original reports

Randomized Double-Blind Placebo-Controlled Study of Olanzapine for Chemotherapy-Related Anorexia in Patients With Locally Advanced or Metastatic Gastric, Hepatopancreaticobiliary, and Lung Cancer

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abstract

PURPOSE Anorexia occurs in 30%-80% of patients with advanced malignancies, which may be worsened with chemotherapy. This trial assessed the efficacy of olanzapine in stimulating appetite and improving weight gain in patients receiving chemotherapy.

METHODS Adults (≥18 years) with untreated, locally advanced, or metastatic gastric, hepatopancreaticobiliary (HPB), and lung cancers were randomly assigned (double-blind) to receive olanzapine (2.5 mg once a day for 12 weeks) or placebo along with chemotherapy. Both groups received standard nutritional assessment and dietary advice. The primary outcomes were the proportion of patients with weight gain > 5% and the improvement in appetite (assessed by the visual analog scale [VAS] and the Functional Assessment of Chronic Illness Therapy system of Quality-of-Life questionnaires Anorexia Cachexia subscale [FAACT ACS]). Secondary end points were change in nutritional status, quality of life (QOL), and chemotherapy toxicity.

RESULTS We enrolled 124 patients (olanzapine, 63 and placebo, 61) with a median age of 55 years (18-78 years), of whom 112 (olanzapine, 58 and placebo, 54) were analyzable. The majority (n = 99, 80%) had metastatic cancer (gastric [n = 68, 55%] > lung [n = 43, 35%] > HPB [n = 13, 10%]). The olanzapine arm had a greater proportion of patients with a weight gain of > 5% (35 of 58 [60%] *v* 5 of 54 [9%], $P < .001$) and improvement in appetite by VAS (25 of 58 [43%] *v* 7 of 54 [13%], $P < .001$) and by FAACT ACS (scores ≥37:13 of 58 [22%] *v* 2 of 54 [4%], $P = .004$). Patients on olanzapine had better QOL, nutritional status, and lesser chemotoxicity. Side effects attributable to olanzapine were minimal.

CONCLUSION Low-dose, daily olanzapine is a simple, inexpensive, well-tolerated intervention that significantly improves appetite and weight gain in newly diagnosed patients on chemotherapy.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Anorexia affects 40%-60% of patients newly diagnosed with cancer.[1] Poor appetite is associated with insufficient oral intake, compromising cancer survival.[2] Anorexia is exacerbated by chemotherapy, compromising the nutritional status of the patient, which may indirectly worsen chemotherapy tolerance and compromise cancer-related outcomes.[3] At the time of diagnosis, patients with certain types of cancers (eg, gastrointestinal tract and lung cancer) are prone to develop anorexia. The incidence of anorexia during chemotherapy ranges from 22% to 56%, depending on the type of cancer and the regimen used.[4-6] Current guidelines on treating anorexia and cachexia recommend dietary counseling; however, there are limited data to support the use of pharmacological agents to stimulate appetite.[7] Megestrol produces modest improvements in appetite at the cost of increased risk of thromboembolism and death.[8] Glucocorticoids temporarily improve appetite and well-being.[9] However, long-term use of steroids leads to several problems and is usually avoided for this indication, except in patients with limited life expectancy. Hence, there is a need to develop agents that can alleviate anorexia, especially among patients receiving chemotherapy.

Olanzapine, an antipsychotic agent with antagonistic effects on dopamine and serotonin receptors, stimulates

CONTEXT

Key Objective

Can continuous, low-dose olanzapine improve appetite and weight gain among newly diagnosed patients with advanced lung and upper gastrointestinal cancer starting chemotherapy?

Knowledge Generated

Olanzapine use significantly improves appetite in patients at high risk of anorexia while on frontline chemotherapy. The proportion of patients achieving weight gain was significantly more with olanzapine than placebo. Olanzapine at these doses was very well tolerated, and these patients had secondary benefits such as improved quality of life, better nutritional status, and reduced chemotherapy toxicity.

Relevance *(C. Zimmermann)*

Low-dose olanzapine in addition to dietary advice should be considered alongside chemotherapy for patients with newly diagnosed advanced lung and upper gastrointestinal cancers to improve appetite and weight gain.*

*Relevance section written by *JCO* Associate Editor Camilla Zimmermann, MD, PhD, FRCPC.

appetite. When initially used in patients with schizophrenia, olanzapine caused weight gain, which was considered an undesirable effect.[10] However, this orexigenic effect was later exploited in patients with anorexia nervosa.[11–13] Appetite stimulation by olanzapine is probably centrally mediated by its action on H1, 5HT2C, 5HT2B, and the D2 receptors.[13] Although a peripheral effect cannot be ruled out, studies attempting to correlate appetite stimulation and ghrelin and leptin levels have shown mixed results.[14,15] Among patients with cancer, olanzapine has been tried in advanced disease as an appetite stimulant.[14,16,17] In one study, the addition of olanzapine enhanced the appetite-stimulating effects of megestrol in patients with advanced gastrointestinal and lung cancers.[17] However, there are no data on the use of olanzapine in chemotherapy-related anorexia in patients with newly diagnosed cancer. Short-duration (1-4 days) olanzapine (doses of 5 or 10 mg per day) has become popular in oncology as a safe, effective, and inexpensive antiemetic.[18] However, appetite stimulation requires a more extended usage of olanzapine, which has also been deemed safe on the basis of long-term data from trials in psychiatry.[10,19] We designed a trial to evaluate the impact of olanzapine on anorexia and weight gain in patients with newly diagnosed cancer receiving chemotherapy.

METHODS

This randomized, double-blind, parallel-group, placebo-controlled trial was conducted in a tertiary care center in South India after the approval of the institutional ethics committee (no: JIP/IEC/2020/029) and registration with the clinical trial registry of India.[20] The trial was conducted per the Indian Council of Medical Research (ICMR) guidelines for good clinical practice in research. Informed consent was obtained from all participants. Anorexia was defined as any subjective loss of appetite within 6 months of diagnosis. If it persisted during chemotherapy, it was considered chemotherapy-related anorexia.

Eligibility

Newly diagnosed patients ≥18 years of age planned for the first cycle of cytotoxic chemotherapy for locally advanced/metastatic gastric, hepatopancreaticobiliary (HPB), or lung cancer were included. Patients with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-3 were eligible, provided they could take an oral diet. Short-duration olanzapine (5 mg once a day on days 1-4) and steroids were used in all randomly assigned patients as per the antiemetic policy at our center. Patients on long-term steroids or antipsychotics were not eligible. Patients receiving conventional cytotoxic agents were eligible for the study. Those patients who were treated with a low dose, oral (metronomic) chemotherapy, or tyrosine kinase inhibitors alone (without injectable cytotoxic chemotherapy) were excluded (detailed inclusion and exclusion criteria are available in the Protocol, online only).

Random Assignment

Patients were randomly assigned 1:1 to one of two treatment groups with a computer-generated block random assignment schedule with variable block sizes. The sequence was created by a statistician uninvolved with patient enrollment and evaluation. The drug was provided in three sealed covers of 30 tablets each. These three covers were sealed in envelopes identified by allocation number labeled by the statistician. Patients were evaluated by clinicians and nutritionists who were blinded to treatment allocation.

