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Treatment Related ToxicityofInduction Chemotherapy Followed By Concurrent Chemoradiotherapy, Surgery and Adjuvant Chemotherapyfor Treatment of Locally Advanced Rectal Cancer

Moamna Mohammed Fahmy, Ahmad Alhosainy, Abdel MotalebMohammed,Bassant Sh.Elshafaay

Department of Clinical Oncology &Nuclear medicine, Faculty of Medicine - Zagazig University, Egypt.

***Corresponding Author:Moamna Mohammed Fahmy**, **Email:** dr.monny.kh@gmail.com

ABSTRACT

Purpose: To decrease the toxicity of induction chemotherapy followed by concurrent chemoradiation,surgery and adjuvant chemotherapy in locally advanced rectal cancer patients.

Method:locally advanced rectal cancer 38 patients recivedneoadjuvant 3 cycles chemotherapy(FOLFOX4)followed by concurrent chemoradiotherapy(CCRT) with capecitabine (median 825 mg/m^2/d BID) and conventional radiotherapy (total dose of 45 Gy was given in 5weeks),followed by surgery then 3 cycles adjuvant chemotherapy(FOLFOX4) at the Clinical Oncology and Nuclear Medicine department, Zagazig University Hospitals from sep. 2019 to sep. 2021.

Results:A total of 38 patients (with a median age of 43 years) were treated. As regard induction chemotherapy grade I toxicity(GI) (Anemia 60.5%,thrombocytopenia 47.4%,leukopenia 23.7%,diarrhea 34.2%,mucositis 23.2% and hand foot syndrome 31.5%) while grade II toxicity was GII(Anemia 21.1%,thrombocytopenia 13.2%,leukopenia 23.7%,diarrhea 15.8%,mucositis 34.2% and hand foot synd 21%)no grade III toxicity(GIII) detected except for 2.6% for both leukopenia, thrombocytopenia and mucositis , no GIV toxicity was detected,theToxicity profile for CCRT GI (Anemia 57.8%,leukopenia 44.7%,thrombocytopenia 47.3%,diarrhea 44.7%,mucositis 26.3%,urinary symptoms 21% and hand foot synd 36.8%) GII toxicity was(Anemia 26.3%,thrombocytopenia 21%,leukopenia 21%,diarrhea 26.3%,mucositis 23.6%,urinary symp 42% and hand foot synd 13.1%)no GIII detected except for 2.6% for both leukopenia and diarrhea , no GIV toxicity wasdetected.Adjuvant chemotherapy toxicity was GI (Anemia 50%,thrombocytopenia 47.3%,leukopenia 52.6%,diarrhea 44.7%,mucositis 42.1% and hand foot synd 39.4%) while GII toxicity was(Anemia 7.9%,thrombocytopenia 10.5%,leukopenia 10.5%,diarrhea 13.1%,mucositis 21% and

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hand foot synd18.4%)no GIII toxicity was detected except for 2.6% for both leukopenia and thrombocytopenia while there was noGIV toxicity.

Conclusions: For locally advanced rectal cancer patients, Neoadjuvant induction chemotherapy followed by concurrentchemoradiotherapywith capecitabine is safe and well tolerable regimen with effective local control that may increase the utilization of neoadjuvant treatment for loclly advanced rectal cancer patients.

Keywords:locallyadvanced,rectalcancer,Neoadjuvant,concurrent chemoradio,FOLFOX4 ,Toxicity.

Introduction

Colorectal cancer is the third most common diagnosed cancer in males and second in females, according to world health organization GLOBOCAN database. In the United States, Annually about 149.500 new cases of large basal cancer are diagnosed, 104.270 of which are colon cancer, and the remainder are rectal cancer.Globally, Australia and New Zeland, Europe, the highest incidence rates, while the lowest rates found in Africa and South central Asia **(1).**

In Egypt, the estimated rate of CRC is 6.5 % of all malignant tumors, **(2),**CRC became the sixth most commonly recorded tumor in the years 2002-2003, regarding the National Cancer Institute registry at Cairo University (**3).** It was 4.2 % in men and 3.8 % in females**(4)**, CRC is also widespread in Egypt, with 14.0 % of all colonoscopies revealing the presence of the disease**(5).**

