A Phase III Randomized, Double-blind, Placebo-controlled, Cross-over Study to Evaluate Olanzapine Combined with Fosaprepitant, Ondansetron, and Dexamethasone for Preventing Nausea and Vomiting in Patients with Testicular Cancer Receiving 5-day Cisplatin Combination Chemotherapy

Clinical study protocol

Scheme No.:

Solution version: 1.3

Version date: October 21, 2021.

Principal investigator: Yanxia Shi

Group leader: Sun Yat-Sen University Cancer Center

Principle Investigator

Signature page

I have read this test protocol (Version no. : 1.3, version date: October 21, 2021) and agree to carry out this test in accordance with the party protocol and relevant attached documents. I will provide the scheme to my research team and conduct relevant discussions with them to ensure that they fully understand the experiment. I may request termination of the study or discontinuation of inclusion at any time for certain pre-specified reasons. I may also stop the study because I need to protect the rights and interests of the subjects. I agree to conduct this trial strictly in accordance with all applicable and current regulations and clinical Trial Quality Management Practices (GCP).

At the same time, AS the main researcher of this experiment, I coordinated the overall process of the experiment.

Name:

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Signature:

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Date:

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Name of test Center:

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Abstract

Title	A Phase III Randomized, Double-blind, Placebo-controlled, Cross-over Study to Evaluate Olanzapine Combined with Fosaprepitant, Ondansetron, and Dexamethasone for Preventing Nausea and Vomiting in Patients with Testicular Cancer Receiving 5-day Cisplatin Combination Chemotherapy
Version number/date	Version 1.3/ 21 October 2021
Categories	Investigator-initiated clinical trial (IIT)
IIT initiator	Professor Shi Yanxia, Cancer Center, Sun Yat-Sen University
Indication	Germ cell tumor
Study population	Men diagnosed with germ cell tumor and treated with 5-day cisplatin (20mg/m2, total 100mg) based chemotherapy
Study design	Phase III Randomized, Double-blind, Placebo-controlled, Self-control, Cross-over Study
Sample size	A total of 75 patients were enrolled in two sequential treatment groups (olanzapine-placebo group and placebo-olanzapine group)
Chemotherapy	EP/BEP/VIP/TIP (cisplatin should be administered with the dose of 20mg/m2 IVD, D1-5, every 3 weeks
Experimental drug	Ondansetron: 8mg IV D1-5 30 minutes before chemotherapy; Dexamethasone: 6mg Po d1-7; Fosappitan: 150mg IVD D1, D4 60 minutes before chemotherapy; Olanzapine/Placebo: 5mg Po D1-7

Inclusion criteria	Patients must meet the following criteria for inclusion: 1) Pathology confirmed germ cell tumor (both spermatogonoma and non-spermatogonoma) and had no chemotherapy before; 2) Men; 3) Age ≥16 years old; 4) ECOG score of physical status 0-2; 5) Chemotherapy regimen containing 5-day cisplatin (20mg/m2, 100mg total; 6) No other nausea, vomiting, or use of any antiemetics within 72 hours prior to enrollment; 7) There are no clear brain metastases or other reasons for long-term systemic use of hormones; 8) The general condition is good, and the blood, liver and kidney functions meet the following standards: Hemoglobin: 90 g/L and above White blood cell count: 3.5 * 109 / L - 10.0 *109 / L Neutrophil count: 1.5* 109/L or above Platelet count: 90* 109/L or above Serum total bilirubin: below 1.5 times the upper limit of normal Serum AST, ALT and ALP: the upper limit of normal is below 2.5 times when the patient is present 9) Ability to read, understand and complete research questionnaires and journals, including visual analog scale (VAS); 10) Understand the study procedure and sign the informed consent in person to participate in the study

Exclusion criteria	Patients who meet any of the following criteria will be excluded: 1) Digestive tract obstruction, water and electrolyte disorder; 2) Have central nervous system diseases (such as primary brain tumors, uncontrolled seizures, any history of brain metastases or strokes); 3) Contraindications to the use of glucocorticoids: ① Viral, bacterial, fungal and other infections that cannot be controlled by antibiotics;② Active gastric or duodenal ulcer;③ Severe hypertension, arteriosclerosis, diabetes; ④ Osteoporosis;⑤ Corneal ulcer;⑥Trauma or surgical repair period, fracture; ⑦Adeno-cortical hyperfunction; ⑧Severe mental illness and epilepsy; ⑨ patients with cardiac or renal dysfunction; 4) Patients with mental disabilities or severe emotional or mental disorders are considered unsuitable for inclusion in the study; 5) In addition to malignancy, the patient has an active infection (e.g. pneumonia, hepatitis) or any uncontrolled infection diseases (such as diabetic ketoacidosis), and the researchers believe may contribute to the study's findings confounding, or exposing patients receiving study drugs to unnecessary risks; 6) The patient is currently using any prohibited drugs, including medicinal marijuana or is currently using alcohol (Chinese Diagnostic criteria for drug dependence); 7) The patient received an unapproved (experimental) drug treatment within the past 4 weeks; 8) Taking oral olanzapine or other psychotropic drugs; 9) A history of hypersensitivity to fosaprepitant, 5-HT3 receptor antagonists or dexamethasone; 10) The patient cannot swallow the drugs; 11) The principal investigator considered the patients unsuitable for the study; 12) Inability or unwillingness to adhere to research

