Olanzapine versus aprepitant for the prophylaxis of chemotherapy-induced nausea and vomiting in breast cancer patients receiving doxorubicin-cyclophosphamide regimen: A prospective, nonrandomized, open-label study

G. Shivaprakash, Karthik S. Udupa, V. Sarayu, Joseph Thomas, Vishal Gupta, L. C. Pallavi, Sudhakar Pemminati

Abstract:
OBJECTIVE: Despite the guideline-directed therapy, complete absence of nausea was noted only in 33% of breast cancer patients on anthracycline-cyclophosphamide regimen. Hence, we sought to compare the efficacy of aprepitant (APT) versus olanzapine (OLP) in preventing chemotherapy-induced nausea and vomiting (CINV) in breast cancer patients on doxorubicin-cyclophosphamide regimen.

PATIENTS AND METHODS: A prospective, open-label, nonrandomized study was conducted at the Department of Oncology. Eighty-three patients completed the study with 43 in the APT group and 40 in OLP group. Data about nausea and vomiting were collected using Multinational Association of Supportive Care in Cancer Antiemesis Tool (MAT). The severity of nausea and vomiting was assessed by the MAT and Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, respectively.

RESULTS: Complete response (no emesis and no rescue medication) was achieved in 81% of the patients in APT group and 85% in the OLP group in the acute period ($P = 0.661$); 74% of patients in APT group and 85% in OLP group had no nausea during the same period ($P = 0.233$). Among the OLP patients who had nausea, 67% had moderately severe and 33% had Severe grade, and in the APT group, severity was equally distributed in mild, moderate, and severe grades. Among the patients who had vomiting, severe (CTCAE) vomiting was noticed in 81% of patients who were treated with APT compared to 50% in OLP group.

CONCLUSION: OLP was found to be an equally effective alternative to APT in the antiemetic prophylaxis of CINV in breast cancer patients receiving chemotherapy with doxorubicin-cyclophosphamide regimen.

Keywords: Breast cancer, chemotherapy, olanzapine

Introduction

Breast cancer ranks first among all cancers in women globally as well as in India, with an incidence rate of 25.8 per 100,000. How to cite this article: Shivaprakash G, Udupa KS, Sarayu V, Thomas J, Gupta V, Pallavi LC, et al. Olanzapine versus aprepitant for the prophylaxis of chemotherapy-induced nausea and vomiting in breast cancer patients receiving doxorubicin-cyclophosphamide regimen: A prospective, nonrandomized, open-label study. Indian J Pharmacol 2017;49:451-7.
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anthracyclines with cyclophosphamide forms the basis of many breast cancer treatment protocols. This combination is known to have a high potential for chemotherapy-induced nausea and vomiting (CINV).[2]

Nausea is being rated as the first and vomiting as the third most distressing side effects of cancer chemotherapy.[3] With the introduction of neurokinin 1 receptor antagonist (NK1RA) as an antiemetic prophylaxis, additional improvement in CINV control was observed, and as a testimony, it was considered as an essential drug in the prophylaxis regimen in all the major international guidelines such as American Society of Clinical Oncology, National Comprehensive Cancer Network, and Multinational Association of Supportive Care in Cancer (MASCC).[4‑6] However, breakthrough CINV persists to the extent of 30%–40% in patients even with guideline-directed prophylactic antiemetics.[7] This is more troublesome in breast cancer patients on chemotherapy as only 33% of the patients achieve the complete absence of nausea despite using aprepitant (APT).[8] Furthermore, factors such as female gender and obesity are known to increase CINV.[9] This prompts us to search for a newer agent. Moreover, the median total cost of APT therapy alone per cycle was found to be 1215 Indian Rupees.[10]

Olanzapine (OLP), a serotonin receptor blocker with a much lower price, can be an effective alternative to NK1RAs. Moreover, phase II study has shown that it is effective in controlling acute as well as delayed CINV in patients receiving moderate to highly emetogenic drugs.[11]

However, there are few studies that have compared OLP with APT in CINV prevention in breast cancer patients receiving anthracycline-cyclophosphamide regimen. Hence, we sought to conduct this study.

