FLOT; To Be Treated as a Highly Emetogenic Regimen or a Moderately Emetogenic One? Comparison of the Emetogenic Potential of FLOT versus FOLFOX and TAC Regimens

Marziyeh Ghorbani
Shiraz University of Medical Sciences Shiraz Institute for Cancer Research
Mehdi Dehghani
Shiraz University of Medical Sciences Medical School
Noushin Fahimfar
Tehran University of Medical Sciences Endocrinology and Metabolism Research Institute
Soha Namazi
Tehran University of Medical Sciences School of Pharmacy
Ali Dehshahri (a.dehshahri@gmail.com)
Shiraz University of Medical Sciences School of Pharmacy

Research Article

Keywords: FLOT, Nausea, Vomiting, Gastric Cancer, Chemotherapy-induced Nausea and Vomiting

Posted Date: November 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1017987/v1

Abstract

Purpose

The current study aimed at investigating the efficacy of aprepitant-containing triple antiemetic regimen in FLOT (Fluorouracil+Leucovorin+Oxaliplatin+Docetaxel) recipients as well as the emetogenic potential of FLOT regimen, through comparison of nausea and vomiting rates in a moderately emetogenic chemotherapy, FLOT, and a highly emetogenic chemotherapy recipients.

Study

Patients planned to receive one of FLOT, FOLFOX (Fluorouracil+Leucovorin+ Oxaliplatin/moderate-emetic-risk), or TAC (Docetaxel+Doxorubicin+Cyclophosphamide/high-emetic-risk) regimens were recruited. All patients were treated with the same triple antiemetic regimen containing aprepitant.

Results

A total of 165 chemotherapy-naïve patients (52 FLOT recipients) were eligible to enter the study. At the end of day five, “complete response” (primary efficacy endpoint) was achieved by 84.6%, 63.5%, and 61.5% of the FLOT-receiving patients in acute, delayed, and overall phases, respectively. A significant difference was seen among the odds of FLOT recipients and FOLFOX recipients concerning “complete response” achievement in delayed (p=0.014) and overall (p=0.017) phases, “no emesis” in delayed (p=0.018) and overall (p=0.010) phases, also “complete protection” in acute (p=0.023), delayed (p=0.009) and overall (p=0.006) phases; however, the difference between the odds of FLOT recipients and TAC recipients, in relation to achieving these endpoints was insignificant. FLOT group showed significantly faster time-to-antiemetic regimen failure and time-to-first emetic episode in comparison to the FOLFOX group, which was insignificant in comparison to the TAC group.

Conclusion

According to the findings, FLOT has to be considered as a high-emetic-risk regimen. To better management of highly emetogenic regimens, antiemetic guidelines recommend adding olanzapine to aprepitant-containing triple antiemetic regimen besides continuing dexamethasone and olanzapine administration on days 2-4.

Introduction:

Frequently reported nausea, vomiting, and retching caused by moderately and highly emetogenic chemotherapy are among the most distressing adverse events from patients’ point of view. Adequate management of these adverse events which are the result of cytotoxic agent administration and cancer itself, is clinically serious due to the high impact on the effectiveness of therapy and, patient’s quality of life and decision to continue the therapy [1, 2].

Several factors affect the incidence and severity of chemotherapy-induced nausea and vomiting (CINV), being divided into patient-related (including age, sex, history of alcohol consumption, motion sickness, history of pregnancy-associated emesis, anxiety, CINV expectation, concomitant use of opioids, and serotonin specific reuptake inhibitors-each of the first three may cause a 10-15% absolute difference in the chance of vomiting with highly emetogenic chemotherapy) and antineoplastic agent-related factors (including intrinsic emetogenicity of the given antineoplastic agent, dose, route of administration and schedule) [3, 4].

Since the strongest prognostic factor for emesis is the emetogenic potential of each chemotherapeutic agent [5], Hesketh et al. [6] proposed a five-level classification based on this factor which was determined by the percentage of patients showing acute emesis when chemotherapy was administered in the absence of antiemetic prophylaxis. This emetogenicity schema was modified to a four-level classification of highly (emetic risk: >90%), moderately (30-90%), low (10-30%) and minimal (<10%) emetogenic agents later in 2004 [7]. Emetic risk determination and appropriate antiemetic prophylaxis selection for antineoplastic combinations are based on the “component antineoplastic agent of greatest emetic risk” [8].

Although Hesketh et al. classification system affords important information that builds the very first steps in proper antiemetic prophylaxis administration and acceptable CINV management in the acute phase, it is accompanied by some limitations; i.e., it underestimates the risk of delayed emesis and, nausea in acute and delayed phases [9] and no row in the table is allocated to each antineoplastic combination for which the net emetogenic potential may be higher than that of the component antineoplastic agent with greatest emetic risk. However, this classification system is not rigid and the trials performed concerning CINV made changes leading to improvement of the system over time. The foremost example of the system improvement is Anthracycline and Cyclophosphamide (AC) combination, which was primarily considered to be moderately emetogenic but its substantial risk of nausea and emesis demonstration by trials led to the elevation of its emetic risk level [7].

The limitations of the Hesketh et al. classification system also seem to become evident when guideline-directed antiemetic regimen for managing FLOT-induced nausea and vomiting fails to meet the expectations.

With its demonstrated superiority over ECF/X (Epirubicin, Cisplatin, Fluorouracil/Capecitabine), the FLOT regimen is accepted as the best standard perioperative treatment in locally advanced (≥cT2 and/or cN+ [10]) gastric cancer -the fifth most common cancer worldwide with over one million estimated new cases annually [11]- and esophagogastric junction (EGJ) cancer [12]. FLOT is also effective in metastatic gastric and EGJ cancers as a docetaxel-based chemotherapy [10].