	protocols
Dose adjustment	See the protocol below for details.
Eliminate drugs	Drugs to be excluded during treatment and observation: phenytoin or carbamazepine, barbiturates, rifampicin or rifambutin, hypericum perforatum, terfenadine, cisapride, amifostine, pimozide, astimidazole, clarithromycin (note: azithromycin, erythromycin and roxithromycin are permitted), ketoconazole or itraconazole (fluconazole is permitted), antiretroviral protease inhibitors; Phenol thiazine drugs (e.g. prochlorazine), phenylbutanone (e.g. haloperidol), olanzapine; Psychotropic drugs, benzamide (e.g. Metoclopramide), domperidone, cannabinol; Herbs with potential antiemetic effects, scopolamine, etc. If the patient develops nausea or vomiting, remedial treatment is permitted with clinically recommended antiemetics.
Outcome Measures	Primary Outcome Complete response (no vomiting and no rescue) rate for the overall phase (1 to 10 days) Secondary Outcomes (1) Minimal nausea, <25 mm on a visual analog scale (VAS) for acute phase ((1-5 days) and delayed phase (6-10 days), and overall phase (1-10 days); (2) Complete response rate for acute and delayed phases; (3) Total control (TC): no vomiting, no rescue antiemetics,

	and no nausea) for acute, delayed, and overall phases; (4) Incidence and severity of nausea were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE); (5) Number of rescue medications; (6) Time to Treatment Failure: time to 1st emetic episode or use of rescue medication; (7) Hospital Anxiety and Depression Scale (HADS), and The Functional Living Index-Emesis (FLIE) questionnaire
Adverse events	The primary endpoint events (vomiting, retching, and nausea) that occurred during the log data collection period (day 1 to morning 11) were not defined as adverse events unless the definition of a severe adverse event was met. Adverse events were graded and recorded according to CTCAE (Version 4.0).
Main Procedure	(1) The screening process begins after the patient signs the written informed consent; (2) The study is characterized by randomized, cross-over, self-control design. For each patient who were randomly divided into experimental group (olanzapine group) or control group (placebo) will cross over the other group in the second cycle of chemotherapy; (3) Patients filled in self-reported diaries and completed visual analogue scales for nausea, as well as HADS and FLIE questionnaires; (4) During the study period, patients may receive "remedial treatment" for nausea or vomiting, and patients requiring remedial treatment are considered to have failed treatment. Patients receiving remedial treatment must continue to receive the study drug and complete the log as directed.
Sample size calculation and statistical analysis	Sample size calculation: The required sample size was calculated to be 75 patients per arm for the study to have a power of 80%, assuming that the CR rate will be 75% in the olanzapine group and 50% in the placebo group, and also assuming a two-sided significance level of 0.05 and 10% ineligible cases. Due to the cross-over, self-control design, the final sample size was 75. Point estimates and confidence intervals for the CR rate will

	be calculated and will be compared between groups by using the Mantel-Haenszel test with adjustment for allocation factors.

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1. Background

Although testicular cancer is rare, accounting for only 1 % of all cancers in males, it is the most common solid tumor among young men in the 20–39 years old. Since the introduction of cisplatin-based chemotherapy in the 1970s, the prognosis of patients with testicular cancer has been dramatically improved, with a 10-year relative survival approaching 95%. However, treatment-related complications, including acute and long-term toxicities remain unsolved.

Cisplatin is a chemotherapy agent with the highest emetic. The risk of emetic is more than 90% when the daily dose of cisplatin is ≥50mg/m^2. While the standard dose of cisplatin is as high as 100mg/m2 in five consecutive days for testicular cancer. Early data showed that patients with germ cell tumor who received multi-day cisplatin chemotherapy experienced vomiting for more than 10 times on the first day and lasted for several days [2]. Severe nausea and vomiting could reduce dietary intake, cause or aggravate other toxicities, such as fatigue, neutropenia, anemia, and finally might interfere with implementation of chemotherapy and anti-tumor efficacy. Therefore, chemotherapy-induced nausea and vomiting (CINV) is one of the most feared side effects experienced by patients with testicular cancer.

The mechanism of CINV has been elucidated in the past decades. The vomiting center is pathological located in the side of the medulla oblongata reticular structure, which directly controls the occurrence of vomiting. Chemotherapeutic drugs can induce the release of a variety of neurotransmitters which bind of their receptors and play an important role in the formation of vomiting. The neurotransmitters associated with CINV include 5-hydroxytryptamine (5-HT), substance P/neurokinin -1 (NK-1), cannabinoid, dopamine, acetylcholine, and histamine. According to the time of vomiting, CINV can be divided into three categories [2-3]: ① Acute nausea and vomiting: nausea and vomiting occurring within 24 hours after chemotherapy. This type of nausea and vomiting is often severe and is mediated by serotonin 3 (5-HT3). In addition, the binding of substance P to its specific receptor NK-1 also plays an important role in acute vomiting. ② Delayed nausea and vomiting: nausea and vomiting 24 hours after the administration of chemotherapy drugs, sometimes lasting for 5-7 days. Delayed CINV may be mediated by various mechanisms, and the main transmitter is substance P.③ Anticipatory nausea and vomiting: caused by conditioned reflex. It occurs when patients see chemotherapy drugs or other things related

to chemotherapy. Anticipatory nausea and vomiting is mainly related to spiritual and psychological factors, and caused by poor control of acute nausea and vomiting.

