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Management of Chemotherapy-Induced Nausea and Vomitting in Breast Cancer Patients: A Prospective Cohort Study

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Abstract

Through a prospective cohort study we aimed to optimize prevention and management of chemotherapy-induced nausea and vomiting (CINV) in the emergence of new therapies for breast cancer patients. We included breast cancer patients treated with moderate emetogenic (MEC) or highly emetogenic chemotherapy (HEC) all stages combined, from April 2021 to November 2021. Patients were required to answer a survey of 32 questions in order to analyze the potential involvement of known and unknown risk factors in the occurrence of CINV. The acute phase of CINV was defined as nausea and vomiting that developed ≤ 24 hours after the start of chemotherapy. Delayed phase of CINV was defined as nausea and vomiting that developed > 24 hours after the start of chemotherapy. The severity of nausea and vomiting was evaluated with common terminology criteria for adverse events (CTCAE) v5.0; publish to date: November 27, 2017. Analysis and results were performed using *JAMOVI* statistical software. In total, 177 patients received chemotherapy, 103 patients(58%) received (HEC), and 74 patients (42%) received (MEC). All patients were female (100%). Risk factors associated to occurrence of CINV included previously known factors: Younger age than 50 years (29,8%), history of pregnancy-related nausea and vomiting (74,7%), alcohol use (no patient reported previous alcohol consumption), failure to adhere to antiemetic treatment guidelines (9,6%). The compliance with treatment score (90,4%) showed a good commitment of the patients in the process of their medical healthcare. Other potential risk factors have been also explored to determine their involvement or not in the occurrence of CINV (cancer stage, performance status, education level, chemotherapy protocols, the use of traditional herbs known as an antibacterial agent and immunity booster in our context). In the acute phase, (78%) of patients experienced nausea and (47,8%) experienced vomiting. In the delayed phase, (37,1%) of patients experienced nausea and only (15,3%) experienced vomiting. The severity of nausea and vomiting was evaluated according to CTCAE v5.0 in both groups HEC and MEC. Only (8,7%) had to stop treatment for non-tolerance (table 1-2). The present study demonstrated that high compliance to treatment guidelines for CINV and individualized care could lead to more optimal management of CINV.

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Introduction

Breast cancer is the most common cancer among women and the leading cause of cancer death worldwide with an estimated 1.7 million cases and 521,900 deaths in 2012 [1-2]. The survival of women with breast cancer has improved since 1974 because of early detection and advances in screening, surgery, chemotherapy regimens, radiation therapy and hormones therapies [3]. Chemotherapy-induced nausea and vomiting are one of the related-treatment side effects feared by cancer patients starting systemic treatment and has a great influence on quality of life. The perception of patients and healthcare providers showed that there is still a significant gap that can be prejudicial in the optimization of antiemetic protocols. According to guidelines we use in our clinical practice the combination of 3 antiemetics for highly emetogenic chemotherapy (HEC) and two for the moderately emetogenic chemotherapy(MEC). The developement of new therapies emerged for HR-positive breast cancer, HER2 and advanced or metastatic breast cancer which led us to reassess our care for CINVs.

Materials and Methods

This is a prospective cohort study that was conducted at the Department of Medical Oncology in Mohammed V Military Teaching Hospital of Rabat, from April 2021 to November 2021(eight months). In consultation we received patients treated with chemotherapy for breast cancer all stages combined. A questionnaire of 32 questions was developed to investigate the

risk factors related to the occurrence of CINV and to evaluate the severity of nausea and vomiting in both HEC and MEC protocols. Patients who received a MEC or HEC protocol were eligible for this study, and the classification of emetogenic risk of anticancer drugs was based on the NCCN Clinical Practice Guidelines in Oncology - Antiemetics v4-. Patients were interviewed in the consultation room by the physician, a total of 177 responses were collected. The inclusion criteria and patient characteristics are summarized below (Table 1), the following patient information's were also collected : medical history, alcohol intake history, level of education, history of psychiatric illness and pregnancy-related nausea and vomiting, common and potential risk factors for CINV, details of antiemetic therapy, blood biochemistry results, performance status, compliance with treatment and the use of traditional herbs which is commonly known as immunity booster in our context.

