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Chemotherapy-Induced Nausea and Vomiting: Situation in Madagascar

Nausées et vomissements induits par la chimiothérapie : situation à Madagascar

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ABSTRACT

Introduction. Chemotherapy-induced nausea and vomiting (CINV) is a major burden of cancer. Knowledge and optimal control of CINV are key factors for better clinical outcomes. Our objectives are to report the prevalence of CINV, to determine the risk factors and to describe their management. **Patients and methods.** This was a three-month descriptive study from 18 October 2018 to 18 January 2019 in the oncology department of the Joseph Ravoahangy Andrianavalona Hospital in Antananarivo, the capital of Madagascar. The study involved cancer patients treated with moderately or highly emetogenic chemotherapy. **Results.** One hundred and thirty-eight patients were included. The mean age of the patients was 50.73 years (± 12.4) with extremes of 18 and 82 years and the sex ratio was 0.21. Breast cancer was in the majority (59.42%). The chemotherapy was highly emetogenic in 67.39% of cases. The prevalence of CINV was 50.72% with a high proportion in the delayed phase. Nausea was associated with vomiting in 52.86% of cases. Female gender and low alcohol consumption were associated with CINV. The combination of odansetron and dexamethasone was used in 92.75% of cases, followed by granisetron and dexamethasone (7.25%). **Conclusion.** Patients were far from being well prepared for chemotherapy. This alarming result reflects our difficulty in adopting the recommendations in the antiemetic guidelines. Access to new antiemetics should be prioritised in low-income countries.

RÉSUMÉ

Introduction. Les nausées et vomissements induits par la chimiothérapie (NVIC) constituent un fardeau majeur du cancer. La connaissance et le contrôle optimal des NVIC sont des facteurs clés pour de meilleurs résultats cliniques. Nos objectifs sont de rapporter la prévalence des NVIC, de déterminer les facteurs de risque et de décrire leur prise en charge. **Patients et méthodes.** Il s'agit d'une étude descriptive de trois mois du 18 octobre 2018 au 18 janvier 2019 dans le service d'oncologie de l'hôpital Joseph Ravoahangy Andrianavalona à Antananarivo, la capitale de Madagascar. L'étude a concerné des patients cancéreux traités par une chimiothérapie modérément ou fortement émétisante. **Résultats.** Cent trente-huit patients ont été inclus. L'âge moyen des patients était de 50,73 ans (± 12,4) avec des extrêmes de 18 et 82 ans et le sex-ratio était de 0,21. Le cancer du sein était majoritaire (59,42%). La chimiothérapie était hautement émétogène dans 67,39% des cas. La prévalence des NVIC était de 50,72% avec une forte proportion en phase retardée. Les nausées étaient associées à des vomissements dans 52,86% des cas. Le sexe féminin et une faible consommation d'alcool étaient associés aux NVIC. L'association de l'odansétron et de la dexaméthasone a été utilisée dans 92,75% des cas, suivie du granisétron et de la dexaméthasone (7,25%). **Conclusion.** Les patients étaient loin d'être bien préparés à la chimiothérapie. Ce résultat alarmant reflète notre difficulté à adopter les recommandations des guides antiémétiques. L'accès aux nouveaux antiémétiques devrait être une priorité dans les pays à faible revenu.

HIGHLIGHTS

What is already known on this topic?
Chemotherapy-induced nausea and vomiting (CINV) are the most reported and feared effects of chemotherapy because they may discourage cancer patients from following their treatment. Few studies on CINV have been conducted in the African population.

What question this study addressed?
Situation of CINV in Madagascar.

What this study adds to our knowledge?
The prevalence of CINV was 50.72% with a high proportion in the delayed phase. The combination of odansetron and dexamethasone was used in 92.75% of cases. Most patients were not prepared for chemotherapy.

How this is relevant to practice, policy or further research?
Reducing the rate of CINV allows for good patient adherence to chemotherapy and reduces health care expenses.

INTRODUCTION

Cancer is a major health problem that has serious effects on patients and their families. These effects are related to the progression of the disease and the side effects of the treatments. Chemotherapy, which is one of the mainstays of treatment, is often associated with unpleasant adverse effects such as nausea and vomiting, pain, hair loss, asthenia and mental disorders (1).

Nausea and vomiting are the most reported and feared effects of chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) has negative impacts on patients' quality of life and nutritional status. They can discourage patients from following chemotherapy regimens (2,3). Knowledge and optimal control of CINV are key factors in ensuring chemotherapy completion and satisfactory clinical outcomes.

In Madagascar, a country located off the southeast coast of Africa, chemotherapy is an important part of cancer treatment. Patients are not spared the effects of chemotherapy. To our knowledge, few studies on CINV have been conducted in the African population. The main objective of the present study is to report the prevalence of CINV in the oncology department of a hospital in Madagascar. The secondary objectives are to determine the risk factors of CINV and to describe their management.

