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Case Report

Feasibility of single low-dose olanzapine with triple antiemetic therapy for prevention of highly emetogenic chemotherapy-induced nausea and vomiting: a single-centre case series

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Abstract

Background: Olanzapine works well as an antiemetic; however, it causes significant somnolence during the day and has additional side effects when used at a standard dose. Our goal was to evaluate the safety and effectiveness of low-dose olanzapine in patients with different cancers following highly emetogenic treatment.

Patients and Methods: This study was a retrospective, single-centre study in an Indian comprehensive cancer centre. Eight patients between the ages of 46 and 70 receiving cisplatin, a high emetogenic chemotherapy (HEC) drug, were chosen for different types of cancers and had an Eastern Cooperative Oncology Group performance level of 0–2. Patients underwent chemotherapy after receiving a prophylactic low-dose oral olanzapine regimen (2·5 mg) in conjunction with a triple antiemetic treatment. In the overall phase (0–120 hours), complete response (CR) and complete control (CC) were the major endpoints. The secondary outcome assessed safety according to the Common Terminology Criteria for Adverse Events V5.0 (CTCAE V5.0).

Results: All the studied patients were reported to have CR and CC. According to CTCAE v5.0, adverse effects grades varied from 0 to 1.

Interpretation: According to this study, prophylactic single low-dosage olanzapine (2·5 mg) was effective enough to prevent vomiting and nausea and reduce the incidence and severity of side effects in patients undergoing HEG; therefore, it should be deemed a new benchmark of care.

Keywords: Olanzapine, Cisplatin, Chemotherapy, Complete Control, Complete Response

Introduction

Nausea and vomiting are well-recognized as prevalent adverse events associated with cancer chemotherapy; however, their significance has often been underestimated. Chemotherapy-induced nausea and vomiting (CINV) can significantly impact patients' adherence to treatment and overall quality of life [1-3]. Prophylactic treatment for CINV typically involves the administration of antiemetic agents with diverse mechanisms of action. These may include medications such as 5-HT3 receptor antagonists (5-HT3 RA), corticosteroids, NK1 receptor antagonists (NK1 RA), olanzapine, and dopamine receptor antagonists, all of which possess antiemetic and anti-nausea properties [1].

Anticancer drugs are categorized based on their emetogenic potential into highly emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), and low and minimal emetic risk regimens. Examples of HEC regimens include high-dose cisplatin, cyclophosphamide, carmustine, dacarbazine, mechlorethamine, streptozocin, and combinations of anthracyclines with cyclophosphamide (AC) [2].

The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend the use of olanzapine in conjunction with NK1 RA, 5-HT3 RA, and dexamethasone for the management of both acute and delayed phases of nausea and vomiting induced by HEC regimens [2].Studies investigating the efficacy of olanzapine in controlling nausea and vomiting in patients undergoing HEC treatment have shown positive outcomes, both as a prophylactic measure and for managing breakthrough CINV in combination with standard antiemetic therapies [4,5].

In clinical settings, olanzapine is commonly prescribed at doses of 5 mg and 10 mg alongside other antiemetics for preventing CINV [2, 6]. Adverse effects like hiccups, dry mouth, somnolence, and constipation, graded as 1-3 according to the Common Terminology Criteria for

Adverse Events (CTCAE), have been observed among users of standard doses of olanzapine potentially impacting patients' quality of life [7-9]. Interestingly, previous studies suggested that dose reduction of olanzapine (2.5 mg) could be effective with fewer adverse effects than the higher dose.[4,9]. Consequently, the present study prospectively analysed the clinical outcomes of patients undergoing HEC treatment in a comprehensive cancer centre who received a single low dose of olanzapine (2.5 mg) as a prophylaxis.

Case Presentation

Patients meeting the criteria for having a cancer diagnosis and being prescribed cisplatin as an HEC regimen, in addition to a reduced dosage of Olanzapine for prophylactic antiemetic purposes, were considered eligible for inclusion. A prospective analysis was conducted on a cohort of eight patients who met the specified eligibility criteria and were treated between October 2022 and March 2023.

The chemotherapy regimens dosage and administration schedule adhered strictly to the authorized protocol. Cisplatin infusion was delivered intravenously at a dosage of 40 mg/m^2 per day, administered once weekly during each treatment cycle. All individuals encompassed in this series of cases underwent cisplatin-based chemotherapy for varying types of cancer, receiving a four prophylactic antiemetic regimen comprising Palonosetron, Dexamethasone, Aprepitant, and a single low dose of Olanzapine (2.5 mg). Adverse events were assessed according to CTCAE v5.0.

