OPEN AIMJ ORIGINAL ARTICLE

Evaluation of The outcome and Toxicity in Patient with Colon Cancer Treated With chemotherapy (Retrospective Study)

Islam Bekhit Ebrahim Salama [1]*M.B.B.Ch; Mohsen Salah El Din Zekry [1]MD; Hesham Abbas Al-Abady [1]MD.

Corresponding Author:
Islam Bekhit Ebrahim Salama
Islam.salama226@gmail.com

Received *for publication December 02, 2021;* ***Accepted*** *March 24, 2022;* ***Published online*** *March 24,2022.*

doi: *10.21608/aimj.2022.109136.1700*

[1]Clinical oncology and neuclear Medicine Department, Faculty of Medicine, Al-Azhar University, Cairo , Egypt.

ABSTRACT

Background: Colo-rectal cancer (CRC) is the third most frequent cancer in the world, and the fourth greatest cause of cancer-related death. Surgery is followed by adjuvant chemo-therapy with either single agent capecitabine or a mixture therapy, chemotherapy toxicity might damage a cancer patients quality of life and lead to treatment cessation early. Hematological, gastrointestinal, constitutional, dermatological, and neurological toxicity are all common.

Aim of The Work: To measure and evaluate chemotherapy toxicity in Colon patients undergoing adjuvant and metastatic treatment.

Patients and Methods: This was retrospective stud y involved 158 cases of colon cancer established adjuvant and palliative chemotherapy and at Clinical Oncology Department, El Hussein Hospital during the period from 2012 till 2018.

Results: We discovered that neurological toxicity is the most commonly reported side effect of chemotherapy, that older patients have a higher incidence of neurological toxicity and fatigue, that females have a higher incidence of anemia (increased Oxaliplatin cumulative dose increases the incidence of neurological toxicity, thrombocytopenia) and renal toxicity, and that older patients have a higher incidence of anemia (increased Oxaliplatin cumulative dose increases the incidence of neurological toxicity, thrombocytopenia) Oxaliplatin-containing regimens have a strong link to neurological toxicity, while capecitabine-containing regimens have a strong link to dermatological damage.

Conclusion: Neurological damage was the most common hazard documented with adjuvant treatment for CRC. Despite the fact that a variety of side effects were identified, the treatment regimes were well accepted, we should be aware of factors that could increase toxicity.

Keywords: *Adjuvant Chemo-therapy; Toxicity; Colorectal cancer.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*
Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

Cancer colon is the 3rd most frequently identified cancer in males and the second in females with 1.8million new patients and almost 861,000 deaths in 2018 agreeing to world health organization. [1] In Egypt, The new database on 2018 showed that the number of new cases of cancer was 128892 cases and the number of new cases of cancer colon was 3477 case which represents 2.7% of the newly discovered cases and this numbers more than numbers of 2017. [1]

As early-stage colon cancer is often asymptomatic, screening is critical for identifying treatable malignant tumor as well as detecting precancerous lesions (adenomatous colon polyps). The broad adoption of colorectal cancer screening has been substantially responsible for the drop in colorectal cancer incidence and mortality rates in recent decades.[2] Adjuvant chemotherapy seeks to eliminate micrometastatic disease present following curative surgical resection. Adjuvant chemotherapy is generally recommended to further decreasing rates of distant metastatic in all cases of stage III tumor and certain cases of stage II tumor. Therapy should be initiated after 8 weeks of surgery with FOLFOX every 2 weeks or XELOX every21 day. [3]

5-Fluorouracil is still the cornerstone of colon cancer chemotherapy regimens, both adjuvant and metastatic. Oral fluoropyrimidines such as capecitabine (Xeloda) and tegafur, in addition to 5-fluorouracil, are increasingly being utilized as monotherapy or in combination with Oxaliplatin (Eloxatin) and irinotecan (Camptosar). A prolonged continuous infusion of fluorouracil (FOLFIRI, FOLFOX) or capecitabine is used in some standard combination regimens (CAPOX, XELOX, and XELIRI).[4]

PATIENTS AND METHODS

This was retrospective study involved a total of 158 patients of colon cancer established adjuvant and palliative chemotherapy at Clinical Oncology Department, El Hussein Hospital during the period from 2012 till 2018.

