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Phase II study of pregabalin for the prevention of chemotherapy induced nausea and vomiting

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Abstract

To evaluate the role of pregabalin in the protection of chemotherapy-induced nausea and vomiting, we performed a phase II randomized, double-blind, placebo-controlled trial to investigate whether pregabalin could improve the complete control of nausea and vomiting (primary end point). We enrolled 82 chemotherapy-naive patients, scheduled to receive moderately and highly emetogenic chemotherapy. All patients received IV ondansetron 8mg, dexamethasone 10mg before chemotherapy on day one and oral dexamethasone 4mg, b.d., on days two and three. Patients were randomly assigned to take pregabalin 75mg or placebo, bd, from the night before chemotherapy to day five. The overall complete response was not statistically significant between the groups (53.7 *versus* 48.8%, respectively, in the pregabalin group and the control group (P=0.65)). There was also no significant difference during the acute phase (first 24 hours) and delayed phase (24-120h): 80.5% *versus* 82.9% (P=0.77), 53.7 versus 51.2% (P=0.82), respectively. There is no role for pregabalin preventing chemotherapy-induced nausea and vomiting. Clinicaltrial.gov registration number: NCT04181346.

Keywords: Nausea. Neurokinin-1 receptor antagonists. Pregabalin. Antiemetics. Cancer.

INTRODUCTION

Patients consistently report that vomiting and nausea are among the most unpleasant and distressing aspects of chemotherapy[1]. This symptom negatively affects patients' nutritional habits, ability to work, and motivation to follow recommended antineoplastic treatment regimens[2,3].

A better understanding of the pathophysiology of vomiting and the introduction of serotonin type 3 receptor antagonists in the 1990s and neurokinin type 1 (NK-1) receptor antagonists in 2000, combined with corticosteroids, have helped to improve the management of this unpleasant side effect[4,5].

The 5-HT3 receptor antagonists have a high therapeutic index in controlling acute chemotherapy-induced nausea and vomiting (CINV), which occurs during the first 24 hours after chemotherapy. However, delayed phase's control (after 24 hours of chemotherapy) remains a challenge and some data shows that the second generation 5-HT3 receptor antagonist palonasetron is better than the first-generation agents ondasetron and granisetron[6-9].

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Many trials established NK-1 receptor antagonists as the most effective drugs for the prevention of acute and delayed nausea and vomiting induced by chemotherapy of high and moderate emetogenic potential (Highly Emetogenic Chemotherapy - HEC and Moderate Emetogenic Chemotherapy - MEC, respectively)[10-12].

Recently, some trials demonstrated that the antipsychotic agent olanzapine significantly improved complete control of nausea and vomiting in patients receiving HEC and MEC[13-17]. Olanzapine blocks multiple neurotransmitters related to the pathophysiology of CINV like dopamine receptors and serotonin receptors[8,15,18]. The role of olanzapine seems to be especially important for nausea control[17].

The guidelines of National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) strongly recommend the combination of corticosteroids, 5-HT3 receptor antagonists, NK-1 receptor antagonists with or without olanzapine as standard regimen for HEC[19-21]. However, even with this combination, almost 30% of patients still present nausea and vomiting[8].

The high cost of oncologic treatment, including antiemetic agents, encourages the search for alternative and cost-effective strategies for the prevention of CINV. Although antiemetic strategies have advanced, there is still a significant gap in our knowledge regarding the potential use of pregabalin in preventing CINV. Currently, there is limited research on this topic, indicating the need for further investigation.

Pregabalin is a structural derivative of the inhibitory neurotransmitter γ-aminobutyric acid, six times more potent than gabapentin. Given the high prevalence of nausea and vomiting associated with current standard chemotherapy regimens, investigating alternative treatments such as pregabalin shows potential for improving patients' quality of life and optimizing healthcare resources by potentially providing a more cost-effective solution. It binds potently to the α2-δ subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P[22,23]. Some of these transmitters are involved on the physiopathology of nausea and vomiting.

Some trials demonstrated that pregabalin may have a role in controlling postoperative nausea and vomiting[24,25]. As far as we are aware, the role of pregabalin in the prevention of CINV hasn't been studied yet.

Against this backdrop, our study aims to address the existing gap by evaluating the specific role of pregabalin in preventing chemotherapy-induced nausea and vomiting. We seek to elucidate the potential benefits of pregabalin within the context of antiemetic strategies for patients undergoing chemotherapy.

