.01	14.12	± 6.70	1.134	0.267
FFM (kg)	46.49	± 10.74	44.74	± 8.99	0.463	0.647
FFM index (kg/m2)	18.48	± 3.11	16.96	± 2.75	1.326	0.197
water (%)	51.91	± 8.67	55.44	± 6.89	1.180	0.249
phase angle	5.12	± 0.91	4.72	± 0.87	1.192	0.244
Laboratory investigation						
Na (mmol/l)	137.60	± 5.84	136.00	± 4.76	0.786	0.439
K (mmol/l)	4.13	± 0.50	4.12	± 0.45	0.062	0.951
Mg (mg /dl)	1.96	± 0.20	1.86	± 0.23	1.216	0.235

Ca (mmol/l)	9.05	±	0.35	8.95	±	0.36	0.805	0.428
Hb (g/dl)	11.17	±	0.64	11.02	±	0.51	0.650	0.521
TLC (/cmm)	4286.67	±	437.31	4276.92	±	319.25	0.066	0.948
Neutrophils (%)	54.60	±	8.19	50.54	±	5.32	1.528	0.139
Albumin (g/dl)	3.83	±	0.45	3.92	±	0.33	0.545	0.591
CRP (mg/l)	26.07	±	3.34	24.05	±	4.72	1.913	0.061

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

Table (3): Shows comparison between both groups in NRS, BIA, and laboratory investigation before third cycle chemotherapy

Before third cycle	Group A (without omega3)			Group B (with omega3)			Tests	
							t / X^2	P-value
NRS	4.54	±	1.27	3.48	±	1.23	3.284	0.002*
<3	19(63.3%)			28(93.3%)			7.954	0.005*
≥3	11(36.7%)			2(6.7%)				
ECOG	1.54	±	0.97	1.15	±	0.90	1.050	0.304
BIA								
wt. (kg)	57.72	±	12.97	64.78	±	13.34	1.368	0.184
BMI (wt/m2)	22.19	±	3.80	25.56	±	4.09	2.177	0.040*
fat mass (kg)	12.95	±	6.75	17.77	±	8.02	1.656	0.111
FFM (kg)	44.32	±	8.88	46.98	±	10.91	0.682	0.502
FFM index (kg/m2)	16.82	±	2.76	18.48	±	3.07	1.423	0.168
water (%)	55.81	±	8.14	52.11	±	8.08	1.164	0.256
Phase angle	4.18	±	0.73	5.20	±	0.91	3.163	0.004*
Laboratory investigation								
Na (mmol/l)	137.31	±	4.52	139.08	±	5.28	0.918	0.368
K (mmol/l)	3.75	±	0.50	4.09	±	0.42	1.864	0.075
Mg (mg /dl)	1.75	±	0.26	1.88	±	0.16	1.456	0.158
Ca (mmol/l)	8.58	±	0.31	8.63	±	0.28	0.656	0.514
Hb (g/dl)	9.96	±	0.84	10.29	±	0.79	1.567	0.122
TLC (/cmm)	3993.77	±	317.64	4138.46	±	272.45	1.894	0.063
Neutrophils (%)	47.82	±	7.60	50.31	±	7.89	1.245	0.218
Albumin (g/dl)	3.79	±	0.29	3.97	±	0.33	2.244	0.028*
CRP (mg/l)	6.69	±	8.34	3.56	±	0.51	2.052	0.045*

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

Table (4): Shows comparison between both groups in NRS, BIA and laboratory investigations before the 6th cycle of chemotherapy

Before 6th cycle	Group A (without omega3)			Group B (with omega3)			Tests	
							T / X^2	P-value
NRS	4.76	±	1.15	2.03	±	1.48	7.978	<0.001**
<3	16(53.3 %)			29(96.7%)			15.022	<0.001**
≥3	14(46.7%)			1(3.33%)				
ECOG	2.23	±	0.60	1.08	±	0.86	3.962	<0.001**
BIA								
wt. (kg)	56.65	±	12.31	65.54	±	12.92	1.796	0.085
BMI (wt/m2)	21.75	±	3.61	26.75	±	4.41	3.163	0.004*
fat mass (kg)	13.10	±	6.43	17.36	±	7.97	1.500	0.147
FFM (kg)	42.73	±	6.19	47.13	±	5.69	2.866	0.006*
FFM index (kg/m2)	16.33	±	2.78	18.53	±	2.85	3.027	0.003*
Water (%)	52.75	±	8.00	56.83	±	7.00	2.411	0.019*
Phase angle	3.78	±	0.48	5.45	±	0.74	6.839	<0.001**
Laboratory investigation								