According to Hesketh et al. classification, FLOT is classified as a moderately emetogenic antineoplastic regimen; however, following the administration of the guideline-directed antiemetic regimen (to control nausea and vomiting caused by moderately emetogenic antineoplastic regimen), the percentage of FLOT recipients with nausea and vomiting, especially in the delayed phase, is much higher than what is

expected according to previous studies on moderately emetogenic chemotherapies, such as FOLFOX regimen [13]. Hence, it is a prerequisite to determine whether the appropriate antiemetic prophylaxis administration and acceptable CINV management have been done correctly or not. In order to address this issue and investigate the FLOT regimen characteristic from an emetogenic potential aspect, we aimed to compare “no emesis”, “complete response (CR)”, and “complete protection (CP)” rates in a group of gastric or EGJ cancer patients receiving FLOT, to the rate of mentioned endpoints in two groups of patients: a group of moderately and a group of highly emetogenic chemotherapy recipients when the same three-drug antiemetic combination with aprepitant was administered to all patients as prophylaxis.

To the best of our knowledge, currently there is no study aimed at specifically assess the efficacy of the aprepitant-containing antiemetic combination in FLOT-receiving patients (the primary objective of this study). Also, no study particularly investigated FLOT regimen characteristic from the emetogenic potential aspect (secondary objective of the current study).

Patients And Methods:

1. Study Design, Inclusion and Exclusion Criteria:

This was a prospective, observational, comparative study conducted between November 2018 and February 2020, at three centers affiliated to Shiraz University of Medical Sciences (SUMS), Shiraz, Iran.

Eligible patients were 18 years and older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, for whom, locally advanced or metastatic gastric or EGJ cancer (1st group), colorectal cancer (2nd group), and breast cancer (3rd group) was diagnosed by oncologist according to the diagnostic tests and were planned to receive their first cycle of neoadjuvant or adjuvant FLOT, FOLFOX, and TAC regimens, respectively (chemotherapy-naïve). Molecular targeted therapy was allowed.

A three-drug antiemetic combination including 125 mg-PO aprepitant, 8 mg-IV ondansetron, and 12mg-IV dexamethasone (30 minutes prior to chemotherapy administration) on day 1 and 80 mg-PO aprepitant on days 2 and 3 was administered to all the patients. Exclusion criteria were defined according to previous studies then, adapted to the research conditions [13, 14]. Additional exclusion criteria were receiving radiation therapy to the abdomen or pelvis within 1 week prior to chemotherapy and treatment with CYP3A4 inducers less than four weeks or an inhibitor or substrate of CYP3A4 one week before chemotherapy administration [15].

This study is conducted in compliance with the principles of the Declaration of Helsinki and the national norms and standards for conducting medical research in Iran .All patients provided written informed consent to participate in the study.

2. Efficacy Endpoints:

The primary efficacy endpoint was the proportion of patients with “CR” (no emesis and no rescue medication use) during 120 hours after initiation of chemotherapy (overall phase) in cycle 1.

Key secondary efficacy endpoints included “CR” during the acute and delayed phases as well as “no emesis” and “CP” (no emesis, no rescue medication use, no more than mild nausea) during acute, delayed, and overall phases in the cycle 1. As exploring rescue medication use, at the end of the study, revealed that all rescue medication consumers had vomiting and/or retching and/or great/severe nausea, “CR” was also defined as no emesis and less than great/severe nausea.

Time-to-antiemetic treatment failure (rescue medication use which was due to emesis or great/severe nausea) and time-to-first emetic episode were other endpoints of this study.

“No significant nausea” (none or mild nausea) rate in acute, delayed, and overall phases is also reported to evaluate the efficacy of the aprepitant-containing antiemetic combination in FLOT-receiving patients.

3. Assessment:

Patients were assessed prior to chemotherapy and then every 24 hours from the start of chemotherapy till the end of day 5. Any nausea, vomiting, and retching occurring within 24 hours after the initiation of chemotherapy was defined as acute, while nausea, vomiting, and retching occurring between 24 and 120 hours after the start of the chemotherapy was defined as delayed.

An emetic episode was defined as any episode of vomiting or retching (non-productive vomiting) or combined vomiting/retching. An interval of at least one minute between two emetic episodes was required to characterize discrete emetic episodes.

Culturally and linguistically adapted, translated-into-Persian version of Rhodes Index of Nausea, Vomiting and Retching (Rhodes INVR) [16] was applied to investigate the frequency and distress (none, mild, moderate, severe, great) of nausea, vomiting, and retching in the round on patient prior to chemotherapy and at the end of the acute phase and also, on daily phone conversations in the delayed phase.

All the patients were trained to take ondansetron in acute and metoclopramide in the delayed phase if an emetic episode and/or great to severe nausea occurred. Rescue medication use was then reported to investigators.

4. Statistical Analysis:

In a trial on FLOT regimen [17], emesis rate was 44.4% (grade 1/2: 40.7% and grade 3/4: 3.7%) and nausea rate was 66.7% (grade 1/2: 61.1% and grade 3/4: 5.6%); so, the incidence of emesis and nausea requiring treatment is assumed 50% (44.4%: all grade emesis plus 5.6%: grade 3/4 nausea) and the other 50% being “CR”. A pilot study including 14 FLOT recipients was performed to choose the expected “CR” rate, which resulted in 71.4% (10/14) “CR”. To set an expected “CR” rate of 70%, a sample size of 50 patients (being 55 patients, assuming 10% drop out or withdraw) is required to provide a power of 80% and overall significance level of 0.05, assuming a two-sided test [18].

Aprepitant-containing antiemetic regimen efficacy in FLOT recipients (the primary objective of the study) was reported as frequency and proportion of patients achieving efficacy endpoints.

In order to present patient characteristics, the only continuous variable, i.e. age, was summarized as mean (Std. Deviation) and categorical variables as frequencies and proportions. To explore characteristics distribution homogeneity among three different antineoplastic regimen groups, one-way ANOVA and chi-square (or Fisher's exact) tests were applied for continuous (age) and categorical variables, respectively.

Inter-group comparison of the number of emetic episodes in acute, delayed and overall phases, separately, was performed using Kruskal-Wallis test and the different group was determined by pairwise comparisons. The Bonferroni correction was used to adjust for multiple comparisons.