Prophylactic medication is the key to control CINV. At present, there are three kinds of drugs widely used in clinical practice: ① 5-HT3 receptor antagonists, which specifically block the binding of 5-HT3 and its receptor, mainly controlling acute nausea and vomiting.② NK-1 receptor antagonist, blocking the binding of substance P to its receptor, has an inhibitory effect both on acute and delayed nausea and vomiting.③ The antiemetic mechanism of dexamethasone is still unknown, but its efficacy in the prevention of acute and delayed vomiting has been widely confirmed, and it has been used as a basic drug for the prevention of CINV. A number of large phase 3 randomized controlled studies and meta-analyses have confirmed that the combined use of 5-HT3 receptor antagonist, NK-1 receptor antagonist and dexamethasone could significantly reduce the occurrence of CINV induced by highly emetogenic chemotherapeutic drugs represented by single-day high dose cisplatin, with the control rate of vomiting is approaching 90%[3, 4].Therefore, this three-drug combination regimen has been recommended by several international and domestic guidelines such as NCCN/ESMO/ MASCC /CSCO for the prevention of highly emetogenic chemotherapeutic drug-associated CINV. For patients undergoing multiple days of highly emetogenic chemotherapy, current guidelines still recommend the use of the triple prophylaxis regimen based on the results of single-day chemotherapy studies. However, this recommendation is not supported by sufficient evidence-based medical evidence. A few small phase II studies have been conducted on CINV associated with multi-day hyperemetogenic chemotherapy. The only one small sample-sized phase III trial demonstrated the efficacy of the triplet combination of NK 1 receptor antagonist,5-HT3 antagonists, and dexamethasone in testicular cancer patients who were treated with 5-day cisplatin combination chemotherapy. Among 71 patients enrolled, 69 could be evaluated. The complete remission rate of vomiting was 42% for patients treated with the triple antiemetic regimen, compared with 13% for patients treated with two drugs combination of 5-HT3 antagonists and dexamethasone [5]. Even if, 42% of overall vomiting control rate is significantly lower than 90% in patients receiving single-day chemotherapy. Moreover, prevention of nausea was extremely poor, and the overall control rate in was only about 25% even for patients treated with the triplet combination [5-7]. Finding a more effective regimen to prevent or reduce CINV for testicular cancer patients receiving 5-day cisplatin combination chemotherapy is urgently needed.

At present, several NK-1 receptor antagonists have been successfully developed and approved for marketing. Aprepitant, the first oral NK1 receptor blocker approved for clinical use, was launched in the United States in March 2003 and entered the Chinese market in September 2013.Forsapitan is the prodrug of aprepitan. In humans, fosaprepitant can be rapidly converted to aprepitan within 30 minutes after the end of intravenous administration of fosaprepitant, so its clinical efficacy is mainly attributed to aprepitan. A randomized, parallel, double-blind, positive-controlled trial demonstrated that fosaprepitant 0.15g intravenously (n=1147) had similar efficacy with aprepitan capsules 3 days orally (n=1175) in patients receiving cisplatin ≥70mg/m2. Fosaprepitant was well tolerated [8]. The most commonly reported adverse reactions in clinical studies included headache and injection site symptoms.

Olanzapine is the second generation of atypical neuroleptics, which is mainly used in the treatment of schizophrenia. Olanzapine antagonizes various vomit-related neurotransmitter receptors, such as dopamine receptor, 5-HT2 receptor, and histamine receptor, and has significant nausea and vomiting prevention effect. Accumulating evidences support the efficacy of olanzapine for prophylaxis of CINV for highly emetogenic chemotherapy. However, most studies focus on solid malignancies and single-day regimens. Moreover, the standard dose of olanzapine (10 mg qd) is associated with high risk of sedation, drowsiness, and fatigue. Subsequent studies showed that lowering olanzapine dose to 5mg per day had similar prophylactic effects on nausea and vomiting compared with 10mg, and significantly reduced the incidence of excessive sedation and drowsiness [9]. Therefore, many researchers suggest that 5mg of olanzapine per day may be a more predictive dose for nausea and vomiting. To improve antiemetic therapies for testicular patients receiving 5-day cisplatin chemotherapy, the current study aims to explore the efficacy and safety of low-dose olanzapine combined with nK-1 receptor antagonist (Fosaprepitant), 5-HT3 receptor antagonist (ondansetron) and dexamethasone quadruplex antiemetics regimen.