Cohort characteristics:

This case series encompasses eight patients diagnosed with different forms of cancer who were administered a therapeutic regimen consisting of cisplatin (an HEC agent) and a lowered dosage of olanzapine for preventive antiemetic purposes. The clinical attributes of these patients are detailed in Table 1.

Table 1: Clinical Attributes of the patients (n=8)

Cases	Gender	Age (Years)	Diagnosis	Site of cancer	Stage	BMI	Alcohol and Tobacco Use	Past Medical History
1	F	57	Squamous cell carcinoma	Cervix	Stage 2(b)	23.1	No	Nil
2	F	38	Squamous cell carcinoma	Cervix	Stage 3 (c1)	25.1	No	Tubectomy
3	F	56	Squamous cell carcinoma	Cervix	Stage 4 (a)	24	No	Nil
4	F	70	Carcinoma (vaginal)	Vaginal	Stage 2	18.6	No	Nil
5	M	57	Squamous cell carcinoma	Vocal card	Stage 3	20.4	No	Nil
6	F	69	Recurrent carcinoma	Left buccal mucosa	Stage 3	22.8	No	Mouth Ulcer
7	F	64	Naso pharynx carcinoma	Pharynx	Stage 3	23.7	No	Cholecystectomy, TAH+BSO, Right TKR
8	F	46	Endometrium adenocarcinoma	Uterus	Stage 3	28.8	No	Hypertension, TAH+BSO

F - Female, M – Male, TAH+BSO - Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy, TKR – Total Knee Replacement.

Data Collection:

The primary endpoints for evaluating the effectiveness of olanzapine dose reduction were the complete response (CR) and complete control (CC) of nausea and vomiting by symptoms reported by the patients for the entire phase (0 to 120 hours). The complete response defines no emesis, no rescue medication while complete control defines no emesis, no rescue medication and no significant nausea. Data for specific individuals were retrieved from the medical records. By documenting the side effects of olanzapine, such as constipation, hiccups, dry cough, and somnolence, and grading them by the CTCAE v5.0, patient safety was evaluated.

Case Summaries:

Case summaries of all eight patients diagnosed with different forms of cancer who were administered a therapeutic regimen consisting of cisplatin (an HEC agent) and a lowered dosage of olanzapine for preventive antiemetic purposes are shown in Table 2. All the patients reported CR and CC during the entire phase (0 to 120 hours). The efficacy of antiemetic with a lowered dosage of olanzapine was 100%. The adverse events are shown in Table 2 and 3. The adverse events were graded based on the CTCAE v5.0. Of the eight patients, three experienced grade 1 adverse events for dry mouth and Somnolence. There were no therapy-related deaths.

Table 2: Case summaries of the patients (n=8)

Cases	Diagnosis	Site of cancer	Stage	Antiemetic Regimen	Chemotherapy Regimen	CR/CC	Adverse Events
1	Squamous cell carcinoma	Cervix	Stage 2(b)	Palo-0.25mg+Dexa-12mg+Apre-125mg+Olanz-2.5mg	Cisplatin - 40mg/m^2	Yes/Yes	No
2	Squamous cell carcinoma	Cervix	Stage 3 (c1)	Palo-0.25 mg + Dexa-16 mg + Apre-80 mg + Olanz-2.5 mg	Cisplatin - 40mg/m^2	Yes/Yes	Grade 1 - Dry mouth
3	Squamous cell carcinoma	Cervix	Stage 4 (a)	Palo-0.25 mg + Dexa-16 mg + Apre-80 mg + Olanz-2.5 mg	Cisplatin - 40mg/m^2	Yes/Yes	Grade 1 - Somnolence
4	Carcinoma (vaginal)	Vaginal	Stage 2	Palo-0.25 mg + Dexa-16 mg + Apre-80 mg + Olanz-2.5 mg	Cisplatin - 40mg/m^2	Yes/Yes	No
5	Squamous cell carcinoma	Vocal card	Stage 3	Palo-0.25 mg + Dexa-16 mg + Apre-80 mg + Olanz-2.5 mg	Cisplatin - 40mg/m^2	Yes/Yes	No
6	Recurrent carcinoma	Left buccal mucosa	Stage 3	Palo-0.25 mg + Dexa-12 mg + Apre-125 mg + Olanz-2.5 mg	Cisplatin - 40mg/m^2	Yes/Yes	No
7	Naso pharynx carcinoma	Pharynx	Stage 3	Palo-0.25 mg + Dexa-8 mg + Apre-125 mg + Olanz-2.5 mg	Gemcitabine - 1000mg/m^2 + Cisplatin - 25mg/m^2	Yes/Yes	Grade 1 - Somnolence
8	Endometrium adenocarcinoma	Uterus	Stage 3	Palo-0.25 mg + Dexa-16 mg + Apre-125 mg + Olanz-2.5 mg	Cisplatin - 40mg/m^2	Yes/Yes	No

Palo – Palonosetron, Dexa – Dexamethasone, Apre – Aprepitant, Olanz– Olanzapine.