Na (mmol/l)	135.38	±	2.63	137.23	±	4.57	1.922	0.059
K (mmol/l)	3.95	±	0.42	4.15	±	0.39	1.911	0.061
Mg (mg /dl)	1.98	±	0.21	2.02	±	0.13	0.887	0.378
Ca (mmol/l)	8.93	±	0.24	9.04	±	0.28	1.634	0.108
Hb (g/dl)	10.14	±	0.92	10.33	±	0.56	0.966	0.337
TLC (/cmm)	4107.92	±	422.88	4284.62	±	401.76	1.659	0.102
Neutrophils (%)	48.38	±	5.81	50.46	±	6.88	1.265	0.210
Albumin (g/dl)	3.59	±	0.24	3.91	±	0.18	5.842	<0.001**
CRP (mg/l)	3.76	±	0.51	1.65	±	0.50	10.625	<0.001**

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

In comparison between both groups according to the toxicity assessment before the 6th cycle, the patients who received omega 3 show more tolerability to chemotherapy with less side effects with also rapid recover. As shown in table (6) the omega3 group patients show significantly better toxicity profile than that of patients in group A as regard (nausea, vomiting, diarrhea, fatigue, anorexia and wt loss).

3. Hospitalization and treatment interruption:

No patients in group B (omega3 group) need hospitalization before 3rd cycle while 4(13%) of patients in group A, need hospitalization before 3rd cycle due to treatment toxicity, with sig. p value.

The patients who need treatment gap was also less in group B than that in group A, with 1(3,33%) vs 3(10%) respectively.

The mean time free of toxicity was higher in group B than that in group A, 2.56±0.50 months vs 2.28±0.45 respectively, with sig. p value.

As regard the need for hospitalization due to treatment toxicity before the 6th cycle only one patient 1 (3,33%) in group B needs hospitalization while in group A the percentage was 36% (11 patients), with sig. p value.

Also one patient in group B 1(3,33%) had treatment gap, while 10(33.3%) patients in group A had treatment gab with sig. p value.

The mean time free of toxicity were also higher in group B than group A, 2.45±0.42 vs 2.0±0.34 months with sig. p value.

4. Discussion:

Colorectal cancer is the major cause of morbidity and mortality in the world. Tumor growth is associated with anorexia-cachexia syndrome which has a large impact on morbidity and mortality, and on patient performance status (**Aoyagi T et al, 2015**)

Chemotherapy interfere with taste, ingestion, swallowing and digest food which leads to hypophagia. Also, chemotherapy agents may cause nausea and diarrhea (**Gangadharan A et al. 2017**).

Nutritional support and early intervention with nutritional supplementation addressing the specific needs of malnourished patient is required to help improve prognosis, reduce the consequences of cancer-associated nutritional decline and may improve outcome in some patients There is evidence suggests that omega 3 supplementation during cancer chemotherapy improves patient outcomes related to chemotherapy tolerability (**Arends, J. et al, 2017**).

Table (5): Shows comparison between both groups according to toxicity assessments before the 3rd cycle of chemotherapy.

Before third cycle	Group A (without omega3)		Group B (with omega3)		Chi-square	
	N	%	N	%	X^2	P-value
Anemia						
No	27	90.0	30	100.0		
Yes					3.158	0.076
G (1-2)	3	10	0	0.0		
G. (3-4)	0	0.0	0	0.0		
Febrile neutropenia						
No	28	93.3	30	100.0		
Yes					2.069	0.150
G (3)	2	6.7	0	0.0		
G (4)	0	0.0	0	0.0		
Diarrhea						
No	19	63.3	26	86.7	4.356	0.037*
Yes						

Before third cycle	Group A (without omega3)		Group B(with omega3)		Chi-square	
	N	%	N	%	X^2	P-value
G (1-2)	11	36.7	4	13.3		
G (3-4)	0	0.0	0	0.0		
Nausea						
No	19	63.3	26	86.7		
Yes					4.356	0.037*
G (1-2)	11	36.7	4	13.3		
G (3)	0	0.0	0	0.0		
Vomiting						
No	26	86.7	30	100.0		
Yes					4.286	0.117
G (1-2)	2	6.7	0	0.0		
G (3-4)	2	6.7	0	0.0		
Fatigue						
No	24	80.0	24	80.0		
Yes					0.000	1.000
G (1-2)	6	20.0	6	20.0		
G (3)	0	0.0	0	0.0		
Anorexia						
No	20	66.7	30	100.0		
Yes					12.000	0.002*
G (1-2)	10	33.3	0	0.0		
G (3-4)	0	0.0	0	0.0		
wt. loss						
No	26	86.7	30	100.0		
Yes					4.286	0.038*
G (1-2)	4	13.3	0	0.0		
G (3)	0	0.0	0	0.0		