Study Intervention

Patients in the intervention group received olanzapine 2.5 mg once a day for 12 weeks. The control group received matching placebo tablets (containing starch). An individualized diet sheet was prepared and provided to all patients, emphasizing the importance of a high-calorie, high-protein,

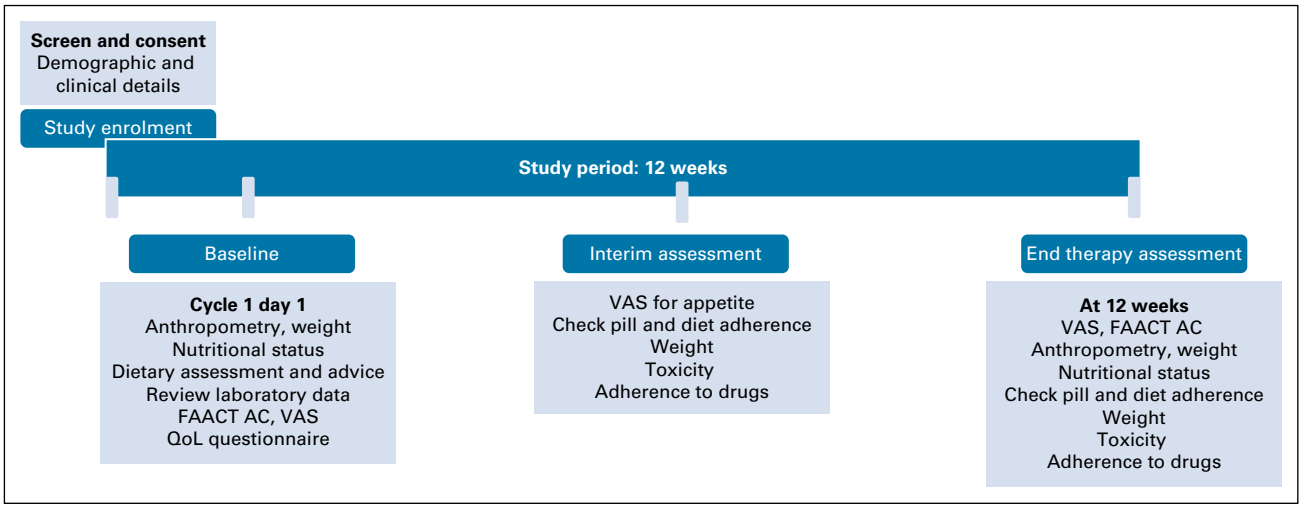

FIG 1. Timelines of assessment during the study period of 12 weeks: Baseline demographic and clinical details were collected before chemotherapy, and eligible patients were screened for consent. The study drug (olanzapine/placebo) was started from cycle 1, day 1 of chemotherapy delivery, along with other supportive medicines. The anthropometry, weight, nutritional assessment, anorexia assessment (VAS and FAACT AC), and QOL assessment were carried out before starting chemotherapy. Subsequently, patients were assessed during each chemotherapy visit for toxicity, side effects of olanzapine, and adherence to the study drug (pill counting and review of the diary). The assessments were repeated at the end of the study period (12 weeks) as above. Since 12 weeks was a fixed assessment point, patients receiving once-in-3-weeks and once-in-2-weeks regimens had their final assessments after four and six cycles, respectively. FAACT AC, Functional Assessment of Chronic Illness Therapy system of Quality-of-Life questionnaires Anorexia Cachexia subscale; QOL, quality of life; VAS, visual analog scale.

nutrient-dense healthy diet. Because most patients hailed from poor economic conditions, the diet sheet stressed home-based foods, and no nutritional supplements were advised or provided.

The intervention started with cycle 1, day 1 of chemotherapy, and continued till the end of 12 weeks (84 days). Chemotherapy was administered in the daycare, and all patients were assessed in the clinic during their follow-up visits. Chemotherapy cycles were delivered once in 2 weeks or 3 weeks, and the post-treatment assessments (at 12 weeks) were planned after six or four cycles, respectively. A delay of upto 7 days was allowed for the end-therapy assessment to account for chemotherapy cycle delays. If the evaluation was delayed (because of chemotherapy delays or other reasons), patients could continue olanzapine for a maximum of 90 days.

Patient Assessment

Patients were evaluated at baseline, during each visit for the chemotherapy cycles, and at the end of the study. The following parameters were recorded at the baseline: weight, height, body mass index, mid-arm circumference, and triceps skin-fold thickness. In addition, the subjective global assessment tool (SGA) was used to document the nutritional status (well-nourished, moderately malnourished, and severely malnourished), and the 24-hour dietary recall was used to calculate the calorie and protein deficit. Symptoms associated with anorexia were assessed using The Functional Assessment of Chronic Illness Therapy system of Quality-of-Life questionnaires Anorexia Cachexia subscale (FAACT ACS) and the visual analog scale (VAS). After 12 weeks (after four cycles in patients on once-in-3-weeks regimens and after six cycles of chemotherapy in those on once-in-2-weeks regimens), weight, anthropometric measures, appetite score, FAACT ACS, and quality of life (QOL) questionnaires were reassessed (Fig 1).

In addition, the global QOL during the study was assessed using the cancer Institute QOL questionnaire version II (CI-QOL), a system developed and validated among Indian patients.[21] The patients were categorized into five groups on the basis of the CI-QOL ranging from "poor" to "high." The methodology of the above assessments is detailed in Appendix 1.

Patients were given a diary for daily self-reporting of adherence. The log was checked at each visit, and patients were encouraged to adhere to trial drug and nutritional advice. Patients were assessed at each scheduled chemotherapy visit for toxicity related to chemotherapy and trial drugs. Toxicities considered to be specifically associated with the trial medicine were drowsiness, headache, dizziness, hyperglycemia, suicidal tendencies, and constipation.

Statistical Analysis

This study hypothesized that supplementing nutritional advice with olanzapine would reduce anorexia and lead to weight gain in patients receiving chemotherapy for advanced lung, gastric, and hepatopancreaticobiliary tract cancers. The primary end point was chosen as the proportion of patients achieving a weight gain of >5% at the end of the study period.[6,17,22] Since a mixed population of lung and upper GI cancers were included, we estimated that about 10% of patients would gain weight (≥5%) during chemotherapy (details of the assumptions and calculations are given in

