

Study Protocol Cover Page

Study Protocol

Official Title:

A Single-Arm, Phase II Prospective Study of Papaverine for Refractory
Paclitaxel-Induced Peripheral Neuropathy

NCT Number:

NCT _____

Document Date:

December 8, 2025

Document Type:

Study Protocol

Version:

Version 1.0

Sponsor/Institution:

the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School
of Medicine

Principal Investigator:

Yinuo Tan

1. Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose-limiting adverse effect of anticancer therapy. Approximately 50% to 90% of patients receiving chemotherapy may develop CIPN, and 30% to 40% may progress to chronic neuropathy. Paclitaxel-related CIPN is particularly common and often persistent, with symptoms including numbness, tingling, burning pain, sensory loss, weakness, and impaired daily functioning. In some patients, symptoms may last for months or even years after completion of chemotherapy.

The pathogenesis of CIPN is not fully understood and is believed to be multifactorial. Proposed mechanisms include injury to dorsal root ganglia and peripheral axons, inflammatory cytokine release, altered neuronal excitability, ion channel dysfunction, microtubule disruption, impaired axonal transport, mitochondrial dysfunction, oxidative stress, immune dysregulation, neuroinflammation, and axonal degeneration. Individual risk factors may include diabetes mellitus, hypothyroidism, renal dysfunction, vitamin deficiency, anemia, advanced age, obesity, alcohol abuse, smoking, fatigue, anxiety, depression, and pre-existing neuropathy. Treatment-related factors such as drug class, cumulative dose, duration of exposure, and concomitant medications also contribute to the risk of CIPN.

Taxane agents are widely used in the treatment of breast cancer, ovarian cancer, lung cancer, and other solid tumors. Paclitaxel-induced CIPN is characterized by a high incidence, dose dependence, predominantly sensory symptoms, and prolonged duration. At present, there is no well-established preventive therapy supported by strong evidence. Duloxetine is the only drug currently recommended by major oncology guidelines for painful CIPN, but its efficacy is limited and its adverse effects, including nausea, somnolence, and dry mouth, restrict its use in some patients. Other drugs such as gabapentin, pregabalin, B vitamins, and mecobalamin have been explored, but convincing evidence remains insufficient. Therefore, there is a substantial unmet need in patients with refractory CIPN who do not respond to standard therapies.

Papaverine is a non-specific vasodilator and smooth muscle relaxant that may improve microcirculatory blood flow in peripheral tissues. One possible mechanism of CIPN involves endoneurial ischemia and hypoxia. By dilating microvessels that supply peripheral nerves, papaverine may enhance blood and oxygen delivery to nerve tissue, promote clearance of toxic metabolites, and facilitate nerve recovery. Preliminary clinical observations by the investigators suggest that papaverine injection may rapidly improve numbness and weakness in some patients with refractory CIPN as early as the day after administration. This phase II exploratory study is designed to preliminarily evaluate the efficacy and safety of papaverine in this patient population and to provide a basis for future confirmatory studies.

2. Study Objectives

Primary Objective

To evaluate the preliminary efficacy of papaverine hydrochloride injection in patients with refractory paclitaxel-induced CIPN, based on changes in patient-reported neuropathy symptoms.

Secondary Objectives

- To evaluate the effects of papaverine on neuropathy signs and quality of life.
- To assess the safety and tolerability of papaverine treatment.
- To explore potential predictive biomarkers of treatment response, such as nerve electrophysiology and inflammatory markers.

3. Study Design

This is a prospective, single-center, single-arm, open-label phase II clinical trial. Eligible participants with refractory paclitaxel-induced CIPN will receive papaverine hydrochloride injection. The study is designed to assess the preliminary therapeutic activity and safety profile of papaverine in this setting.

4. Study Population

4.1 Inclusion Criteria

Participants must meet all of the following criteria:

1. Age 18 to 75 years, regardless of sex.
2. Histologically or cytologically confirmed malignancy.
3. Prior treatment with a paclitaxel-containing chemotherapy regimen, including but not limited to paclitaxel, docetaxel, nab-paclitaxel, or paclitaxel polymeric micelles, with chemotherapy completed at least 4 weeks before enrollment.
4. Persistent and clinically significant peripheral neuropathy considered by the investigator to be mainly caused by paclitaxel, with sensory neuropathy graded as NCI-CTCAE version 5.0 grade 2 or higher.

