Effectiveness of antiemetics in control of antineoplastic chemotherapy-induced emesis at home

Efetividade de antieméticos no controle da emese induzida pela quimioterapia antineoplásica, em domicílio

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Abstract

Objective: Evaluating if antiemetics are effective in the prevention or treatment at home, of chemotherapy-induced emesis.

Methods: In total, were included 42 women with breast cancer in moderately emetogenic chemotherapy, using dexamethasone/ondansetron before each cycle. The frequency of nausea and vomiting was obtained by applying the instrument in the pre-chemotherapy period, and 24h, 48h, 72h and 96h after chemotherapy. The use of antiemetics was considered in accordance with adherence to medical prescription.

Results: All patients (n = 42, 100%) reported emesis at some point. Only five cases (11.9%) were anticipatory. In the first 24 hours (acute emesis), 38 (90.5%)ayed), emesis was reported by all despite the regular use (n = 20, 47.6%) or not (n = 22, 52.4%) of antiemetics (ondansetron, dexamethasone and metoclopramide/or dimenhydrinate).

Conclusion: Antiemetics were not effective in the prevention or treatment at home, of chemotherapy-induced emesis.

Resumo

Objetivo: Avaliar se antieméticos são eficazes na prevenção ou tratamento da emese induzida pela quimioterapia antineoplásica, em domicílio.

Métodos: Foram incluídas 42 mulheres com câncer de mama, em quimioterapia moderadamente emetogênica, submetidas à dexametasona/ondansetrona antes de cada ciclo. A frequência de náuseas e vômitos foi obtida por instrumento aplicado nos tempos pré-quimioterapia e 24h, 48h, 72h e 96h pós-quimioterapia. O uso de antieméticos foi considerado conforme adesão à prescrição médica.

Resultados: Todas as pacientes (n=42, 100%) relataram emese em algum momento. Apenas cinco casos (11,9%) foram antecipatórios. Nas primeiras 24h (emese aguda), 38 (90,5%) apresentaram náuseas associadas (n=20, 47,6%) ou não (n=18, 42,8%) a vômitos e, após este período (tardio), a emese foi referida por todas, apesar da utilização regular (n=20, 47,6%) ou não (n=22, 52,4%) de antieméticos (ondansetrona, dexametasona, metoclopramida e/ou dimenidrinato).

Conclusão: Os antieméticos não foram eficazes na prevenção ou no tratamento da emese induzida pela quimioterapia, em domicílio.

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Introduction

Nausea and vomiting can be manifested in a variety of conditions, for example, in cases of drug poisoning.[1] In cancer chemotherapy, the drugs used are potent inducers of nausea and vomiting, which represent the most uncomfortable and stressful adverse effects in view of the patients themselves.[2]

Several drugs are used in the prevention and treatment of chemotherapy-induced emesis. Antagonists of serotonin receptors (5-HT3) such as ondansetron and granisetron are widely prescribed in hospitals, outpatient clinics and for use at home.[1] However, despite proven efficacy, the 5-HT3 antagonists do not show satisfactory results in about 20 to 30% of patients in antiemetic treatment.[3] In this context, the use of corticosteroids associated with the 5-HT3 antagonist is recommended, in view of greater efficacy in the control of emesis.[4] Other drugs, such as metoclopramide hydrochloride and dimenhydrinate have also been used, however, without clearly defined efficacy.[5]

Despite the introduction of antiemetic drugs considered effective, such as NK-1 receptor antagonist - aprepitant, an inadequate control of chemotherapy induced nausea and vomiting (CINV) is still observed and may persist until about five days after chemotherapy.[3,6] Without effective prophylaxis, prolonged nausea and vomiting can result in dehydration, electrolyte imbalance, malnutrition, aspiration pneumonia and increased rates of hospitalization. Moreover, these symptoms can be so distressing that end up affecting the quality of life of patients, leading them to even stop the treatment. Therefore, the effective and well tolerated antiemetic therapy is essential in patients receiving intensive chemotherapy.[7]

Thus, we consider that despite the recommendations made by consensus, the occurrence of CINV is still common, probably due to the ineffectiveness of antiemetic drugs or the combination of them. Given this, this study aims to assess the impact of antiemetic drugs currently used for the control of emesis in patients with breast cancer undergoing moderately emetogenic chemotherapy.