Objectives

Primary objective
To compare the efficacy of OLP versus APT in the prophylaxis of CINV in breast cancer patients receiving doxorubicin-cyclophosphamide regimen.

Patients and Methods

A prospective, open-label, nonrandomized study was carried out over a period of 18 months (November 2014–April 2016) in the Department of Oncology at a tertiary care center. The study was conducted after obtaining informed consent from all the participants and institutional human ethical committee clearance (Letter No. IEC 537/2014). Highly emetogenic anticancer drugs were those as defined by Hesketh; Level 4 and Level 5 drugs associated with emesis-producing frequency of 60%–90% and more than 90%, respectively.[2]

Subject selection

Inclusion criteria
1. Adults aged 18 years and above
2. Chemotherapy-naive breast cancer patients receiving doxorubicin and cyclophosphamide regimen in the adjuvant setting
3. Patients who were on either OLP or APT as one of the antiemetic prophylaxis
4. Patients who were on medications such as antibiotics and motility enhancers such as metoclopramide shall be included only after a washout period of 7 days.

Exclusion criteria
1. Patients who were on antiemetics other than palonosetron, dexamethasone, and OLP/APT as an antiemetic prophylaxis regimen
2. Concurrent radiation therapy scheduled within 8 days of day 1 of the study
3. Patients suffering from tumors with brain metastasis, gastrointestinal tumors
4. Patients diagnosed with serious psychiatric conditions
5. Patients on antipsychotic drugs such as chlorpromazine, risperidone, quetiapine, clozapine, phenothiazine, or butyrophenone
6. Patients with acute surgical conditions such as small bowel obstruction, appendicitis, and pancreatitis
7. Acutely ill patients such as serious liver and renal disorders and serious cardiac disorders with left ventricular ejection fraction <50%
8. Pregnant and lactating women.

Methods

Chemotherapy-naive patients who satisfied the selection criteria were included in the study. Patients on highly emetogenic anticancer drug combination, cyclophosphamide with doxorubicin, were followed up for 5 days immediately postchemotherapy.

The two treatment groups were APT and OLP. Baseline demographic characteristics such as age, body mass index (BMI), history of alcohol and tobacco consumption, comorbid illness, and habits were obtained from all the patients. The included patients received the following treatment in the two groups:

Aprepitant
- Day 1: Capsule APT 125 mg per oral, injection palonosetron intravenous 0.25 mg, and tablet dexamethasone 12 mg per oral 30 min before chemotherapy
- Day 2–3: Capsule APT 80 mg per oral once daily and dexamethasone 8 mg per oral once daily.
Olanzapine

- Day 1: Tablet OLP 10 mg per oral, injection palonosetron intravenous 0.25 mg once daily, and tablet dexamethasone per oral 12 mg on day 1, 30 min before chemotherapy
- Day 2–3: Tablet OLP 10 mg per oral once daily and dexamethasone 8 mg per oral once daily.

**Primary efficacy endpoint**

The proportion of patients achieving complete response (CR) which is defined as a number of patients who achieved no emesis and no requirement of rescue medication following either the APT or OLP as prophylactic antiemetics.

Patients in both the groups were observed for 5 days for nausea and breakthrough emesis immediately after first chemotherapy cycle. CR and treatment failure (time to occurrence of emesis or start of rescue therapy) during 0–24 h immediately after chemotherapy and during delayed phase (24 h–day 5) of postchemotherapy were noted. Data were collected, and nausea and vomiting were assessed using MASCC Antiemesis Tool (MAT). MAT is an established tool to assess CINV. It includes questions on occurrence and frequency of nausea and vomiting and also on the intensity of nausea. The severity of vomiting was graded (mild, moderate, and severe) by Common Terminology Criteria for Adverse Events (CTCAE version 4.03) after obtaining information such as appetite, status on the oral intake of food, need for intravenous fluids, or total parenteral nutrition.

The intensity of nausea was assessed in a 100-mm scale measuring the severity of nausea. Patients were asked to mark a score on a scale of 0–10 that exactly resembled their experience during each episode of nausea.