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2. Purpose

To investigate the efficacy and safety of low dose of olanzapine in combination with fosaprepitant, ondansetron, and dexamethasone compared with placebo in combination with fosaprepitant, ondansetron, and dexamethasone in the prevention of nausea and vomiting in patients with testicular cancer receiving 5-day cisplatin chemotherapy

2.1 Primary Outcome

Complete response (no vomiting and no rescue) rate for the overall phase (1 to 10 days)

2.2 Secondary Outcomes

(1) Minimal nausea, <25 mm on a visual analog scale (VAS) for acute phase ((1-5 days) and delayed phase (6-10 days), and overall phase (1-10 days);
(2) Complete response rate for acute and delayed phases;
(3) Total control (TC): no vomiting, no rescue antiemetics, and no nausea) for acute, delayed, and overall phases;
(4) Incidence and severity of nausea were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE);
(5) Number of rescue medications;
(6) Time to Treatment Failure: time to 1st emetic episode or use of rescue medication;
(7) Hospital Anxiety and Depression Scale (HADS), and The Functional Living Index-Emesis (FLIE) questionnaire

3. Study the population

Men diagnosed with germ cell tumor and treated with 5-day cisplatin (20mg/m2, total 100mg) based chemotherapy

3.1 Inclusion Criteria

Patients must meet the following criteria for inclusion:

1) Pathology confirmed germ cell tumor (both spermatogonoma and non-spermatogonoma) and had no chemotherapy before;
2) Men;

3) Age ≥16 years old;
4) ECOG score of physical status 0-2;
5) Chemotherapy regimen containing 5-day cisplatin (20mg/m2, 100mg total;
6) No other nausea, vomiting, or use of any antiemetics within 72 hours prior to enrollment;
7) There are no clear brain metastases or other reasons for long-term systemic use of hormones;
8) The general condition is good, and the blood, liver and kidney functions meet the following standards:
   Hemoglobin: 90 g/L and above
   White blood cell count: 3.5 * 109 / L - 10.0 *109 / L
   Neutrophil count: 1.5* 109/L or above
   Platelet count: 90* 109/L or above
   Serum total bilirubin: below 1.5 times the upper limit of normal
   Serum AST, ALT and ALP: the upper limit of normal is below 2.5 times when the patient is present
9) Ability to read, understand and complete research questionnaires and journals, including visual analog scale (VAS);
10) Understand the study procedure and sign the informed consent in person to participate in the study

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded:

1) Digestive tract obstruction, water and electrolyte disorder;
2) Have central nervous system diseases (such as primary brain tumors, uncontrolled seizures, any history of brain metastases or strokes);
3) Contraindications to the use of glucocorticoids: ① Viral, bacterial, fungal and other infections that cannot be controlled by antibiotics;② Active gastric or duodenal ulcer;③ Severe hypertension, arteriosclerosis, diabetes; ④ Osteoporosis;⑤ Corneal ulcer;⑥Trauma or surgical repair period, fracture; ⑦Adeno-cortical hyperfunction; ⑧Severe mental illness and epilepsy; ⑨ patients with cardiac or renal dysfunction;
4) Patients with mental disabilities or severe emotional or mental disorders are considered unsuitable for inclusion in the study;
5) In addition to malignancy, the patient has an active infection (e.g. pneumonia, hepatitis) or any uncontrolled infection diseases (such as diabetic ketoacidosis), and the researchers believe may contribute to the study's findings confounding, or exposing patients receiving study drugs to unnecessary risks;

6) The patient is currently using any prohibited drugs, including medicinal marijuana or is currently using alcohol (Chinese Diagnostic criteria for drug dependence);
7) The patient received an unapproved (experimental) drug treatment within the past 4 weeks;
8) Taking oral olanzapine or other psychotropic drugs;
9) A history of hypersensitivity to fosaprepitant, 5-HT3 receptor antagonists or dexamethasone;
10) The patient cannot swallow the drugs;
11) The principal investigator considered the patients unsuitable for the study;
12) Inability or unwillingness to adhere to research protocols

4. Study design

Phase III Randomized, Double-blind, Placebo-controlled, Self-control, Cross-over Study

4.1 sample size calculation

The required sample size was calculated to be 75 patients per arm for the study to have a power of 80%, assuming that the CR rate will be 75% in the olanzapine group and 50% in the placebo group, and also assuming a two-sided significance level of 0.05 and 10% ineligible cases. Due to the cross-over, self-control design, the final sample size was 75.

4.2 Double-blind random design

The trial was designed in a double-blind fashion.

that is, at the beginning of randomization, the true status of the treatment will remain blind to the subjects, the investigator, the data analyst, the sponsor, and all medical personnel involved in the treatment or clinical evaluation. Olanzapine tablets and placebo tablet simulators used by patients will use identical packaging, administration method, label, appearance, taste and smell to hide the true situation of therapeutic drugs. After unified packaging, drug numbers will be given uniformly. The blind is kept with the randomizer.