Methods

This is an observational, longitudinal study carried out in the outpatient chemotherapy at the Hospital do Câncer of the Universidade Federal de Uberlândia, in the state of Minas Gerais, southeastern Brazil, between February and November 2013.

Forty-two women with an initial diagnosis of breast cancer, regardless of tumor staging and on chemotherapy treatment (initial or ongoing) were included. It was a non-probabilistic convenience sample, consecutively drawn until reaching the number of subjects in accordance with sample size calculation (95% CI and 5% alpha error II).

All patients were followed for three consecutive cycles of chemotherapy - adriamycin (A) and cyclophosphamide (C) with or without fluorouracil (AC or FAC, respectively) - totaling 126 evaluated cycles. Immediately before each cycle, all received the same antiemetic therapy (ondansetron plus dexamethasone) administered intravenously, according to the Brazilian Consensus of Nausea and Vomiting (Consenso Brasileiro de Náuseas e Vômitos).[8]

Clinical data were obtained from information on the medical records of patients, such as age (years), tumor staging (initial - I, IIa; advanced - IIb, III or IV), as well as antiemetics and anticancer drug (generic name) prescribed to use at home. The latter information was updated according to ongoing treatment.

The daily monitoring to measure the frequency of nausea and vomiting and the routine use of antiemetics was initiated before the completion of each cycle of chemotherapy, and for four days after the end of it. The survey instrument was developed by the authors, based on the Functional Living Index of Emesis.[8] The interviews were conducted before the start of chemo and 24, 48, 72 and 96 hours (days one, two, three and four,

respectively) after completion of chemotherapy, by phone, when patients were already at home. The instrument was applied for three consecutive cycles of chemotherapy, following this same procedure.

The emesis was considered anticipatory when presented prior to the chemotherapy session; acute when occurring in the first 24 hours after chemotherapy and delayed, when nausea and/or vomiting occurred 24 hours after completion of the cycle.[9]

In the data analysis, three groups of patients were formed in accordance with the routine use of antiemetics at home: (1) Regular: use according to medical prescription, following the prescribed dosage; (2) Irregular: use without obeying the association of antiemetics and/or the recommended dosage, and (3) Self-medication: addition of some antiemetic to their everyday use, as well as using what had been prescribed or using only the antiemetic that they considered as the most effective.

Statistical analysis was performed with the use of Microsoft Office Excel 2007 and the GraphPad Prism 5. The results were expressed in mean ± standard deviation (±SD) and median with minimum and maximum values or absolute and relative frequencies.

The development of study followed the national and international standards of ethics in research involving human beings.

Results

In total, were included 42 women with mean age of (±SD) 48.3 ± 10.1 years, ranging between 29 and 73 years. Breast cancer was diagnosed, mostly at an advanced stage (n=26, 61.9%). In all cases there were reports of nausea and/or vomiting at some point of the chemotherapy treatment, despite the regular use of antiemetics (n=20, 47.6%) or not (n=22, 52.4%) by 100% of the study population (Table 1).

Considering the time of emesis occurrence, only five cases (11.9%) were anticipatory. However, in the first 24 hours after chemotherapy, 38 (90.5%) women had nausea associated with vomiting (n=20, 47.6%) or only nausea (n=18, 42.8%), and after this period, emesis was reported by all patients (n=42, 100%) (Table 1).