Table 1: Patients characteristics

	N	(%)
Age (years)		
>50	52	(29,8)
<50	125	(70,2)
Gender		
Male	0	(0,0)
Female	177	(100,0)
Level of Education		
Illiterate	65	(36,7)
Educated population	77	(43,5)
Higher education	35	(19,8)
History of Pregnancy-Related Nausea and Vomiting	133	(74,7)
Stage		
I	5	(2,8)
II	120	(67,4)
III	19	(10,7)
IV	30	(17,4)
Recidivism	3	(1,7)
PS		
0	136	(76,4)
1	31	(18)
2	7	(3,9)
3	3	(1,7)
HEC (n=103)		
AC	57	(55,3)
EC	30	(29,1)
FEC	16	(15,5)
HEC prophylactic regimen		
3 antiemetics	95	(85,6)
2 antiemetics	16	(14,4)
Others	0	(0)
Docetaxel	19	(25,7)
Paclitaxel	15	(20,3)
Capecitabine	15	(20,3)
TC	17	(23)
Vinorelbine	5	(6,8)
Carboplatine	3	(4,1)
MEC prophylactic regimen		
2 antiemetics	39	(63,9)
3 antiemetics	22	(36,1)
Others	0	(0)

Grade of Nausea (ctcae v5) :		
I	136	(76,8)
II	38	(21,5)
III	3	(1,7)
IV	0	(0)
V	0	(0)
Grade of Vomitting (ctcae v5) :		
I	156	(89,1)
II	16	(9,1)
III	3	(1,7)
IV	0	(0)
V	0	(0)
Compliance with Treatment	161	(90,4)
Stopping Treatment Following Cinv	10	(5,6)
Traditional Herbs	12	(6,8)

AC : doxorubicin + cyclophosphamide, EC :epirubicin + cyclophosphamide,
FEC : fluorouracil epirubicin + cyclophosphamide, TC : docetaxel + cyclophosphamide

The risk factors for CINV in collected data sets were analyzed by logistic regression analysis (Table 2), all reported p values of ≤ 0,05 were considered statistically significant. Analysis were carried out with *JAMOVI software*.

Table 2: Binomial logistic regression analysis of risk factors

Variables	Acute Nausea (<24h)	Delayed Nausea (>24h)	Acute Vomiting (<24h)	Delayed Vomiting (>24h)
Age (years):				
<50 ans	*p* <0,001 OR=7 ; 95% CI [3,609-13,579]	*p*=0,187	*p*<0,001 OR=2,565 ; 95% CI [1,584-4,153]	*p*=0,006 OR=0,528; 95% CI [0,334-0,835]
> 50 ans	p <0,001 OR=3,13 ; 95% CI [2,17-4,51]	p<0,001 OR=0,524 ; 95% CI [0,377-0,729]	P=0,067	p<0,001 OR=0,113 ; 95% CI [0,067-0,19]
Level of education :				
Illiterate	p<0,001 OR 7,250; 95% CI [3,462-15,183]	p=0,326	p=0,326	p<0,001 OR 0,294; 95% CI [0,165-0,523]
Educated population	p<0,001 OR 4,750; 95% CI [2,216-10,18]	p=0,786	p=0,08	p=0,002 OR 0,353; 95% CI [0,183-0,682]
Higher education	p<0,001 OR 3,35; 95% CI [2,033-5,52]	p=0,OO8 OR 0,554; 95%CI [0,357-0,858]	p=0,453	p<0,001 OR 0,1; 95% CI [0,0489-0,21]
Stage:				
I	p=0,988	p=0,657	p=0,981	p=0,215
II	p<0,001 OR 3,405; 95% CI [2,3605 - 4,91]	p=0,036 OR 0,719; 95% CI [0,5275-0,979]	p=0,484	p<0,001 OR 0,26; 95% CI [0,178 – 0,378]
III	p<0,001 OR 7; 95% CI [2,45534-19,957]	p=0,082	p= 0,017 OR 2,556; CI 95% [1,1825-5,523]	p=0,01 OR 0,3478; 95% CI [0,15559–0,778]
IV	p<0,001 OR 6; 95% CI [2,32799-15,46]	p=0,003 OR 0,296; 95% CI [0,135-0,652]	p= 0,014 OR 0,4; 95% CI [0,192-0,833]	p<0,001 OR 0,294; 95% CI [0,00403 – 0,215]
Performance status:				

