



**COMPARATIVE STUDY BETWEEN THE CLINICAL EFFECT OF PALONOSETRON
AND GRANISETRON AS ANTIEMETIC THERAPY IN COMBINATION WITH
DEXAMETHASONE IN PATIENTS RECEIVING HIGHLY EMETOGENIC
CHEMOTHERAPY REGIMENS**

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting (CINV) are considered the main fear for both oncologists and patients. It dramatically affects the quality of life, especially food intake and nutritional status. we can observe CINV in highly emetogenic chemotherapy (HEC) such as AC protocol in breast cancer patients or cisplatin-based regimens in other cancer types. This study aimed to evaluate the antiemetic efficacy of palonosetron (PALO) over Granisetron (GRA) in combination with dexamethasone for multiple high emetogenic risk (HER) anti-cancer agents, especially in chemotherapy regimens in Egyptian breast cancer patients and Cisplatin-based regimens in other diseases. **Patients and Methods:** All patients received dexamethasone in combination with the 5-HT₃ receptor antagonist. Patients' clinical and biochemical characteristics were recorded, and blood samples were drawn to monitor serum substance P and serotonin in correlation with chemotherapy-induced nausea and vomiting (CINV). MASCC antiemetic tool in the acute phase (0hr-24hr) and delayed phase (24hr-120hr) was used to evaluate patient outcomes in both stages after each chemotherapy cycle. **Results:** In (PALO) group, only 7.84% of patients showed acute vomiting, and 11.76 % showed acute nausea, whereas 43.75 % of patients showed acute vomiting and 89.06 % showed acute nausea in (GRA) group (P<0.0001). For delayed CINV, 23.53 % of patients showed delayed vomiting, and 47.06 % showed delayed nausea in (PALO) group, while 82.81 % of patients showed delayed emesis, and 92.19 % showed delayed nausea in (GRA) group (P<0.0001). Besides that, 45.10% of patients in (PALO) required additional rescue medications (domperidone 10 mg oral three times per day plus trimebutine 200mg oral three times per week both for five days), while 95.24 % in the (GRA) group used the same medications. Adverse events of both antiemetic drugs (PALO and GRA) were mostly mild to moderate, with relatively low rates among the two groups. **Conclusion:** Palonosetron, combined with dexamethasone, is more effective than Granisetron and dexamethasone combination against both acute and delayed emesis induced by highly emetogenic cisplatin-based chemotherapy and highly emetogenic combination of cyclophosphamide and anthracyclines (AC).

KEYWORDS: CINV, HEC, Palonosetron, Granisetron, Supportive care, Pharmacokinetics, cancer pharmacology.

1. BACKGROUND

Chemotherapy-induced nausea and vomiting (CINV) is the most problematic issue in oncology supportive care plan. It can lead to disruption of oral intake, a decline in nutritional status, discontinuation or interruption of chemotherapy, and compromised life quality.^[1] This can be clearly observed in highly emetogenic chemotherapy (HEC) such as AC protocol in breast cancer patients or cisplatin-based regimens in other cancer types. This study aimed to achieve reasonable emetic control via a Comparison of the clinical outcome of palonosetron

(PALO) and Granisetron (GRA) in combination with dexamethasone for multiple high emetogenic risks (HER) anti-cancer agents, especially in chemotherapy regimens in breast cancer and Cisplatin-based regimens.^[2] Moreover, 70–80% of chemotherapy-receiving patients experience CINV due to the lack of appropriate antiemetic control. Therefore, the effective management of CINV is a priority for this large group of patients.-

CINV control has improved since the evolution of the serotonin receptor antagonists (5-HT₃)(RAs) and the neurokinin 1 (NK1) RA aprepitant.^[5] In 2005 granisetron (GRA) and ondansetron were introduced to the market as first-generation serotonin receptor antagonists; however, CINV's prophylaxis with those agents against acute CINV. The antiemetic action is decreased in the delayed phase of CINV. In a previous meta-analysis, if another dose of 5HT-3 receptor antagonist is administered beyond 24 hrs. of the chemotherapy cycle, it will be ineffective.^[6] Palonosetron, the second generation of serotonin receptor antagonists with higher affinity and binding capacity than those of the first generation, especially Granisetron.^[7]