In the study, severity scores were graded as mild (scores 1–4), moderate (scores 5–7), and severe (scores 8–10).

**Statistical analysis**

Statistical analysis was performed by SPSS version 20.0 (IBM Corp: Armonk, NY). Categorical data were expressed as a percentage and continuous data as mean ± standard deviation. Fisher’s exact test and Chi-square test were applied wherever applicable. A $P \leq 0.05$ was considered statistically significant.

**Results**

Figure 1 is a flow diagram to show the distribution of study patients. A total of 91 eligible patients participated in the study. Fifty-one patients received APT and grouped into the APT group, and 40 patients received OLP as prophylaxis and grouped to OLP group. Seven patients expired and one patient was unwilling to continue in the APT group. Hence, a total of 43 patients in APT group and all the 40 patients in the OLP group completed the study. Eleven patients in the APT group had breakthrough emesis, and among them, eight patients required the rescue therapy. Six patients developed breakthrough emesis in OLP group, and all required rescue therapy.

The minimum age of the patients was 18 years and the maximum age was 70 years. The average age of the patients who participated in the study was 46 years. The overall mean BMI of the patients was 23 kg/m$^2$. Overall, 65% of the patients were American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) stage IIIa; 75% among OLP and 57% among APT were diagnosed as having stage IIIa. About 73% in the APT group and 75% in OLP group had no comorbidities associated, and overall, 97% of the patients had no habits such as tobacco smoking or chewing [Table 1].

Overall, a total of 66 (80%) did not have nausea, and 17 (20%) patients had nausea. Among 43 patients who took APT, 32 patients (74%) had no nausea while 11 patients (26%) had nausea. In the OLP group, out of 40 patients, 34 patients (85%) had no nausea, and six patients (15%) had nausea. Among the APT-treated group, 35 (81%) patients achieved CR (no vomiting episodes and no rescue medication use), while 34 (85%) patients among OLP group achieved a CR. All the six patients in the OLP group who had nausea also had vomiting, but in APT group, three among 11 patients with nausea did not have associated episodes of vomiting. Surprisingly, all patients had acute nausea and/or vomiting, but none of the patients in both the groups had nausea or vomiting from the 2nd day of postchemotherapy till 5th follow-up day. The difference between the two treatment groups was insignificant,

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Table 1: Baseline demographic characteristics

| Character                  | Aprepitant (n=51) | Olanzapine (n=40) | Total (n=91) |
|----------------------------|-------------------|-------------------|--------------|
| Age in years               | 45±12             | 47±9.4            | 46±11        |
| BMI                        | 22±4              | 24±3.9            | 23±4         |
| AJCC TNM stage             |                   |                   |              |
| TNM stage Iib              | 7 (14)            | 5 (12.5)          | 12 (13)      |
| TNM stage IIIa             | 29 (57)           | 30 (75)           | 59 (65)      |
| TNM stage IIIb             | 15 (29)           | 5 (12.5)          | 20 (22)      |
| Comorbidity                |                   |                   |              |
| No comorbidity             | 37 (73)           | 30 (75)           | 67 (74)      |
| HTN                        | 2 (4.4)           | 2 (5)             | 4 (4)        |
| DM                         | 1 (1.7)           | 4 (10)            | 5 (5.5)      |
| DM+HTN                     | 3 (5)             | 2 (5)             | 5 (5.5)      |
| Retropositive              | 2 (4.4)           | 0                 | 2 (2)        |
| Others                     | 6 (11)            | 2 (5)             | 8 (9)        |
| Habits (tobacco smoking/   |                   |                   |              |
| chewing/alcohol)           | No                | 49 (96)           | 39 (98)      | 88 (97) |
| Yes                        | 2 (4)             | 1 (2)             | 3 (3)        |

Age and BMI are expressed in mean±SD. Staging, comorbidity, habits, are expressed as number (n) and percentage in parenthesis. HTN=Hypertension, DM=Diabetes mellitus, AJCC=American Joint Committee on Cancer, TNM=Tumor, node, and metastasis, SD=Standard deviation, BMI=Body mass index

though nearly 11% increase in patients who achieved no nausea and 4% increase in patients who achieved the CR were found in OLP group as compared to APT group [Figure 2].

