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ORIGINAL ARTICLE

The role of neoadjuvant FLOT chemotherapy with and without omega 3 in locally advanced gastric carcinoma

Lamiss Mohamed Abdel Aziz[1], Tarek Salah[2], Fatma Gharib[1]

[1]Tanta University, Dept. of Clinical Oncology, Tanta, Egypt. [2]Tanta Cancer Institute, Dept. of Surgical Oncology, Tanta, Egypt.

Summary

Purpose: *Gastric is the third leading cause of cancer-related deaths worldwide with two third of the cases presented in advanced stage with resultant increased morbidity and mortality. The purpose of the study was to investigate the nutritional intervention with and without omega 3 fatty acids.*

Methods: *Forty two cases were randomized into two groups: group; A: FLOT neoadjuvant chemotherapy with omega 3 and group B: FLOT chemotherapy alone in the period from July 2018 to July 2019. We evaluated the radicality of surgical interference, overall response, nutritional status, treatment delivery and toxicity.*

Results: *The radicality, overall response the SGA score and the bioelectrical impedance parameters were higher in those who received omega 3 with chemotherapy and toxicity was less which was statistically significant.*

Conclusions: *Omega 3 administrations during chemotherapy in gastric cancer increased the chemotherapy tolerability and decreased the treatment gap between cycles and hence improved gastric cancer resection.*

Key words: *gastric, FLOT, neoadjuvant, omega 3*

Introduction

Worldwide the fifth most common type of malignancy and the third leading cause of cancer-related death is gastric cancer [1-2]. About two thirds of the cases present in advanced stage [3].

To improve response and resectability, perioperative chemotherapy has been used based on many trials with no improvement on survival [4,5].

A new regimen (FLOT) has emerged for early or low burden locally advanced metastatic gastric cancer repeated every 2 weeks (oxaliplatin, leucovorin, docetaxel and 5-fluorouracil). This regimen improved survival but at the expense of increased toxicity [6]. Malnutrition that occurs in malignancy is different from pure starvation as it is characterized by protein loss and inflammatory status that results in bad quality of life [7,8].

Omega 3 fatty acids supplementation is found to decrease the tumor associated inflammatory markers [9-11]. In many studies such as a study carried out on patients with colorectal cancer who received supplementary omega 3 , the group receiving supplementation showed prolonged time to disease progression [12] .

Also, in patients with esophageal carcinoma, receiving omega 3 supplementation decreases the side effects of chemotherapy [13].

So, in our study we tested the role of omega 3 supplementation with FLOT neoadjuvant chemotherapy in locally advanced gastric cancer to reduce the treatment interruptions.

Methods

From July 2018 to July 2019, 42 patients with histopathologically confirmed stage III-IVa locally advanced unresectable gastric adenocarcinoma according to the

Corresponding author: Lamiss Mohamed Abdel Aziz Sad, MD. Oncology Department, Tanta University, Tanta, Nast City, abrag afifi, Cairo, Egypt
Tel: +20 01224151806, Fax: +20 403407734, Email: lamissmohamed2@yahoo.com
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criteria of the American Joint Committee on Cancer (AJCC) TNM stage classification (8th edition) for gastric cancer [14] were randomized into 2 groups. In group A 21 patients received neoadjuvant chemotherapy with omega 3 and in group B 21 patients received neoadjuvant chemotherapy without omega 3.

The study was carried out in Tanta University, Department of Oncology, Eligibility for the study entry required patients to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and good hematological, hepatic, renal and cardiac function. Written informed consent was taken from all patients.

Treatment plan

Group A (21 patients): four cycles (FLOT) neoadjuvant chemotherapy (85 mg/m^2 of oxaliplatin intravenous infusion; 200 mgm/m^2 intravenous infusion of leucovorin; 50 mg/m^2 intravenous infusion of docetaxel followed by 24-h intravenous infusion of 2600 mg/m^2 of 5-fluorouracil) with omega 3.

Two grams omega 3 were given to patients in the same day of first cycle of chemotherapy and continued throughout the whole cycles.

Group B (21 patients) received four cycles of the same neoadjuvant chemotherapy without omega 3.