Table 1. Age group, tumor staging, and the occurrence and treatment of emesis

Variables	Measures or frequencies
Age (years)	
Mean ± SD	48.3 ± 10.1
Median (min - máx)	46(29-73)
Tumor staging	
Initial+	16(38.1)
Advanced*	26(61.9)
Nauseas and/or vomiting	
None**	-
Only nausea	14(33.33)
Only vomiting	-
Nausea and vomiting	28(66.7)
Type of nausea and/or vomiting*	
Antecipatory	5(11.9)
Nausea	4(9.5)
Nausea and vomiting	1(2.4)
Acute	38(90.5)
Nausea	18(42.8)
Nausea and vomiting	20(47.6)
Delayed	42(100)
Nausea	22(52.4)
Nausea and vomiting	20(47.6)
Routine of use of antiemetics at home	
Regular**	20(47.6)
Irregular***	20(47.6)
Self-medication****	2(4.8)

+Stages I, IIa; *Stages IIb, III and IV; **No episode of CINV; *Rating of nausea and/or vomiting according to the time of occurrence, pre (anticipatory emesis) and/or post (acute emesis – first 24h - or delayed – after 24h) chemoterapy; ** Use of antiemetic in accordance with the prescription, following the prescribed dose; *** Use of the prescribed antiemetic however, not obeying the association of antiemetics and/or the recommended dosage; **** Addition of some antiemetic into their routine use, as well as using what had been prescribed, or using only the antiemetic they considered as the most effective

Linking nausea and vomiting with the regularity of use of antiemetics (Table 2) showed that among the group who regularly followed the prescription (n=20), in almost 100% (n=19, 95%) emesis occurred in the first 24 hours and continued thereafter (delayed emesis). A similar result was observed for the groups with irregular use (n=20) or the self-medication group (n=2), where acute and delayed emesis occurred in 85% (n=17) and 100% (n=2) of cases, respectively.

Considering the total of cycles evaluated isolatedly (n = 126), nine antiemetic regimens were listed according to association among drugs or not: (A) ondansetron; (B) ondansetron, and dexamethasone; (C) ondansetron, dexamethasone and metoclopramide hydrochloride; (D) metoclopramide

Table 2. Type of nausea and vomiting according to use of antiemetics at home

Type of nausea and/or vomiting	Regular** (n=20) n(%)	Irregular*** (n=20) n(%)	Self-medication+ (n=2) n(%)
Acute			
Only nausea	-	-	-
Vomiting	-	-	-
Nausea and vomiting	-	-	-
Dealyed			
Only nausea	1(5.0)	2(10.0)	-
Only vomiting	-	-	-
Nausea and vomiting	-	1(5.0)	-
Acute and delayed			
Only nausea	7(35.0)	4(20.0)	-
Only vomiting	-	-	-
Acute nausea and delayed NV*	2(10.0)	4(20.0)	1(50.0)
Acute NV and delayed nausea*	3(15.0)	4(20.0)	1(50.0)
Nausea and vomiting	7(35.0)	5(25.0)	-

*NV - nausea and vomiting; ** Use of antiemetic in accordance with the prescription, following the prescribed dose; *** Use of the prescribed antiemetic however, not obeying the association of antiemetics and/or the recommended dosage; + Addition of some antiemetic into their routine use, as well as using what had been prescribed, or using only the antiemetic they considered as the most effective; The hyphen (-) indicates no occurrence for the group

hydrochloride; (E) dexamethasone and metoclopramide hydrochloride; (F) metoclopramide hydrochloride and ondansetron; (G) dexamethasone; (H) dexamethasone and dimenhydrinate; (I) dimenhydrinate (Table 3).

Ondansetron was used after 94 cycles isolatedly (n=41, 32.5%) or associated with dexamethasone (n=40, 31.7%), or together with dexamethasone and metoclopramide hydrochloride (n=4, 3.2%), or only associated with metoclopramide hydrochloride (n=9, 7.2%). The schemes A and B were the most frequent (32.5% and 31.7%, respectively) when compared to the others.

A high occurrence of acute and/or delayed emesis (n = 106, 84.1%) was observed for the different antiemetic regimens. Only two patients reported no use of antiemetics in one of the three analyzed cycles, and another patient reported not having used any medication in two consecutive cycles (data not shown in Table 3). For these cases, were found reports of both the occurrence of emesis (delayed nausea, delayed nausea and vomiting) as the lack thereof.