Participants were randomized to treatment order (Olanzapine or placebo first). Randomization was performed by an independent researcher. For each participant, treatment conditions were assigned and sealed in opaque envelopes (O for Olanzapine first and P for placebo first) and provided to the dispensing pharmacist. Participant codes were allocated sequentially as participants enrolled, and treatments were prepared and allocated by a pharmacist not affiliated with the study. The pharmacist

preparing the treatments did not interact with the researchers or participants, and treatments were collected by the research assistants. Participants, physicians and study researchers were blinded to medication allocation. Unblinding of treatment occurred after the final participant evaluation. Data were coded by one researcher to indicate which treatment was received first, and those data screened for outliers and missing data. Data were analyzed by a separate researcher blinded to treatment allocation.

5. Research program

5.1 Steps and process

(1) The screening process begins after the patient signs the written informed consent

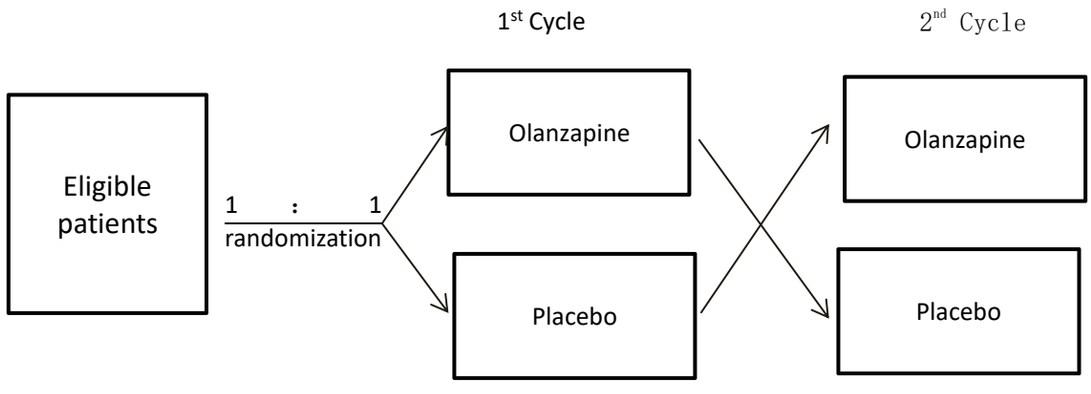
(2) Patients were randomly divided into different treatment order groups (Olanzapine or placebo first)

(3) 2 to 10 days after chemotherapy, log by patients to patients from the beginning chemotherapy drug infusion 0 hours (1 day) to 10 days (240 hours) to monitor the effectiveness of, should be in the log report within 24 hours before the onset of vomiting, use of salvage therapy and a review of daily nausea, should also be recorded Any vomiting or vomiturition attack, as well as the use of rescue drug time and date. At days 2 to 6, the visual analog scale (VAS) was used to record the assessment of nausea in the previous 24 hours.

(4) Patients filled in self-reported diaries and completed visual analogue scales for nausea 2 to 10 days after chemotherapy, as well as Hospital Anxiety and Depression Scale (HADS) and Functional Living Index-Emesis (FLIE) questionnaires of 1 to 10 days on day 11.

(5) Patients may receive "remedial treatment" for nausea or vomiting during the study period, and those requiring remedial treatment are considered to have failed because the primary endpoint is complete remission. However, patients receiving remedial treatment must continue to receive the study drug and complete the log as directed

5.2 the flow chart



5.3 Administration schedule

Chemotherapy regimens

EP regimen

Cisplatin: 20mg/m ^{2}ivd, D1-5

Etoposide: 100mg/m^2 D1-5

BEP regimen

Cisplatin: 20mg/m ^{2}ivd, D1-5

Etoposide: 100mg/m^2 D1-5

Bleomycin：30,000 U IV D1,D3,D5

VIP regimen

Cisplatin: 20mg/m ^{2}ivd, D1-5

Etoposide: 75mg/m^2 D1-5

Ifosfamide：1.2g/m^2 D1-5

Mesna：60% total amount of Ifosfamide, divided into 3 points after 0,3, 6 hours IV

TIP regimen

Cisplatin: 20mg/m ^{2}ivd, D1-5

Etoposide: 75mg/m^2 D1-5

Paclitaxel/Nab-paclitaxel：200-250mg/m^2 D1

Mesna：60% total amount of Ifosfamide, divided into 3 points after 0,3, 6 hours IV

Preventive antiemetic program

Eligible patients will be randomized to receive prophylactic antiemetic therapy with olanzapine or placebo combined with a triplet regimen of of NK 1 receptor antagonist,5-HT3 antagonists, and dexamethasone as follows:

Ondansetron: 8mg IV D1-5 30 minutes before chemotherapy;

Dexamethasone: 6mg Po d1-7;

Fosaprepitant: 150mg IVD D1, D4 60 minutes before chemotherapy;

Olanzapine/Placebo: 5mg Po D1-7

6. Exclude medication

Drugs eliminated to use during treatment and observation include: phenytoin and carbamazepine, barbiturate drugs, rifampicin, hypericum perforatum, hypericum perforatum，fexofenadine，cisapride，amifostine, Pimozide, astemizole,

clarithromycin (note: allows the use of azithromycin and erythromycin and Roxithromycin), Ketoconazoleor itraconazole (allows the use of fluconazole), Nucleoside Reverse Transcriptase Inhibitors， Phenolthiazide (e.g. prochlorazine), phenylbutanone (e.g. haloperidol), olanzapine psychotropic drugs, benzamide (e.g. metoclopramide), domperidone, cannabinol, herbs with potential antiemetic effects, scopolamine, etc. However, if the patient develops nausea or vomiting and requires "remedial treatment, clinically recommended antiemetics may be used.