Logistic regression was applied not only to adjust for covariates (including age, sex, BMI (Body Mass Index), concomitant opioid consumption, concomitant tobacco/cigarettes consumption, motion sickness, CINV expectation, alcohol consumption, neoadjuvant/adjuvant chemotherapy, stage of cancer and history of pregnancy-associated emesis) in assessing antineoplastic regimen effect on the risk of acute, delayed and overall CINV, being expressed as odds ratios (OR) with 95% confidence intervals but also, to explore the risk factors for CINV. Hence, univariable analysis was performed primarily, then multivariable logistic regression analysis (Wald's test) by the backward method was performed on items with a significance level of less than 20%.

Cox proportional hazards regression analysis was performed to estimate hazards ratios (HR) and 95% confidence intervals for the time-to-antiemetic regimen failure (vomiting, retching, or severe nausea occurrence) and time-to-first emetic episode, concerning the different antineoplastic regimens.

All reported *p*-values correspond to two-sided tests and those *p*-values lower than 0.05 were considered to be statistically significant. Statistical analysis was carried out using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results:

1. Patients:

Among a total of 182 chemotherapy-naïve patients who were enrolled in this study, 165 patients (63 patients in the TAC group, 52 patients in FLOT group and 50 patients in FOLFOX group) met the eligibility criteria and were included in the analysis. In the TAC group, migraine was the leading cause of exclusion while in the FLOT group, tumor site causing obstruction resulted in patients' ineligibility.

The mean age (Std. Deviation) of the patients in the FOLFOX, FLOT, and TAC groups were 57.34 (11.621), 55.60 (12.693), and 42.57 (7.219), respectively. The other baseline characteristics of the patients are described in Table 1. The Low rate of positive alcohol consumption, concomitant use of opioids, and motion sickness may lead to the lack of power in testing the relationship between these factors and CINV occurrence.

Table 1
Patient Characteristics

Characteristics	FOLFOX (N=50) n (%)	FLOT (N=52) n (%)	TAC (N=63) n (%)	Total (N=165) n (%)
Sex				
Male	28 (56.0)	36 (69.2)	0 (0.0)	64 (38.8)
Female	22 (44.0)	16 (30.8)	63 (100)	101 (61.2)
BMI				
Underweight (<18.5 kg/m^2)	5 (10.0)	17 (32.7)	0 (0.0)	22 (13.3)
Normal (18.5-24.9 kg/m^2)	24 (48.0)	29 (55.8)	25 (39.7)	78 (47.3)
Overweight (25-29.9 kg/m^2)	12 (24.0)	4 (7.7)	27 (42.9)	43 (26.1)
Obese (30-39.9 kg/m^2)	9 (18.0)	2 (3.8)	11 (17.5)	22 (13.3)
Alcohol Consumption				
Almost Daily	1 (2.0)	3 (5.8)	0 (0.0)	4 (2.4)
None	49 (98.0)	49 (94.2)	63 (100.0)	161 (97.6)
Concomitant Use of Opioids				
Positive	2 (4.0)	9 (17.3)	2 (3.2)	13 (7.9)
Negative	48 (96.0)	43 (82.7)	61 (96.8)	152 (92.1)
Concomitant Use of Tobacco/Cigarettes				
Positive	10 (20.0)	17 (32.7)	13 (20.6)	40 (24.2)
Negative	40 (80.0)	35 (67.3)	50 (79.4)	125 (75.8)
Motion Sickness				
Positive	5 (10.0)	1 (1.9)	12 (19.0)	18 (10.9)
Negative	45 (90.0)	51 (98.1)	51 (81.0)	147 (89.1)
CINV Expectation				
Positive	11 (22.0)	9 (17.3)	34 (54.0)	54 (32.7)
Negative	39 (78.0)	43 (82.7)	29 (46.0)	111 (67.3)
Neoadjuvant/Adjuvant Chemotherapy				

Characteristics	FOLFOX (N=50)	FLOT (N=52)	TAC (N=63)	Total (N=165)
	n (%)	n (%)	n (%)	n (%)
Neoadjuvant	21 (42.0)	35 (67.3)	29 (46.0)	85 (51.5)
Adjuvant	29 (58.0)	17 (32.7)	34 (54.0)	80 (48.5)
Stage of Cancer				
I	1 (2.0)	6 (11.5)	22 (34.9)	29 (17.6)
II	5 (10.0)	8 (15.4)	27 (42.9)	40 (24.2)
III	25 (50.0)	15 (28.8)	14 (22.2)	54 (32.7)
IV	19 (38.0)	23 (44.2)	0 (0.0)	42 (25.5)
History of Pregnancy-Associated Emesis				
Positive	11 (52.4)	8 (53.3)	38 (69.1)	57 (62.6)
Negative	10 (47.6)	7 (46.7)	17 (30.9)	34 (37.4)

2. Efficacy of Aprepitant-Containing Triple Antiemetic Regimen in FLOT Recipients:

The primary efficacy endpoint, “CR”-overall phase, was achieved in 61.5% (32/52) of FLOT recipients. The percentage of the FLOT-receiving patients achieving other efficacy endpoints in acute, delayed, and overall phases are shown in Fig. 1.

3. FLOT Regimen Characteristic from Emetogenic Potential Aspect:

In order to explore the emetogenic potential of the FLOT regimen (secondary objective of the current study), we compared “CR”, “no emesis” and “CP” rates in acute, delayed, and overall phases among FLOT and each of FOLFOX and TAC groups. The frequency and proportion of the patients achieving each endpoint are shown in Table 2.