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

In our study, the mean NRS score before the third cycle was lower in the group B than that in group A (3.48±1.23 and 4.54 ± 1.27 respectively) with p-value was significant. Also in our study, this significant value increased before the 6th cycle (2.03 ±1.48 and 4.76±1.15 and respectively), in comparison of our result to **Ziętarska M et al, 2017** (which include 114 Oncologic patients randomly divided into two groups first group included 47 patients who treated by high-energy, high-protein, oral liquid nutritional supplements (ONS group) and second group included 48 patients (Control group)) the mean NRS was higher in control group (2.6 ± 0.5) than oral nutritional support (ONS) group (2.5 ± 0.6) with no significance this may be due to no omega 3 used in the ONS group.

Table (6): Shows comparison between both groups according to toxicity assessments before the 6th cycle of chemotherapy

Before the 6th cycle	Group A (without omega3)		Group B (with omega3)		Chi-square	
	N	%	N	%	X^2	P-value
Anemia						
No	28	93.3	30	100.0		
Yes					2.069	0.150
G. (1-2)	2	6.7	0	0.0		
G. (3-4)	0	0.0	0	0.0		
Febrile neutropenia						
No	28	93.3	30	100.0		
Yes					2.069	0.150
G (3)	2	6.7	0	0.0		
G (4)	0	0.0	0	0.0		

Diarrhea						
No	16	53.3	30	100.0		
Yes					18.261	<0.001**
G (1-2)	14	46.7	0	0.0		
G (3-4)	0	0.0	0	0.0		
Nausea						
No	18	60.0	26	86.7		
Yes					5.455	0.020*
G (1-2)	12	40.0	4	13.3		
G (3-4)	0	0.0	0	0.0		
Vomiting						
No	18	60.0	30	100.0		
Yes					15.000	<0.001**
G (1-2)	12	40.0	0	0.0		
G (3-4)	0	0.0	0	0.0		
Fatigue						
No	16	53.3	30	100.0		
Yes					18.261	<0.001**
G (1-2)	14	46.7	0	0.0		
G (3)	0	0.0	0	0.0		
Anorexia						
No	20	66.7	30	100.0		
Yes					12.000	0.002*
G (1-2)	9	30.0	0	0.0		
G (3-4)	1	3.3	0	0.0		
Weight loss						
No	18	60.0	30	100.0		
Yes					15.000	<0.001**
G (1-2)	10	33.3	0	0.0		
G (3)	2	6.7	0	0.0		

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

In our study we observed that before the 6th cycle, the mean value of the performance status score (ECOG) was lower (better) in group B (patients received omega 3) (1.08 ± 0.86) than that in group A (2.23 ± 0.6) with significant p-value. Our result was matched with **de Quadros Camargo et al, 2019** (which included 51 patients randomly divided into two groups one group received fish oil tablet by dose of 1.5 gm daily and second group received placebo olive oil tablet) who revealed that the mean value of the performance status score was better in fish oil group than placebo group with significant p-value. In contrast, in **Ziętarska M et al, 2017**, the mean performance status score (karnofsky) was higher in oral nutritional support group than that in control group, but with no significance p value between the two groups this may be due to omega 3 not specified to one group and / or duration of follow up was more short than our study.

Table (7): Shows comparison between both groups according to hospitalization, treatment gap and time free of toxicity before the 3rd cycle of chemotherapy

Before third cycle	Group A (without omega3)	Group B (with omega3)	Tests	
			t / X^2	P-value
Hospitalization due to toxicity	4(13.33%)	0(0.0%)	4.286	0.038*
Treatment gap	3(10%)	1(3.33%)	3.158	0.076
Time free of toxicity (mon.)	2.28±0.45	2.56±0.50	2.280	0.026*

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

Table (8): Shows comparison between both groups according to hospitalization, treatment gap, and time free of toxicity before the 6th cycle of chemotherapy

Before 6th cycle	Group A (without omega3)	Group B (with omega3)	Tests	
			t / X^2	P-value
Hospitalization due to toxicity	11(6.7%)	1(3.33%)	10.417	<0.001**
Treatment gap	10(3.3%)	1(3.33%)	9.017	0.003*
Time free of toxicity (mon.)	2.0±0.34	2.45±0.42	4.561	<0.001**