METHODS

We performed in our institution, *Instituto Brasileiro de Controle do Câncer - IBCC Oncologia* Clinic, a prospective, double-blind, placebo-controlled study, from September 2019 to February 2020. All the randomized patients provided written informed consent. All personnel involved in the study were blinded to the assigned treatment. This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the *Instituto Brasileiro de Controle do Câncer* Research Ethics Board (IBCC -CEP) (Ethics approval number:1.250.884). Informed consent was obtained from all individual participants included in the study. Clinicaltrial.gov registration number: NCT04181346.

INCLUSION AND EXCLUSION CRITERIA

Patients aged 18 years or older with cancer who were scheduled to receive their first cycle of

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moderate to highly emetogenic chemotherapy, as previously defined, were included[26]. The following regimens were included: doxorubicin (60 mg/m^2) + cyclophosphamide (600mg/m^2), carboplatin (AUC5) + paclitaxel (175mg/m^2), docetaxel (75mg/m^2) + cyclophosphamide (600mg/m^2) and doxorubicin (60mg/m^2).

Additional eligibility criteria were: an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (on a 5-point scale, with 0 indicating no symptoms and higher numbers indicating increasing disability); serum creatinine level of 2.0mg per deciliter (177µmol per liter) or less; an aspartate or alanine aminotransferase level that was no more than 3 times the upper limit of the normal range, and an absolute neutrophil count of at least 1,500 per cubic millimeter; no nausea or vomiting in the 24 hours before enrollment; no severe cognitive compromise; no regular use of corticosteroids, opioid, benzodiazepines, tricyclic antidepressant or cannabinoids within 30 days before randomization; no known brain metastasis; no chronic alcoholism; no known hypersensitivity to pregabalin.

TREATMENT

All patients received intravenous ondansetron 8 mg, dexamethasone 10mg before chemotherapy on day one and dexamethasone twice a day on days two and three. Patients were randomly assigned, with a block-balanced randomization list, to take pregabalin 75mg or placebo, twice a day, from the night before chemotherapy to day five.

DEFINITIONS OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Episodes of vomiting or retching were recorded by the patients on diary cards from the beginning of chemotherapy infusion (0 hour) until the morning of day 6 (120 hours). An emetic episode was defined as a single instance of vomiting or retching; distinct episodes were separated by at least one minute. The use of rescue therapy, defined as any medication taken to treat established nausea or emesis, was also recorded. Permitted rescue medications included 5-HT3-antagonists, phenothiazines and antihistaminics.

Nausea was assessed on a 100 mm horizontal visual-analogue scale in the patient diary with the heading: *"How much nausea have you had over the past 24 hours?"* The left-hand end (0 mm) of the scale was labelled "no nausea" and the right-hand end was labelled "nausea as bad as it could be". Every 24 hours, the patients indicated the degree of nausea during the previous 24 hours by placing a vertical mark on the line scale. During the day before chemo and five days after, telephone contact was made by study site personnel to confirm that patients were taking study medications appropriately, maintaining accurate record and to give orientation.

Complete protection (CP) from nausea and vomiting was defined as the absence of moderate or severe nausea and the absence of any episode of vomiting and no use of rescue medication. Complete protection was further defined as either acute (Acute Complete Protection- ACP), when occurring during the first 24 hours after chemotherapy; delayed (Delayed Complete Protection - DCP), when occurring during the period from days 2 through 5 after chemotherapy; or overall, when occurring over the entire period of the study (first 120 hours).

Any adverse events were registered on the diary cards and checked on the post-study visit, which occurred after day six of chemotherapy, using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Patients answered the Functional Living Index-Emesis (FLIE) questionnaire before the initiation of chemotherapy infusion on day one and after day six of chemotherapy[27]. The FLIE questionnaire is a validated patient-reported measure of the impact of CINV on daily life.

STATISTICAL METHODS

The primary end points of this study were complete protection from both vomiting and nausea during the entire period of study (day one to day five) and complete protection during

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the delayed period. The secondary end points were to evaluate the adverse events other than episodes of vomiting or nausea, and to evaluate the impact of nausea and vomiting on quality of life (QoL) using the FLIE questionnaire.

Statistical analyses were carried out using *Stata 12*. For all binary outcome efficacy measures, comparison between the pregabalin regimen and the control regimen was made using logistic regression. We evaluated associations between categorical variables using the X^2 test. Because we wanted to test whether the addition of pregabalin was superior to placebo, we used one sided significance tests with a significance threshold of P≤0.05.