Chemotherapy related factors and patient demographics considered as the main issue, as this study is regarded as the only study that deals with Egyptian patients representing the middle eastern Caucasian population and also using dual therapy, not the triplet regimen for economic concerns, which gives a reasonable chance to get an insight about the cost-effectiveness of the regimen used. Highly emetogenic chemotherapy regimens result in acute vomiting (acute CINV) episodes in over 90% of patients during the first 24-hour of administering chemotherapy, especially if they are not receiving proper antiemetic treatment.^[8] Several patient demographics contribute to the higher risk of developing CINV, e.g., young age, female gender, history of alcoholism, previous exposure to chemotherapy, vomiting, and nausea episodes with the prior anti-cancer drug regimen.^[9]

Poor control of acute CINV events results in an increased incidence of delayed CINV, which typically peaks in severity between day two and day four post-chemotherapy, depending on the agent's emetogenicity level (s) used. 5-HT₃ receptors play a central role in CINV, and inhibiting these receptors using HT₃ -5 receptors antagonists is a cornerstone for treating and managing CINV.^[9,10] Among the various types of available antiemetic agents, they are considered first-line therapy for CINV control due to known efficacy and safety compared to alternatives.^[1,11] Due to novel pharmacokinetic features of palonosetron(PALO) as a second-generation serotonin receptor antagonists such as prolonged half-life and more allosteric binding sites in Comparison with Granisetron (GRA).^[12] we conducted this study to compare two serotonin receptor antagonists' clinical outcomes with dexamethasone to prevent and manage CINV.^[13]

2. PATIENTS AND METHODS

2.1. Study design

An open-label randomized trial was carried out, including 115 patients receiving at least four cycles of highly emetogenic chemotherapy regimens. All patients received dexamethasone combined with the serotonin receptor antagonist in a parallel assignment into two arms palonosetron (PALO) arm and Granisetron (GRA)

arm. (PALO) arm patients received an intravenous infusion of 0.25 mg palonosetron (5 ml) + 16 mg dexamethasone (4 ml) mixed on 100 ml NS before administering highly emetogenic chemotherapy. While in (GRA) arm, patients received an intravenous infusion of 1 mg granisetron hydrochloride (1 ml) + 16 mg dexamethasone (4 ml) mixed on 100 ml NS before administration of highly emetogenic chemotherapy. We used this dual regimen in fixed doses and did not use an adjusted dose regimen to prevent bias or any confounding factors, ensure unifying all criteria, and insight into PALO's pharmacokinetic properties. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of Tanta - Egypt

2.2. Inclusion criteria

Eligible patients were men and women aged between 20 to 60 years diagnosed with malignant disease (breast cancer and lung cancer mainly) when they give consent. Besides, patients should have been naive to chemotherapy upon recruitment and scheduled to receive four cycles of highly emetogenic chemotherapy (cisplatin ≥ 50 mg/m² or AC/EC) on day 1, according to NCCN guidelines 2017.^[14] Patients also should be with (ECOG) scores for performance status of 0 to 2, hepatic function ([AST] and [ALT] within normal range), and renal function (creatinine clearance ≥ 60 mL/min).

2.3. Exclusion criteria

Patient(s) with one of the following should be rejected; severe (requiring hospitalization) and uncontrollable complications ex (Symptomatic heart failure, severe arrhythmia, active infection, any other uncontrolled medical illness), and asymptomatic metastases to the brain. Besides, seizure disorder needing anticonvulsants, malabsorption disease, gastric outlet stenosis, or intestinal obstruction should be considered for exclusion. Also, ongoing emesis or (CTCAE) grade 2 or greater nausea, known hypersensitivity to ingredients of the study drug, namely palonosetron (PALO) or granisetron hydrochloride (GRA) injection, or other 5-HT₃ receptor antagonists or dexamethasone are considered as exclusion reasons.

2.4. Outcomes and measures

Primary Outcome Measures include complete response (no vomiting events and no added supportive medication) in acute and delayed nausea and vomiting. Simultaneously, the secondary outcome measures include evaluating possible side effects according to the FDA (nervous system disorders: Headache-Dizziness, Gastrointestinal disorders: Constipation – Diarrhea). Patients' clinical and biochemical characteristics were recorded, and blood samples were drawn to monitor serum substance P (SP) and serotonin (5-HT₃) in

correlation with CINV incidence using ELISA kits. Those measured parameters (SP and 5HT-3) provide insight into the difference between PALO and GRA mechanistically. Besides, (MASCC) antiemetic tool in the acute phase (0 hr-24 hr) and delayed phase (24 hrs.the -120 hrs.) was used to evaluate patients' outcomes in both phases after each chemotherapy cycle.