Significant level: Non sig. >0.05 Sig. <0.05* High sig. <0.001**

In our study we observed that before the 6th cycle, the maintenance of the mean value of free fatty mass (FFM) was higher in group B than group A (42.73 ± 6.19 and 47.13 ± 5.69 respectively) with significant p-value. Our results was in agreement with **Sánchez-Lara K et al, 2014** (this study analyzed 112 patients with NSCLC who randomly divided into two groups, control group included 46 patients and oral nutritional support (ONS - EPA) group included 46 patients) who revealed that mean value of FFM decreased in the control group but increased in the ONS-EPA group (42.0 ± 13 and 37.8 ± 9 respectively) with significant p-value. In contrary, **Mocellin M.C. et al, 2013** (this study included 11 CRC patients were randomly assigned into two study groups, control group with 5 patients and experimental (received fish oil 2 g/day) group with 6 patients) showed different results than our study, there was no significant changes in the mean value of FFM of both groups (50.2±13.8 in control group and 50.5±9.0 in experimental group) this may be due to use of only 150 mg of EPA and DHA instead of 2gm with lesser duration of follow up.

In our study we observed that before the 6th cycle, the mean value of Free fatty mass index was higher in group B (18.53 ± 2.85) than group A (16.33 ± 2.78) with significant p-value. In contrast to this, in **Mocellin M. C. et al, 2017** Olive oil group showed a reduction in the mean value of FFM index during the study period but Fish oil group showed maintenance of the FFM index (17.8 ± 2.0 and 18.0 ± 2.0 respectively) and there was no significant p-value this may be due to less period of follow up and/ or less dose of EPA and DHA (1.5 gm) than our study.

In our study we observed that before the 6th cycle, the mean value of phase angle was maintained or increased in group B with omega 3 (5.45 ± 0.74) and decreased in group A (3.78 ± 0.4) and with significant p- value.

In contrast to this, **Sánchez-Lara K et al, 2014** revealed near no changes in the mean value of phase angle of both groups 5.9 ± 2.2 in control group and 6.0 ± 2.0 in ONS group this may be due to more short duration of trial or due to the patients suffered from NSCLC and treated by another types of chemotherapy.

In our study before the last 6th cycle, patients presented with higher mean albumin level in the group B (3.91 ± 0.18) than the group A (3.59 ± 0.24) with significant p-value. This result matched with **Ziętarska M et al, 2017** which reported that higher mean albumin level after 3 months of follow up with significant p-value in ONS group than control group (39.15 ± 4.28 g /L in ONS group and 35.9 ±5.30 g/L in control group).

In our study after completion of follow-up (near 6 months) the group B reported lower mean CRP level (1.65 ± 0.50) than the group A (3.76 ±0.51) with significant p-value. This result matched with **Camargo C. Q et al, 2016** who showed significant anti inflammatory effect of omega 3 in investigated trials.

In our study before the 6th cycle, there were no significant p-value in mean electrolytes levels and mean values CBC between the two groups with more or less maintained their values in the 2 groups. Similar to **Ziętarska M et al, 2017**.

In our study we found that before the 6th cycle, statistically significance in minimizing chemotherapy induced toxicity according to CTCAE v 5 in group B. As regard diarrhea, it was observed with grade 1-2 for few days with lower incidence in the group B (0%) than the group A (46.7 %) with significant p-value, this matched with **Mocellin M. C. et al, 2017** (who used Quality of Life questionnaire (QLQ-C30)) who revealed that in CRC patients the mean value of diarrhea scale was 27.8±40.0 in olive group and 17.5±32.1 in fish oil group with significance. In contrary to **Sánchez-Lara K et al, 2014**, revealed that the mean value of diarrhea scale equal to 8.6±14 in control group and 12.0 ± 12 in ONS group with no significance this may be due to GIT symptoms not frequently associated with NSCLC as CRC patients.

In our study we found that before the 6th cycle the nausea was lower in the incidence and intensity with significant p-value after omega3 supplementation before the third and the last cycles in the group B (13.3 % before third cycle and 13.3 % before last cycle) than the group A (36.7 % before third cycle and 40 % before last cycle), similar to **van der Meij BS et al, 2012** (this double-blind experiment included 40 patients with stage III NSCLC randomized to two

groups, one group received a protein- and energy-dense oral nutritional supplement containing omega 3 (interventional group) (n=20) and another group received an isocaloric supplement (control group) (n=20)) who revealed that the difference between two groups in the mean value of nausea and vomiting scale was -16.0 with significant p-value.

In contrast to our study, **Mocellin M. C. et al, 2017** (who used Quality of Life questionnaire (QLQ-C30)) CRC patients revealed that the mean value of nausea and vomiting scale was 23.1 ± 29.8 in olive group and 16.7 ± 30.4 in fish oil group with no significant p- value between both groups this may be due to use only 1.5 gm of EPA and DHA instead of 2 gm with more short duration.