It was estimated that a total of 82 subjects would be required for a two-way parallel trial to detect a treatment effect, assuming a 30% difference in the proportion of patients experiencing complete control of nausea and vomiting between arms, with a significance level of 5% and a power of 80%.

RESULTS

Of the 97 potential patients, 88 were able to participate. Nine were excluded due to the use of benzodiazepine, tricyclic antidepressant or chronic alcohol consumption, and six refused to participate. From September 2019 to February 2020, 82 patients were consecutively randomized, of whom 41 to the experimental group (pregabalin) and 41 to the Control Group (placebo) (Figure 1). The baseline characteristics of eligible patients were similar between groups (Table 1).

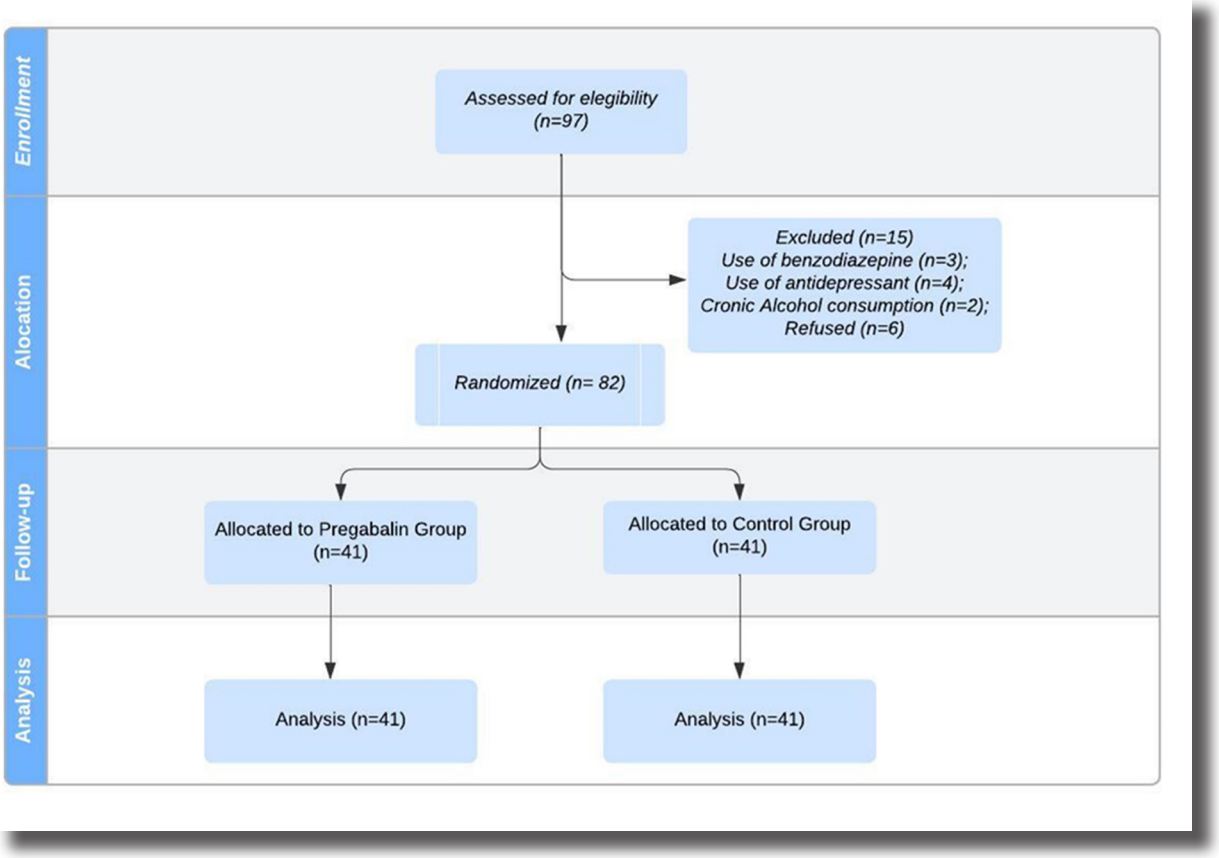

Figure 1 - Flowchart of the patient's selection.

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Table 1 - Demographic and clinical characteristic of patients.