3. RESULTS

Table 1: Demographic and clinical characteristics of the two groups of patients receiving either (PALO) or (GRA).

	PALO arm	GRA arm	P-value
Number of patients	51	64	
	30 Females (58.8%) 21 Males (41.2%)	39 Females (60.18%) 25 Males (39.06%)	
Chemotherapy protocols	(AC) 52.9% (CISPLATIN) 47.1%	(AC) 59.3% (CISPLATIN) 40.6%	
Age in years (mean± SD)	47.49 ±9.22	49.88 ± 8.96	0.164
Alanine transaminase(U/L)	32.48 ±13.7	33.59 ± 19.05	0.7280
Aspartate transaminase (U/L)	31.05 ± 13.48	31.09 ± 15.09	0.988
Hemoglobin (g/dL)	11.52 ± 1.21	11.7 ± 1.13	0.415
Platelet count (*10 ³ /uL)	277.36 ± 74.94	294.91 ± 81.71	0.238
Serum creatinine (mg/dL)	0.72 ± 0.24	0.71 ± 0.2	0.84
Total bilirubin (mg/dL)	0.48 ± 0.35	0.46 ± 0.22	0.654
Total leucocyte count (*10 ³ /uL)	7.1 ± 3.4373	6.61 ± 1.88	0.325
Absolute neutrophilic count(*10 ³ /uL)	4.32 ± 2.49	4.08 ± 1.72	0.551

115 patients (n = 51 in the PALO arm; n =64 in the GRA arm) were included in the study cohort for the efficacy analyses. The baseline characteristics of the patients are shown in Table 1. The distribution of males and females was comparable between the two treatment arms (58.8 % [30/51 patients] in the PALO arm vs. 60.18 % [39/64] in the GRA arm were female), as was the age distribution (mean age ± SD) (47.49 ±9.22 in the PALO arm vs.

Moreover, we evaluate rescue medication usage if nausea and vomiting episodes occurred for the population in the two arms PALO and GRA. Medications used in these consequences are mainly Metoclopramide 10 mg oral 2 times per day for 2 days and Trimebutine 200 mg oral 3 times per day for 5 days.

49.88 ± 8.96 in the GRA arm, respectively). Before study initiation, all of the patients in two arms were chemotherapy-naïve. A similar proportion of patients in both study arms received cisplatin (47.1% vs. 40.6%, respectively) or AC/EC (52.9% vs. 59.3 %, respectively).

Mann-Whitney U test was used in statistical analysis MASCC antiemetic tool analysis.

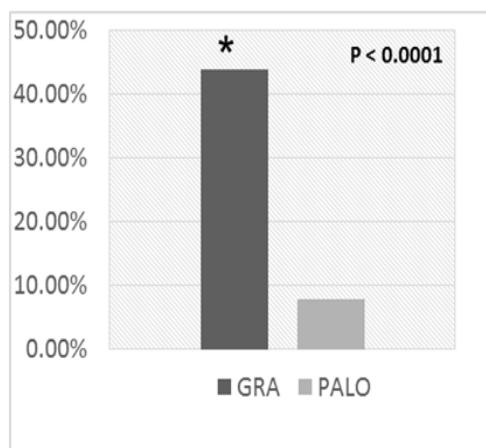


Fig.1A percentage of patients reporting acute vomiting during first 24 hrs. of chemotherapy. Stars over column indicate statistical significance (P <0.0001)

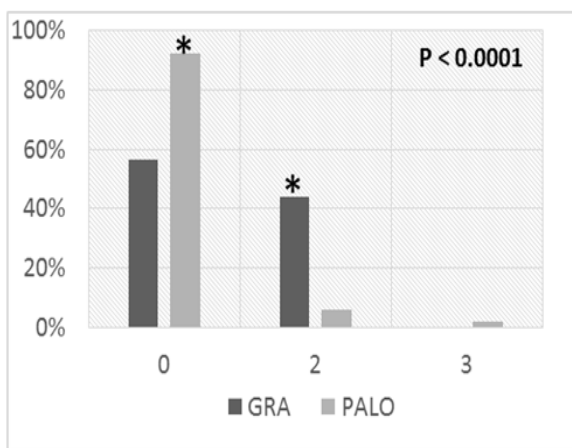


Fig.2B percentage of patients reporting acute vomiting during first 24 hrs. Of chemotherapy(Y-axis) versus the frequency of vomiting incidence. Stars over column indicate statistical significance (P <0.0001)