0	p<0,001 OR 3,744; 95% CI [2,629-5,33]	p=0,093	p=0,165	p<0,001 OR 0,283; 95% CI [0,1657 – 0,343]
1	p<0,001 OR 4,857; 95% CI [2,153-10,96]	p=0,022 OR 0,464; 95% CI [0,240-0,896]	p=0,277	p<0,001 OR 0,171; 95% CI [0,0721 – 0,408]
2	p=0,178 OR 3; 95% CI [0,606-14,86]	p=1	p=0,484	p=0,097
3	p=0,989	p=1	p=0,341	p=0,341
HEC (n=103)				
AC	p<0,001 OR 4,56. 95% CI [2,656-7,84]	p=1	p=0,142	p<0,001 OR 0,254.95% CI [0,151 – 0,425]
EC	p<0,001 OR 6,667 ; 95% CI [2,827-15,72]	p=0,378	p=0,004 OR 2,538; 95% CI [1,336- 4,82]	p<0,001 OR 0,278; 95% CI [0,138– 0,560]
FEC	p <0,001 OR 13; 95% CI [3,0856-54,77]	p=0,988	p<0,001 OR 6,250 ; 95% CI [2,1752-17,958]	p=0,578
HEC prophylactic regimen				
3 antiemetics	p<0,001 OR 4,92;95% CI [3,201-7,56]	p=0,328	p=0,01 OR 1,54; 95% CI [1,11-2,14]	p<0,001 OR 0,364; 95% CI [0,253-0,522]
2 antiemetics	p=0,003 OR 20;95% CI [2,6846-149]	p=0,514	p=0,004 OR 6; 95% CI [1,7674-20,369]	p=0,006 OR 0,176 ; 95% CI [0,0517-0,602]
MEC (n=74)				
Docetaxel	p=0,117	p=0,004 OR 0,118 95% CI [0,0272-0,509]	p=0,008 OR 0,118 95% CI [0,0546-0,643]	p=1
Paclitaxel	p=0,442	p=0,996	p=0,206	p=1
Capecitabine	p=0,046 OR 3,667; 95% CI [1,02294-13,14]	p=0,019 OR 0,167; 95% CI [0,0373-0,745]	p=0,121	p=1
TC	p=0,046 OR 3,667.95% CI [1,02294-13,14]	p=0,996	p=0,007 OR 0,133. 95% CI [0,0305-0,583]	p=1
Vinorelbine	p=0,215	p=0,657	p=0,215	p=1
Carboplatine	p=0,571	p=0,571	p=0,571	p=1
MEC prophylactic regimen				
2 antiemetics	p<0,001 OR 3,875;95% CI [1,7812-8,430]	p<0,001 OR 0,147;95% CI [0,0575-0,376]	p=0,009 OR 0,393; 95% CI [0,196-0,789]	p=1
3 antiemetics	p=0,670	p=0,002 OR=0,1;95% CI [0,0234-0,428]	p=0,007 OR 0,222;95% CI [0,0752-0,657]	p=1
Compliance with treatment	p=0,002 OR 10 ; 95% CI [2,3381-42,77]	p=0,016 OR 3,40;95% CI [1,2544-9,216]	p=0,003 OR 6,333;95% CI [1,8742- 21,402]	p=1
Use of traditional herbs	p<0,001 OR 3,85;95% CI [2,782-5,32]	p=0,073	p=0,386	p<0,001 OR 0,231;95% CI [0,165- 0,323]

All reported *p* values (≤ 0,05) were considered statistically significant

Results

In the whole study 177 women had breast cancer of different stages, the characteristics of patients are listed below (Table 1). The majority (76,4%) had a Performance Status of zero. All patients were female (100%). 125 patients were over 50 years old. Stage II breast cancer represented (67.4%) of the study population. 103 patients received HEC (doxorubicin + cyclophosphamide, epirubicin + cyclophosphamide, fluorouracil epirubicin + cyclophosphamide) for which the AC protocol was the most used, and 74 patients received MEC (Docetaxel, paclitaxel , capecitabine, docetaxel, cyclophosphamide, vinorelbine and carboplatin) of which docetaxel was the most widely used anti-cancer drug in our practice followed by paclitaxel and capecitabine at equal rates (20.3%).

Almost the half of patients were educated, (36,7%) were illiterate and the rest had a higher education. The compliance with treatment score of (90,4%) showed a good commitment of the patients in the process of their medical healthcare which reassures us to carry out the treatment properly. Twelve patient used traditional herbs according to their beliefs of its benefits completely ignoring the danger of possible toxic interactions with anti cancer drugs. More than half of the patients experienced grade I nausea and vomiting according to CTCAE v5.0 and only (21.5%) and (9.1%) had grade II nausea and vomiting respectively.