Characteristics	Pregabalin (n=41)	Placebo (n=41)
Male sex (%)	1 (1.2%)	1 (1.2%)
Age*	51.4 + 10.7	52.1 + 11.8
ECOG 0 (%)	41 (100%)	41 (100%)
Type of cancer (%)		
Breast	39 (95.1%)	35 (85.4%)
Ovarian	1 (2.4%)	2 (4.9%)
Uterus	0 (0%)	2 (4.9%)
Endometrium	1 (2.4%)	1 (2.4%)
Head and neck	0 (0%)	1 (2.4%)
Type of chemotherapy (%)		
Doxorubicin (60mg/m^2) + Cyclophosphamide (600mg/m^2)	38 (92.7%)	35 (85.4%)
Carboplatin (AUC5) + paclitaxel (175mg/m^2)	2 (4.9%)	5 (12.2%)
Docetaxel (75mg/m$^{2)}$ + Cyclophosphamide (600mg/m^2)	1 (2.4%)	0 (0%)
Doxorubicin (60mg/m^2)	0 (0%)	1 (2.4%)
Clinical stage (%)		
I	2 (4.9%)	2 (4.9%)
II	16 (39%)	16 (39%)
III	23 (56.1%)	20 (48.8%)
IV	0 (0%)	3 (7.3%)
Intention of treatment (%)		
Neoadjuvant	28 (68.2%)	23 (56.1%)
Adjuvant	13 (31.7%)	16 (39%)
Palliative	0 (0%)	2 (4.9%)

*The results are expressed as number of patients (percent) or mean + SD; ECOG: Eastern Cooperative Oncology Group.

The majority of patients were female and received highly emetogenic chemotherapy (98.8%), all of them had ECOG 0 (100%). Only 2.4% of patients had metastatic disease.

The primary end point of overall complete response (Figure 2) was not statistically different between the Experimental and Control Groups (53.7 *versus* 48.8%, P=0.65). There was also no difference in the acute phase (80.4% *versus* 82.9%, P=0.77) and delayed phase 53.7% *versus* 51.2%, P=0.82) (Figure 2/Table 2).

No serious adverse events were observed, and no patient discontinued medication (Table 3). On the FLIE questionnaire, there was no significant difference between the treatment groups.

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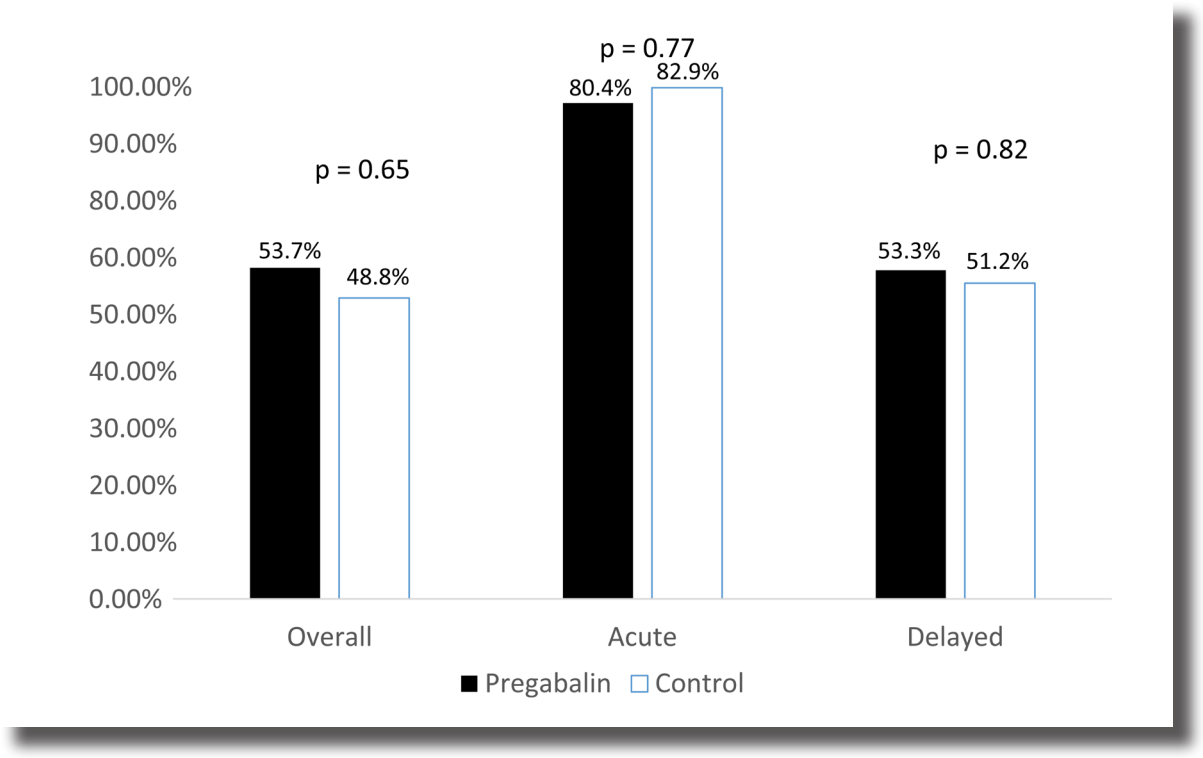