PATIENTS AND METHODS

Study characteristics

This was a descriptive study conducted over a period of three months, from October 18, 2018 to January 18, 2019, in the oncology department of the Joseph Ravoahangy Andrianavalona University Hospital. The hospital is located in Antananarivo which is the capital of Madagascar.

Study population and inclusion/exclusion criteria

The study involved patients seen in consultation in this department. Patients aged 18 years and older, histopathologically diagnosed with cancer and treated with moderately or highly emetogenic chemotherapy were included. Patients undergoing radiotherapy were excluded.

Studied parameters

We collected sociodemographic characteristics, history of chronic ethylism, history of CINV during previous chemotherapy cycles, history of vomiting in pregnancy, types of cancer and chemotherapy regimens, signs of CINV, and antiemetics used.

Chemotherapy-induced nausea and vomiting

CINV occurring within 24 hours of chemotherapy initiation was acute CINV. CINV occurring 24 hours to five days after chemotherapy initiation was delayed CINV. CINV occurring a few days before chemotherapy was anticipated CINV (4). Nausea and vomiting were classified into five grades according to the 2009 Common Terminology Criteria for Adverse Events (table 1) (5).

Table 1: 2009 Common Terminology Criteria for nausea and vomiting

Grade	Nausea	Vomiting
0	–	–
1	Loss of appetite without change eating habits	1 - 2 episodes in 24 hours (5 minutes apart)
2	Reduction of food intake without weight loss, dehydration or malnutrition	3 - 5 episodes in 24 hours (5 minutes apart)
3	Insufficient caloric or fluid intake, parenteral nutrition or intravenous hydration ≥ 24h	≥ 6 episodes in 24 hours, parenteral feeding or intravenous hydration ≥ 24h
4	–	Vital risk
5	–	Death

The emetogenicity of cancer chemotherapy was classified as moderate and high. This classification is based on the frequencies of CINV without antiemetics, as reported in the literature. Moderately emetogenic chemotherapy has a risk of CINV of 30-90% and highly emetogenic chemotherapy has a risk above 90% (6).

Statistical analysis

Data were entered using Excel® software and analyzed using Epi Info® software. Quantitative variables were presented as means and qualitative variables were expressed as frequencies and percentages. The chi-square test was used and values with $p < 0.05$ were considered statistically significant.

Table 2: Chemotherapy regimens **(N = 138)**

Regimens	**N (%)**
5-fluorouracile, adriblastine, cyclophosphamide	48 (34,78)
Carboplatine, paclitaxel	20 (14,49)
Paclitaxel	13 (9,42)
Cyclophosphamide, methotrexate, 5-fluorouracile	11 (7,97)
Docetaxel	8 (5,8)
5-fluorouracile, oxaliplatine	7 (5,07)
Adriblastine, bleomycine, vinblastine, dacarbazine	7 (5,07)
Carboplatine	4 (2,9)
Gemcitabine	3 (2,17)
Others	17 (12,32)

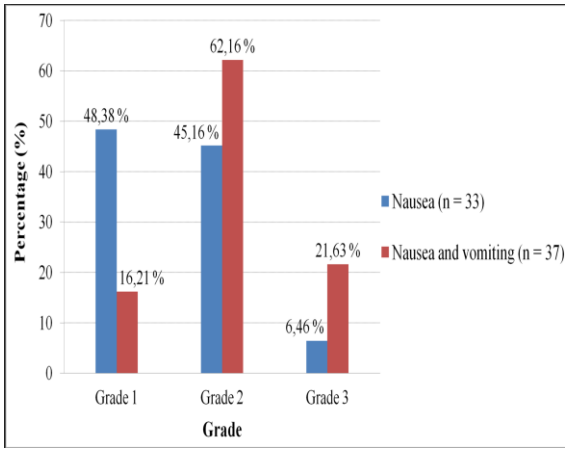

Figure 2: Classification of chemotherapy-induced nausea and vomiting by grade

Ethics approval

The present study was authorized and validated by our institution, CHU-JRA. The guidelines of the Declaration of Helsinki and the anonymity of the patients were respected.

RESULTS

Patient characteristics

One hundred and thirty-eight patients were included. The mean age of the patients was 50.73 years (± 12.4) with extremes of 18 and 82 years. The age range [50 - 69] years was the majority (54.35%). The sex ratio was 0.21 with 114 women (82.61%). Regular alcohol consumption was noted in 14.49% of cases. Forty-one percent of women (41.22%) reported a history of vomiting in pregnancy.

Cancer and chemotherapy regimens

Breast cancer was found in 59.42% of cases, followed by colon cancer (7.97%) and cervical cancer (6.52%) (figure 1).