158 suitable patients identified histopathologically confirmed carcinoma of colon .

The inclusion criteria were Patient with pathology confirming cancer colorectal either histologically or cytological, Patient younger than 70 years, Performance status 0 – 3 WHO. Received adjuvant chemotherapy or received palliative chemotherapy at clinical oncology department of El Hussein university hospital. -Follow up the patients for 2years as a progression free survival

Patients were omitted from the study if they had experienced - Patient who has double malignancy, Pathology other than colorectal cancer, Performance status 4 WHO and patient treated with surgery only were also excluded.

Defining the charts of included patients, data had been retrieved from the archive and the following data will be collected, Patient related data: Age, sex, family history, special habits (eg. smoking) ,comorbidity and performance status.

Disease related dated: Date of first diagnosis, extent of disease, histopathology including type of pathology, grade, Ras mutation test and site of metastases.

Treatment related data: (surgery and chemotherapy), (Type of surgery. Chemotherapy (regimens, number of cycles ,response and related toxicities -Progression free survival from data of starting treatment till 2 years, progression, death or last follow up. Overall survival from date of diagnosis till date of death

The statistical software for social science (SPSS) version 22 was used to collect, reviews, code, and enter the data. Quantitative data was provided as mean, standard deviations, and ranges, whereas qualitative data was presented as numbers and percentages. When the predicted count in any cell was less than 5, the Chi-square test and/or Fisher exact test were used to compare the groups' qualitative data. The CI was established to 9 5% So, the p-value was considered significant as the following:

$p > 0.05$: Non-significant (NS);$p < 0.05$: Significant (S); $p < 0.01$: Highly significant (HS). One-sided log-rank of Kaplan—Meier survival estimates had been used for statistical analysis of progression survival and progression free survival, while the unpaired T test and one way ANOVA test were used in the univariate analysis of the variables.

RESULTS

	Studied cases (No.= 158)		
		Frequency	Percent
Neurotoxicity	Yes	121	76.6%
	No	37	23.4%
Neurotoxicity grade (collective)	G1&G2	102	64.6%
	G3&G4	19	12.0%
	No	37	23.4%
Neurotoxicity grade	G1	14	8.9%
	G2	88	55.7%
	G3	12	7.6%
	G4	7	4.4%
	No	37	23.4%
	Total	158	100.0%
GIT toxicities	Yes	108	68.4
	No	50	31.6
Nausea	Yes	49	31.0
	No	109	69.0
Nausea grade (collective)	G1&G2	47	29.7
	G3&G4	2	1.3
	No	109	69.0
Nausea grade	G1	30	19.0
	G2	17	10.8
	G3	1	.6
	G4	1	.6
	No	109	69.0
Vomiting	Yes	44	27.8
	No	114	72.2
Vomiting grade (collective)	G1&G2	44	27.8
	No	114	72.2
Vomiting grade	G1	36	22.8
	G2	8	5.1
	No	114	72.2
Diarrhea	Yes	86	54.4
	No	72	45.6
Diarrhea grade (collective)	G1&G2	76	48.1
	G3&G4	10	6.3
	No	72	45.6
Diarrhea grade	G1	39	24.7
	G2	39	24.7
	G3	5	3.2
	G4	3	1.9
	No	72	45.6
	Total	158	100.0%

Table 1: Distribution of studied cases as regards neurotoxicity & its grade

The results revealed that the mean age of cases was 47.07± 12.9 years and ranged from 18 and 75 years. In relation to sex, more than half of the patients were female (59.5%), while (40.5%) were males. Table (1)