Table 2
Frequency and Proportion of the Patients, Achieving Each Efficacy Endpoint

Efficacy Endpoint	FOLFOX (N=50) n (%)	FLOT (N=52) n (%)	TAC (N=63) n (%)
Acute Phase			
No Emesis	49 (98.0)	46 (88.5)	58 (92.1)
Complete Response	48 (96.0)	44 (84.6)	54 (85.7)
Complete Protection	48 (96.0)	44 (84.6)	52 (82.5)
Delayed Phase			
No Emesis	46 (92.0)	38 (73.1)	45 (71.4)
Complete Response	42 (84.0)	33 (63.5)	35 (55.6)
Complete Protection	40 (80.0)	29 (55.8)	31 (49.2)
Overall Phase			
No Emesis	45 (90.0)	37 (71.2)	43 (68.3)
Complete Response	41 (82.0)	32 (61.5)	33 (52.4)
Complete Protection	39 (78.0)	28 (53.8)	27 (42.9)

Comparison among FLOT and each of FOLFOX and TAC groups, concerning endpoint-achieving rates, was performed using logistic regression to adjust for covariates. As shown in Table S_1. (Online Resource 1, which presents the odds of achieving each endpoint; adjusted for covariates), the odds ratios indicate the significant difference among FLOT and FOLFOX regimens and non-significant difference among FLOT and TAC in relation to the rates of “CR”, “no emesis” and “CP” in the delayed and overall phases, also “CP” in the acute phase. The difference is significant among FLOT and FOLFOX, also, FLOT and TAC concerning “CR” and “no emesis”, in the acute phase. To explain in detail:

The odds of the FOLFOX recipients achieving “CR” in the overall phase is 3.145 times as high as the odds of FLOT recipients (95%C.I.: 1.232-8.025, *p*=0.017) while the odds of TAC recipients is only 1.006 times as high as the odds of FLOT recipients (95%C.I.: 0.446-2.271, *p*=0.989). Since the patients in the FOLFOX group are 3.398 times more likely to achieve “CR” in the delayed phase (95% C.I.: 1.284-8.990, *p*=0.014), patients in the TAC group are only 1.099 times (95%C.I.: 0.480-2.519, *p*=0.823) more likely than FLOT group.

The odds of achieving “no emesis” in the overall phase is 365.8% higher if the patients are receiving FOLFOX (OR=4.658, C.I.: 1.455-14.910, *p*=0.010) as opposed to the ones receiving FLOT. The odds for achieving this endpoint is 89.6% higher if the patient is planned to receive TAC (OR=1.896, C.I.: 0.671-

5.361, *p*=0.228) as opposed to the patients in the FLOT group. While individuals in the FOLFOX group show more than 300% increase in the odds of achieving “no emesis” in the delayed phase (OR=4.237, C.I.: 1.287-13.946, *p*=0.018), the ones in the TAC group show only a 7.9% decrease (OR=0.921, C.I.: 0.405-2.094, *p*=0.844) in comparison to patients in FLOT group.

In comparison to FLOT recipients, the odds of achieving “CP” in the overall phase is 3.784 and 2.354 times greater for FOLFOX (C.I.: 1.459-9.816, *p*=0.006) and TAC (C.I.: 0.782-7.088, *p*=0.128) patients, respectively. The FOLFOX recipients’ odds of achieving “CP” in the delayed phase is approximately three and a half fold greater (OR=3.428, C.I.: 1.355-8.669, *p*=0.009) than the FLOT recipients’ odds and TAC recipients’ odds is more than one and a half fold higher (OR=1.672, C.I.: 0.674-4.149, *p*=0.267) than FLOT recipients’ odds.

While antineoplastic regimen is the only significantly associated factor (multivariable logistic regression) with “no emesis” in the delayed phase, antineoplastic regimen and sex are both the statistically significant associated ones with “no emesis” in acute and overall phases, also “CR” and “CP” in the acute phase. Antineoplastic regimen and CINV expectation are statistically significant predictive factors for “CR” not only in the delayed phase but also in the overall phase.

Antineoplastic regimen, age, and CINV expectation are significantly associated with “CP” in the delayed phase, and antineoplastic regimen, age, and sex are the significant predictive factors for “CP” in the overall phase.

As mentioned earlier, the history of pregnancy-associated emesis was explored only in 55.15% (91/165) of the patients who had pregnancy experience and it was statistically significant in the univariable analysis only for “CR” in delayed and overall phases. Hence, multivariable logistic regression (Backward-Wald’s test) was performed again on these endpoints including all previously recognized significant predictive factors (*p*-value<0.2 in univariable analysis except sex) and history of pregnancy-associated emesis. The outcome clarifies that the FOLFOX recipients’ odds of achieving “CR” in the delayed phase is more than seven and a half fold greater (OR=7.723, C.I.: 1.474-40.454, *p*=0.016) than the FLOT recipients’ odds and TAC recipients’ odds is two folds higher (OR=2.035, C.I.: 0.598-6.924, *p*=0.256) than FLOT recipients’ odds. In comparison to FLOT recipients, the odds of achieving “CR” in the overall phase is 8.829 and 3.225 times greater for FOLFOX (C.I.: 1.702-45.812, *p*=0.010) and TAC (C.I.: 0.856-12.149, *p*=0.084) patients, respectively. Significant predictive factors are as follows: “CR”-delayed phase: CINV expectation, “CR”-overall phase: antineoplastic regimen, history of pregnancy-associated emesis, and CINV expectation.

Time-to-antiemetic prophylaxis failure (vomiting, retching, or great/severe nausea occurrence) was analyzed using Cox proportional hazards regression, adjusting for sex, age, CINV expectation, antineoplastic regimen, and stage of cancer. The results reveal that while the rate of failure in the FLOT group is 2.63 times as fast as the rate in the FOLFOX group ($HR_{(FOLFOX/FLOT)}$=0.380, C.I.: 0.172-0.842, *p*=0.017), the rate of failure is 1.38 times as fast as the rate in TAC group ($HR_{(TAC/FLOT)}$=0.724, C.I.: 0.365-

1.439, p=0.357), denoting the significant difference among FLOT and FOLFOX regimens and non-significant difference among FLOT and TAC regimens Fig. 2.

This analysis was performed for the second time, in 55.15% (91/165) of the patients with pregnancy experience, to adjust not only for age, CINV expectation, antineoplastic regimen, and stage of cancer but also, for the history of pregnancy-associated emesis (as it was a significant factor in the univariable analysis of “CR”-overall phase). The results indicate that the failure rate in the FLOT group is 3.650 and 1.580 times as fast as the rate of failure in FOLFOX ($HR_{(FOLFOX/FLOT)}$=0.274, C.I.: 0.084-0.887, p=0.031) and TAC ($HR_{(TAC/FLOT)}$=0.633, C.I.: 0.305-1.314, p=0.220) groups, respectively.