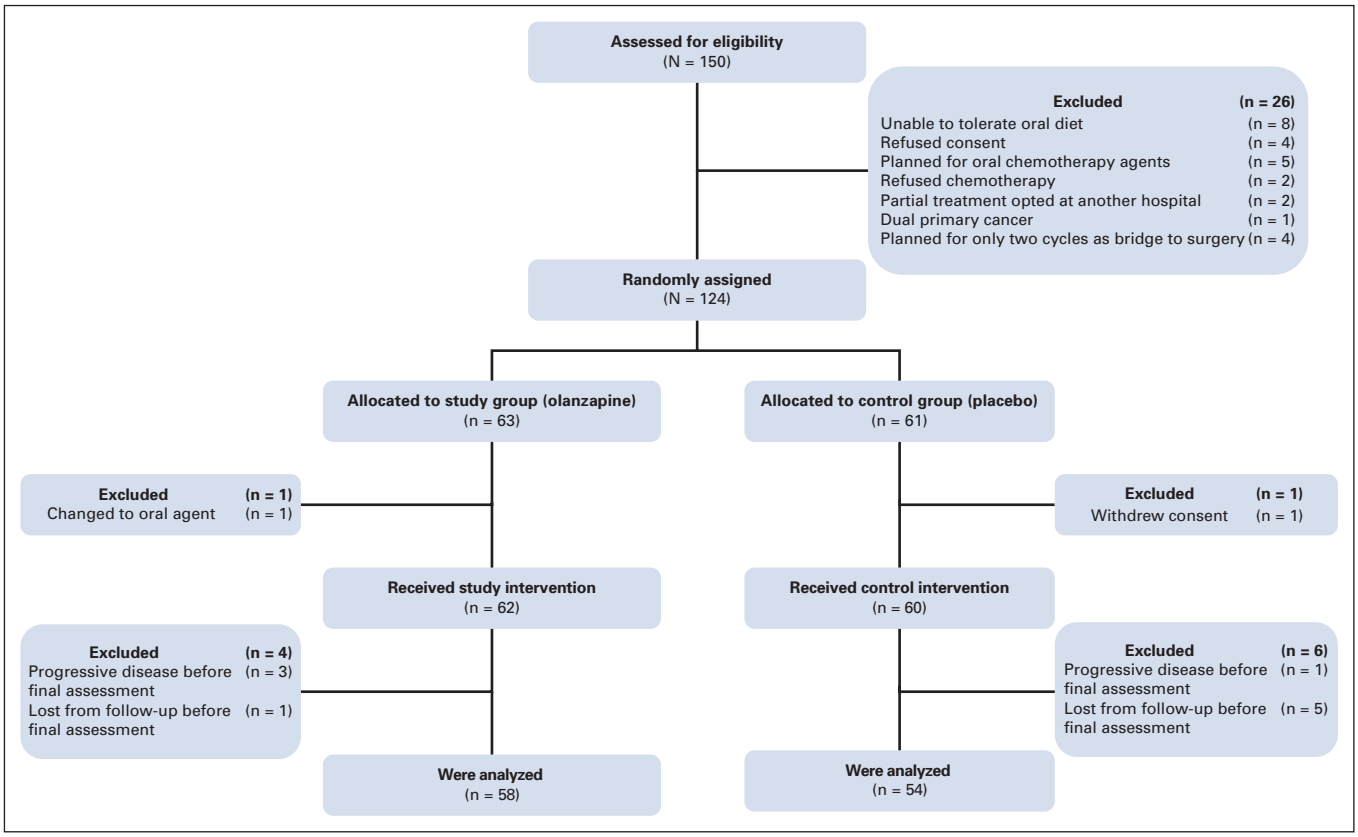

FIG 2. CONSORT diagram showing the evaluation, random assignment of patients, and their evaluation for efficacy.

Appendix 1). With a power of 80% and type I error of 5%, we needed 62 patients in each group to demonstrate an improvement in proportion gaining weight from 10% to 30%.

The baseline characteristics were presented using descriptive statistics. The proportions of patients achieving weight gain, improvement in anorexia, nutrition, and QoL status were compared between the two groups using the chi-square or Fisher exact test. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS Inc, Chicago, IL).

RESULTS

Baseline Features

During the study period (between November 2020 and June 2022), 150 patients were screened, and 124 were enrolled (the olanzapine arm had 63 patients, and the placebo arm had 61 patients). Among the randomly assigned patients, 58 patients in the olanzapine group and 54 in the placebo group were eligible for assessing the primary end point of weight gain at 12 weeks (Fig 2). Baseline clinical characteristics were similar between the groups (Tables 1 and 2). The median age was 55 years, and two-thirds were male. Gastric cancer was the most common subtype (55%), followed by lung (35%). Most patients (84%) had stage IV disease and were treated with palliative intent. The proportion of patients receiving highly emetogenic (14 [23%] in olanzapine and 15 [25%] in the placebo group) and moderately emetogenic chemotherapy (49 [77%] and 46 [75%]) was similar. The dose of chemotherapy was modified for poor performance or poor nutrition in cycle one for some patients on the basis of the clinician's decision. Thus, 23 (37%) and 21 (34%) patients in the olanzapine and placebo groups, respectively, were started at reduced doses of chemotherapy (75% of the calculated dose; Appendix Table A1, online only).

On nutritional assessment (Table 2), one-third were underweight, and almost all patients reported anorexia at baseline. Most patients could meet only about 50% of the recommended daily calorie intake. More than half the patients reported weight loss of >5% from prediagnosis weight (57% in olanzapine and 59% in placebo). Almost three quarters of the patients had below average or poor QOL.

Appetite and Weight

The primary end points of weight gain and appetite were assessable in 58 patients in the olanzapine arm and 54 patients in the placebo arm. The primary analysis was done only with evaluable patients and is presented below. A separate analysis considering all randomly assigned patients is detailed in Appendix Table A6.

TABLE 1. Baseline Characteristics

Parameter	Olanzapine, n = 63	Placebo, n = 61
Age, years, median (range)	55 (24-74)	55 (18-78)
Sex, No. (%)		
Male	40 (64)	39 (64)
Female	23 (36)	22 (36)
ECOG PS, No. (%)		
1	47 (74)	44 (72)
2	13 (21)	15 (25)
3	3 (5)	2 (3)
Diagnosis, No. (%)		
Gastric	34 (54)	34 (56)
Lung	22 (35)	21 (34)
HPB[a]	7 (11)	6 (10)
Stage (AJCC), No. (%)		
3	10 (16)	15 (25)
4	53 (84)	46 (75)
Type of therapy, No. (%)		
Neoadjuvant	10 (16)	15 (25)
Palliative	53 (84)	46 (75)
Chemotherapy cycles, No. (%)		
Once in 3 weeks[b]	42 (67)	44 (72)
Once in 2 weeks[c]	21 (33)	17 (28)
Antiemetic use, No. (%)		
OAOD	14 (23)	15 (25)
OOD	49 (77)	46 (75)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HPB, hepatopancreaticobiliary; OAOD (for highly emetogenic chemotherapy), olanzapine (5 mg once daily on days 1-4), aprepitant (125 mg once a day on day 1, and 80 mg once a day on days 2 and 3), ondansetron (8 mg three times a day for 3-5 days), and dexamethasone (8 mg IV on day 1 and 8 mg orally once daily on days 1-3); OOD (for moderately emetogenic chemotherapy), olanzapine (5 mg once daily on days 1-4), aprepitant (125 mg once a day on day 1, and 80 mg once a day on days 2 and 3), ondansetron (8 mg three times a day, for 3-5 days), and dexamethasone (8 mg IV on day 1 and 8 mg orally once daily on days 1-3).