7. Efficacy evaluation

7.1 Effectiveness evaluation indicators

Efficacy parameters included the number of vomiting episodes, daily assessment of nausea symptoms, and use of remedial therapy recorded in patients' diary from the beginning of chemotherapy (0 h on day 1) to day 10 (approximately 240 h) after chemotherapy.

FLIE questionnaires were recorded on day 11.

The primary time frame was 10 days after initiation of chemotherapy infusion, include: overall CINV (day1-10), acute CINV (day 1 to 5), and delayed CINV(day 6 to 10).

7.2 Safety evaluation indicators

Adverse events: Events associated with the primary end point (vomiting, retching, and nausea) during the data collection period from day 1 to the morning of day 11 were not defined as adverse events unless the definition of a severe adverse event was met. Adverse events were graded and recorded according to CTCAE (Version 4.0).

8. Screening and baseline visits

Patients signed written informed consent before screening. Any procedure such as tumor assessment out of screening window, if researchers believe is reasonable and acceptable, this procedure may not be repeated. The data of qualified patients can only be filled in the CRF table according to the inclusion criteria. All patients who have signed written informed consent will be screened from 28 days to 24 hours prior to the start of study treatment. Including the following:

- 28 ~ 1 days

Signed written informed consent: Date

Demographic characteristics: age, sex

History: including gastrointestinal disease, hypertension, thromboembolic disease, cardiovascular disease, kidney disease, other major diseases, alcohol intake;

Cancer and treatment history: time of first visit; Primary diagnosis of germ cell tumor (date, pathological subtype, TNM stage); Previous treatment (surgical excision of the primary tumor); Previous chemotherapy (regimen, type [adjuvant, neoadjuvant], time, course of treatment, dose).

Drug combination: medications that may be related to the occurrence of an adverse event or related to the management of an adverse event need to be recorded.

Physical examination: A complete physical examination should include head, eyes, ears, nose, throat, cardiovascular, skin, musculoskeletal, respiratory, digestive, genitourine-urinary and nervous systems; Abnormalities observed at baseline should be recorded in the CRF table in the corresponding section of the general history and baseline conditions; A local, symptom-oriented physical examination should be performed during subsequent visits; Abnormal signs that change from baseline should be recorded in the patient notes; New or malignant abnormalities should be recorded as adverse events in the adverse event related section of the CRF table

Height and weight

ECOG score

Whole-body imaging (when clinically indicated)

ECG

-7 ~ 1 day

Laboratory tests (date, value): blood routine, biochemical, tumor markers.

Patients with fertility requirements should have sperm cryopreservation before chemotherapy.

9. Evaluation during the study

9.1 Assessment of acute vomiting:

The time and date of any episodes of vomiting or retching or use of rescue drugs in the previous 24 hours were recorded in the patient's diary on day 2 from the beginning of chemotherapy at 0h on day 1 to 120h after chemotherapy (day 5).

The visual analog scale (VAS) was used to record the nausea assessment in the previous 24 hours.

Adverse events were graded and recorded according to CTCAE (Version 4.0), and patients experience serious nausea or vomiting can receive remedial treatment. Patients requiring remedial therapy were considered to have failed treatment. However, patients receiving remedial treatment must continue to receive the study drug and complete the log as directed.

9.2 Follow-up evaluation of delayed vomiting

Patients were contacted after chemotherapy (day 6 to 10) and reminded to record vomiting or retching events in the previous 24 hours, remedial treatment, and daily assessment of nausea using VAS in the patients' diary. Patients were required to complete HADS and FLIE questionnaires immediately after logging on day 11.During the study period, adverse events were graded and recorded according to CTCAE (Version 4.03), and patients received "remedial treatment" for nausea or vomiting. Patients requiring remedial therapy were considered to have failed treatment. However, patients receiving remedial treatment must continue to receive the study drug and complete the log as directed.

10. Termination and exit criteria

The investigator reserves the right to discontinue or withdraw patients from the study at any time. In addition, patients have the right to withdraw from the study at any time and for any reason. Reasons for discontinuing the study drug or withdrawing from the study may include, but are not limited to, the following:

The patient withdraws informed consent at any time.

The researchers determined that there was a medical event that could endanger patient safety if the study continued. The researchers say early withdrawal from the study would be of greatest benefit to patients.

Patients did not comply with the study protocol.

Every effort should be made to obtain information on patients dropping out of the study. The main reasons for withdrawal from the study should be recorded in the CRF table. Patients should not be followed up for any reason after informed consent is withdrawn. Patients who drop out of the study should not be replaced by other patients.