			Age (years)		p value
			<50 (n=78)	>=50 (n=80)	
Neurotoxicity					
Neurotoxicity grade	G1&G2	no	50	52	0.367
		%	64.1%	65.0%	
	G3&G4	no	12	7	
		%	15.4%	8.8%	
	no	no	16	21	
		%	20.5%	26.3%	
Hematological toxicities					
Anemia grade	G1&G2	no	24	29	0.810
		%	30.8%	36.3%	
	no	no	52	49	
		%	66.7%	61.3%	
	G3&G4	no	2	2	
		%	2.6%	2.5%	
Neutropenia grade	G1&G2	no	16	20	0.794
		%	20.5%	25.0%	
	no	no	49	47	
		%	62.8%	58.8%	
	G3&G4	no	13	13	
		%	16.7%	16.3%	
Thrombocytopenia grade	G1&G2	no	12	9	0.444
		%	15.4%	11.3%	
	no	no	66	71	
		%	84.6%	88.8%	
Organ affection					
Hepatic toxicity	G1&G2	no	13	14	0.889
		%	16.7%	17.5%	
	no	no	65	66	
		%	83.3%	82.5%	
Renal toxicity	G1&G2	no	2	10	0.018
		%	2.6%	12.5%	
	no	no	76	70	
		%	97.4%	87.5%	
Fatigue grade	G1&G2	no	11	15	0.546
		%	14.1%	18.8%	
	no	no	63	63	
		%	80.8%	78.8%	
	G3&G4	no	4	2	
		%	5.1%	2.5%	
Hypotension toxicity	yes	no	3	1	0.364
		%	3.8%	1.3%	
	no	no	75	79	
		%	96.2%	98.8%	
GIT toxicities					
Nausea grade	G1&G2	no	23	24	0.609
		%	29.5%	30.0%	
	no	no	55	54	
		%	70.5%	67.5%	
	G3&G4	no	0	2	
		%	0.0%	2.5%	
Vomiting grade	G1&G2	no	20	24	0.541
		%	25.6%	30.0%	
	no	no	58	56	
		%	74.4%	70.0%	
Diarrhea grade	G1&G2	no	29	47	0.020
		%	37.2%	58.8%	
	no	no	44	28	
		%	56.4%	35.0%	
	G3&G4	no	5	5	
		%	6.4%	6.3%	

Table 2: Association between age of the studied group and toxicity

There was no significant association between age of the studied group and Neurotoxicity grade.There was no significant association between age of the studied group and anemia grade . Also, there was no significant association between age of the studied group and neutropenia grade and there was no significant association between age of the studied group and thrombocytopenia grade (p= 0.444). Table (2)

			Sex		p value
			Male (n=64)	female (n=94)	
Neurotoxicity					
Neurotoxicity grade	G1&G2	no	40	62	0.802
		%	62.5%	66.0%	
	G3&G4	no	9	10	
		%	14.1%	10.6%	
	no	no	15	22	
		%	23.4%	23.4%	
Hematological toxicities					
Anemia grade	G1&G2	no	16	37	0.025
		%	25.0%	39.4%	
	no	no	48	53	
		%	75.0%	56.4%	
	G3&G4	no	0	4	
		%	0.0%	4.3%	
Neutropenia grade	G1&G2	no	11	25	0.022
		%	17.2%	26.6%	
	no	no	47	49	
		%	73.4%	52.1%	
	G3&G4	no	6	20	
		%	9.4%	21.3%	
Thrombocytopenia grade	G1&G2	no	10	11	0.476
		%	15.6%	11.7%	
	no	no	54	83	
		%	84.4%	88.3%	
Organ affection					
Hepatic toxicity	G1&G2	no	6	21	0.034
		%	9.4%	22.3%	
	no	no	58	73	
		%	90.6%	77.7%	
Renal toxicity	G1&G2	no	3	9	0.255
		%	4.7%	9.6%	
	no	no	61	85	
		%	95.3%	90.4%	
Fatigue grade	G1&G2	no	10	16	0.894
		%	15.6%	17.0%	
	no	no	51	75	
		%	79.7%	79.8%	
	G3&G4	no	3	3	
		%	4.7%	3.2%	
Circulatory problems					
Hypotension toxicity	yes	no	3	1	0.304
		%	4.7%	1.1%	
	no	no	61	93	
		%	95.3%	98.9%	
GIT toxicities					
Nausea grade	G1&G2	no	12	35	0.011
		%	18.8%	37.2%	
	no	no	52	57	
		%	81.3%	60.6%	
	G3&G4	no	0	2	
		%	0.0%	2.1%	
Vomiting grade	G1&G2	no	22	22	0.131
		%	34.4%	23.4%	
	no	no	42	72	
		%	65.6%	76.6%	
Diarrhea grade	G1&G2	no	32	44	0.393
		%	50.0%	46.8%	
	no	no	30	42	
		%	46.9%	44.7%	
	G3&G4	no	2	8	
		%	3.1%	8.5%	