Multimodality approach of neoadjuvantchemoradiotherapy (nCCRT) followed by total mesorectal excision (TME) and postoperative adjuvant chemotherapy has been accepted worldwide as the standard treatment for patients with locally advanced rectal cancer. This therapeutic approach markedly reduced the local recurrence rate from 35% to 5%-10% and significantly improved overall survival **(6).**

Neoadjuvant radiotherapy is more favorable because of better tolerance, low toxicity and more dose-response relationship**(7).** Therefore, the efficacy of adjuvant chemotherapy in rectal cancer treatment remains controversial. With the purpose of improving patient survival, delivery of chemotherapy before surgery had been proposed to treat occult micrometastases early and increase treatment compliance**(8).**

Toxicity of irradiation depends on treatment volume and dose**(9).** In rectal cancer treatment, acute toxicity of chemo-radiotherapy mainly consists of hematological, genitourinary, and gastrointestinal **(10)**

Capecitabine, a pro-drug of 5-flourouracil is an oral carbamate, which changes into 5-flouro-uracil within tumor via enzyme thymidine phos-phorylase**(11).** The capecitabine preferential activation in tumor cell reduces systemic acquaintanceto 5-flourouracil and possibly enhances safety and efficacy, oral capecitabine could achieve dosing that approximates to continuous 5-florouracil infusional regimens. During radiation therapy,

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thymidine phosphorylase enzyme is up regulated within tumor cells leading to a synergistic effect of capecitabine with radiotherapy**(12).**

STUDYDESIGN AND PARTICIPANTS

Our study is a phase II prospective study including 38 patients with locally advanced rectal cancer and pathologically proven adenocarcinoma, who presented to Clinical Oncology & Nuclear Medicine Department, zagazig University Hospitals during the period from Sep.2019 to Sep. 2021.The patients were treated by neoadjuvant chemotherapy:3 cycles folfox-4 2weeks after the end of induction chemotherapy patients started CCRT which is capcitabine 825 mg/ m² twice daily 5d/week during radiotherapy.Three-dimensional conformal RT to the whole pelvis was given with high-energy photon beams (15 MV) from Electalinear accelerator (precise plan TPS)for a total dose of 45 Gy over 5 weeks by conventional fractions Patients referred for surgical consultation 6-8 weeks after the end of CCRT. The aim was performing total mesorectal excision (TME) with trial of sphincter preservation if possible. Patients received adjuvant chemotherapy Folfox- 4 regimen for 3 cycles.

Inclusion criteria

1- ≥ 18 years old.
2- ECOG(Eastern Cooperative Oncology Group) performance status 0-2.
3- Histologically proved adenocarcinoma of rectum.
4- TNM stage II – III based on (MRI) of the pelvis.
5- Operable disease.
6-Normal liver, renal and bone marrow functions.
7- Informed consent had been signed.

Exclusion criteria

1- Performance status (PS)> 2 by EasternCooperative Oncology Group (ECOG).
2- Pregnant or lactating patients. .
3- Other cancers.-
5- Inflammatory bowel disease.

Treatment:

The Prospective study was conducted to 38 patients of newly diagnosed locally advanced cancer rectum patientsreffered to the Clinical Oncology & Nuclear Medicine Department, Zagazig University Hospitals, from sept 2019 to sept 2021. The patients was treated by neo-adjuvant chemotherapy:3 cycles folfox4 After 2weeks from the end of induction chemotherapy patients started CCRT which is capcitabine 825 mg/ m² twice daily 5d/week during radiotherapy.Three-dimensional conformal RT to the whole pelvis was given with high-energy photon beams (15 MV) from a linear accelerator for a total

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dose of 45 Gy over 5 weeks byfractionation ,six to eight week later our patients underwent surgical consultation total mesorectal excision (TME) with atrial of sphincter preservation, Patients received adjuvant 3 cycles of Folfox- 4.

The target volumes were deliniated according to The RTOG anorectal contouring atlas .