Nausea was graded from the MAT scale score as mild, moderate, and severe, with a score of 1–4, 5–7, and 8–10, respectively. Patients in the APT-treated group had a nearly equal number of patients in all the grades. In OLP-treated group, majority had nausea of moderate severity (67%) and 33% had a severe grade. There was no difference in severity noted between the two groups. Eighty-five percent of OLP group and 74% among the APT group did not have nausea. There was no nausea during the delayed phase of the study [Figure 3].

Vomiting was graded according to the CTCAE grading; mild/moderate as Grade I/II and severe as Grade III and above. Patients in the OLP-treated group were equally distributed in both the grades (mild-to-moderate and severe), while 81% of patients in the APT group had vomiting of the severe grade. However, it was not significant (P = 0.159) when compared to OLP group. None of the patients had vomiting during the delayed phase of the study [Figure 4].

Discussion

The patient demographic characteristics are presented in Table 1. Age and BMI were comparable in both the groups, with a mean age of 46 years and BMI of 23 kg/m². The majority of the patients were AJCC

Figure 2: Proportion of patients achieving no-nausea and no-vomiting at different study phase. Values are expressed as a percentage. P ≤ 0.05 is considered statistically significant. D5: Day 5 of chemotherapy

Figure 3: Severity of nausea in patients following aprepitant and olanzapine prophylaxis. Values are expressed as a percentage. P ≤ 0.05 is considered statistically significant. Mod = Nausea of moderate severity (score 5–7); Sev: Nausea of severe (score 8–10)

Figure 4: Severity of vomiting in patients following aprepitant and olanzapine prophylaxis. Mild-to-moderate = CTCAE Grade I and II; Severe = CTCAE Grade 3. P value set at ≤0.05. CTCAE: Common Terminology Criteria for Adverse Events
TNM breast cancer stage IIIa in both the groups. Despite screening facilities and adequate education initiatives, the figure is still startling. This finding is similar to earlier reports.[14] Surprisingly, 74% of the total participants had no associated comorbidity, and 97% of them had no habits which are risk factors for cancer such as tobacco smoking/chewing and alcohol intake. Only 3% in the APT group and 2% in OLP group had habits such as alcohol and tobacco intake. This observed lower rate of risk factors might be due to the general lower pattern of prevalence of risky habits in Indian females. Studies have shown that prevalence of tobacco is only 15% and alcohol consumption is <1% in Indian women.[15] As it is socially unacceptable, many women may not report it by self-reporting. Men report regular smoking, tobacco chewing, and alcohol use more likely than women.[16] Comorbidities such as associated diabetes mellitus, hypertension, and other serious illness were present only in 27% of patients in APT group and 25% in OLP group and were comparable [Table 1].

Emetogenicity of the chemotherapy combination for acute emesis is classified as Level 1–5 by Hesketh. By Level 1 being least, it is defined as the proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis in <10%; Level 2 with 10%–30%; Level 3 with 30%–60%; Level 4 with 60%–90%, and Level 5 with more 90%. In our study, all the patients received emetogenic chemotherapy combination regimen graded Level 4 and Level 5. Adriamycin is widely used in breast carcinoma, multiple myeloma, acute lymphoblastic leukemia, and Hodgkin’s and Non-Hodgkin’s lymphoma.[17] Cyclophosphamide is classified under alkylating agent and used broadly in lymphoma, ovarian carcinoma, and along with Adriamycin in breast cancer.[18] Cyclophosphamide in combination with an anthracycline-like Adriamycin is considered as highly emetogenic.[2]

CR (patients achieving no emesis, no rescue) in APT and OLP group in acute (0–24 h) and delayed (24 h–day 5) periods following chemotherapy was presented in Figure 2. Nearly 74% of patients in APT group and 85% in OLP group had no nausea. The proportion of patients without nausea or vomiting was more in OLP group, but compared to APT group, the difference was not statistically significant. Nearly 81% in the APT group and 85% in the OLP group attained a CR. The findings were similar to a study done by Navari et al., which included different cancer types that were treated with various emetogenic anticancer regimens. The study showed CR achieved was 97% in acute period (24-h postchemotherapy) in OLP group and 87% in the APT group.[18] The study concluded that OLP and APT were comparable and that OLP is equally efficient to APT in the prophylaxis of chemotherapy.