Table 3: association between sex of the studied group and neurotoxicity and Hematological toxicities

Our results showed that there was no significant association between Folfox protocol of the studied group and neurotoxicity, anemia, neutropenia, thrombocytopenia, Circulatory problems, nausea and diarrhea grade. there was no significant association between Degramount protocol of the studied group and neurotoxicity, anemia, neutropenia, thrombocytopenia, Circulatory problems, nausea and diarrhea grade ,that there was no significant association between Xelox protocol of the studied group and neurotoxicity, anemia, neutropenia, thrombocytopenia, hepatic toxicity, renal toxicity, fatigue grade, Hypotension toxicity, nausea, vomiting grade There was significant association between Xelox protocol and hand foot syndrome. (p= 0.001). There was significant association between Xelox protocol and diarrhea grade (p= 0.027). Table (3).

Prognostic factors	Total no	No of events	Cumulative survival% at 3 years	Cumulative survival% at 5 years	Median survival time (months)	P value
Whole group	140	90	49.6%	28.7%	34.9	-
Sex						
male	59	43	42.4%	21.0%	31.5	0.082
female	81	47	66.4%	54.8%	34.2	
Age (years)						
<50	68	44	50.8%	29.6%	36.9	0.713
>=50	72	46	48.3%	28.2%	34.9	
Special habits (smoking)						
yes	56	38	44.2%	27.0%	31.9	0.391
no	84	52	53.1%	29.3%	38.2	
Family history						
yes	68	40	54.8%	37.4%	37.4	0.027
no	72	50	44.8%	19.7%	30.8	
DM presence						
yes	22	18	36.4%	NR	25.8	0.016
no	118	72	52.1%	31.8%	37.3	
HTN presence						
yes	14	10	42.9%	NR	31.5	0.475
no	126	80	50.4%	28.9%	36.9	
IHD presence						
yes	3	3	NR	NR	22.5	*
no	137	87	50.7%	29.4%	36.9	
Comorbidities presence						
yes	56	38	46.4%	27.1%	31.5	0.473
no	84	52	51.5%	29.8%	36.9	
Symptoms (IO)						
yes	40	26	48.7%	26.4%	34.9	0.753
no	100	64	50.0%	29.7%	32.8	
Symptoms (bleeding per rectum)						
yes	110	71	46.2%	29.2%	32.4	0.434
no	30	19	62.1%	29.1%	40.0	
Symptoms (constipation)						
yes	87	53	52.7%	31.0%	37.4	0.303
no	53	37	44.6%	25.0%	31.9	
colonoscopic biobsy						
yes	105	70	48.4%	28.2%	34.6	0.378
no	35	20	53.4%	32.4%	39.3	
Laterality						
right side	42	26	53.6%	32.5%	37.2	0.679
left side	98	64	48.0%	27.0%	34.8	
Grade						
II	105	55	57.0%	40.6%	40.2	<0.001
III	35	35	28.6%	NR	26.5	
Staging						
stage2,3A &3B	112	62	54.3%	38.6%	39.3	<0.001
stage3C	28	28	32.1%	NR	27.4	
Pathology (T)						
T2&T3	94	55	45.9%	34.8%	32.4	0.573
T4	46	35	56.5%	20.6%	37.3	
LN ratio						
<=0.2353	68	33	62.2%	47.4%	42.4	0.001
>0.2353	72	57	37.9%	11.0%	31.7	
Surgery type						
RT hemicolectomy	39	23	52.6%	36.0%	36.9	0.127
LT hemicolectomy	17	13	26.9%	17.9%	26.1	
others	84	54	53.0%	27.8%	39.3	
Folfox						
yes	90	61	47.4%	24.6%	34.6	0.532
no	50	29	53.7%	35.8%	37.3	
Degramont						
yes	29	12	70.5%	51.9%	NA	0.024
no	111	78	44.5%	23.2%	32.4	
Xelox						
yes	24	17	38.9%	22.2%	27.3	0.197