In our study we found that before the 6th cycle the vomiting was lower in the incidence and intensity with significant p-value after omega3 supplementation in the group B (0%) than the group A (40%) similar to **van der Meij BS et al, 2012** who revealed that the difference between two groups in the mean value of nausea and vomiting scale -16.0 with significant p-value.

In contrast to our study, **Mocellin M. C. et al, 2017** CRC patients revealed that the mean value of nausea and vomiting scale was 23.1 ± 29.8 in olive group and 16.7 ± 30.4 in fish oil group with no significant p- value between both groups this may be due to use only 1.5 gm of EPA and DHA instead of 2 gm with more short duration.

As regard fatigue, in our study we found that before the 6th cycle (after near 5 months of omega3 supplement) lower incidence of fatigue in the group B (0%) than the group A (46.7%) with significant p-value, our result was agreement with **Sánchez-Lara K et al, 2014** who revealed that the mean value of fatigue scale was 34.7 ± 20 in control group and 32.3 ± 24 in ONS group with significant p-value. In contrast **Mocellin M. C. et al, 2017** the mean value of fatigue scale of CRC patients was 25.9 ± 34.9 in olive group and 26.9 ± 29.2 in fish oil group with no significance this may be due to use of only 1.5 gm of EPA and DHA instead of 2 gm with more short duration.

As regard Anorexia our study showed that before the last 6th cycle (after near 5 months of omega3 supplement), lower incidence and intensity of anorexia in the group B (0%) than group A (33.3%) with significant p-value, this matched with **Mocellin M. C. et al, 2017** results regard CRC patients, the mean value of loss of appetite scale was 33.3 ± 45.7 in olive group and 22.8 ± 38.6 in fish oil group with significance.

As regard weight loss, before the 6th cycle the study showed lower incidence and intensity of weight loss in the group B (0%) than group A (40%) with significant p-value, similar to **Mocellin M. C. et al,**

2017 who reported that during the follow-up, equal number of patients lost weight in both groups but in the patients with fish oil supplementation there was significantly minimizing the mean value of weight lost when compared to olive oil (fish oil -2.81 ± 2.8 kg and olive oil -5.57 ± 3.6 kg). Also, **Bonatto SJ et al, 2012** revealed that the mean value of change in weight over the 8 week period of follow up was higher in control group (-2.5 ± 0.8 kg) than fish oil group ($+1.7 \pm 0.9$ kg) with significant p-value.

In our study before the 6th cycle we found that incidence of anemia was less in B group (0%) than A group (6.7) with no significant p-value. This result matching with **Ziętarska M et al, 2017** who revealed that on follow up delayed administration of the next chemotherapy cycle or half-dose reduction due to thrombocytopenia, leucopenia or neutropenia were reported in 3 patients in the ONS group and 7 in the Control group with no significance.

In our study before the 6th cycle we found that incidence of febrile neutropenia was less in B group (0%) than A group (6.7%) with no significant p-value. This result matching with **Ziętarska M et al, 2017** who revealed that on follow up delayed administration of the next chemotherapy cycle or half-dose reduction due to thrombocytopenia, leucopenia or neutropenia were reported in 3 patients in the ONS group and 7 in the Control group with no significance.

In our study before the third cycle, the number of the patients in the group B who need to hospitalization and need to delay next cycle due to chemotherapy toxicity (0% and 3.33% of patients respectively) were less than the group A (13.33% and 10% of patients respectively) with significant p-value. Also, before the last cycle the number of the patients who need to hospitalization and need to delay next cycle due to chemotherapy toxicity were less in the group B (3.33% and 3.22% respectively) than the group A (6.7 % and 3.3% respectively) with significant p-value.

In contrast to our results **Ziętarska M et al, 2017**, reported that delay in administration of the next chemotherapy cycle in 3 patients in ONS group and in 7 patients in control group with no significant p-value this may be due to no use of omega3 by 2gm daily.

In our study before the 6th cycle, the time free of toxicity was longer in the group B (2.45 ± 0.42 months) than the group A (2.0 ± 0.34 months) with significant p-value. Our result was agreement with **Ziętarska M et al, 2017** who revealed that delay of chemotherapy for an average of 7 days was need in 14 patients in the ONS group and 10 patients in the Control group.

Conclusion:
Administration of omega 3 (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) concomitant with chemotherapy in colorectal cancer

effective in improving the nutritional status (including lean body mass and phase angle) and increase the tolerability of chemotherapy with decrease the need of treatment gap and hospitalization between cycles.

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2/24/2020