[a]HPB cancers; hepatocellular carcinoma = 1, periampullary carcinoma: 2, cholangiocarcinoma: 3, pancreatic: 2, and gallbladder: 5.

[b]Once-in-3-weeks regimens: CAPOX, paclitaxel carboplatin, pemetrexed carboplatin/cis (details in Appendix Table A1).

[c]Once-in-2-weeks regimens: Gemcitabine oxaliplatin, FLOT4, DOX (docetaxel, oxaliplatin, capecitabine; details in Appendix Table A1).

Weight gain. The proportion of patients with >5% weight gain after 12 weeks was 60% (35 of 58 patients) versus 9% (5 of 54 patients), favoring olanzapine (Fig 3A). Correspondingly, the proportion of patients suffering weight loss at the end of the study period was lower with olanzapine (14% *v* 59%, Fig 3B). The mean weight in the olanzapine group increased from 53 kg (SD ± 8.86) to 55.7 kg (SD ± 9.05) at the end of the study. Patients on olanzapine had a higher increase in mean weight at the interim evaluation and the completion of the study (Fig 3C, Table 3, and Appendix Table A7).

Appetite

The proportion of patients with an improvement in appetite assessed using the VAS from baseline to week 12 was significantly higher in the olanzapine group (43% *v* 13%; $P < .001$). At the end of treatment, FAACT ACS score >37 (cutoff validated in previous trials as predictive of anorexia[24]) was seen in 13 (22%) of 58 patients in the olanzapine group as compared with 2 (4%) of 54 patients in the placebo group ($P = .004$). Adherence to the trial medication was 90% and 93%, respectively, in the olanzapine and placebo groups.

Nutrition, Calorie Intake, and QOL

Nutrition scores, as assessed by SGA, had improved among 25 of 58 (43%) in olanzapine as compared with 5 of 54 (9%) in the placebo group (<0.0001). The number of patients who remained in or worsened to group C (severely malnourished) as per SGA was 7 (12%) in olanzapine compared with 21 (39%) in the placebo group ($P = .001$; Appendix Table A5). Similarly, the number of patients who could achieve an adequate calorie intake of more than 75% of the required calories and protein was 30 (52%) in the olanzapine group versus 10 (18%; $P < .0001$) in the placebo group (Table 3).

TABLE 2. Patient Anthropometry and Nutritional Characteristics at Baseline

Variable	Olanzapine, n = 63, No. (%)	Placebo, n = 61 No. (%)
Weight loss >5%[a]		
Yes	36 (57)	36 (59)
No	16 (25)	11 (18)
Previous weight unknown	11 (18)	14 (23)
Anorexia[b]		
Yes	59 (94)	52 (85)
No	4 (6)	9 (15)
BMI (kg/m^2; median, range)	20.7 (13-30)	20.6 (13.7-33.8)
Underweight, <18.5	22 (35)	17 (28)
Normal, 18.5-22.9	32 (51)	35 (57)
Overweight and obese ≥23	9 (14)	9 (15)
SGA score		
A: Well nourished	16 (25)	14 (23)
B: Moderately malnourished	27 (44)	25 (41)
C: Severely malnourished	18 (28)	20 (33)
Missing information	2 (3)	2 (3)
Quality of life category[c]		
1: Very low	18 (29)	14 (23)
2: Low	20 (32)	20 (33)
3: Average	19 (30)	22 (36)
4: High	4 (6)	3 (5)
Missing information	2 (3)	2 (3)
FAACT A/CS (score > 37)		
Yes	—	—
No	63 (100)	61 (100)
Proportion of calorie intake met[d]		
≤50%	26 (41)	24 (39)
51%-75%	32 (51)	31 (51)
>75%	5 (8)	6 (10)

Abbreviations: CI-QOL, Cancer Institute Quality of Life tool; FAACT A/CS, FAACT Anorexia Cachexia subscale; SGA, subjective global assessment; VAS, visual analog scale.

[a]Within 6 months of diagnosis.

[b]Anorexia: history of loss of appetite or weight at diagnosis.

[c]Using CI-QOL; scoring as per categories mentioned in Appendix 1 (there were no patients in the "very high" category of QoL).

[d]Recommended energy (30 kcal/kg/day) and protein(1 g/kg/day) were calculated for an individual at baseline, which was taken as 100%. The 24-hour dietary recall captured detailed information on foods and beverages consumed to assess the total dietary intake. Thus, the proportion of energy and protein requirements met by the patient was calculated.

Improvement in the QOL score as compared with baseline was seen in 44 (70%) patients in the olanzapine group compared with 27 (50%) in the placebo group ($P = .003$). At the end of the study, a lower proportion of patients in the olanzapine group had poor or average QOL scores.

Tolerance of Chemotherapy and Safety

Most toxicities were nonhematological and were equally distributed between olanzapine and placebo groups (85% *v* 88%, respectively). However, the proportion of patients with ≥grade 3 toxicities was lower with olanzapine (7 of 58 [12%] *v* 20 of 54 [37%], $P = .002$; Table 3). Doses in the second cycle were modified in 16 (28%) patients in the olanzapine group, of whom 12 (75%) had an increase in the dose of chemotherapy to 100%. In the placebo group, 21 (39%) had dose modification at cycle 2, of whom only three (14%) patients had an increase in chemotherapy dosage. Thus, chemotherapy tolerance was significantly better in the olanzapine group. Toxicities attributable to the trial drug were