The significant difference among FLOT and FOLFOX and insignificant difference among FLOT and TAC was repeated when Cox proportional hazards regression was also used for time-to-first emetic episode analysis, adjusting for sex, age, antineoplastic regimen, and stage of cancer. The outcome reveals that in FLOT recipients, emesis occurred more than three and a half fold as fast as emesis occurrence in patients receiving FOLFOX ($HR_{(FOLFOX/FLOT)}$=0.268, C.I.: 0.096-0.746, p=0.012) and more than one and a half fold as fast as emesis occurrence in TAC recipients ($HR_{(TAC/FLOT)}$=0.575, C.I.: 0.258-1.283, p=0.177) Fig. 3. In addition, in female patients, emesis occurred faster than the male patients ($HR_{(male/female)}$=0.338, C.I.: 0.138-0.824, p=0.017). Also, as reported previously [19], most of the patients who showed emesis, started vomiting and/or retching within the first three days.

Kruskal-Wallis test was performed to compare the number of emetic episodes among groups and assisted in achieving the secondary objective of the current study. As shown in Table 3, the difference between the number of emetic episodes is statistically significant in the delayed (p=0.012) and overall (p=0.011) phases and pairwise comparison revealed that FOLFOX is the different regimen. In the acute phase, the number of emetic episodes is not significantly different among groups (p=0.161).

Table 3
Comparison of the Number of Emetic Episodes Among the Regimen Groups in Different Phases

CINV Evaluation Phase	Kruskal-Wallis Test (p-value)	Pairwise Comparison of Antineoplastic Regimens		
		Regimens	Sig.	Adj. Sig. (Bonferroni Correction)
Acute Phase	0.161	-	-	-
Delayed Phase	**0.012**	*FOLFOX-FLOT*	**0.012**	**0.036**
		FLOT-TAC	0.960	1.000
		FOLFOX-TAC	**0.007**	**0.022**
Overall Phase	**0.011**	*FOLFOX-FLOT*	**0.010**	**0.030**
		FLOT-TAC	0.997	1.000
		FOLFOX-TAC	**0.007**	**0.021**

Discussion:

Over the last few decades, a better understanding of the complicated multifactorial pathophysiology of CINV, which involves interaction among different neurotransmitters and receptors in the central nervous system and gastrointestinal tract, caused important advances in CINV management, however, CINV prevention often remains suboptimal particularly for chemotherapy-induced nausea in delayed phase [20, 21]. Therefore, there is an ongoing effort involved in paving the way to better CINV management, from improving emetic risk determination to finding new targets to design antiemetic agents.

A novel scenario in CINV management is FLOT-induced nausea and vomiting. Although the FLOT regimen is considered to be moderately emetogenic, guideline-directed antiemetic combination to manage moderately emetogenic chemotherapy does not meet the expectations when administered to FLOT recipients. This can be considered as the main reason to perform the present study aiming at investigating the efficacy of aprepitant-containing triple antiemetic regimen in FLOT recipients and FLOT characteristic from the emetogenic potential aspect by comparing FLOT recipients to moderately (FOLFOX) and highly (TAC) emetogenic chemotherapy recipients. FOLFOX and FLOT are almost alike (both are platinum-based agents which are characterized by their ability to induce delayed nausea and vomiting) except for the rate of 5-FU administration (2600mg/m^2-administered in 20 hours in FLOT and 2400mg/m^2-administered in 40 hours in FOLFOX) and the presence of docetaxel in FLOT combination so it seems to be the best choice among moderately emetogenic regimens. TAC, being at the top of the highly emetogenic agents list in the emetogenic potential classification table, is the best choice among highly emetogenic regimens.

The percentage of FOLFOX-receiving patients achieving “CR” and “CP” in the acute, delayed, and overall phases are almost consistent with that of a previous study involving 187 patients in the aprepitant-receiving arm, by Nishimura and his colleagues [13]. The percentage of TAC-receiving patients achieving “CR” in the delayed and overall phases is almost consistent with a study by Warr et al. [22], in which, 98.6% of the patients in the aprepitant arm (n=438), received anthracycline and cyclophosphamide.

Previous studies indicated that the acute CINV is more manageable than the delayed CINV [23, 24] that led to the concentration mostly on delayed CINV management as in the current study; we focused on FLOT emetogenic behavior mostly in the delayed and overall phases and the three sets of analyses denoted the similarity of FLOT regimen characteristic to TAC from the emetogenic potential aspect and different characteristic of FLOT in comparison to FOLFOX mostly in the delayed and overall phases; acceptable CINV management is seen in the acute phase (minimum percentage of patients achieving endpoints is 84.6%).

The difference among FLOT and FOLFOX from emetogenicity potential aspect may be due to higher administration rate of 5-FU in FLOT recipients (which is an antineoplastic agent-related factor, affecting the incidence and severity of CINV), the higher dose of 5-FU in FLOT protocol, or due to the presence of docetaxel in FLOT regimen. Docetaxel and 5-FU are agents of low-emetic risk however may synergistically increase the overall emetic risk of antineoplastic combination; Overall, more investigation is required.

According to the results of the current study, FLOT has to be considered as a highly emetogenic regimen; so, adding an NK_1 receptor antagonist to the antiemetic combination prior to chemotherapy is a necessity. In order to better management of CINV caused by non-AC highly emetogenic combinations, ASCO [25], MASCC/ESMO [26] and the last update of NCCN [27] recommend adding olanzapine to the triple antiemetic regimen (an NK1 receptor antagonist, a serotonin (5-HT3) receptor antagonist, dexamethasone) besides continuing dexamethasone and olanzapine on days 2-4.

It should also be noted that as the Hesketh et al. [6] emetic-risk classification system is based on acute emesis, this system seems to be a poor predictor of CINV in the delayed phase [28] and there is a need to allocate a row to each antineoplastic combination in the table of emetogenic level. Also, since the net emetogenic potential may be higher than that of the component antineoplastic agent with greatest emetic risk, the emetogenic level of the antineoplastic combination should be determined by designing appropriate clinical trials.