11. Statistical analysis

The primary and secondary endpoints of the study were provided in a descriptive and exploratory manner data.

11.1 Study Population

The intentional-to-treat group (ITT) is a set of subjects based on the principle of intentionality analysis, which shall mainly include all subjects randomized to be treated

on the basis of randomization and shall be the primary population used for effectiveness analysis.

The eligible population (PP) will include all patients who are randomized to receive the study drug at least once and who strictly follow the study protocol. The reporting analysis plan excluded patients with severe protocol violations from the PP population. The PP population provided only a supportive analysis of clinical effectiveness. PP population analysis is not necessary if PP population reaches 95% or more of ITT population.

The safety cohort (SS) will include all patients enrolled in the randomization who received the study drug at least once, and if the randomization cohort is inconsistent with the cohort actually receiving treatment, the safety cohort will be based on the cohort actually receiving treatment.

11.2 Statistical Analysis

The statistical description and statistical test were determined according to the properties of the analysis indicators, and the number of cases and incidence of classification variables were analyzed by the list of classification variables. X2 test, Fisher's exact probability method or contingency table data statistical analysis were used for the comparison of classification variables between the two groups. Kaplan-meier method was used to calculate the time until the first vomiting and curve was drawn.

For the security data statistical analysis plan, all security parameters are described in the form of tables and summary tables. Adverse events and laboratory parameters were assessed according to the National Cancer Institute Standard Classification System for Commonly Used Terminology for Adverse Events (NCI CTC) (V4.03). The safety data analyzed included the incidence of all reported adverse events and serious adverse events (regardless of their relevance) and the incidence of all surgery-related adverse events.

11.3 Processing of exit or missing data

In this study, we expected two types of missing data. The first category is "complete absence"; That is, the patient did not receive any post-treatment evaluation. Post-treatment was defined as receiving cisplatin on day 1.This may occur in patients who dropped out of the study early (due to adverse events or lack of efficacy or for other reasons).The second category is "partial absence", that is, the patient had a post-treatment evaluation, but data were missing for several days. In the main analysis, category 1 missing data were treated as non-evaluable cases in the full set of analyses. For the missing data of category 2, the "forward method" is used to fill in the missing data in each period.

11.4 Analysis Plan

The analysis was planned after the last patient completed study treatment and observation, and the main analysis parameters were primary end points and secondary end points.

12. Adverse event reporting and recording

12.1 Definition

Adverse Event (AE): The term adverse event covers the appearance or worsening of any syndrome, symptom, syndrome, or disease that occurs during the observation period of a clinical study and affects the health of the subject. The term also includes clinically relevant conditions discovered during laboratory or other diagnostic procedures, such as the need for unplanned treatment, or lead to withdrawal from the trial. Adverse events may be new disease, treatment status, worsening of symptoms or signs, or accompanying disease progression, the role of control drugs, or combination of one or more factors unrelated to participation in a trial. So the term "adverse event" does not imply a causal relationship with the experimental drug.

The protocol stipulates that any unexpected medical event that occurs outside the follow-up period is not an adverse event.

Pre-existing diseases, symptoms (such as cancer or other diseases) or medically significant abnormalities confirmed by laboratory tests or instruments (such as electrocardiograms) should not be considered as adverse events. However, the emergence of new symptoms and exacerbations of pre-existing conditions should be considered as adverse events. In addition, if an emerging abnormality confirmed by laboratory tests or instrumentation has clinical implications for the patient, it may reduce the use of the investigational drug.

It should be considered an adverse event if the dose, delay treatment or discontinue treatment, or cause a serious adverse event (SAE) as defined below.

Serious adverse event (SAE): an adverse event occurring at any dose of the experimental drug or at any time during observation:

A) Resulting in death;
B) Immediate life-threatening, that is, in the investigator's opinion, the occurrence of an event that poses a risk of death to the patient (excluding an event in which a hypothetical exacerbation of the illness would result in death);
C) Requiring hospitalization or prolonged hospitalization;

D) Disability refers to an event clinically determined to result in permanent or severe disability/disability. Disability refers to a person's apparent loss of ability to live a normal life;
E) Birth defects (defects in the child after birth due to the use of medical products before fertilization or during pregnancy;
F) Medically significant (meaning an event that does not immediately endanger life or cause death or require hospitalization, but may endanger patients or require measures to prevent one of the consequences defined above); Medical treatment is required to prevent permanent loss or damage. Such events include allergic bronchospasm that requires emergency room or home care, hemodystrophy or convulsions that do not require hospitalization.

12.2 Expected range of adverse events

Common adverse reactions:

Digestive system: anorexia, hiccups, constipation, diarrhea, nausea and vomiting, duodenal ulcer perforation, etc. Nervous system: muscle weakness, disorientation, anxiety, etc.

Skin: rash, Stevens-Johnson syndrome, etc.

Others: such as flushed face, weakness, fatigue, upper respiratory tract infection, tachycardia, pelvic pain, bone pain, myalgia, hypokalemia, bradycardia, etc.