Figure 2 - Percent of patients achieving complete response of nausea and vomiting. For each group, n=41.

Table 2 - Patients reaching control of nausea, control of vomiting and complete control by study phase and Treatment Group.

Treatment Group	Acute (day 1)			Delayed (days 2-5)			Overall (days 1-5)		
	Pregabalin n=41	Placebo n=41	P-value	Pregabalin n=41	Placebo n=41	P-value	Pregabalin n=41	Placebo n=41	P-value
No emesis	37 (90.2%)	37 (90.2%)	1.0	34 (82.9%)	31 (75.6%)	0.41	32 (78%)	30 (73.2%)	0.6
No nausea	32 (78%)	34 (82.9%)	0.57	22 (53.6%)	23 (56.1%)	0.82	22 (53.7%)	22 (53.7%)	1.0
No rescue	37 (90.2%)	37 (90.2%)	1.0	28 (68.2%)	33 (80.5%)	0.20	28 (68.3%)	31 (75.6%)	0.46
Complete control	33 (80.5%)	34 (82.9%)	0.77	22 (53.7%)	21 (51.2%)	0.82	22 (53.7%)	20(48.8%)	0.65

Note: Number of patients in each group (percent). Complete protection indicates no emesis, no nausea and no rescue therapy.

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Table 3 - Adverse events*.

Adverse events	Pregabalin	Placebo
Stomachache	3 (7.32%)	5 (12.2%)
Dizziness	2 (4.88%)	2 (4.88%)
Hypersalivation	1 (2.44%)	0 (0%)
Heartburn	0 (0%)	1 (2.44%)
Weakness	6 (14.63%)	6 (14.63%)
Rash	1 (2.44%)	0 (0%)
Constipation	2 (4.88%)	3 (7.32%)
Tremor	1 (2.44%)	0 (0%)
Neuropathy	1 (2.44%)	1 (2.44%)
Sleepiness	2 (4.88%)	1 (2.44%)

*Number of patients (percent). None of the variables differed significantly between Groups (p>0.05).

DISCUSSION

In this pilot randomized clinical trial, the addition of pregabalin to ondansetron and dexamethasone during the first cycle of moderately and highly emetogenic chemotherapy did not improve complete control of CINV compared to placebo. There was no statistically significant difference in the complete response primary end point.

Pregabalin and gabapentin are antiepileptic drugs that are structurally similar to gamma-aminobutyric acid (GABA), although neither has activity in GABAergic systems. Both share the same mechanism of action, which is based on the fact that alpha 2/delta calcium voltage-gated channels (VGCC) reduce the flow of neuronal calcium[28,29].

The antiemetic properties of gabapentinoids has been tested before, specially gabapentin. The first evidence that gabapentin may have some activity as an antiemetic drug was demonstrated by Guttuso *et al.* In patients with refractory CINV, gabapentin decreased the degree of delayed nausea in 66.7% of patients. It was postulated that gabapentin might mitigate tachykinin neurotransmitter activity and lead to physiologic activity similar to that seen with NK-1 receptor antagonists, making it a potential intervention for delayed nausea and vomiting[30].

At our institution, we conducted a prospective, double-blinded, placebo-controlled study that demonstrated the efficacy of adding gabapentin to ondansetron and dexamethasone in preventing CINV for moderately and highly emetogenic chemotherapy (65% *versus* 42.5%; P=0.04). The trial

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showed that acute complete control rate and use of gabapentin were independent factors for achieving overall complete response. The benefit of gabapentin was higher in the delayed phase[31].

However, the Phase III Alliance trial revealed that gabapentin did not significantly improve delayed chemotherapy-induced nausea and vomiting. Both the gabapentin and placebo groups reported satisfactory symptom control. In contrast to Cruz *et al.*'s trial, where most patients received a higher dose of gabapentin (900mg), the patients in this study received a lower dose (600mg). It is unclear whether this difference in dosage may have contributed to the lack of activity observed. It is well established that there is a dose-response relationship of gabapentinoids in the treatment of postherpetic neuralgia and partial seizures[32].