Target volume:

- GTV(gross target volume): Primary tumor and/ or clinically positive nodes greater than 1 cm.
- CTV(Clinical target volume): LNs at risk for T3 tumor including common iliac , internal iliac and presacral LNs as well as the entire mesorectum. For T4 tumor ,also include coverge of external iliac LNs while inguinal LNs covered only in tumors extending to the distal anal canal or lower third vagina.
- PTV(planning target volume): PTV = CTV + 1 cm.
- OAR(organs at risk): The organs at risk included the urinary bladder, femoral heads, and small intestine. It was delineated according to the uniform consensus guidelines from an RTOG consensus panel.

Dose /Fractionation:

Conventional fractionation 1.8gy/fr/day,5days,per week to a total dose of 45 Gyof 15Mv photon energy was given to all patients pre- operatively, followed by boost dose 9 Gy over 1 week to the tumor bed only for patients with residual tumor or pathological specimen examination with positive surgical margins.

CCRT was started after 2 weeks of neoadjuvant chemotherapy.

Machine:

Treatment with 15 MV photon beams was delivered with an MLC-equipped megavoltage linear accelerator.

Chemotherapy:

Induction chemotherapy 3 cycles folfox-4 regimen, concurrent chemo-radiotherapy with capecitabine 825 mg/ m^2 twice daily 5d/week during radiotherapy and adjuvant chemotherapy was 3 cycles folfox-4 regimen.

Surveillance and follow-up:

Full physical examination, routine laboratory evaluation with tumor markers (CEA, CA19-9), plain chest radiography will be done each visit.

Pre surgical restaging will done 4–6 weeks after end of neo-adjuvant CRT by CT scan or MRI examination.

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Then reevaluated by another radiological examination 2 months after ending the whole course of treatment, then every 3months during 1st year and every 6months during 2nd year.

And colonoscopy annually for the 1st three years,then every 3 years after that.

Toxicities were assessed according to the National Cancer Institute/Common Terminology Criteria of adverse events (CTCAE/NCI), version 4.0. Patients were followed up weekly during the treatment course for recording acute toxicities.

Grade 3 or higher toxicity (diarrhea, cystitis or abdominal pain) was treated by treatment interruption and supportive medication (anti-diarrheal, analgesics, anti-inflammatory, or antibiotics when necessary) and restart treatment once symptoms reduced to grade 1.

Statistical Analysis:

The DFS(disease free survival) was calculated in patients who surgically operated, completed their adjuvant course and/or achieved response. It was calculated from the end of treatment till the occurrence of recurrence. The OS was calculated from the time of diagnosis till death or last time the patient seen. Data entry and analyses were performed using SPSS statistical package version 24 (SPSS, Inc., Chicago, IL, USA). The quantitative data were presented as a mean, median and range. The qualitative data were presented as number and percentage. The chi-square test (/2) was used to get the association between variables of qualitative data. The P value of 0 0.05 and 0 0.001 indicate significant and highly significant results respectively at confidence interval 95%.

RESULTS

Patients and Tumor Characteristics:Patients age ranged between 18-68 years, the median was 43 years,most patients were between 40-60 years(50%) then between 18-40 years(34%) then>60 years(15%),Males were 15 patients representing 39.5%,while females were 23 representing 60.5% and 27 patient (71%) presented with ECOG 1 and 11 patients(29%) presented with ECOG 2(table 1). From pretreatment proctoscopy, imaging and pathological findings, most patients were grade 2 they were(27 patients), most patients were adenocarcinoma (25 patients), most of patients also were at lower third of the rectum(15 patient), most of patients with annular mass(14 patients) and most of patients masses were more than 5cm in greatest dimension (22 patients). Table (2)

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Table (1): Patients characteristics:

Age (years)		
Mean ± SD	46.22 ± 14.37	
Median (Range)	43 (28 – 69)	
	No.	%
18 – 40 years	13	34.2
40 – 60 years	19	50.0
>60 years	6	15.8
Sex		
Male	15	39.5
Female	23	60.5
ECOG		
1	27	71
2	11	29
Total	38	100.0

Table (2) Tumor characteristics of preoperative proctoscopy and imaging findings:

		No.	%
Tumor grade	G I	8	21.1
	G II	27	71.1
	G III	3	7.9
Histological subtype	Adenocarcinoma	25	65.8
	Mucinous	6	15.8
	Signet ring	7	18.4
Site of tumor	Lower 1/3	15	39.5
	Middle 1/3	9	23.7
	Upper 1/3	14	36.8
Distantance from anal verge	<5 cm	15	39.5
	5 – 10 cm	9	23.7
	> 10 cm	14	36.8
Gross pattern	Fungating	13	34.2
	Ulcerating	11	28.9
	Annular	14	36.8
Largest dimension (cm)	Mean ± SD	9.21 ± 1.38	
	Median (Range)	8 (6-10)	
	≤ 5 cm	16	42.1
	> 5 cm	22	57.9

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Induction chemotherapy toxicity profile isGI (Anemia 60.5%,thrombocytopenia 47.4%,leukopenia 23.7%,diarrhea 34.2%,mucositis 23.2% and hand foot synd 31.5%) while GII toxicity was(Anemia 21.1%,thrombocytopenia 13.2%,leukopenia 23.7%,diarrhea 15.8%,mucositis 34.2% and hand foot synd 21%)no GIII detected except for 2.6% for both leukopenia, thrombocytopenia and mucositis ,GIV was absent, Most of these toxicities are grade 1 and 2 and well tolerated.

Toxicity profile for CCR GI (Anemia 57.8%,leukopenia 44.7%,thrombocytopenia 47.3%,diarrhea 44.7%,mucositis 26.3%,urinary symptoms 21% and hand foot synd 36.8%) GII toxicity was(Anemia 26.3%,thrombocytopenia 21%,leukopenia 21%,diarrhea 26.3%,mucositis 23.6%,urinary symp 42% and hand foot synd 13.1%)no GIII detected except for 2.6% for both leukopenia and diarrhea ,GIV was absent(table 4).Noadjuvant concurrent chemotherapy related toxicity:Most of these toxicities are grade0, 1 and 2 and and well tolerated.

Adjuvant chemotherapy toxicity was GI (Anemia 50%,thrombocytopenia 47.3%,leukopenia 52.6%,diarrhea 44.7%,mucositis 42.1% and hand foot synd 39.4%) while GII toxicity was(Anemia 7.9%,thrombocytopenia 10.5%,leukopenia 10.5%,diarrhea 13.1%,mucositis 21% and hand foot synd 18.4%)no GIII detected except for 2.6% for both leukopenia, thrombocytopenia while G IV toxicity was absent(table 5).most of them toierable G0,Iand II (Table 5).

Table (3): Neoadjuvant chemotherapy related toxicity of the studied locally advanced rectal cancer patients.

Chemotherapy related toxicity	Grade 0	Grade 1	Grade II	GradeIII	Grade IV
Hematological toxicities					
WBCs(Leukopenia)	12 (31.6%)	16 (42.1%)	9 (23.7%)	1 (2.6%)	0 (0%)
RBCs(Anemia)	7 (18.4%)	23 (60.5%)	8 (21.1%)	0 (0%)	0 (0%)
Platelts(Thrombocytopenia)	12 (31.6%)	19 (47.4%)	5 (13.2%)	1 (2.6%)	1 (2.6%)
Non-hematological toxicities					
Diarrhea	18 (47.4%)	13 (34.2%)	6 (15.8%)	0 (0%)	1 (2.6%)
Mucositis	14 (36.8%)	9 (23.7%)	13 (34.2%)	1 (2.6%)	1 (2.6%)
Hand foot syndrome	18 (47.4%)	12 (31.5%)	8 (21%)	0 (0%)	0 (0%)

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Table (4): Neoadjuvantconcurrenetchemoradiotherapy related toxicity of the studied locally advanced rectal cancer patients.

CCR related toxicity	Grade0	GradeI	Grade II	Grade III	Grade IV
Hematological toxicities					
WBCs	12 (31.5%)	17 (44.7%)	8 (21%)	1 (2.6%)	0 (0.0%)
RBCs	6 (15.7%)	22 (57.8%)	10 (26.3%)	0 (0.0%)	0 (0%)
Platelets	12 (31.5%)	18 (47.3%)	8 (21%)	0 (0.0%)	0 (0.0%)
Non-hematological toxicities					
Diarrhea	10 (26.3%)	17 (44.7%)	10 (26.3%)	1 (2.6%)	0 (0.0%)
Mucositis	19 (50.0%)	10 (26.3%)	9 (23.6%)	0 (0.0%)	0 (0.0%)
Urinary symptoms	14 (36.8%)	8 (21%)	16 (42.%)	0 (0.0%)	0 (0%)
Hand foot syndrome	19 (50%)	14 (36,8)	5 (13,1%)	0 (0.0%)	0 (0%)