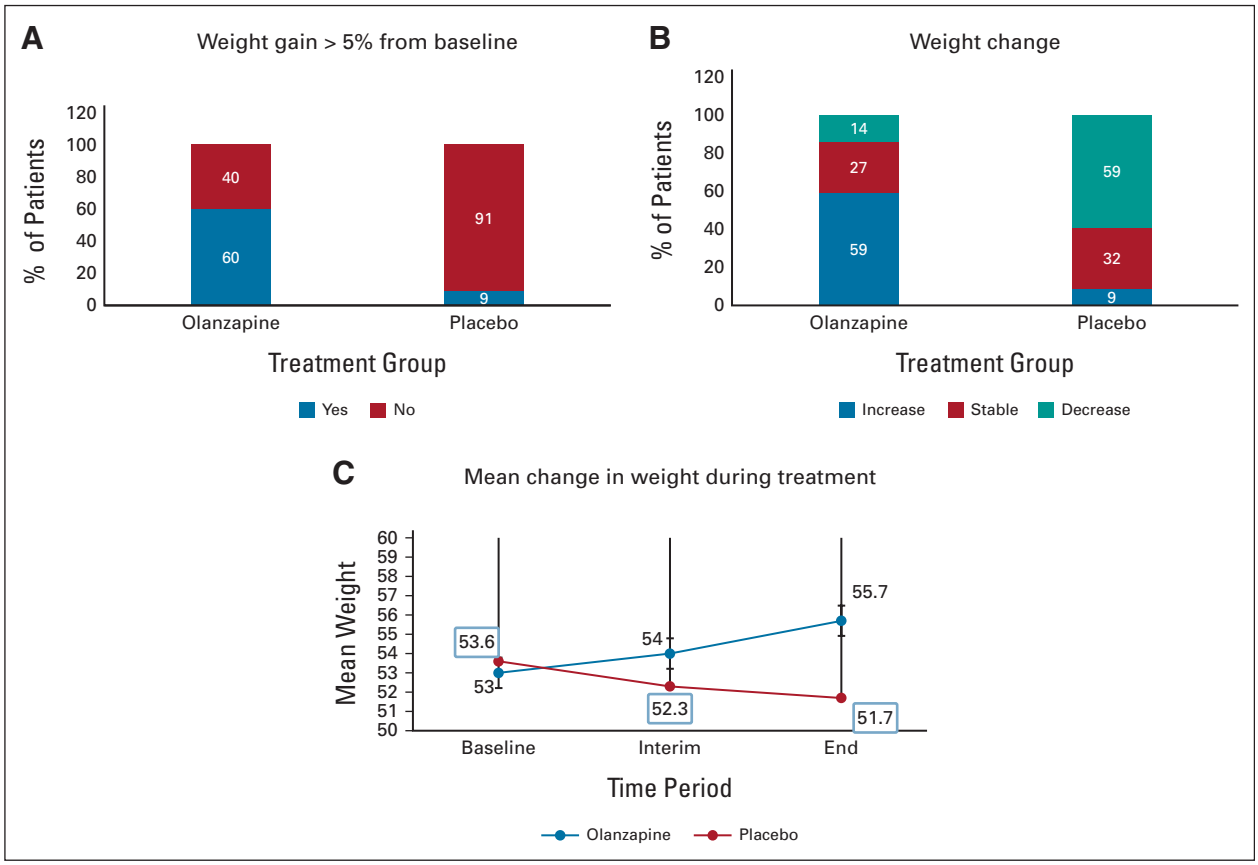

FIG 3. The changes in weight between the intervention (olanzapine) and standard therapy (placebo) groups during the study. (A) The primary end point (>5% gain of weight) was achieved by 35 of 58 (60%) of patients in olanzapine compared with 5 of 54 (9%) in the placebo arm. (B) The change in weight at the end of the study showing a greater proportion of weight gain with olanzapine and a significant proportion of patients losing weight in the placebo arm. (C) Mean weight and its change during the study showing a trend of increasing mean weight in the olanzapine group and decreasing weight in the placebo group. Patients in the olanzapine group had an increase in mean weight from 53.1 kg (±8.9) to 55.7 kg (±9.0), $P < .001$ (paired t test). Patients in the placebo group had a decrease in mean weight from 53.6 kg (±9.9) to 51.7 kg (±9.7), $P < .001$ (paired t test).

seen in 13 (23%) patients in the olanzapine group and 8 (15%) in the placebo group. Only one patient had a grade 3 headache in the olanzapine group. This was later attributed to the development of brain metastasis. Two patients with grade 3 hyperglycemia were in the placebo group, which could be managed with modifications of oral hypoglycemic drugs (detailed toxicity data available in Appendix Tables A2-A4).

DISCUSSION

Very few studies are available addressing the problem of anorexia in patients with newly diagnosed cancer receiving chemotherapy. This study aimed to demonstrate improvement in appetite in patients with newly diagnosed cancer on chemotherapy using low-dose continuous olanzapine. We demonstrated that a higher proportion of patients receiving olanzapine had appetite improvement compared with placebo (43% *v* 13%). Weight gain occurred in 60% of patients receiving olanzapine (compared with 9% with placebo). On the other hand, 59% of patients in the placebo group suffered some weight loss (compared with 9% with olanzapine). The use of olanzapine was also associated with better nutrition, QOL, and less chemotherapy toxicity.

Short-term olanzapine use (as for antiemesis) has not demonstrated weight gain.[25,26] Longer use is needed for appetite stimulation and weight gain. There were concerns about additional toxicity with continuous dosing since olanzapine was also used as an antiemetic in all our patients. However, adverse events attributable to olanzapine were mild and manageable. There were only two patients who reported drowsiness, which was mild and short lasting. Although recent studies suggest that olanzapine may be taken at night to reduce drowsiness, we did not specify this in our protocol.[27] We used a lower dose of olanzapine for antiemesis (5 mg once daily on days 1-4) than most clinical trials (10 mg once daily on days 1-4).[26,27] We used a very low dose of 2.5 mg per day of olanzapine for appetite stimulation. This dose was also lower than earlier studies of olanzapine in anorexia, where 5 mg per day was used.[17] These could be the reasons for our study's

TABLE 3. Comparison of Primary and Secondary End Points

Variable	Olanzapine, n = 58, No. (%)	Placebo, n = 54, No. (%)	*P*
Weight gain >5%			
Yes	35 (60)	5 (9)	<.0001
No	23 (40)	49 (91)	
FAACT A/CS (score > 37)			
Yes	13 (22)	2 (4)	.004
No	45 (78)	52 (96)	
Improvement in VAS[a]			
Yes	25 (43)	7 (13)	<.001
No	33 (57)	47 (87)	
End of treatment SGA			
A: Well nourished	32 (55)	14 (26)	<.001
B: Moderately malnourished	19 (33)	19 (35)	
C: Severely malnourished	7 (12)	21 (39)	
Change in SGA[b]			
Increase	25 (43)	5 (9)	<.001
Stable	32 (55)	40 (74)	
Decreased	1 (2)	9 (17)	
Calories met (%) at 12 weeks[23]			
≤50%	9 (16)	15 (28)	<.001
51%-75%	19 (32)	29 (54)	
>75%	30 (52)	10 (18)	
End of treatment CI QOL score			
Poor	2 (3)	12 (22)	<.001
Below average	14 (24)	25 (47)	
Average	29 (50)	16 (29)	
Above average	12 (21)	1 (2)	
High	1 (2)	—	
Chemotherapy toxicity (CTCAE) grade ≥ 3			
Yes	7 (12)	20 (37)	.002
No	51 (88)	34 (63)	

Abbreviations: cal, calories; CI QOL, Cancer Institute Quality of life score; CTCAE, common terminology criteria for adverse events version 3.0; FAACT A/CS, FAACT Anorexia Cachexia subscale; SGA, subjective global assessment; VAS, visual analog scale.

[a]Increase in VAS more than three points from baseline.