Previously known risk factors for acute (≤24H) and delayed (>24H) phase of chemotherapy-induced nausea and vomiting (younger age, pregnancy related nausea and vomiting, compliance with treatment, chemotherapy regimens, antiemetics) were significantly associated to the occurrence of CINV. Failure of adherence to treatment guidelines was clearly a common risk factor for acute nausea and vomiting but also delayed nausea. Additionally, we explored other potential risk factors that we found associated to CINV (all levels of education were significantly correlated to acute nausea). We noticed that the use of traditional herbs (E.g. thyme, ginger infusion) was significantly correlated to acute nausea and delayed vomiting (Table 2).

Discussion

In our study we found that almost all patients (90,4%) received highly or moderate chemotherapy for breast cancer in compliance with treatment guidelines (Table 1). The cancer care team efforts on daily practice to ensure adherence to treatment deserve special mention especially that compliance with treatment guidelines is dependent to healthcare providers. The INSPIRE study conducted to evaluate the impact of guideline-consistent/guideline-inconsistent CINV prophylaxis (GCCP/GICP) on the incidence of no CINV after cycle 1 of highly or moderately emetogenic chemotherapy (HEC or MEC) showed that increased adherence to antiemetic guidelines could significantly reduce the incidence of CINV after HEC and MEC [4].

Nausea and vomiting are the most troubling side effects that cancer patients tend to fear most because it greatly affects their quality of life and can lead to discontinuation of treatment. Multiple studies have been carried out for the development of new antiemetics to provide effective relief from chemotherapy-induced nausea and vomiting. The American Society of Clinical Oncology (ASCO) in 2014, demonsrated that antiemetics were voted by physicians, patients, and the public as one of the "Top 5 Advances in 50 Years of Modern Oncology" [5]. Another cancer society showed that prophylaxis should be the main objective of antiemetic therapy [6-7]. Chemotherapy emetogenicity and patient risk factors must be taken into consideration in the management of CINV [8].

Among the 103 patients who received HEC in our study, the AC and EC protocols were significantly correlated to the occurrence of acute nausea and delayed vomiting, FEC protocol was also significantly correlated to acute nausea and vomiting. In the MEC group: Docetaxel, TC and capecitabine were significantly correlated to the occurrence of CINV. Despite the high rate of compliance to treatment guidelines (90,4%), the results of statistical analysis (table 2) are evocative of a significant correlation between chemotherapy emetogenicity and patient risk factors [9-10].

A European prospective observational study evaluated the predictive power of personal and treatment-related characteristics in the development of CINV, found that following evidence-based clinical antiemetic guidelines is of paramount importance, alongside treating patients with increased risk for CINV more aggressively, which both could lead to more optimal CINV management [11].

The common patient risk factors of CINV according to an overview of chemotherapy-induced nausea and vomiting and evidence-based therapies include younger age than 50 years, female gender, history of motion sickness and/or pregnancy-related nausea and vomiting, alcohol intake (eg, ≥5 drinks per week) tends to lower the risk of CINV use, chemotherapy regimens, emesis with prior chemotherapy and failure to adhere to antiemetic treatment guidelines [12-13].

In addition to known risk factors whose involvement in the occurrence of CINV has been confirmed by our analysis, we demonstrated that performance status (0, 1 and 2), cancer stage (II, III and IV) were also associated to CINV. The use of herbal medicine was significantly correlated to acute nausea, an important traditional factor that should be addressed in greater depth, especially in African countries and also promote awareness around possible toxic interactions with anti cancer drugs.

Study Limits

Our analysis did not include gender as variable. In literature female gender appears to be a factor with a higher risk generally associated to CINV [14].

When conducting this study, we found that the use of traditional herbs was significantly correlated to CINV, but we can't draw valid conclusions because of insufficient sample size for statistical analysis.

Conclusion

In conclusion, compliance with treatment guidelines was good and led to reduce the severity of chemotherapy-induced nausea and vomiting according to CTCAE v5.0. The results of the use of traditional herbs may suggest that further studies are needed to develop more individualized care based on each patient's risk and varieties among countries.

Conflicts of Interests

The authors declare there are no conflicts of interest.

Author's Contribution

All the authors contributed in this study.

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