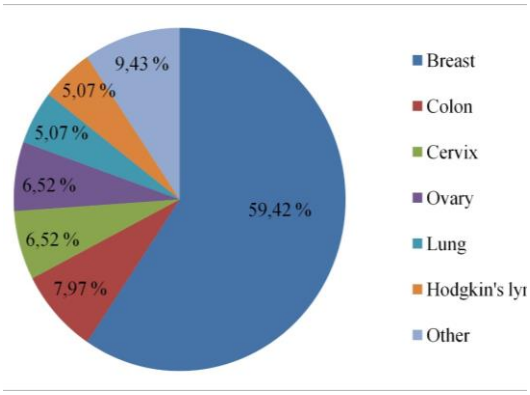

Figure 1: Types of cancer diagnosed

The combination of 5-fluorouracil, adriblastine, and cyclophosphamide was the most used (34.78%) (table 2). Chemotherapy was highly emetogenic in 67.39% of cases and moderately emetogenic in 32.61% of cases.

Chemotherapy-induced nausea and vomiting

Twenty-one patients (15.28%) had experienced CINV during previous cycles. Seventy patients had CINV, a prevalence of 50.72%. The prevalences of acute and delayed CINV were 13.79% and 36.96%, respectively. Anticipatory CINV was not found in any patient. Among the patients with CINV, nausea was isolated in 47.14% and associated with vomiting in 52.86%. Nausea was grade 1 in 48.38% of cases and vomiting was grade 2 in 62.16% of cases (figure 2). Figure 3 shows the distribution of patients by type of NVIC and chemotherapy emetogenicity. Female gender and the absence of chronic alcoholism were significantly correlated with the occurrence of CINV (table 3).

In the management of CINV, the combination of odansetron and dexamethasone was the most commonly used (92.75%), followed by granisetron and dexamethasone (7.25%).

Table 3 : Risk factors for chemotherapy-induced nausea and vomiting

Parameter	**Variables**	**CINV**	**No CINV**	**Total**	**p**
		(n = 70)	**(n = 68)**	**(N = 138)**	
Age (years)	< 50	35 (60,34)	23 (39,66)	58	0,054
	≥ 50	35 (43,75)	45 (56,25)	80	
Gender	F	63 (55,26)	51 (44,74)	114	0,02
	M	7 (29,17)	17 (70,83)	24	
History of CINV	Yes	12 (57,14)	9 (42,86)	21	0,522
	No	58 (49,57)	59 (50,43)	117	
Chronic alcoholism	Yes	6 (30)	14 (70)	20	0,044
	No	64 (54,24)	54 (45,76)	118	
History of vomiting in pregnancy		**(n = 63)**	**(n = 51)**	**(N = 114)**	
	Yes	30 (63,83)	17 (36,17)	47	
	No	33 (49,25)	34 (50,75)	67	0,123

DISCUSSION

Cancer and chemotherapy regimens

Breast cancer was in first place (59.42%). Indeed, according to the Global Cancer Observatory in 2020, breast cancer ranks first worldwide, all ages and genders combined (7). In Madagascar, epidemiological studies have reported the same result (8,9). The combination of 5-fluorouracil, adriblastine and cyclophosphamide was the most used chemotherapy protocol (34.78%). This is a first-line protocol in the treatment of breast cancer.

Chemotherapy-induced nausea and vomiting

The prevalence of CINV was 50.72%, which is higher compared to the literature where it is reported in 40% of patients despite antiemetic prophylaxis (10). Our result is explained by the fact that some first-line antiemetics are not available in Madagascar. The lack of knowledge of antiemetic recommendations by some clinicians may also explain this result.

The predominance of delayed CINV (36.96%) is similar to other studies. CINV during the delayed phase is reported in 20-50% of patients and is often underestimated after highly or moderately emetogenic chemotherapy (11,12). Anticipatory CINV, usually reported in 8-14% of patients was not found in our study (13).

Nausea was frequently associated with vomiting (52.86%). In other studies, isolated nausea was the majority (58%), followed by nausea and vomiting (29%) and vomiting alone (13%) (14).

Mechanisms of chemotherapy-induced nausea and vomiting

The vomiting center is located in the medulla oblongata (15). Neurotransmitters stimulate this center via two pathways: peripheral and central. The peripheral pathway is derived from vagal afferents of the gastrointestinal tract. The central pathway is secondary to pain, vestibular disturbance and emotional factors. The response to vomiting is controlled by neurotransmitters and receptors. Serotonin or 5-hydroxytryptamine (5-HT) is the most important. Upon exposure to chemotherapy agents, 5-HT is secreted by enterochromaffin cells and binds to 5-HT3 receptors on vagus nerve terminals. Substance P is another potent regulator, binding to neurokinin-1 (NK-1) receptors. Dopamine release and dopamine receptor signaling are also involved.