[b]Change in SGA, increase: change from B to A or C to A, B; stable: no change compared with baseline; decrease: change from A to B, C or B to C (see Appendix Table A5 for details).

low incidence of drowsiness. This study also showed the safety of a more prolonged intake of olanzapine (12 weeks) in patients with newly diagnosed cancer starting chemotherapy. Previous studies had also used olanzapine for a longer duration without significant toxicities.[17] The phase I study by Naing et al[14] had not specified the duration of intake of olanzapine but demonstrated that upto 20 mg dose per day would be safe to use. However, we chose the dose of 2.5 mg per day on the basis of data that showed that weight gain is achieved even with lower doses.[16]

Although weight gain is not a direct measure of the orexigenic impact of olanzapine, we chose this as the primary end point as it would be more objective than measuring changes in appetite. An increase in weight of >5% was deemed significant as this is associated with improved survival in lung cancer.[6] Improvement in anorexia was demonstrated using two separate scales, the VAS and FAACT ACS version. 2.0 (anorexia subscale). The effect of olanzapine on appetite in this study has certain advantages (low toxicity and weight gain) compared with those observed earlier with corticosteroids and progestins.[7,9] The trials using glucocorticoids suggested short-lasting improvements in appetite and well-being, but increased weight was rare.[9] Progestational agents have been more extensively studied and seem to have

more sustained effects than steroids. However, the current guidelines do not recommend the routine use of progestins because of concerns about increased toxicity and even death.[9]

Several factors determine food intake; appetite is one of the key determinants. The proportion of patients achieving >75% intake of recommended daily calories at the end of the study was 52% versus 18% favoring olanzapine. Improvement in nutritional status occurred in 43% (*v* 9%) of patients receiving olanzapine. Only one patient on olanzapine suffered a worsening nutritional status while nine patients receiving placebo worsened. Patients with cancer with SGA category C nutritional status have a poor prognosis.[28] The proportion of patients who were in SGA category C reduced from 28% to 12% in the olanzapine group. It increased from 33% to 38% among those who received a placebo. Although there are no data on serial assessments of SGA in patients with cancer during therapy, the improvement in the SGA status might be expected to affect therapy outcomes positively. Another effect of better appetite and food intake is improved QOL. QOL improvement was seen in 70% (*v* 50%) of those who received olanzapine. The effect of better nutrition was also associated with better tolerance of chemotherapy in the form of reduced grade 3-4 toxicities.

There are a few limitations to this study. A heterogeneous group of cancers (gastric, lung, and HPB) were included. However, these were chosen because these cancers have a high baseline incidence of anorexia which could be worsened with cytotoxic chemotherapy. Although the chemotherapy regimens were also different, the antiemetic regimens were homogenous (Table 1). The proportion of patients receiving highly and moderately emetogenic chemotherapies was similar between the groups. The study assessed the improvement in weight and symptoms of anorexia over 12 weeks. Thus, we do not have information on the sustainability of weight gain beyond 12 weeks. Although we had enrolled 124 patients, only 112 were eligible for final analysis (Fig 2). Although additional enrollment could have been planned, the overall recruitment was slower than planned (because of the COVID-19 pandemic), and we had to stop recruitment at the preplanned number. However, an intention-to-treat type analysis, including patients not assessed for the end point, continued to show the benefit of olanzapine over placebo for the primary end points (Appendix 1). Anorexia measurement is subjective and difficult to judge using single instruments. Hence, in this study, we used several direct and indirect measures to gauge the impact of the intervention. In addition to improved appetite, we also demonstrated increased calorie intake, better nutritional status, weight gain, and reduced chemotherapy toxicity in patients receiving olanzapine. Thus, despite the limitations mentioned, this study makes a strong case for considering olanzapine as an add-on agent in patients at risk of anorexia and cachexia during chemotherapy.

Olanzapine demonstrated stimulation of appetite and better oral intake in patients receiving chemotherapy. This resulted in a more significant proportion of patients achieving weight gain during therapy. This trial was conducted in a tertiary center where an experienced dietician was available who could assess and closely follow the nutrition status of the patients. Similar expertise may not be available at all centers. At the same time, this was a double-blind study, and the impact of olanzapine was achieved in addition to the effects of the dietary advice provided. In addition, since olanzapine is inexpensive and well-tolerated, we believe that olanzapine can be considered an add-on therapy in patients starting chemotherapy who are at risk of developing anorexia in all centers. Future studies could look at various cancers in a multicentric setting and long-term end points such as patient survival.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Double-Blind Placebo-Controlled Study of Olanzapine for Chemotherapy-Related Anorexia in Patients With Locally Advanced or Metastatic Gastric, Hepatopancreaticobiliary, and Lung Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

APPENDIX 1

Assessment of Parameters

Weight was recorded using digital standing scales in metric measure. Patients were instructed to wear light, comfortable clothing while recording weight. Any heavy clothing or shoes/jewelry which was worn and the patient was uncomfortable removing during the time of weight record was noted while measuring. It was ensured that patients were not supporting their weight while standing on the weighing machine. Weight was recorded in kilograms to the nearest 0.1 kg. The same weighing machine was used for pretreatment and post-treatment weight records; however, the time of measuring weight was dependent on patient visits, which was variable.

Height was measured using a stadiometer in centimeters (cm) using the metric system.

BMI was calculated by dividing weight (in Kg) by the square of the body height (in m^2) expressed in units of kg/m^2.

Midarm circumference was measured using a centimeter measuring tape at the midpoint between the olecranon and acromion with the arm hanging straight down. The unit of measurement is a centimeter. A value between 23 and 25 was considered normal, as defined in previous studies.

Triceps skin fold thickness was measured using a standard skinfold caliper at the midarm over the triceps by grasping the skin fold of the patient by the examiner and applying a caliper at the right angle. The unit of measurement is a millimeter.

Nutrition assessment tool: Subjective global assessment was used to assess the nutritional status of patients at baseline and after 12 weeks of treatment. It is a scored nutritional assessment tool validated for patients with cancer, categorizing them as well-nourished, moderately malnourished, and severely malnourished. This tool includes BMI, weight changes, symptoms related to food intake, functional capacity and its difference, some comorbidities, and physical examination of muscle/fat deficit and edema.

Dietary evaluation: Recommended energy (30 kcal/kg/day) and protein (1 g/kg/day) were calculated for an individual at baseline, which was set as the target dietary requirement and was considered 100% for them.[29,30] Using the 24-hour dietary recall, detailed information on foods and beverages consumed was captured to assess total dietary intake. The proportion of energy and protein requirements met was calculated by subtracting the required calorie/protein percentage from the calories/protein the patient was already consuming. A calorie intake proportion of more than 75% was considered the minimum necessary calorie target.[23] At 12 weeks, using the 24-hour recall, the calories consumed by the patient were calculated. The percentage consumed after the intervention was compared with the baseline calculation of recommended calories.

Assessment of Anorexia

Symptoms associated with anorexia were assessed using The Functional Assessment of Chronic Illness Therapy system of Quality-of-Life questionnaires Anorexia Cachexia subscale (FAACT ACS), mentioned as additional concerns in version 4. The scales are primarily designed for patient self-administration but can be administered in an interview format. As the scoring system was unavailable in Tamil (the local language), we administered it in an interview format for all patients. The score ranges from 0-48. FAACT ACS was scored as per scoring guidelines. License and permission were obtained before the initiation of the study. A validated cutoff of <37 was used to define anorexia.[22]

A visual analog scale (VAS) was used as an additional measure of change in appetite. The patients scored this from 0 to 10, with 10 being normal/good appetite and 0 being no appetite. To compare the improvement in appetite between the groups, we considered a $\geq$3-point improvement in VAS to be clinically relevant. This was based on a previous study that used a similar cutoff (Navari et al)[17]

Assessment of the Health-Related Quality of Life

The Cancer Institute quality of life questionnaire version II, an indigenously developed and validated scoring system for patients with cancer in India, was used in our study.[21] A total of 41 items on different domains covered general well-being, physical well-being, psychological well-being, interpersonal relationship, sexual and personal ability, cognitive well-being, optimism, belief, economic well-being, informational support, patient-physician relationship, and body image. Thirty-nine items were on a Likert four-point scale and two on a ten-point semantic scale. Twenty-one questions have direct scoring, and 20 questions have reverse scoring. The maximum possible score is 180, and the minimum score is 42—the higher the score, the better the quality of life. Furthermore, the final scores can be represented in predefined norms as categorical variables that can be used to compare the two treatment groups. There are five defined norms: below 99 (very low), 99-117 (low), 118-146 (average), 147-165 (high), and above 165 (very high) quality of life.[21]

Chemotherapy Toxicity and Delay

During chemotherapy, any delay of more than five days from the scheduled cycles was defined as a delay. A decrease in dose, delay in the chemotherapy schedule for more than five days, or inability to complete the planned number of chemotherapy cycles, were defined as poor tolerance to chemotherapy.