no	116	73	53.8%	30.1%	37.2	
D. delay c4						
yes	113	73	51.4%	28.6%	37.2	0.536
no	27	17	46.9%	29.8%	33.6	
D. delay c5						
yes	113	72	51.0%	28.7%	37.2	0.449
no	27	18	43.7%	29.5%	27.4	
Dose delay c6						
yes	107	69	51.7%	28.5%	37.3	0.536
no	33	21	42.9%	30.3%	30.8	
red.dose c2						
yes	48	28	55.7%	39.4%	40.6	0.094
no	92	62	46.2%	22.4%	33.6	
red dose c3						
yes	50	30	53.5%	37.8%	40.2	0.168
no	90	90	47.4%	22.9%	34.6	
Neurotoxicity						
yes	112	69	51.6%	30.9%	37.2	0.230
no	28	21	41.9%	21.0%	31.4	
Hematological toxicities						
yes	70	33	47.8%	24.1%	34.8	0.770
no	70	28	50.9%	32.0%	36.9	
GIT toxicities						
yes	93	59	40.6%	29.4%	31.3	0.139
no	47	31	65.9%	29.0%	40.9	
Circulatory problems						
yes	52	40	53.8%	20.3%	37.1	0.596
no	88	50	47.2%	37.0%	32.4	
Dermatological toxicities						
yes	56	39	58.4%	20.9%	39.8	0.746
no	84	51	43.7%	33.8%	31.7	

Table 4: prognostic factors of progression-free survival (PFS), Cumulative survival% at 3 years, Cumulative survival% at 5 years and Median survival time

The predictors of progression-free survival (PFS). We identified six independent factors as significantly predictive of progression-free survival. It was found that family history, presence of DM, grade III, stageII,IIIA &IIIB, LN ratio ≤0.2353, GIT toxicities and Degramont protocol were significant independent factors associated with decreased progression-free survival. Table (4)

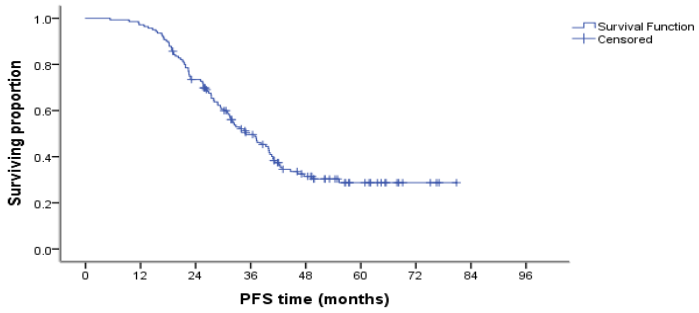

Fig. 1: Kaplan–Meier curve of PFS for survival time

DISCUSSION

In 2016, colorectal cancer is predicted to be the third highest reason of cancer death in the United States, with 134 490 new cases and 49 190 fatalities. While colorectal cancer incidence and mortality rates among persons aged 50 and older have dropped in recent years in the United States, the similar trend has not been seen among patients aged 20 to 49. The lower mortality rate among those aged 50 and up may be due to the usage of colorectal cancer screening, which is recommended for adults in this age group. [5] As regard Distribution of studied cases as regards neurotoxicity & its grade, our results revealed that 121 (76.6%) of studied cases had neurotoxicity. 88 (55.7%) of studied cases had grade 1 neurotoxicity, 14 (8.9%) cases had grade 2, 12 (7.6%) of cases had grade 3 and 7 (4.4%) of cases had grade 4.

Toxicity of peripheral nervous system is a well-known adverse effect of Oxaliplatin, which limits its applicability. In agreement with our results Wiela-Hojeńska et al., [6] reported that 75.0 percent of the treated cases affected by neurotoxicity, among whom 8.3 percent established intolerable paresthesia and/or significant loss of muscle strength (severity grade 3). They also reported that symptoms were significantly more severe in patients who were administered more cycles of the FOLFOX-4 regimen

Also, Argyriou et al., [7] According to the NCI-CTC v3 neurosensory criteria, 146 of 170 patients (85.9%) had acute OXLIPN (Oxaliplatin-induced peripheral neuropathy), and 123 of 170 patients (72.4 percent) later displayed varied degrees of chronic, cumulative OXLIPN. Twenty-three individuals who received acute OXLIPN did not experience cumulative neurotoxicity at the end of treatment.