Emesis was not observed in 18 (14.3%) cycles of chemotherapy and in the vast majority of these (n = 16, 88.9%), some antiemetic drug was used in association with others or not (Table 3). A total of 12 different women had cycles with no emetic episodes, of which six (50%) had two cycles without complaints of emesis and the rest (n = 6, 50%) had only one cycle without complaint. Despite these reports, it is noteworthy that all patients had nausea and/or vomiting at some point, and in most cases was used an identical antiemetic regimen to that prescribed in the cycles without reports of emetic episodes.

Table 3. Occurrence of emesis and the used antiemetic drug regimens

Emesis	Schemes								
	A** n(%)	B*** n(%)	C**** n(%)	D+ n(%)	E+ n(%)	F+++ n(%)	G++++ n(%)	H***** n(%)	I****** n(%)
No emesis	6(14.6)	6(15.0)	-	-	-	-	3(37.5)	1(33.3)	-
Acute									
Nausea	2(4.9)	1(2.5)	-	-	-	-	1(12.5)	1(33.3)	-
Vomiting	-	-	-	-	-	-	-	-	-
NV*	-	1(2.5)	-	-	-	-	-	-	-
Delayed									
Nausea	2(4.9)	6(15.0)	-	-	1(16.7)	1(11.1)	3(37.5)	-	-
Vomiting	-	-	-	-	-	-	-	-	-
NV*	2(4.9)	3(7.5)	1(25.0)	2(20.0)	-	1(11.1)	-	-	-
Acute and delayed									
Nausea	13(31.7)	9(22.5)	-	4(40.0)	1(16.7)	2(22.2)	1(12.5)	1(33.3)	-
Vomiting	-	-	-	-	-	-	-	-	-
AN e DNV#	2(4.9)	3(7.5)	1(25.0)	2(20.0)	4(66.7)	1(11.1)	-	-	-
ANV and DN##	7(17.1)	7(17.5)	2(50.0)	2(20.0)	-	1(11.1)	-	-	-
NV*	7(17.1)	4(10.0)	-	-	-	3(33.3)	-	-	1(100)
Total	41(32.5)	40(31.7)	4(3.2)	10(7.9)	6(4.8)	9(7.2)	8(6.3)	3(2.9)	1(0.8)

*Nausea and vomiting; #Acute nausea and delayed nausea and vomiting; ##Acute nausea and vomiting and delayed nausea; **Use of ondansetron only; ***Us e of ondansetron associated with dexamethasone; ****Association of ondansetron, dexamethasone and metoclopramide hydrochloride; +Use of metoclopramide hydrochloride only; ++Use of metoclopramide hydrochloride associated with dexamethasone; +++Uso de ondansetron associated with metoclopramide hydrochloride; ++++Use of dexamethasone only; *****Use of dexamethasone associated with dimenhydrinate; ******Use of dimenhydrinate only; The hyphen (-) indicates no occurrence for the group

Discussion

The limit of the results of this study is related to the observational design that does not allow establishing relations of cause and effect.

Nurses acting in oncology should know the chemotherapy drugs used, their possible side effects and the impact triggered by treatment, to ensure quality care. Therefore, it is essential showing the oncology teams about the high incidence of emesis even with an established antiemetic therapy, in order to help in the treatment of patients with similar conditions.

Despite the use of antiemetic drugs in specialized services, both in outpatient clinics as at home, in agreement with the consensus, the control of these symptoms is not yet satisfactory.[3,6,10] Such statement was demonstrated in the results of this study when it was observed that all participants had nausea with or without vomiting, either pre or post chemotherapy. A study of 178 American patients also showed the high occurrence of emesis, since in their results, 34% and 58% of participants experienced acute and delayed nausea and vomiting, respectively.[11]

It has been discussed and accepted that the emetogenic profile of chemotherapy drugs is primarily responsible for the intensity and duration of emesis.[8] Among the 42 studied patients, all have experienced emetic episodes, revealing that despite one of the schemes being composed by fluorouracil, the addition of this chemotherapy drug did not alter the emetogenic profile of the protocol (data not shown). It is known that in chemotherapy regimens including more than one drug, the degree of emetogenicity is given by the combination of the chemotherapy drug with the highest emetogenic degree, plus the degree of emetogenicity of the other drugs.[9]