References:

1. Rhodes VA, McDaniel RW (2001) Nausea, vomiting, and retching: complex problems in palliative care. CA-Caner J Clin 51(4):232–248. quiz 49-52 doi: 10.3322/canjclin.51.4.232
2. Kovács G, Wachtel AE, Basharova EV et al (2016) Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately

or highly emetogenic chemotherapy: a randomised, phase 3, double-blind, double-dummy, non-inferiority study. Lancet Oncol 17(3):332–344. doi: 10.1016/s1470-2045(15)00520-3

3. Warr D (2014) Prognostic factors for chemotherapy induced nausea and vomiting. Eur J Pharmacol 722:192–6. doi: 10.1016/j.ejphar.2013.10.015
4. Ettinger DS, Armstrong DK, Barbour S, Antiemesis et al (2012) JNCCN J Natl Compr Cancer Netw 10(4):456–485. doi: 10.6004/jnccn.2009.0039
5. Pater J, Slamet L, Zee B et al (1994) Inconsistency of prognostic factors for post-chemotherapy nausea and vomiting. Support Care Cancer 2(3):161–6. doi: 10.1007/BF00417474
6. Hesketh PJ, Kris MG, Grunberg SM et al (1997) Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 15(1):103–109. doi: 10.1200/jco.1997.15.1.103
7. Roila F, Hesketh PJ, Herrstedt J (2006) Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol. ;17(1):20-8. doi: 10.1093/annonc/mdj078
8. Hesketh PJ, Kris MG, Basch E et al (2017) Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 35(28):3240–3261. doi: 10.1200/JCO.2017.74.4789
9. Navari RM, Aapro M (2016) Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting. N Engl J Med 374(14):1356–1367. doi: 10.1056/NEJMra1515442
10. Al-Batran SE, Homann N, Pauligk C et al (2019) Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 393(10184):1948–1957. doi: 10.1016/s0140-6736(18)32557-1
11. World Health Organization (2020) : International Agency for Research on Cancer. Stomach Cancer. The Global Cancer Observatory. https://gco.iarc.fr/today/fact-sheets-cancers.[updated December, ; cited July 12, 2021].
12. Uson Junior PLS, Santos VM, Bugano DDG et al (2019) Systematic review and meta-analysis of docetaxel perioperative chemotherapy regimens in gastric and esophagogastric tumors. Sci Rep 9(1):15806. doi: 10.1038/s41598-019-52334-y
13. Nishimura J, Satoh T, Fukunaga M et al (2015) Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based chemotherapy (SENRI trial): a multicentre, randomised, controlled phase 3 trial. Eur J Cancer 51(10):1274–1282. doi: 10.1016/j.ejca.2015.03.024
14. Bubalo JS, Herrington JD, Takemoto M et al (2018) Phase II open label pilot trial of aprepitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic FOLFOX chemotherapy for the treatment of colorectal cancer. Support Care Cancer 26(4):1273–9. doi: 10.1007/s00520-017-3950-y
15. Zhang L, Lu S, Feng J et al (2018) A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant

regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). Ann Oncol 29(2):452–8. doi: 10.1093/annonc/mdx698

16. Moradian S, Shahidsales S, Ghavam Nasiri MR et al (2014) Translation and psychometric assessment of the Persian version of the Rhodes Index of Nausea, Vomiting and Retching (INVR) scale for the assessment of chemotherapy-induced nausea and vomiting. Eur J Cancer Care (Engl) 23(6):811–8. doi: 10.1111/ecc.12147
17. Al-Batran SE, Hartmann JT, Hofheinz R et al (2008) Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 19(11):1882–7. doi: 10.1093/annonc/mdn403
18. Oyama K, Fushida S, Kaji M et al (2013) Aprepitant plus granisetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients with gastric cancer treated with S-1 plus cisplatin. J Gastroenterol 48(11):1234–1241. doi: 10.1007/s00535-012-0746-1
19. Hesketh PJ, Gralla RJ, du Bois A et al (1998) Methodology of antiemetic trials: response assessment, evaluation of new agents and definition of chemotherapy emetogenicity. Support Care Cancer 6(3):221–7. doi: 10.1007/s005200050157
20. Yang MJ, Xu HR, Li H et al (2020) Comparison of Pharmacokinetics of Aprepitant in Healthy Chinese and Caucasian Subjects. Drug Des Devel Ther 14:1219–1226. doi: 10.2147/dddt.s243924
21. Aapro M (2018) CINV: still troubling patients after all these years. Support Care Cancer 26(Suppl 1):5–9. doi: 10.1007/s00520-018-4131-3
22. Warr DG, Hesketh PJ, Gralla RJ et al (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 23(12):2822–2830. doi: 10.1200/jco.2005.09.050
23. Escobar Y, Cajaraville G, Virizuela JA et al (2015) Incidence of chemotherapy-induced nausea and vomiting with moderately emetogenic chemotherapy: ADVICE (Actual Data of Vomiting Incidence by Chemotherapy Evaluation) study. Support Care Cancer 23(9):2833–2840. doi: 10.1007/s00520-015-2809-3
24. Baba Y, Baba H, Yamamoto S et al (2017) Chemotherapy-induced nausea and vomiting is less controlled at delayed phase in patients with esophageal cancer: a prospective registration study by the CINV Study Group of Japan. Dis Esophagus 30(2):1–7. doi: 10.1111/dote.12482
25. Hesketh PJ, Kris MG, Basch E et al (2020) Antiemetics: ASCO Guideline Update. J Clin Oncol 38(24):2782–2797. doi: 10.1200/jco.20.01296
26. Aaparo MGR, HJ, Molassiotis A, Roila F, MASCC/ESMO Antiemetic, Guidelines *MASCC: Multinational Association for Supportive Care in Cancer*. https://www.mascc.org/antiemetic-guidelines. [updated July, 2019; cited May, 2021]
27. NCCN Antiemesis Panel Members. NCCN Guidelines Version 2.2020, Antiemesis. *NCCN: National Comprehensive Cancer Network.* https://www.nccn.org/professionals/physician_gls/default.aspx. [updated April 23, 2020; cited December, 2020]

28. Jordan K, Gralla R, Jahn F et al (2014) International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): Content and implementation in daily routine practice. Eur J Pharmacol 722(0):197–202. doi: 10.1016/j.ejphar.2013.09.073