Furthermore, Argyriou et al., [8] Acute neuropathy is present in the majority of Oxaliplatin-treated individuals (86%) and is precipitated by exposure to cold. It is usually brief and disappears within hours or days.

In addition, Ruzzo et al., [9] Neutropenia was the most common fluoropyrimidines-related side event, followed by diarrhea. They also reported that thrombocytopenia occurred in 1.2 percent of the individuals analysed and anemia in 0.4 percent.

43ee3While the study by Wiela-Hojeńska et al., [6] reported that in cases treated with FOLFOX-4 regimen, there were 76.7% of patients have Nausea/vomiting 41% of them were grade 1

I 41.7 % of cases had Diarrhea of them 27.1 of grade 1, while in patients treated with CLF-1 regimen there were 78.7% of patients have Nausea/vomiting 31.7% of them were grade 3 and 50 % of cases had Diarrhea of them 18.8% for of grade 2 and 3 each.

Whereas Keefe et al., [10]reported that Cumulative incidence of diarrhea was 30 % at Cycle 1 for the FOLFOX regimens, but 50 % in the smaller FOLFIRI group. By Cycle 4, the cumulative incidences were 50 and 90 %, respectively.

The variation in the incidence of these side effects may be attributed to the variation in sample size, age and genetic factors.

Furthermore, Bruera et al., [11] reported that preventive increasing G3-5 toxicities were: asthenia 14%, diarrhea 17%,neutropenia 17%, mucositis 6%, hypokalemia 7%, hyper transaminasemia 7%, nausea/vomiting, hypo albuminemia, anemia, Our results revealed that there was no significant association between age of the studied group and Neurotoxicity grade, anemia grade, neutropenia grade, thrombocytopenia grade, nausea grade, vomiting grade. Diarrhea grade 1&2 and Oral mucositis was significantly higher in age group ≥50 years compared to age <50 years

Our results were reinforced by Argyriou et al., [7] as they stated that there was no significant association between age with the studied group and acute Oxaliplatin-induced peripheral neuropathy.

In contrast to our results Wiela-Hojeńska et al., [6] reported that a statistically significant correlation was demonstrated between the patient's age and the incidence of some of the side effects of the FOLFOX-4 regimen.

In disagreement with our result Molassiotis et al., [12] reported that there was no significant association between age of the studied group and Neuro toxicity grade. That was supported by the study Bandos et al., [13] who reported that older age somewhat contributed to chemotherapy- induced peripheral neuropathy. Thrombocytopenia 3%, respectively. One case of toxic death (3%) was observed.

Our results showed that there was no significant association between Folfox protocol of the studied group and neurotoxicity, anemia, neutropenia, thrombocytopenia, Circulatory problems, nausea and diarrhea grade.

While the study by Wiela-Hojeńska et al., [6] reported that Paresthesia was also revealed to be a neurotoxic effect of the FOLFOX-4 regimen after termination of therapy. A statistically significant relationship was observed between the use of vitamin supplements and the incidence and severity of the toxicity of the FOLFOX-4 regimen.

Regarding prognostic factors of overall survival, Cumulative survival% at 3 years, Cumulative survival% at 5 years and Median survival time, our results revealed that 61 (43.6%) were died. The median follow up was 31.39 months. We identified five independent factors as significantly predictive of decreased survival. It was found that presence of DM, grade III, stage2, 3A &3B, LN ratio ≤0.2353 and GIT toxicities were independent factors associated with decreased survival. We also identified six independent factors as significantly predictive of progression-free survival. It was found that family history, presence of DM, grade III, stage2,3A &3B, LN ratio ≤0.2353, GIT toxicities and Degramont protocol were significant independent factors associated with decreased progression-free survival.

In disagreement with our results the study by Rambach et al., [14] reported that sex was significantly associated with the overall survival (p=.04).

Our results were in line with Manjelievskaia et al., [15] who reported that among patients who received surgery and postoperative systemic chemotherapy, no significant differences were observed in survival between age groups. In addition, the HR was not lower for surgery and chemotherapy than the HR for surgery alone, given age group and tumor stage.

Furthermore, our result was supported by the study by Rambach et al., [14] reported that age was not significantly associated with the overall survival (p=.651).