OLP, which is an atypical antipsychotic agent, acts by blocking dopamine, serotonin, α-1 adrenergic, histamine, and muscarinic receptors. Dopamine and serotonin are known neurotransmitters involved in CINV, and antagonistic actions of OLP at these receptors may be responsible for its efficacy in CINV. A systematic review assessed six randomized clinical trials involving OLP, with three each for prophylaxis and treatment of CINV. The results showed the clinical superiority of OLP compared to other group. The study concluded OLP as an effective agent for prevention of CINV and also as a treatment for delayed nausea.[19]

OLP besides its clinical efficacy in CINV has also shown to be less expensive compared to APT in many studies.[19,20] However, other studies have shown that APT regimen to be more cost-effective if the cost per quality-adjusted life year was evaluated. The study observed that APT in the regimen added 15 h of perfect health per cycle (0.63 quality-adjusted life days) in patients receiving highly emetogenic chemotherapy.[21] However, any cost benefits should be carefully deciphered as it depends on various factors such as use of generic pharmaceuticals, insurance, and specific governmental policies in the region. A cost analysis incorporated into future clinical trials involving OLP with APT would provide more evidence on pharmacoeconomics.

Substance P, a neuropeptide which is present in neurons of brainstem, nucleus tractus solitarius and area postrema, mediates its emetic effect through NK1 receptors. APT acts by blocking NK1 receptors to produce its antiemetic effect.[22] APT has shown promising clinical efficacy in the prevention of acute and delayed CINV associated with highly emetic and moderately emetic chemotherapy.[23]

There were no episodes of delayed nausea or vomiting in both groups. Nausea and/or vomiting occurred only during the first 24 h of postchemotherapy in all the study participants. The reason for this is not known. It is known that prevention and optimal control of acute CINV successfully prevent delayed vomiting.[24] Research has also established substance P as a causative agent in delayed emesis and the use of NK1 antagonist along with granisetron and dexamethasone effectively controls emesis during 2–5 days of postchemotherapy in patients on a highly emetogenic anticancer regimen.[25]

The severity of nausea was measured using MAT scale, which was graded as mild, moderate, and severe with score range 1–4, 5–7, and 8–10, respectively. In OLP-treated group, majority had nausea of moderate
severity (67%) and 33% had a severe grade. In APT group, 36% of the patients had severe-grade nausea and 64% with mild-to-moderate-grade nausea [Figure 3].

The vomiting was graded according to CTCAE guidelines; mild/moderate as Grade I and II and severe as Grade III and above.[13] Among patients who had vomiting despite APT or OLP prophylaxis, 81% of the patients had severe vomiting in the APT group and 50% in OLP group. The difference was not statistically significant (P = 0.159). There was no vomiting in the delayed phase in either of the groups [Figure 4].

Studies have shown despite using prophylactic antiemetics as per guidelines, 30%–50% of patients develop breakthrough CINV.[9] In our study, six patients in the OLP and eight patients in the APT group had breakthrough emesis constituting about 15% and 19%, respectively. The current treatment guidelines for breakthrough CINV recommends using an antiemetic drug that is distinct from the group that was used for the prophylaxis of CINV and suggests it to be used uninterruptedly and not on as required basis.[5,26,27]

**Conclusion**

OLP and APT were comparable, and OLP is equally efficient in preventing CINV compared to APT. Since OLP is less expensive than APT, we advocate OLP as an effective alternative to APT for antiemetic prophylaxis in breast cancer patients on doxorubicin-cyclophosphamide regimen.

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**Conflicts of interest**

There are no conflicts of interest.

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