Preparation of tablets and administration. The olanzapine and matching placebo were given in sealed envelopes containing 30 tablets each. The placebo tablets contained starch and were identical in shape, size, and color to the olanzapine tablets. These were repackaged into separate envelopes of 30 each and done by investigators not involved in the patient assessment (L.G. and M.S.). Although the assessment was planned at 12 weeks (84 tablets), an additional six tablets were provided to account for delays in the evaluation due to chemotherapy delays and other logistic issues. The patients took the tablets daily, and their compliance was checked with the diary maintained by the patient at every visit.

Sample size calculation and statistical analyses. The primary end point was chosen as the proportion of patients achieving a weight gain of more than 5% at the end of the study period. This has been used earlier in studies of anorexia and is associated with survival in patients with lung cancer.[6,17] The proportion of patients with lung cancer gaining $>5\%$ weight after chemotherapy was 17%.[6] There are limited data on the proportion of GI cancers gaining weight, as most patients suffer weight loss.[21] Since we used a mixed population of patients with lung and GI cancers, we estimated that about 10% of patients would gain weight ($>5\%$) during chemotherapy in the control arm.

On the basis of the earlier study of adding olanzapine to megestrol, there was an absolute 35% improvement in the proportion of patients gaining weight.[17] Since our study was in newly diagnosed patients receiving frontline chemotherapy, we estimated that the effect size might be lesser, so an absolute 20% improvement in the proportion achieving weight gain was assumed. With a power of 80% and type I error of 5%, to demonstrate an improvement in proportion gaining weight from 10% (in control) to 30% (in olanzapine), we needed 62 patients in each group. The patient demographic, clinical, and treatment characteristics were presented using descriptive statistics. The categorical variables were analyzed using the chi-squared test/Fisher's exact test and continuous variables using *t* test/Wilcoxon test. The difference was considered significant at a P value of $<.05$. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS Inc, Chicago, IL).

Compliance with study drugs. A total of 124 patients were randomly assigned, of whom 112 received the study drug (olanzapine, 58 and placebo, 54). Data could not be collected from 12 patients (See consort diagram Fig 2). Of the 112 patients, nine had a delay in chemotherapy of more than 3 days (3-10 days) because of the logistics

of being unable to visit the hospital on the assigned day of chemotherapy. Ten patients skipped trial drugs at some point, and the rest were completely adherent. Of the 10 patients who missed the trial drug, six were in the olanzapine arm and four in the placebo arm, yielding complete adherence in 52 of 58 (90%) in olanzapine and 50 of 54 (92.5%) in placebo arms, respectively.

Three of the six patients who missed trial medicine in the olanzapine arm forgot to take the tablets for 3, 3, and 7 days, respectively. One patient misplaced the drug and missed three doses. One skipped medication for 4 days because of nausea. One patient skipped for 7 days with no particular reason stated.

Among the patients in the placebo group, four missed the pills for the following reasons and duration: Two missed because of nausea and vomiting for 3 and 4 days, respectively. One patient forgot to take medication for 4 days, and one misplaced pills in the last week (7 days) before the response assessment.

TABLE A1. Additional Parameters at Baseline Compared Between the Study Groups

Variable	Olanzapine, n = 63, No. (%)	Placebo, n = 61, No. (%)
Comorbidities		
Yes	13 (20)	16 (26)
No	50 (80)	45 (74)
The intent of therapy		
Curative	10 (16)	15 (25)
Palliative	53 (84)	46 (75)
Smoking		
Yes	23 (37)	23 (37)
No	40 (64)	38 (63)
Alcohol		
Yes	22 (35)	16 (26)
No	41 (65)	45 (74)
Chemotherapy schedule		
Once in 3 weeks[a]	42 (67)	44 (72)
Once in 2 weeks[b]	21 (33)	17 (28)
Chemotherapy protocol		
CAPOX	20 (33)	20 (34)
FLOT (5 FU, oxaliplatin, docetaxel)	8 (13)	7 (11)
DOX	6 (9)	7 (11)
GEMOX/GemCap	6 (9)	7 (11)
Paclitaxel and carboplatin	4 (6)	4 (7)
Pemetrexed and carboplatin	19 (30)	14 (23)
Pemetrexed and cisplatin	0	2 (3)
Chemotherapy dosage (%) administered in cycle 1[c]		
100%	40 (63)	40 (66)
75%	23 (37)	21 (34)

Abbreviations: CAPOX, capecitabine and oxaliplatin; DOX, docetaxel, oxaliplatin, capecitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; GEMOX, gemcitabine and oxaliplatin.

[a]Once in 3 weeks: CAPOX, paclitaxel carboplatin, pemetrexed carboplatin/cis, Gemcap (gemcitabine and capecitabine).

[b]Once in 2 weeks: Gemcitabine oxaliplatin, FLOT4 (5FU, leucovorin, oxaliplatin, docetaxel), DOX (docetaxel, oxaliplatin, capecitabine).

[c]Reason for dose reduction in the first cycle: ECOG PS 2 or greater.

TABLE A2. Toxicities Attributed to Trial Drug

Variable	Olanzapine, n = 58	Placebo, n = 54	P
Any-grade toxicity present, No. (%)	13 (23)	8 (15)	.26
Hyperbilirubinemia/transaminitis, No.	3	1	
Constipation, No.	3	2	
Hyperglycemia, No.	4[a]	3	
Drowsiness, No.	2	1	
Headache, No.	1	1	
Suicidal tendencies, No.	0	0	
Cardiac complications, No.	0	0	
Grade 2 toxicity, No.	6	3	
Grade ≥3 toxicity, No.	1[b]	2[c]	

NOTE. The toxicities listed in this table were specifically assessed as those likely to be caused by olanzapine and were explicitly looked for during the follow-up visits.

[a]One patient had newly diagnosed type 2 diabetes mellitus during therapy.

[b]The patient in olanzapine arm with grade 3 headache had disease progression with new brain metastasis.

[c]Two patients who were known to have diabetes and developed grade 3 hyperglycemia (which improved with modification of oral hypoglycemic drugs).