Moreover, Wagner et al., [16] reported that in patients with metastatic colorectal cancer, an association between treatment with FOLFOX or trifluridine/tiperacil and improved median survival in patients with neutropenia (media survival in patients with grade III/IV neutropenia versus without neutropenia for FOLFOX 20. versus 12.5 months, p<.001; for trifluridine/ tiperacil 9.8 versus 4.4 months) has been reported.

CONCLUSION

The most generally toxicity stated during adjuvant treatment in CRC was neuro- logical toxicity. While a change of contrary reactions were reported the treatment regimens were tolerated but we should take care of factors that may in- crease certain toxicity.

REFERENCES

1. GLOBCON Cancer fact sheets colorectal cancer cited on MAY, 2019.
2. Cancer Facts & Figures. American Cancer Society. Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. Accessed: February 19, 2020.
3. Bertelsen CA. Complete mesocolic excision an assessment of feasibility and outcome. *Dan Med. J*. 2017; 64(2).
4. Arkenau HT, Arnold D, Cassidy J, Diaz-Rubio E, Douillard JY, Hochster H, et al. Efficacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: a pooled analysis of randomized trials. *J Clin Oncol*. 2008 ; 26(36):5910-7.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: *a cancer journal for clinicians*. 2016; 66(1): 7-30.
6. Wiela-Hojeńska A, Kowalska T, Filipczyk-Cisarż E, Łapiński Ł, Nartowski K. Evaluation of the toxicity of anticancer chemotherapy in patients with colon cancer. *Advances in Clinical and Experimental Medicine*. 2015; 24(1):103-11.
7. Argyriou AA, Cavaletti G, Briani C, Velasco R, Bruna J, Campagnolo M, et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. *Cancer*. 2013; 119(2): 438-44.
8. Argyriou AA, Kyritsis AP, Makatsoris T, Kalofonos HP. Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. *Cancer management and research*. 2014; 6:135.
9. Ruzzo A, Graziano F, Galli F, Giacomini E, Floriani I, Galli F, et al. Genetic markers for toxicity of adjuvant oxaliplatin and fluoropyrimidines in the phase III TOSCA trial in high-risk colon cancer patients. *Scientific reports*. 2014; 4(1):1-7.
10. Keefe DM, Elting LS, Nguyen HT, Grunberg SM, Aprile G, Bonaventura A, et al. Risk and outcomes of chemotherapy-induced diarrhea (CID) among patients with colorectal cancer receiving multi-cycle chemotherapy. *Cancer chemotherapy and pharmacology*. 2014; 74(4):675-80.
11. Bruera G, Ricevuto E. Toxicity syndromes, patient-related clinical indicator of toxicity burden induced by intensive triplet chemotherapy-based regimens in gastrointestinal cancers with metastatic disease. *Frontiers in oncology*. 2020; 10:172.
12. Molassiotis A, Cheng HL, Leung KT, Li YC, Wong KH, Au JS, et al. Risk factors for chemotherapy- induced peripheral neuropathy in patients receiving taxane- and platinum- based chemotherapy. *Brain and behavior*. 2019; 9(6):e01312.
13. Bandos H, Melnikow J, Rivera DR, Swain SM, Sturtz K, Fehrenbacher L, et al. Long-term peripheral neuropathy in breast cancer patients treated with adjuvant chemotherapy: NRG Oncology/NSABP B-30. JNCI: *Journal of the National Cancer Institute*. 2018; 110(2):djx162.
14. Rambach L, Bertaut A, Vincent J, Lorgis V, Ladoire S, Ghiringhelli F. Prognostic value of chemotherapy-induced hematological toxicity in metastatic colorectal cancer patients. *World journal of gastroenterology: WJG*. 2014; 20(6):1565.
15. Manjelievskaia J, Brown D, McGlynn KA, Anderson W, Shriver CD, Zhu K. Chemotherapy use and survival among young and middle-aged patients with colon cancer. *JAMA surgery*. 2017; 152(5):452-9.
16. Wagner AD, Grothey A, Andre T, Dixon JG, Wolmark N, Haller DG, et al. Sex and adverse events of adjuvant chemotherapy in colon cancer: an analysis of 34 640 patients in the ACCENT database. *JNCI: Journal of the National Cancer Institute*. 2021; 113(4):400-7.