5. Failure of standard treatment, defined as prior treatment with at least one standard CIPN medication, such as duloxetine at a dose of at least 60 mg/day, pregabalin at a dose of at least 150 mg/day, or gabapentin at a dose of at least 900 mg/day, administered for at least 4 weeks without meaningful symptom improvement, or discontinued because of intolerable adverse effects.
6. Eastern Cooperative Oncology Group performance status of 0 to 2.
7. Adequate major organ function, including hematologic, hepatic, and renal function.
8. Voluntary participation with written informed consent provided before study entry.

4.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded:

1. Other clear causes of peripheral neuropathy, including uncontrolled diabetes mellitus with HbA1c greater than 7.0%, severe renal insufficiency, vitamin B12 deficiency, thyroid dysfunction, or history of alcohol abuse.
2. Known allergy to papaverine or any of its excipients.
3. Contraindications to papaverine, such as complete atrioventricular block.
4. Ongoing treatment with another investigational drug that may affect neurological function.
5. Pregnancy or breastfeeding.
6. Severe hepatic or renal dysfunction, defined as ALT or AST greater than 3 times the upper limit of normal, or serum creatinine greater than 2 times the upper limit of normal.
7. Any other condition that, in the investigator's judgment, makes the participant unsuitable for the study.

5. Study Treatment

5.1 Investigational Product

Papaverine hydrochloride injection

5.2 Dose and Administration

Papaverine hydrochloride injection will be administered at a dose of **120 mg**, diluted in **100**

mL of 0.9% sodium chloride solution, by intravenous infusion once daily. Treatment consists of **1 treatment day followed by 6 days of rest, and 7 days constitute one cycle.**

5.3 Treatment Duration

After completion of one cycle, efficacy will be evaluated. Participants who derive clinical benefit and tolerate therapy well may continue to receive a second cycle. A maximum of **3 cycles** of free study treatment will be provided under the study protocol. Continued use beyond the protocol-defined treatment period, if considered beneficial, may be discussed jointly by the treating physician and the patient and may be provided outside the study at the patient's own expense.

5.4 Concomitant Medications

- Continued use of previously prescribed neurotrophic agents, such as mecobalamin, is allowed if the dose remains stable.
- Initiation of new agents or dose escalation of existing agents that may affect neuropathy assessment is prohibited during the study period.
- Other vasoactive drugs and systemic corticosteroids are prohibited, except for short-term local use when clinically necessary.
- Analgesic agents for CIPN-related pain, such as gabapentin, must remain at a stable dose and be carefully documented.

6. Study Procedures and Assessments

6.1 Study Flow

The study includes a screening period, baseline assessment, treatment period, on-treatment visits, and end-of-treatment/safety follow-up. The general sequence is:

Screening (informed consent and eligibility assessment) → Baseline (Day 0) → Intervention treatment (Day 1 / Day 8 / Day 15) → On-treatment visits (Week 1 and Week 2) → End-of-treatment and safety visit (Week 3 ± 3 days)

6.2 Screening Period (Day -14 to Day -1)

- Written informed consent
- Eligibility review

- Medical history
- Physical examination
- Laboratory tests
- Baseline questionnaire assessments

6.3 Baseline (Day 0)

- Confirmation of eligibility
- Completion of baseline assessments

6.4 Treatment Period (Day 1 to Day 15)

Participants will receive papaverine in the inpatient setting, outpatient clinic, or day ward as appropriate. Vital signs and acute adverse reactions will be monitored during treatment.

6.5 Efficacy Assessment Time Points

Assessments will be performed at:

- Day 1 (the day after the first administration)
- Day 8 \pm 3 days
- Day 15 \pm 3 days
- Post-treatment follow-up: 3 weeks after end of treatment, Day 22 \pm 3 days

6.6 Assessments

The following assessments will be performed according to the study schedule:

- Medical history and physical examination
- ECOG performance status
- Vital signs
- Laboratory tests
- NCI-CTCAE v5.0 sensory neuropathy assessment
- EORTC QLQ-CIPN20
- Numeric Rating Scale for pain and symptom severity
- Adverse event recording

7. Outcome Measures

7.1 Primary Efficacy Endpoint

Change from baseline in the **EORTC QLQ-CIPN20 sensory subscale score**.