Table 1. Patient characteristics

Characteristics	*Group A (FLOT+omega 3)* *n (%)*	*Group B (FLOT)* *n (%)*	*p value*
Age (years)			0.057
<53	10 (47.6)	16 (76.2)	
≥53	11 (52.4)	5 (23.8)	
Sex			0.217
Female	12 (57.1)	8 (38.1)	
Male	9 (42.9)	13 (61.9)	
ECOG performance status			0.008*
0-1	21 (100)	15 (71.4)	
2	0 (0)	6 (28.6)	
Pathology			0.516
Adenocarcinoma	13 (61.9)	8 (38.1)	
Mutinous	5 (23.8)	3 (14.1)	
Signet ring	2 (9.5)	0 (0)	
Others	1 (4.8)	10 (47.6)	
Differentiation			0.562
Well	1 (4.8)	3 (14.3)	
Moderate	6 (28.6)	6 (28.6)	
Poor	14 (66.7)	12 (57.1)	
T staging			0.679
T3	18 (85.7)	17 (81)	
T4	3 (14.3)	4 (19)	
N staging			0.038*
N1	20 (95.2)	15 (71.4)	
N2	1 (4.8)	6 (28.6)	
N3	0 (0)	0 (0)	
TNM staging			0.079
III	18 (85.7)	13 (61.9)	
IVa	3 (14.3)	8 (38.1)	
Surgery			0.061
Total gastrectomy	9 (42.9)	15 (71.4)	
Subtotal gastrectomy	12 (57.1)	6 (28.6)	
Radicality			0.004*
R0	18 (85.7)	9 (42.9)	
R1	3 (14.3)	12 (57.1)	
R2	0 (0)	0 (0)	

Asterisks denote statistical significance

All patients received nutritional counseling throughout the whole treatment period by the nutritional team.

Evaluation of response was done after 4 chemotherapy cycles when patients were restaged. Patients who showed a realistic change of margin-free R0 of primary tumor underwent total or subtotal distal gastrectomy with D2 lymphadenectomy. Patients who did not respond continued another four cycles of chemotherapy.

Nutritional assessment

Nutritional assessment was done using subjective global assessment [15]. Evaluation of nutritional parameters was done using the Tanita mcv870, a machine used for assessment of body composition. Patients with 2-3 points (A) had no malnutrition, patients with 4-8 points (B) had moderate malnutrition, and patients more than 9 points had severe malnutrition (C). Bioelectrical analysis was used to acquire data about weight, body mass index (BMI), fat-free mass, extracellular water and phase angle.

Evaluation of toxicity

The toxicity was evaluated according common toxicity criteria for solid tumors version 4 [16].

Evaluation of efficacy outcomes

Three weeks after the fourth cycle of chemotherapy, evaluation of treatment response was done using contrast CT and MRI abdominopelvic or upper gastrointestinal endoscopy and was classified according to response evaluation criteria (RESIST) version 1.1 [17].

Table 2. Correlation between response and line of treatment

Response	*Treatment*		*Total*	*p value*
	Group A (FLOT+Omega 3) %	*Group B (FLOT only)* %	%	
CR	75.0	25.0	100.0	
PR	88.9	11.1	100.0	0.000*
SD	9.5	61.9	35.7	
PD	0.0	23.8	11.9	
Total	50.0	50.0	100.0	

Asterisk denotes statistical significance

Table 3. Comparison between two treatment groups after 4 cycles of chemotherapy with different bioelectrical impedance analysis

Characteristics	*Group A (FLOT+omega 3)* *n (%)*	*Group B (FLOT only)* *n (%)*	*p value*
Subjective global assessment			0.000*
A	10 (47.6)	0 (0)	
B	11 (52.4)	3 (23.8)	
C	0 (0)	18 (76.2)	
Performance status			0.008*
0-1	21 (100)	15 (71.4)	
2	0 (0)	6 (28.6)	
Weight, kg			0.002*
<59	6 (28.6)	16 (71.4)	
≥59	15 (71.4)	5 (23.8)	
BMI			0.002*
< 25	4 (19)	14 (66.7)	
> 25	17 (81)	7 (33.3)	
FFM (kg)			0.549
<31.5	1 (4.8)	2 (9.5)	
≥31.5kg	20 (95.2)	19 (90.5)	
Phase angle			000*
<4.1	0 (0)	19 (90.5)	
≥4.1	21 (100)	2 (9.5)	

Asterisks denote statistical significance

Absence of cancer on microscopic examination in all margins were considered as R0 resection.

Statistics

IBM SPSS statistical package version 23 was used for statistical analyses. Unpaired T-test was used to compare quantitative data. Fisher exact test and chi-square test were used for tables 2x2. Values less than 0.05 were considered statistically significant [18].

Results

Forty-two cases with locally advanced gastric carcinoma stage III and IVa were randomized into two groups where group A received 4 cycles FLOT neoadjuvant chemotherapy with omega 3 and group B received 4 cycles FLOT neoadjuvant chemotherapy without omega 3. Table 1 shows the characteristics of both treatment groups. The factors with statistical difference in both treatment groups were performance status, N stage, and radicaility of surgical interference after 4 cycles of neoadjuvant chemotherapy.

The overall response was higher in group A than in group B (90.5% versus 14.3%, respectively, which was statistically significant) with complete response in 14.3% and 4.8% in group A and B, respectively, which was also statistically significant (p=0.000; Table 2).