Table 3: Grading of adverse events based on CTCAE v5.0

Adverse effects	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hiccups	None	None	None	Not applicable	Not applicable
Dry mouth	1	None	None	Not applicable	Not applicable
Somnolence	2	None	None	None	None
Constipation	None	None	None	None	None

DISCUSSION

This case series conducted a retrospective analysis of eight patients who received a diagnosis of various types of cancer and were treated with a therapeutic protocol involving cisplatin (an HEC agent) along with a reduced dose of olanzapine for prophylactic antiemetic management.

Chemotherapy-induced nausea and vomiting (CINV) are frequently observed adverse reactions in patients with malignant tumours [10]. The etiology of CINV is associated with various neurotransmitters and receptors within the central nervous system and the gastrointestinal tract, including 5-hydroxytryptamine and its receptors, dopamine and its receptors, substance P, and the neurokinin-1 (NK-1) receptors [11]. The administration of chemotherapy drugs can impact intestinal chromaffin cells via the bloodstream or by direct influence on the intestinal mucosa, leading to the release of serotonin. Consequently, activation of serotonin on the chemoreceptor trigger zone induces the release of additional neurotransmitters. These neurotransmitters then stimulate the vomiting centre, resulting in oesophageal, diaphragmatic, and abdominal muscle movement and increased salivary gland secretion, culminating in vomiting. Moreover, the binding of substance P to the NK-1 receptor can contract smooth muscle, contributing to vomiting. Furthermore, vomiting can involve histamine, acetylcholine, and other neurotransmitters [12].

Olanzapine, due to its mechanism of blocking multiple neurotransmitter receptors, can serve as a broad-spectrum antiemetic for nausea and vomiting induced by various factors among patients with advanced cancer or in palliative care settings[13]. Olanzapine exhibits inhibitory effects on several neurotransmitter

receptors, including serotonergic 5-hydroxytryptamine (5-HT) type 2a, type 2c (5-HT2c), type 3 (5-HT3), and type 6 (5-HT6) receptors; dopaminergic D1, D2, D3, and D4 receptors; catecholamine alpha one adrenergic receptor; histamine H1 receptors; and acetylcholine muscarine receptor. By blocking these receptors associated with specific neurotransmitters, olanzapine demonstrates antiemetic efficacy, particularly towards 5-HT2c, 5-HT3, and dopaminergic D2 receptors. Numerous studies have highlighted the significant preventive impact of standard dose of olanzapine (5 mg and 10 mg)on CINV [14, 15]. The predominant adverse reaction associated with olanzapine is the occurrence of somnolence and fatigue, potentially leading to a deterioration in the overall well-being of individuals [15].

All of the cases under study had reported CC and CR of nausea and vomiting, demonstrating the effectiveness of preventive low-dose olanzapine in conjunction with triple antiemetic medications. Within this series of cases, an analysis was conducted on the prevalent adverse effects of olanzapine, which included hiccups, somnolence, dry cough, and constipation. It was observed that none of these effects were classified as grade 2 or higher. Specifically, only two instances of grade 1 somnolence and one case of grade 1 dry mouth were reported, both of which were shown to have a positive influence on the overall quality of life.

This case series explored efforts to mitigate the adverse events associated with standard dosages of olanzapine while preventing breakthrough symptoms in higher doses. A study indicated that 2.5 mg of olanzapine was equally effective as 10.0 mg in antiemetic properties. Furthermore, the lower dosage decreased daytime drowsiness among patients undergoing HEC, suggesting it could establish a new standard of care [16].

The primary constraints of the present study encompass its retrospective nature and the limited number of participants gathered from a single healthcare facility. Future studies with larger sample sizes are recommended to ascertain the practicality and benefits of utilizing a low dose of olanzapine.

Conclusion

According to this study, prophylactic single low-dosage olanzapine (2.5 mg) was effective enough to prevent vomiting and nausea and reduce the incidence and severity of side effects in patients undergoing HEC; therefore, it should be deemed a new benchmark of care.

ABBREVIATION

CINV- Chemotherapy Induced Nausea and Vomiting.

HEC- Highly Emetogenic Chemotherapy

CTCAE – Common Terminology Criteria for Adverse Events

CR- Complete Response

CC- Complete Control

QOL- Quality of Life

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