12.3 Indicators related to the judgment of causality between adverse events and drugs

The related indexes for judging the causal relationship between adverse events and drugs: ① Whether there is a reasonable sequential relationship between the start time of medication and the occurrence time of suspected adverse reactions.② Whether the suspected adverse reactions are consistent with the known adverse reaction types of the drug.② Whether the suspected adverse reactions can be explained by the patient's pathological status, drug combination, combined therapy, and previous therapy.④ Stop the drug or reduce the dosage, whether the suspected adverse reactions can be alleviated and disappear.⑤ Whether the same reaction occurs again after exposure to the same drug.

Judgment of causality between adverse events and drugs: According to the above five indicators, the analysis of causality is positive, probable, possible, suspicious and unlikely (level 5.)

1. Definitely relevant	Events follow a reasonable chronological sequence from the time of administration. The event resolved when treatment was discontinued. Adverse events (AE) have been shown to recur with repeated administration (re-excitation).
2. Probably related	Events occurred in a reasonable chronological sequence from the time the experimental drug was administered. The event resolved when treatment was discontinued. The event cannot reasonably be interpreted as a known symptom of the patient's clinical state or as an event triggered by another drug/treatment.
3. It may be relevant	Events occurred in a reasonable chronological sequence from the time the experimental drug was administered. The event was consistent with a known response to the investigational drug, but could have been caused by the patient's clinical status or other drug/treatment.
4. Probably not	Events did not follow a reasonable chronological sequence from the time the experimental drug was administered. Events may be caused by documented pre-existing conditions, concomitant treatment, or the patient's clinical status.
5. Definitely not	The event must be caused by the patient's clinical status or other medications/treatments.

12.4 Management of adverse events

12.4.1 Record of adverse events

Adverse events

Researchers should explain and require patients to truthfully report the changes in their condition after medication. Doctors should avoid leading questions. Any adverse events that occur during the study, including abnormal laboratory tests, must be carefully questioned and followed up. All adverse events must be determined in terms of their nature, severity and relevance to the drug. Investigators should follow up to observe and record the outcome of all adverse events, and follow up patients who dropped out of the trial due to adverse events until the adverse events were resolved. For each event, the following information is recorded in the Adverse Events (AE) section of the Case Report Form (CRF):

Severity: Adverse events are classified as major adverse events or non-major adverse events.

AE: Whenever possible, the specific diagnosis of the event should be recorded. If diagnosis is not possible, record each sign or symptom separately, e.g., nausea and vomiting as two adverse events. If an event occurs more than once, and there is an appropriate time interval to indicate symptoms that could be considered for recurrence, each adverse event should be recorded separately on the case report form.

Start date: Records the start date of the event. If an abnormal change in laboratory tests is reported as an adverse event (AE), the date of collection of the first laboratory sample indicating a change in the condition is recorded as the start date of the event. The commencement date of a serious adverse event was defined as the date on which the event began to meet the criteria for a serious adverse event.

End Date: Record the end date of the event. If abnormal changes in laboratory tests are reported as an adverse event, the date of collection of the first sample after the event, on which the test would indicate a return to the pre-event state or a return to normal levels, is recorded as the event stop date.
Relationship with the experimental drug

Therapeutic intervention: Record any therapeutic intervention necessary in the concomitant care section of the CASE Report Form (CRF) and indicate whether it is pharmacological or non-pharmacological.

Outcomes:

(1) Event remission without sequelae -- the patient recovers from an adverse event without observing any sequelae.

(2) Event remission with sequelae -- patients recovered from the adverse event, but with some sequelae (described in the AE section of CRF)

(3) The event is not alleviated -- the event still exists. Patients should be followed until definitive results are available. Follow-up information was recorded in the AE section of the CRF when follow-up data were collected. If the incident is serious, fill out the follow-up SAE report.)

(4) Death -- The patient died of adverse events. (List the main causes of death in the AE section of the case report form and, if feasible, attach an autopsy report to the case report form)

Actions taken in relation to the test drug:

(1) None -- No actions taken in relation to the test drug.

(2) Discontinuation/adjustment -- suspend the trial drug and resume it when the patient's symptoms are relieved.

(3) Discontinue -- permanently discontinue the use of the investigational drug.

12.4.2 Report of serious adverse events

Serious adverse event (SAE) should be actively treated or rescued, and should be notified by telephone/fax within 24 hours, and fill out a report on the "serious adverse events," a book Geared to the needs of the local pharmaceutical supervisory and administrative department, the state drug administration at the provincial level, clinical research and ethics committee report. The sponsor and its client CRO will immediately inform the participating hospitals and ensure that all legal and regulatory requirements of the reporting procedures are met.

Organization	Contact	Phone
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Drug Clinical Trial Ethics Committee, Cancer Center, Sun Yat-sen University		+862087343565

State Food and Drug Administration	Drug Research and Supervision Department, Safety Supervision Department	（010）68313344-1013

Contact information for serious adverse event reporting is as follows:

When a death occurs, the investigator should write a comprehensive description of the death on the SAE form, and Keep an SAE report at the base with CRF. If an autopsy is performed, the investigator should voluntarily obtain a copy of the autopsy report and keep a copy of the autopsy report at the site with the CRF.