Bioelectrical impedance analysis after 4 cycles of neoadjuvant chemotherapy in group A and B, were more than 59 kg in group A than in group B (71.4% versus 23.8% with p value = 0.02). Body mass index was higher in group A than in group B (81% versus 19%, respectively, which was statistically significant with p=0.002). Phase angle was significantly higher in group A than in group B (p=0.000; Table 3).

Table 4. Details of drug delivery according to treatment group

Characteristics	*Group A (FLOT+omega 3)* *n (%)*	*Group B (FLOT)* *n (%)*	*p value*
Hospitalization due to toxicity/cycle	0 (0)	15 (71.4)	0.000*
Treatment gap	1 (4.8)	10 (47.6)	0.002*

Asterisks denote statistical significance

Table 5. Treatment toxicity

Characteristics	*Group A (FLOT+omega 3)* *n (%)*	*Group B (FLOT)* *n (%)*	*p value*
Anemia			0.147
Grade 1+2	0 (0)	2 (9.5)	
Grade 3+4	0 (0)	0 (9.5)	
Febrile neutropenia			0.147
Grade 3	0 (0)	2 (9.5)	
Grade 4	0 (0)	0 (9.5)	
Diarrhea			0.000*
Grade 1+2	0 (0)	15 (71.4)	
Grade 3+4	0 (0)	0 (0)	
Nausea			0.000*
Grade 1+2	0 (0)	12 (57.1)	
Grade 3+4	0 (0)	0 (0)	
Vomiting			0.000*
Grade 1+2	0 (0)	12 (57.1)	
Grade 3+4	0 (0)	0 (0)	
Fatigue			0.000*
Grade 1+2	0 (0)	14 (57.1)	
Grade 3+4	0 (0)	0 (0)	
Weight loss			0.000*
Grade 1+2	0 (0)	10 (47.6)	
Grade 3+4	0 (0)	2 (9.5)	

Asterisks denote statistical significance

On assessing the patient nutritional status using subjective global assessment of patient and clinician generated scores, the patients in group B receiving neoadjuvant chemotherapy without omega 3 were severely malnourished with performance status 2 which was statistically significant (p=0.000 and 0.000 respectively; Table 3).

Treatment interruptions due to toxicity and hospital admission in patients not receiving omega 3 group B were higher and statistically significant (p=0.002 and 0.000 respectively; Table 4).

The toxicity was higher in group B as regard nausea, vomiting, fatigue, diarrhea and weight loss which were statistically significant (p=0.000; Table 5).

Discussion

Gastric carcinoma is one the most important cancers causing increased morbidity and mortality worldwide [19]. Anorexia and cachexia caused by the disease results in increased morbidity, treatment interruptions, hospital admission, bad performance status and increased mortality [20]. Also the role of Helicobacter pylori is a known cause of gastric inflammation resulting in gastric cancer [21].

Nutritional counseling and early intervention after screening of gastric cancer patients followed by subjective global assessment may avoid the hazardous effects of cancer chemotherapeutic agents and hence treatment interruptions with resultant increase of the therapeutic outcome [22].

In investigating the role of omega 3 in gastrointestinal cancers it was found that it improved the immune response, maintained body weight and therapeutic ratio [23].

FLOT neoadjuvant chemotherapy has improved the therapeutic response in potentially resectable metastatic gastric carcinoma with low burdens [6]. So the aim of our study was to investigate the role of neoadjuvant FLOT chemotherapy with and without omega 3.

In our study, before the start of chemotherapy there was no statistically significant difference between the two groups except for N stage where N2 stage was higher in the group A than in the group B, but when combining the T and N stage in the TNM stage no statistically significant difference in performance status was noticed.

The performance status was higher in group A patients than in group B patients and this coincided with other authors [23-25].

The radicality of surgical intervention of gastric cancer was significantly higher in group A that received omega 3 treatment in contrast to those who received treatment without omega 3 (p=0.004) and this coincided with the reports of other authors [26,27].

The factors with statistical difference in both treatment groups were performance status, N stage, and radicality of surgical intervention after 4 cycles of neoadjuvant chemotherapy.

The overall response was significantly higher in group A compared with group B (90.5% versus 14.3%, respectively) with complete response in 14.3% and 4.8% in group A and B, respectively (p=0.000). This was nearly similar to Batran et al study but in that study the patients did not receive omega 3 [28].

Treatment interruptions due to toxicity and hospital admission in patients not receiving omega 3 (group B) were significantly different (p=0.002 and 0.000, respectively). The toxicity was higher in group B as regard nausea, vomiting, fatigue, diarrhea and weight loss which were significantly different, coinciding to reports of many authors [23-28].

The use of omega 3 reduced the neoadjuvant treatment toxicity and decreased treatment interruptions, resulting in increased resectability. However, large number of cases are required to verify the results of the present study.

Conflict of interests

The authors declare no conflict of interests.

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