Figures

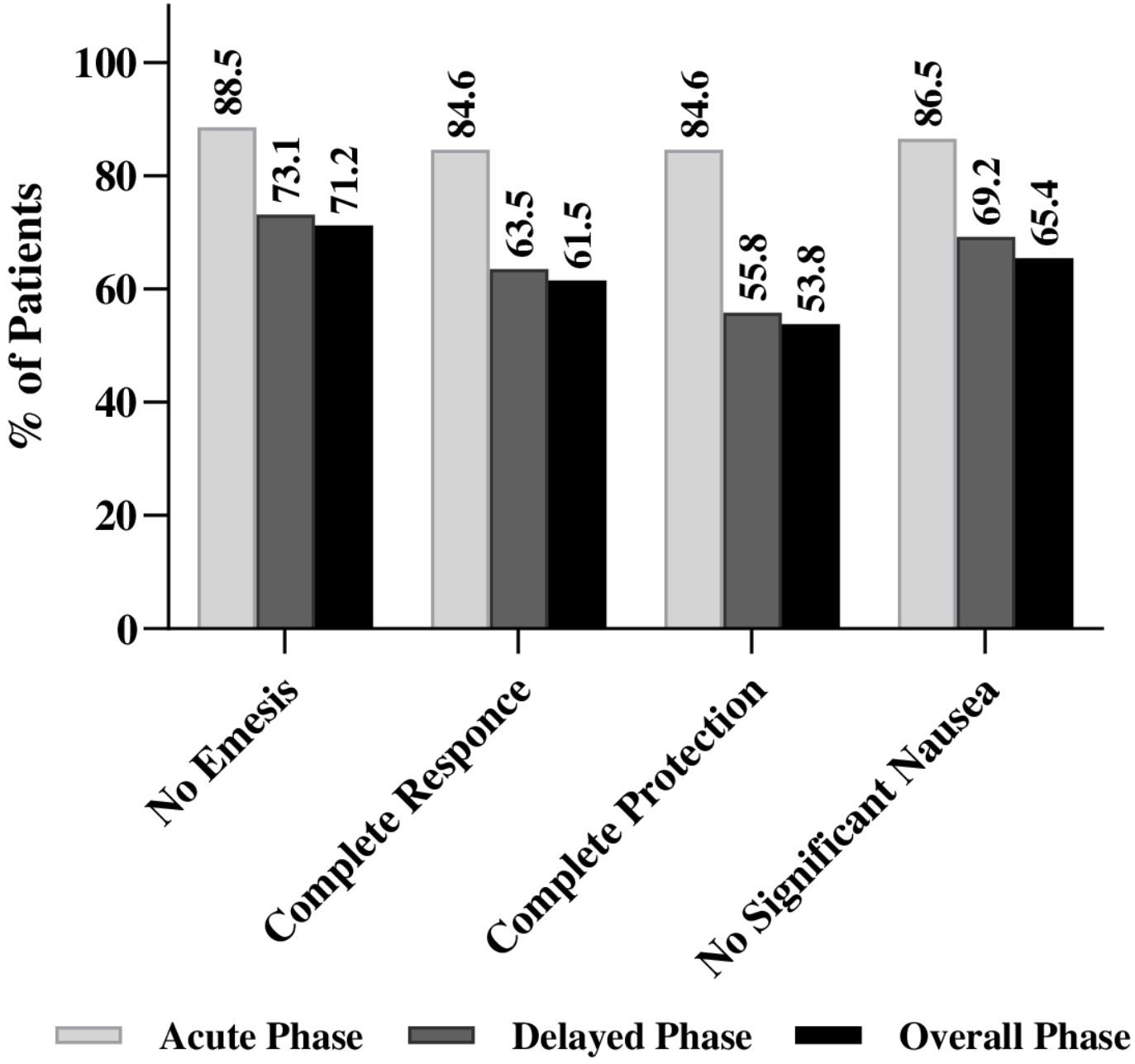

Figure 1

The proportion of the patients with “no emesis”, “complete response”, “complete protection” and “no significant nausea” in acute, delayed, and overall phases in the FLOT-receiving group (N=52)