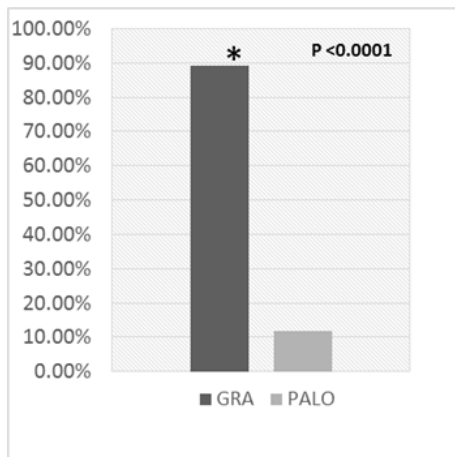


Fig.3C percentage of patients reporting acute nausea during first 24 hrs. of chemotherapy. Stars over column indicate statistical significance (P <0.0001)

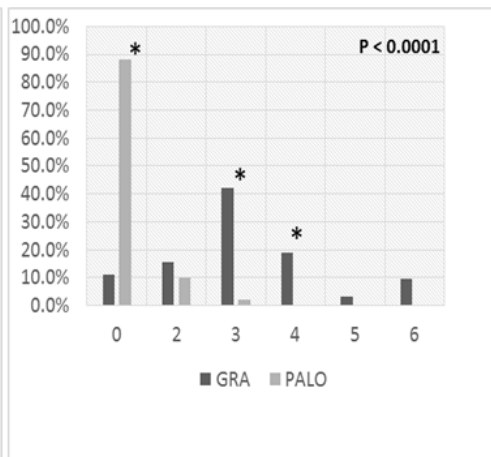


Fig.4D percentage of patients reporting acute nausea during first 24 hrs. of chemotherapy(Y-axis) versus the intensity of nausea incidence on intensity scale (1 to10). Stars over column indicate statistical significance (P <0.0001)

As shown in (Fig.1A and 2B) for the PALO arm, 11.76 % of patients showed acute nausea, and only 7.84 % showed acute vomiting, whereas 82.81% of patients showed acute vomiting and 89.06 % showed acute nausea in the GRA arm (P < 0.0001) figures 1A and 2B. While in (Fig.3C and 4D) for PALO arm, 11.8 % of

patients reported acute nausea, and only 7.8 % showed acute vomiting in different degrees. In Comparison, in the GRA arm, 43.80 % of patients showed acute vomiting, and more than 89.1% reported acute nausea (P < 0.0001).

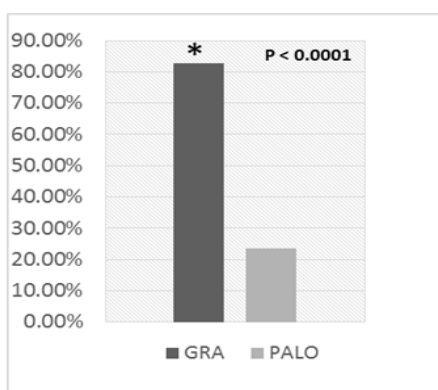


Fig.1A percentage of patients reporting delayed vomiting during first 24 hrs. of chemotherapy. Stars over column indicate statistical significance (P <0.0001)

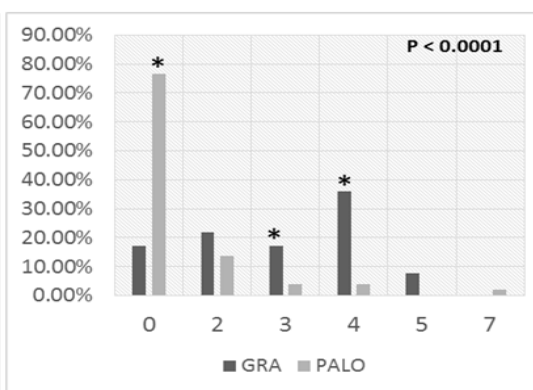


Fig.2B Percentage of patients reporting delayed vomiting during first 24 hrs. Of chemotherapy (Y-axis) versus the frequency of vomiting incidence. Stars over column indicate statistical significance (P <0.0001)