Acute CINV is mediated by 5-HT3 receptors. Delayed CINV is mediated by binding of substance P to NK-1 receptors in the central nervous system. Anticipatory CINV is probably mediated by a combination of physiological and psychological mechanisms. Thus, antiemetics act at these receptors (4). On the other hand, the mechanism of nausea is less well understood because of its subjective nature. It usually precedes vomiting and together they may have the same neurotransmitters and receptors. Other hypotheses including histamine and muscarinic receptors have been suggested (16).

Factors associated with chemotherapy-induced nausea and vomiting

Age is a risk factor for CINV. Patients with younger ages have a higher risk than older patients (10,17,18,19). This correlation was not significant in our study although the prevalence of CINV was high in patients younger than 50 years.

Female gender was related to the occurrence of CINV. This result is similar to the literature (10,17,19). The female predominance could be attributed to hormonal implications.

It has been reported that patients with low alcohol intake or those who do not drink have a higher risk of developing CINV (10,17,18). Chronic alcohol consumption is a beneficial factor, explained by altered dopamine metabolism and lower plasma concentrations of cytotoxic agents. Although observed in our results, the lack of precise definition and measurement of alcohol consumption could be a bias.

Patients who have experienced nausea and vomiting during previous chemotherapy regimens are at high risk for their next chemotherapy cycles (10,20). In women, a history of nausea and vomiting during previous pregnancies is a risk factor (10,21,22). In our study, these factors were not associated with the occurrence of CINV. Other risk factors have been demonstrated but were not evaluated in our study. Anxiety, impaired general condition, morning sickness, Asian origin, short sleep duration and early cycles of chemotherapy are risk factors for CINV (10,17,20,22). Cardiovascular comorbidities reduce the risk of acute and delayed CINV.

Management of chemotherapy-induced nausea and vomiting

The Multinational Association of Supportive Care in Cancer and European Society for Medical Oncology (MASCC/ESMO) guidelines revised in 2016 recommend the combination of 5-hydroxytryptamine receptor antagonist (5-HT3RA) and dexamethasone for the prevention of CINV associated with moderately emetogenic chemotherapies (23). For patients treated with highly emetogenic chemotherapies or anthracycline- or carboplatin-based regimens, the combination of 5-HT3RA, neurokinin-1 receptor antagonist (NK1RA), and dexamethasone is recommended [23]. Among the 5-HT3RA are ondensetron, granisetron and tropisetron. Palonosetron is a second-generation 5-HT3RA, which is more effective (24). NK1RA are aprepitant, fosaprepitant and rolapitant. Similar recommendations have been issued by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO), with the addition of olanzapine (25).

Dopamine receptor antagonists (metoclopramide, chlorpromazine) are widely used, but high dosages can lead to extrapyramidal reactions. Other adjuvant medications such as benzodiazepines and cannabinoids have been shown to be effective, particularly in managing anticipatory symptoms and anxiety (26).

In Madagascar, as reported in our study, only odensetron, granisetron and corticosteroids can be used. NK1RA and

palonosetron are not available. However, the majority of patients receive highly emetogenic chemotherapy. The absence of NK1RA may explain the high prevalence of CINV. This context reflects our difficulty in adopting the recommendations in the antiemetic guidelines.

Limitations and strengths of the study

Our study has limitations. Several factors such as sleep duration, performance status, body mass index, dietary habits, tumor stage, and refractory CINV were not assessed. Some parameters were based on questioning, such as history of vomiting in pregnancy. However, according to the study, patients were far from being well prepared for chemotherapy. The prevalence of CINV was high. CINV was delayed in the majority of cases. NK1RA were not available despite the high emetogenicity of the therapeutic agents used.

Efforts should be made to improve the management of chemotherapy side effects. The delayed phase of CINV should not be underestimated after highly or moderately emetogenic chemotherapy. Antiemetics should be continued for a few days after initiation of chemotherapy. Access to newer antiemetics, including NK1RAs, should be favored in low-income countries.

CONCLUSION

The prevalence of CINV is alarming. However, only 5-HT3RA and corticosteroids are the available antiemetics. It is therefore essential to facilitate access to new antiemetics in low-income countries. Reducing the rate of CINV allows for good patient adherence to chemotherapy and reduces health care resources.

DATA AVAILABILITY

Additional data can be requested by contacting the corresponding author.

CONFLICT OF INTEREST

No conflict of interest between co-authors.

AUTHORS' CONTRIBUTIONS

TJB Norohery : data collection, writing the draft. RMF Randrianarisoa : writing-editing. NOTF Andrianandrasana : critical revision. HMD Vololontiana, F Rafaramino : visualization, validation.

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