Table (5): Adjuvant chemotherapy related toxicity of the studied locally advanced rectal cancer patients:

Chemotherapy related toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicities					
WBCs	13 (34.2%)	20 (52.6%)	4 (10.5%)	1 (2.6%)	0 (0%)
RBCs	16 (42.1%)	19 (50%)	3 (7.9%)	0 (0%)	0 (0%)
Platelets	15 (39.4%)	18 (47.3%)	4 (10.5%)	1 (2.6%)	0 (0%)
Non-hematological toxicities					
Diarrhea	16 (42.1%)	17 (44.7%)	5 (13.1%)	0 (0%)	0 (0%)
Hand foot syndrome	16 (42,1%)	15 (39,4%)	7 (18,4%)	0 (0%)	0 (0%)
Mucositis	14 36.8%)	16 (42.1%)	8 (21%)	0 (0%)	0 (0%)

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IV.DISCUSSION

CRC is the third most often recognized cancer in the world, behind lung and breast cancer. In developed regions and countries, such as Europe, North America, and Australia, the greatest rates (60%) are seen. In developing areas, such as Africa and South-Central Asia, the rate was lower. In 2008, over 1.200000 new CRC patients were diagnosed worldwide, with 608,700 deaths, so that it is the 4th most reported reason for cancer death, reporting about 8.0 % of all cancer deaths **(13).** In the United States, CRC is the 4th more reported cancer **(14).**

The multidisciplinary approach of neoadjuvantchemoradiotherapy (nCRT) followed by total mesorectal excision (TME) and postoperative adjuvant chemotherapy has been accepted worldwide as the standard treatment for patients with locally advanced rectal cancer. This therapeutic approach markedly reduced the local recurrence rate from 35% to 5%- 10% and significantly improved overall survival **(15).**

The results obtained in our study showing pCR in 21.1% near to the results of **STAR-01 double armed study** (performed on 747 patients received 50.4 Gy RT with 5-FU with or without weekly oxaliplatin 60 mg/m2) showing pCR in 16% of patients of both arms, while it showed higher toxicity levels as GIII- IV toxicity were recorded in 24% of first arm patients versus 8% only of second arm patients as reported by **(16*).***

While the response rate in our study was21.1% better than the response of the Korean phase II study (which studied 31 patients received concomitant CRT by using the same modified FOLFOX regimen with RT as our study) showing 77% overall response with 13% pCR. However, they succeeded to perform SSS in 93% of their patients, and CRM was positive in 6.5% only of patients. Toxicity rates were relatively higher, showing GIII diarrhea in 19% of patients but no deaths secondary to toxicity occurred as recorded by**(17).**

The RadiOxCape study (single armed study on 40 patients received 45 Gy conventional pelvic RT with concomitant CAPOX chemotherapy; oxaliplatin (50 mg/m^2) IV weekly and Capecitabine (825 mg/m^2 twice day) orally on each day of RT). The most frequent grade III, IV adverse event was diarrhea, occurring in 30% of patients as reported byMachielsJ,etal while in our study there was no grade IV toxicity and grade III toxicity was 2.6% only***(18).***

In one of capecitabine escalating doses concurrent chemoradiation phase 1 studies reported by Dunst et al, in which hand foot syndrome was found as dose limiting toxicity with capecitabine dose of 1000mg/m2 twice a day during radio-therapy(19).

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Another phase 1 study by Ngan et al, has shown grade 3 diarrhea and skin reaction as dose limiting toxicity with capecitabine 1000mg/ m2 twice a day concurrent with radiotherapy(20). In our study This difference observed in toxicity profile may be attributed to the lower dose of capecitabine i.e. 825mg/m2 twice daily, used in our study.

CONCLUSION

For locally advanced rectal cancer patients, neoadjuvant induction chemotherapy followed by concurrentchemoradiotherapy with capecitabine is safe and well tolerable regimen with effective local control that may increase the utilization ofneoadjuvant treatment for loclly advanced rectal cancer patients.

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