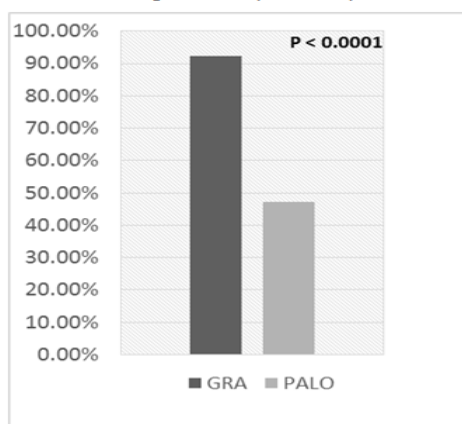


Fig.3C percentage of patients reporting delayed nausea during first 24 hrs. of chemotherapy. Stars over column indicate statistical significance (P <0.0001)

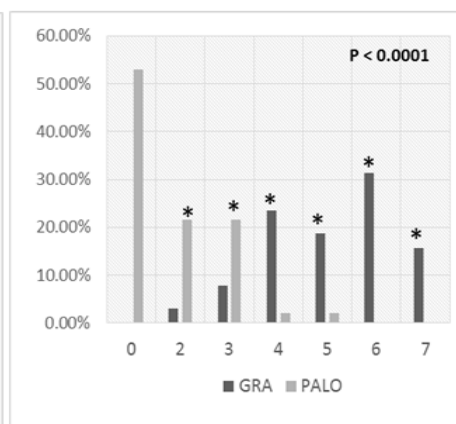


Fig.4D percentage of patients reporting delayed nausea during first 24 hrs. of chemotherapy(Y-axis) versus the intensity of nausea incidence on intensity scale (1 to10). Stars over column indicate statistical significance (P <0.0001)

For delayed CINV in (Fig.1A and 2B), 23.53 % of patients showed delayed vomiting, and 47.06 % showed delayed nausea in the PALO arm. In comparison, 82.81% of patients showed delayed emesis, and 92.16 % showed delayed nausea in the GRA arm ($P < 0.0001$). When we look at (Fig. 3C and 4D) we can find that 23.5% of patients in the PALO arm reported delayed vomiting while 82.80% in the GRA arm showed the same event; also, 47.10 % of patients in the PALO arm showed delayed nausea versus 96.9 % in the GRA arm with variable intensities ($P < 0.0001$).

Besides that, 45.10% of patients in (PALO) required additional rescue medications (dompridone 10 mg oral three times per day plus trimibutine 200mg oral three times per week both for five days), while 95.24 % in the (GRA) group used the same medications ($P < 0.0001$) (Fig.1A for rescue medication percentage of usage).

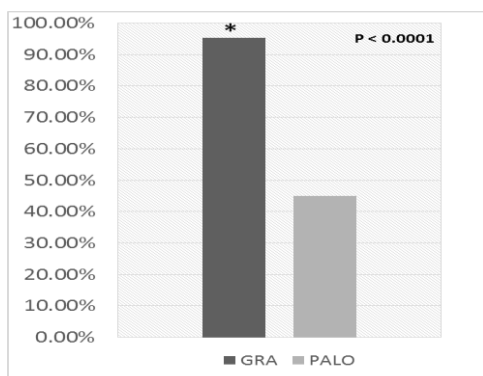


Fig. 1: A percentage of rescue medication usage in GRA and PALO groups. Stars over column indicate statistical significance.

Table 2: Serum concentration of substance P and serotonin in the two groups of patients.

	PALO Group		GRA group		P-value
	Number	Mean ± SD	Number	Mean ± SD	
Substance P	27	0.489 ± 0.0251	29	0.493 ± 0.0112	0.4835
Serotonin	26	1.735 ± 0.132	30	1.631 ± 0.131	0.0046