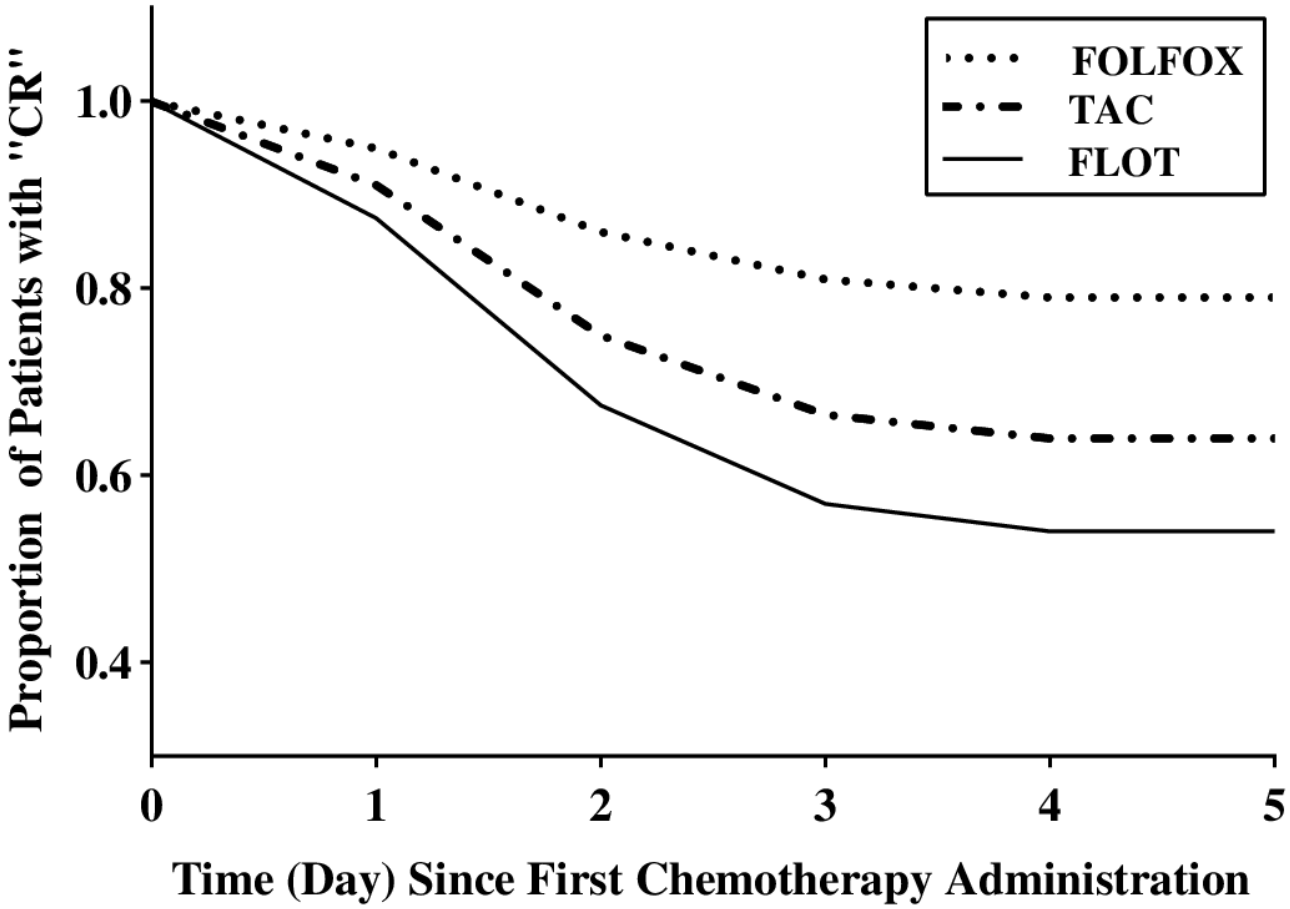

Figure 2

Plot for Cox proportional hazards model compares the proportion of patients with “CR” between different antineoplastic regimens, at any point of time in the overall phase, adjusted for covariates

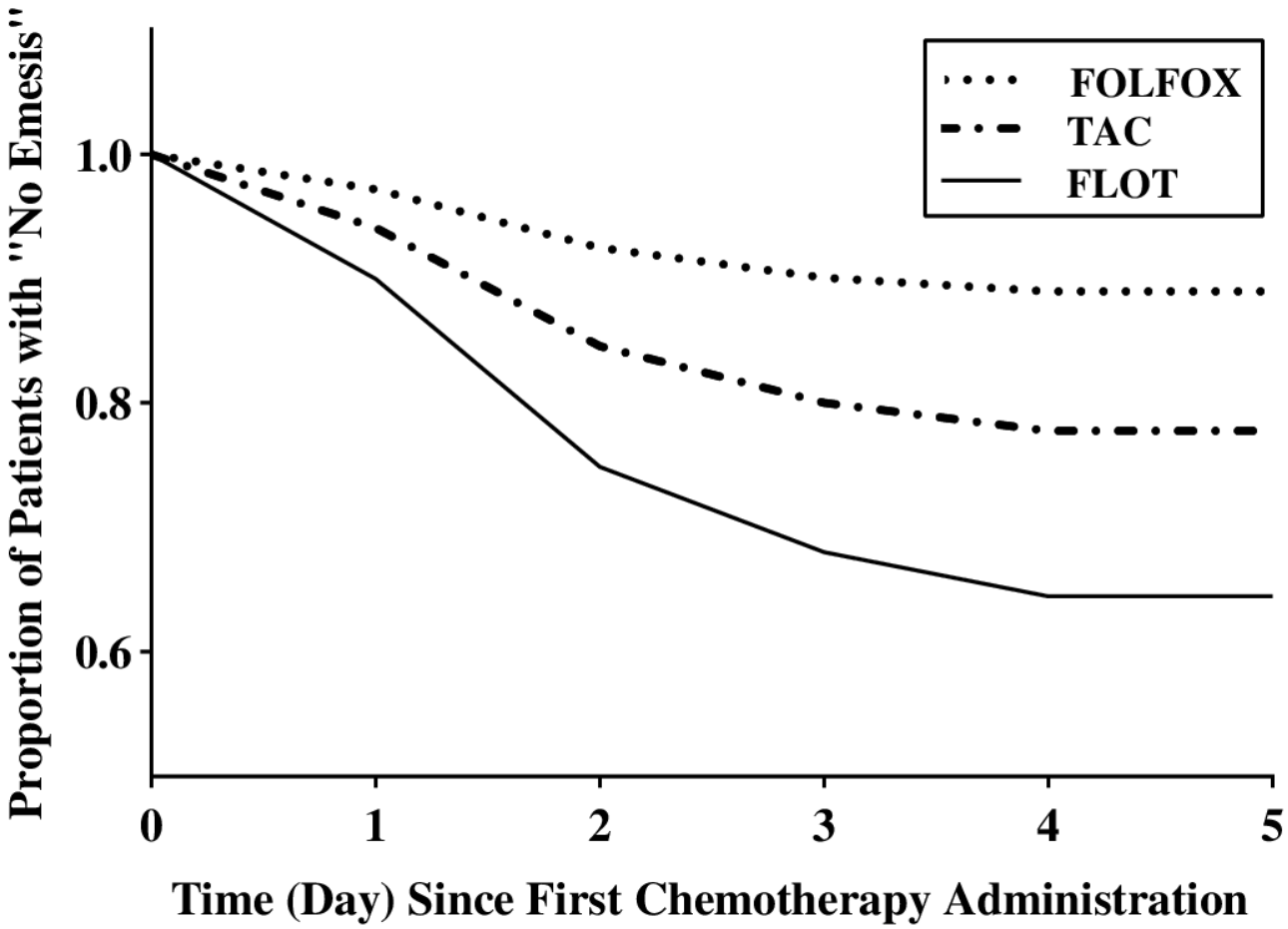

Figure 3

Plot for Cox proportional hazards model compares the proportion of the patients with “no emesis” between different antineoplastic regimens, at any point of time in the overall phase, adjusted for covariates

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- OnlineResource1.pdf