TABLE A3. Chemotherapy Toxicity and Tolerance

Variable	Olanzapine, n = 58, No. (%)	Placebo, n = 54, No. (%)	P
Delay in the chemotherapy schedule[a]			.30
No	55 (95)	48 (89)	
Yes	3 (5)	6 (11)	
Chemotherapy dose modification in the second cycle			
Yes	16 (28)	21 (39)	
The dose increased in the second cycle[b]	12/16 (75)	3/21 (14)	< .001
The dose decreased in second cycle[c]	4/16 (25)	18/21 (86)	< .001
Chemotoxicity (any grade)	33 (57)	48 (89)	
Chemotherapy toxicity (CTCAE grade ≥ 3)			.002
Yes	7 (14)	20 (37)	
No	51 (86)	34 (63)	
Toxicity details	n = 33	n = 48	
Hematological	5 (15)	6 (12)	.52
Nonhematological	28 (85)	42 (88)	
Toxicity grade (CTCAE)			
1	6 (18)	4 (8)	
2	20 (60)	24 (50)	
3	7 (22)	20 (42)	

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events version 5.0 was used; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Delay in scheduled chemotherapy was defined as delay by more than or equal to 5 days due to toxicity or any other reason.

[b]Primarily due to improvement in ECOG PS.

[c]Primarily due to toxicity or worsening of ECOG PS.

TABLE A4. Details of Chemotherapy Toxicity

Toxicity	Olanzapine, n = 58, No. (%)	Placebo, n = 54, No. (%)
All grades		
Nausea, vomiting	14 (24)	23 (42)
Diarrhea	1 (2)	5 (9)
Constipation	2 (3)	3 (6)
Jaundice	2 (3)	—
Anemia	3 (5)	6 (11)
Thrombocytopenia	2 (3)	—
Fatigue	7 (12)	11 (20)
Hand-foot syndrome	0	2 (4)
Mucositis	2 (3)	1 (2)
Neuropathy	0	1 (2)
Headache	1 (2)	—
Palpitation	1 (2)	—
Febrile neutropenia	1 (2)	2 (6)
Others	1 (2)	1 (2)
Grade 3 or higher		
Nausea, vomiting	1 (2)	2 (4)
Anemia	2 (3)	5 (9)
Fatigue	2 (3)	6 (11)
Headache	1 (2)	—
Febrile neutropenia	1 (2)	1 (2)
Mucositis	—	1 (2)
Diarrhea	—	4 (8)
Hyperglycemia	—	1 (2)

TABLE A5. Change in SGA at 12 Weeks

SGA Change at 12 weeks	Olanzapine, n = 58, No. (%)	Placebo, n = 54, No. (%)
Improved		
B to A	14 (24)	3 (6)
C to B	9 (16)	2 (4)
C to A	2 (3)	—
Stable	32 (55)	40 (74)
Decrease		
A to B	—	2 (4)
A to C	—	—
B to C	1 (2)	7 (13)

Abbreviation: SGA, subjective global assessment.

TABLE A6. Intention-to-Treat Analysis

Variable	Olanzapine, n = 63, No. (%) Nonevaluable Patients, n = 5	Placebo, n = 61, No. (%) Nonevaluable Patients, n = 7	P[a]
Assumption: All nonevaluable patients (in both arms) did not achieve weight gain or improvement in appetite			
Weight gain >5%			
Yes	35 (56)	5 (8)	< .001
No	28 (44)	56 (92)	
FAACT A/CS (score > 37)[b]			
Yes	13 (21)	2 (3)	.0030
No	50 (79)	59 (97)	
Improvement in VAS[c]			
Yes	25 (40)	7 (12)	< .001
No	38 (60)	54 (88)	
Assumption: All nonevaluable patients (in both arms) achieved the primary end point (weight gain or improvement in appetite)			
Weight gain >5%			
Yes	40 (63)	12 (20)	<.001
No	23 (37)	49 (80)	
FAACT A/CS (score >37)[b]			
Yes	18 (29)	9 (15)	.062
No	45(71)	52 (85)	
Improvement in VAS[c]			
Yes	30 (48)	14 (23)	.0041
No	33 (52)	47 (77)	
Assumption: All the nonevaluable patients in the olanzapine group failed to achieve weight gain and improved appetite while all the nonevaluable patients in the placebo group achieved weight gain/appetite improvement			
Weight gain >5%			
Yes	35 (56)	12 (20)	<.001
No	28 (44)	49 (80)	
FAACT A/CS (score > 37)[b]			
Yes	13 (21)	9 (15)	.391
No	50 (79)	52 (85)	
Improvement in VAS[c]			
Yes	30 (48)	7 (12)	<.001
No	33 (52)	54 (88)	
Assumption: All nonevaluable patients in the olanzapine group achieved weight gain and improved appetite while all the nonevaluable patients in the placebo group failed to achieve weight gain/appetite improvement			
Weight gain >5%			
Yes	40 (63)	5 (8)	<.001
No	23 (37)	56 (92)	
FAACT A/CS (score > 37)[b]			
Yes	18 (29)	2 (3)	<.001
No	45 (71)	59 (97)	
Improvement in VAS[c]			
Yes	25 (40)	14 (23)	.044
No	38 (60)	47 (77)	

NOTE. All the randomly assigned patients were included in the denominator. Assumptions were made regarding the primary outcome measures for the nonevaluable patients as per 4 possible scenarios. For the evaluable patients, the outcome was assigned as per the assessment.

Abbreviations: FAACT A/CS, FAACT Anorexia Cachexia subscale; VAS, visual analog scale.

[a]Chi-square test except that the Fisher test was used whenever cell numbers were <5.

[b]The proportion of patients who achieved a score of >37 at 12 weeks were considered.

[c]Improvement in the VAS for assessment of appetite of >3 points from baseline was considered as yes.

TABLE A7. Change in Nutritional Parameters (continuous variables)

	Olanzapine, n = 58, Median (range)		Placebo, n = 54, Median (range)	
Parameter	**Baseline**	**End of Study**	**Baseline**	**End of Study**
Weight (kg)	53 (34-69)	56 (31-73)	53 (33-77)	51.5 (32-73)
BMI (kg/m^2)	20.7 (13-30)	21.6 (13.8-32.4)	20.6 (13.7-33.8)	20.1 (13.8-30.3)
QOL score[a]	113 (77-154)	132 (89-166)	115 (79-162)	112 (80-147)
FAACT A/CS	17 (4-28)	33.5 (11-48)	14 (7-37)	20 (7-39)
VAS[b]	4 (1-7)	6 (2-9)	4 (1-7)	3 (1-8)
Energy (cal%)[c]	52 (26-100)	75 (22-100)	54 (30-84)	60 (31-100)
Protein (g %)[c]	38 (12-71)	62 (15-100)	36 (16-72)	49 (23-84)

Abbreviations: cal, calories; CI QOL, Cancer Institute Quality of life score; FAACT A/CS, FAACT Anorexia Cachexia subscale; VAS, visual analog scale.
[a]CI-QOL assessment.
[b]VAS for assessment of appetite showing the actual score.
[c]The proportion of estimated daily requirements met on the basis of the 24-hour recall.