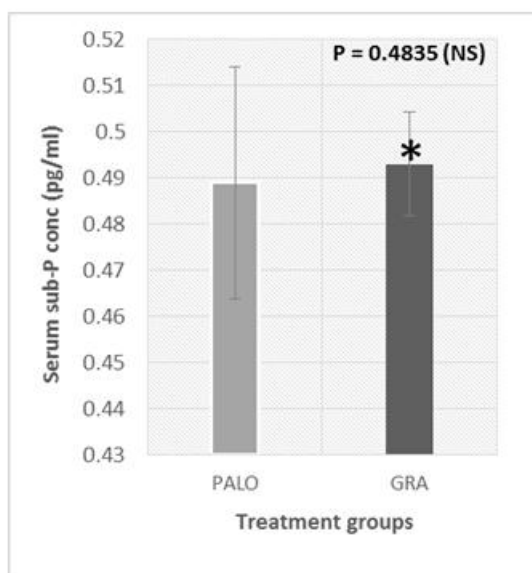


Fig.1A difference between serum sub-P conc in GRA and PALO groups. Stars over column indicate statistical insignificance

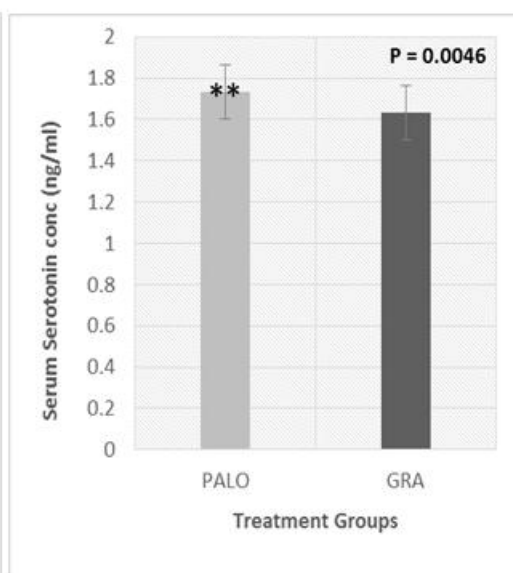


Fig.2B difference between serum serotonin conc in GRA and PALO groups. Stars over column indicate statistical significance

For evaluating serum biomarkers, an independent T-test was used to compare serum substance P and serotonin concentrations in the two groups of patients (Table 2). Mean serum concentration \pm SD for substance P was (0.489 ± 0.0251 in PALO arm vs. 0.493 ± 0.0112 in GRA arm $P = 0.4835$) (Fig.1A). This means that there is no significant statistical difference between the concentration of substance P between the two arms. The mean serum concentration was (1.735 ± 0.132 in the PALO arm vs. 1.631 ± 0.131 in GRA arm $P = 0.0046$) for serotonin (Fig.2B). The previous results showed a significant increase in serotonin serum concentration in the PALO arm. In contrast, serum substance P concentration in the PALO arm was less than that of the GRA arm without statistical significance.

4. DISCUSSION

In a phase III study, CINV was considered the major fear of chemotherapy, especially during highly emetogenic chemotherapy.^[11] Considering the various effects of anti-cancer drugs, such as the dopamine D2 receptor in the chemoreceptor trigger zone (CTZ) and neurokinin-1 (NK-1), a combination of antiemetic agents needs to be assessed.^[15,16] Though the effectiveness of 5-HT₃-receptor antagonists (RAs) against CINV proved to be enhanced in combination with dexamethasone in several clinical trials, the best standard treatment for delayed emesis is known to be 5-HT₃ RAs in the triplet regimen with aprepitant and dexamethasone.^[17,18] Palonosetron showed superiority versus Granisetron in adequate CINV control. Complete response (no emetic episodes and no supportive medication) in acute and delayed nausea and vomiting is the primary outcome measure in this study. This clinical parameter was superior in (PALO) group compared to (GRA) group in acute and delayed CINV phases.^[19,20] These findings were also supported by another study conducted by Simino *et al.*^[21]

Palonosetron shows both high affinity and unique allosteric binding with the 5-HT₃-receptor, which shows a strong antagonism. Because allosteric interactions can induce receptor conformation changing, it is speculated that palonosetron's dual action on the 5-HT₃-receptor could induce augmentation of its inhibitory effect at the primary receptor binding site.^[22,23] Besides that, structural data showing the orientation of palonosetron in 5-HT₃ receptor binding sites, combined with functional data in the 5-HT₃ receptor, gives us a reason for the high-affinity long-lived actions of this compound. These are likely because of some interactions formed with binding site residues and its presence as an effective compartment in the binding pocket, made possible by the tricyclic ring structure.^[24]