7.2 Secondary Efficacy Endpoints

- Change from baseline in **EORTC QLQ-CIPN20 total score** and subscale scores (sensory, motor, and autonomic) at Day 1, Day 8, Day 15, and Day 22.
- Daily symptom diary using an **11-point Numeric Rating Scale (NRS)** to record the worst severity of numbness, pain, and tingling.
- Change in **NCI-CTCAE v5.0 sensory and motor neuropathy grades**.
- Change in **EORTC QLQ-C30** quality-of-life scores.

7.3 Exploratory Endpoints

- Changes in nerve conduction velocity and amplitude before and after treatment.
- Changes in serum inflammatory markers, such as IL-6 and C-reactive protein.

7.4 Safety Endpoints

- Incidence, type, and severity of papaverine-related adverse events graded according to CTCAE v5.0.
- Incidence of serious adverse events.
- Proportion of participants discontinuing treatment early and reasons for discontinuation.

8. Sample Size Calculation

The sample size is based on a single-group target-value design (Simon single-stage design).

The assumptions are as follows:

- Null hypothesis: response rate **$P \leq 15\%$**
- Alternative hypothesis: response rate **$P \geq 40\%$**

- One-sided alpha: **0.05**
- Power: **80%**

Based on these assumptions, **36 evaluable participants** are required. Assuming a dropout rate of **20%**, the final planned enrollment target is **43 participants**.

Decision Rule

Among 36 evaluable participants:

- If **11 or more** participants are considered responders, papaverine will be regarded as having sufficient potential for further study.
- If **10 or fewer** participants are considered responders, the treatment effect will be considered insufficient to support further investigation.

9. Adverse Event Recording and Management

All adverse events will be recorded from the time of signing informed consent until the last follow-up visit. Adverse events will be graded according to **CTCAE version 5.0**. The relationship of each adverse event to study treatment will be assessed by the investigator as definite, very likely, possible, unlikely, unrelated, or unknown. Serious adverse events must be reported to the ethics committee within **24 hours**.

Adverse events of special interest related to papaverine include:

- Hypotension
- Flushing
- Dizziness
- Palpitations
- Elevated liver enzymes
- Gastrointestinal discomfort, including nausea, vomiting, and abdominal pain
- Injection-site reactions

10. Analysis Populations

10.1 Full Analysis Set (FAS)

All enrolled participants who receive at least one dose of study treatment will be included in the primary efficacy analysis.

10.2 Per-Protocol Set (PPS)

Participants in the FAS without major protocol deviations, who complete at least 70% of treatment and complete the primary endpoint assessment, will be included in sensitivity analyses.

10.3 Safety Set (SS)

All participants who receive at least one dose of study treatment will be included in the safety analysis.

11. Data Management and Confidentiality

Case report forms will be established, and designated study personnel will be responsible for data entry and verification to ensure the accuracy and completeness of study data. Study results, whether positive or negative, are planned to be presented at academic conferences and prepared for publication in peer-reviewed journals. All study procedures will comply with applicable confidentiality requirements.

12. Ethical Considerations

This study will be conducted in accordance with the principles of the **Declaration of Helsinki** and the requirements of **Good Clinical Practice (GCP)** in China. The protocol, informed consent form, and any other relevant documents must be approved by the institutional ethics committee before study initiation. All investigators involved in the study must receive GCP training.

13. Schedule of Assessments

Assessment	Screening	Baseline (D0)	D1	D8 ± 3 days	D15 ± 3 days	D22 ± 3 days
Informed consent	X					
Demographics	X					
Medical history / Physical exam	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Laboratory tests	X	X				
NCI-CTCAE v5.0 sensory neuropathy	X	X	X	X	X	X
EORTC QLQ-CIPN20	X	X	X	X	X	X
NRS symptom assessment	X	X	X	X	X	X
Adverse events	X	Continuous	Continuous	Continuous	Continuous	Continuous

14. Appendices

The following appendices may be attached in the full uploadable version if needed:

ECOG Performance Status Scale

EORTC QLQ-C30

EORTC QLQ-CIPN20

Visit Schedule Table