The management of emesis, particularly at the late stage of post chemotherapy, is a challenge.[12] It is known that first-generation 5-HT3 antagonists such as the ondansetron, which is the drug used in most cycles evaluated in this study, often fails to adequately control the late symptoms.[10] In addition, other drugs such as metoclopramide hydrochloride at high doses, associated with dexamethasone are less effective than the use in combination of a 5-HT3 antagonist and dexamethasone,[13] reinforcing the concept that antiemetics such as metoclopramide hydrochloride and also dimenhydrinate have low therapeutic index,[8] and there are few reports of use of this drug. It is noteworthy that all the women interviewed in this study had delayed emesis, which shows the poor control provided by the antiemetics used by this population.

It was also observed that the frequency of use of the prescribed antiemetic did not influence the control of emesis. However, some studies support the idea that due to irregular use of prescribed medication, some patients may not be benefiting from the treatment of prophylaxis.[11] Women taking the prescribed antiemetics irregularly argued that followed this routine for not having the habit of using any medication on a regular basis, for considering it unnecessary in face of the discomfort caused by emesis, and due to side effects of antiemetics.

Besides the features of chemotherapeutic agents and routine use of prescribed antiemetic, factors intrinsic to patients also increase the risks for developing nausea and vomiting, namely: the female gender, younger than 50 years, history of low alcohol consumption, history of nausea and vomiting in previous chemotherapy treatments, history of motion sickness, nausea and vomiting during previous pregnancy.[10,14] In this study, it is noteworthy that the studied population is comprised of women only, with average age under 50 years, which may be contributing factors to the high incidence of emesis.

Due to not being adequately controlled, nausea and vomiting affect the quality of life and adherence to the proposed treatment.[7] In another study, the authors indicated that, without the use of prophylactic antiemetic therapy, chemotherapy can trigger severe nausea and vomiting, which can lead patients to wish to stop treatment.[11]

Besides the negative impact on quality of life and influence on adherence to treatment, emesis may exert a burden on the health system, generating increased costs, whether with other medicines,

unscheduled medical consultations, and hospitalizations that may be required.[11]

The goal of antiemetic therapy is the complete prevention of emesis. In this context, adherence to new practices that enable better control of symptoms becomes necessary. Studies have shown that combinations of new drugs such as palonosetron (serotonin receptor antagonist of the second generation) and aprepitant (NK-1 receptor antagonist) can offer a better protection.[10,11,15]

Apart from drugs, complementary medicines and integrative practices can be associated with treatment such as herbal medicines, homeopathy, acupuncture, relaxation, aromatherapy and others. It is noteworthy that in addition to having these services provided, patients should be counseled regarding their effectiveness and encouraged to carry them out.[8]

The nursing consultation is also of great importance. Nurses, as members of a multidisciplinary team, are a facilitating bridge on quality care and form a channel of communication and orientation, thus assisting effectively in the control of emesis. These professionals should be able to identify the risks to which patients are subjected, aiming at planning an assistance focused on preventing and minimizing these side effects.

The results showed that antiemetics were not able to prevent or treat chemotherapy-induced emesis, which shows that despite the recommendations made by consensus, nausea and vomiting remain one of the most prevalent side effects of chemotherapy.

Given the above, it is necessary to optimize the treatment with antiemetics, providing new drugs with proven effectiveness, new forms of complementary and alternative therapies and the institution of systematic nursing consultation, impacting in greater control of emesis and consequently positively influencing the quality of life of patients.

Conclusion

Antiemetics were not effective in the prevention or treatment at home, of chemotherapy-induced emesis.

Collaborations

Castro MC; Araújo AS; Mendes TR; Vilarinho GS and Mendonça MAO declare to have contributed to the project design, analysis and interpretation of data, drafting the article, critical revision of the important intellectual content and final approval of the version to be published.

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