This study evaluated palonosetron administration in a dose of 0.25 mg in four chemotherapy cycles, either AC/EC or Cisplatin. The analyzed biomarkers (serum samples of sub-P and 5HT-3) confirmed the maintenance of palonosetron's efficacy combined with dexamethasone in patients receiving repeated cycles of HEC, and this

approach is similar to the one conducted by Kimura *et al.* in 2015.^[25] The serum serotonin concentrations in (PALO) arm were significantly higher than those of (GRA) arm. This significant difference in serotonin serum concentration between the two treatment arms can be justified by the higher binding affinity and longer half-life of palonosetron. Our data support the hypothesis of the effective blockade of receptor binding sites for palonosetron (PALO) over Granisetron (GRA), leaving a higher concentration of serotonin in the blood in (PALO) arm in Comparison with (GRA) arm.

Several investigators have reported cross-talk between NK1 and 5-HT₃ receptor signaling pathways.^[26-28] NK1 antagonists block vagal afferent activation by substance P, and 5-HT₃ receptor antagonists block vagal afferent activation by serotonin. This cross-talk raises the possibility that palonosetron's unique efficacy as a 5-HT₃ receptor antagonist may be partly due to differential inhibition of the cross talk.

Our study results revealed lower substance P levels in the PALO arm comparing with the GRA arm so that the possibility of cross-talk mechanism can be reasonable despite the statistical insignificance. In both in vitro and in vivo studies, palonosetron inhibited NK1 receptor activation from substance P, a potent NK1 agonist.^[29] This inhibition was dose-dependent and was not seen in parallel experiments with granisetron or ondansetron. Taken together, Palonosetron is a structurally unique, pharmacologically distinct agent with various properties from the first-generation 5-HT₃ RAs.

The Economic impact is needed to be considered in choosing a 5-HT₃ RA, especially in developing, low-income countries like Egypt. Direct medical costs were obtained from health hospitals' ministry via a cost-effectiveness report issued in September 2017 in which deterministic sensitivity analyses were conducted. Total costs for (PALO) and (GRA) were 777.417 EGP and 747.282, respectively. Quality-Adjusted Life Year (QALY) for PALO was 1.243 versus 1.206 for ondansetron 32 mg (as 4 doses of standard 8 mg dose) while (PALO) is a single 0.25 mg. The incremental cost-effectiveness ratio (ICER) for (PALO) versus (GRA) was 814.572 EGP/QALY. Although PALO cost is higher than other 5-HT₃ RA such as GRA and ondansetron.^[5] However, this study showed that PALO is a cost-effective choice when compared to GRA in CINV prevention. when we consider the antiemetic regimen efficacy and the complete response achieved throughout the study, especially in the delayed phase of CINV, we can say that the total care plan cost (PALO) is equal to or near the care plan in (GRA).^[30,31]

5. CONCLUSION

Our study demonstrates that palonosetron combined with dexamethasone is more effective than granisetron and dexamethasone combination against CINV, especially induced by highly emetogenic cisplatin-based

chemotherapy and highly emetogenic combination of cyclophosphamide and anthracyclines (AC). We recommend palonosetron plus dexamethasone as an effective combination in prophylaxis and CINV treatment in acute and delayed phases. Besides all previous, these results comply with many clinical trials performed in this approach and also MASCC and ESMO clinical practice guidelines update 2016.

In conclusion, both vomiting and nausea in the few days after chemotherapy remain a significant medical obstacle. More effort should be made by medical team members, especially clinical pharmacy individuals, to monitor therapy effectiveness and help the medical team achieve a suitable and reliable care plan.

6. Declarations

Funding: No funding was received to assist with the preparation of this manuscript.

Conflicts of interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval: Approval was obtained from the ethics committee of Tanta university. The procedures used in this study adhere to the tenets of the Declaration of Helsinki 1964.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary material.

Code availability: N/A

Authors' contributions

1. Mohamed Ahmed Mahrous: checking and optimizing of supportive care plan for all patients, also assurance of proper patient recruitment and teaching them about study care plan according to declaration of Helsinki and finally access different clinical response.
2. Gamal Abd Elkhalek Elazab: supervision all the clinical pharmacy interventions and clinical outcome measures as a professor of clinical pharmacy in faculty of pharmacy.
3. Hesham Ahmed Tawfik: as a professor and chairman of medical oncology department in Faculty of Medicine Tanta university, he played an important role in designing of study protocol also a major percentage of study population recruited from this Department.

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