Although pregabalin and gabapentin share similarities in their pharmacokinetic and pharmacodynamic profiles, there are significant differences between them. Pregabalin has more predictable pharmacokinetics, a higher binding affinity to its target receptor, greater potency, and a steeper dose-response curve in neuropathic pain. In contrast to gabapentin, pregabalin's dose-response curve does not plateau even at recommended dosage levels. Studies indicate that pregabalin may have fewer side effects and be more effective than gabapentin for neuropathic pain[33].

As an antiepileptic, pregabalin may be more effective than gabapentin, on the basis of the magnitude of the reduction in the seizure frequency[34]. Pregabalin's great affinity to calcium channels results in the release reduction of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P[29]. Since the blockage of serotonin, substance P and dopamine receptors plays an important role in the pathophysiology of nausea and vomiting, it was speculated that pregabalin could have an antiemetic activity.

Pregabalin has been studied for its effectiveness in reducing acute postoperative pain. However, the results have been conflicting, possibly due to variations in dosage and surgery type. Administering pregabalin during the perioperative period has been shown to significantly reduce the need for opioids within the first 24 hours after surgery[35]. Additionally, it has been found to decrease postoperative vomiting, although it may increase the risk of visual disturbances. A meta-analysis focused on the effect of preoperative pregabalin in preventing postoperative nausea and vomiting (PONV) and concluded that it leads to a significant reduction in PONV. Therefore, pregabalin should be considered as part of a multimodal approach to postoperative pain relief and a potential preventive measure for PONV[36]. The antiemetic property of pregabalin is small and might be an indirect effect, caused by the reduction of opioids consumption and consequently decreasing the opioid-related adverse events.

Pregabalin remains a drug with high costs for both patients and the healthcare system. One limitation of our trial is that the Brazilian government does not fund NK1 antagonists due to their high cost. Another limitation is our current understanding of pregabalin's mechanisms of action as an antiemetic. To validate the results of this study, more high-quality clinical trials should be conducted. These trials should be randomized, controlled, multicenter, double-blind, and have larger sample sizes. The primary outcome of these trials should be the antiemetic effect of pregabalin. That is the reason our control arm was constituted only for a doublet regimen with corticosteroid and 5HT3RA.

Comparative evaluation of triplet antiemetic schedule versus doublet antiemetic schedule in chemotherapy-induced emesis showed a better control with three drugs[21]. Now, there is evidence that a quartet regimen including olanzapine, NK1RA, 5HT3RA

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and corticosteroids achieved a better control of CINV[17]. The cost of anti-emetic drugs is a concern, particularly in developing countries where many of these drugs are unaffordable. The cost of drugs to treat a specific cancer symptom can vary widely, and many of these drugs are expensive. The high number of products used and their frequency among cancer patients can significantly contribute to patients' financial burden. Therefore, patients and clinicians should evaluate the risk--benefit ratio of a prescription, particularly given the limited data supporting the use of some drugs.

CONCLUSION

In conclusion, pregabalin is not effective in controlling chemotherapy-induced nausea and vomiting. Further work is warranted to investigate other antipsychotic drugs for the prevention of chemotherapy induced nausea and vomiting. Further evaluation is necessary for promising antiemetic agents, such as pregabalin. Besides that, studies to evaluate the effects of different combinations of antiemetics (using older and newer combinations of agents) and determine the optimal combination for prevention and control of CINV.

CREdiT author statement

Conceptualization: Rossi, CS; Cruz, FJSM. Methodology: Rossi, CS; Cruz, FJSM. Validation: Rossi, CS; Cruz, FJSM. Statistical analysis: Cruz, FJSM; Giglio, AD. Formal analysis: Rossi, CS; Cruz, FJSM; Giglio, AD. Research: Rossi, CS. Writing-elaboration of the original draft: Rossi, CS; Cruz, FJSM; Giglio, AD; Yamada, AMTD. Writing-review and editing: Rossi, CS; Cruz, FJSM; Giglio, AD; Yamada, AMTD. Visualization: Rossi, CS; Cruz, FJSM; Giglio, AD; Yamada, AMTD. Supervision: Rossi, CS; Cruz, FJSM; Giglio, AD; Yamada, AMTD. Project administration: Rossi, CS.

All authors read and agreed to the published version of the manuscript.

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