A Multicenter Evidence-Based Clinical Study on the Safety and Efficacy of Wenyang Tongbi Formula in the Treatment of Chemotherapy-Induced Polyneuropathy

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V1.0

1. Introduction / Background

Chemotherapy-induced peripheral neurotoxicity (CIPN) refers to damage to the peripheral nervous system caused by specific chemotherapeutic agents (e.g., vinca alkaloids, taxanes, platinum compounds). It manifests primarily as limb numbness, pain, and paresthesia, often persisting long-term with limited therapeutic options. While duloxetine is currently the only agent recommended by the American Society of Clinical Oncology (ASCO), its clinical use is restricted by adverse effects (fatigue, drowsiness, gastrointestinal reactions) and limited efficacy (approximately 40% of patients showed no response in a Japanese study).

Mecobalamin, a vitamin B12 preparation, is widely used clinically for preventing and treating peripheral neuritis and neuropathy due to its low side-effect profile and cost-effectiveness. Breast cancer is the most prevalent malignant tumor in women globally. Taxane-based regimens are primary treatments, yet approximately 60% of patients develop CIPN, impairing mobility and quality of life. For colorectal cancer, oxaliplatin (a third-generation platinum drug) offers superior efficacy and lower toxicity than cisplatin/carboplatin but induces peripheral neurotoxicity characterized by cold sensitivity in 85–95% of patients. Given the distinct mechanisms and manifestations of taxane- and oxaliplatin-induced CIPN, comparing the effects of Wenyang Tongbi Formula holds significant clinical value.

In Traditional Chinese Medicine (TCM), CIPN falls under "Bi Zheng"

(Impediment Syndrome), primarily attributed to Yang deficiency, collateral obstruction, and toxin-stasis accumulation. Wenyang Tongbi Formula (Patent No. ZL202310257730.9), comprising Astragali Radix, Cinnamomi Ramulus, Paeoniae Radix Alba, Bombyx Batryticatus, Polygoni Bistortae Rhizoma, Curcumae Longae Rhizoma,and Clematidis Radix, is a patented prescription of our institution. It tonifies Qi, warms Yang, unblocks collaterals, and resolves toxins. Previous pilot studies indicate it effectively reduces CIPN severity grades and improves KPS scores via oral administration or external foot baths. This trial aims to provide high-level evidence for this novel treatment.

2. Objectives and Study Design

2.1 Objectives

To evaluate the efficacy and safety of Wenyang Tongbi Formula in treating CIPN (manifesting as numbness, pain, temperature sensation changes, and paresthesia) and to explore its underlying mechanisms.

2.2 Study Period

January 2026 – December 2028.

2.3 Study Design

(1)Overall Design: A prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial. A total of 144 patients (64 breast cancer, 80 colorectal cancer) will be enrolled and allocated 1:1 to treatment or control groups via stratified block randomization (stratified by center).

Interventions last 42 days, with assessments at baseline, Day 21, Day 42, and a 1-month post-treatment follow-up.

(2) Sample Size Calculation:

The sample size is based on the comparison of two proportions (primary outcome: overall response rate) with α=0.05 (two-sided) and power (1-β)=80%.Breast Cancer Cohort:Based on historical data (control: 26.31%, treatment: 63.15%), n=28 per arm. With 10% dropout, 32 per arm (total 64). Colorectal Cancer Cohort: Based on historical data (control: 35.71%, treatment: 68.18%), n=36 per arm. With 10% dropout, 40 per arm (total 80). Total:144 patients.

(3) Inclusion & Exclusion Criteria:

Inclusion: ① Age 18–80 years; ② Life expectancy ≥3 months; ③ KPS ≥60 with adequate organ function; ④ Histologically confirmed breast or colorectal cancer; ⑤ Receiving taxane- or oxaliplatin-based chemotherapy; ⑥ CIPN ≥ Grade 2 (NCI-CTCAE); ⑦ TCM Pattern: "Yang Deficiency and Collateral Obstruction with Toxin-Stasis Accumulation Pattern" (per Guidelines for Clinical Research of New TCM Drugs), presenting with limb numbness, flaccidity, pain, limited movement, cold extremities, fatigue, pale complexion, aversion to cold, edema, preference for warm drinks, clear copious urine/nocturia, loose stools, pale-dark tongue with thin white coating/distended sublingual veins, deep-thin-rough pulse.

Exclusion:① Allergy to study drugs/excipients or history of ≥3 allergies; ② Severe psychiatric disorders or pre-existing neuropathies (diabetic, hypothyroid, renal, radiculopathy, Charcot-Marie-Tooth, Guillain-Barré); ③ Used CIPN-related TCM within 30 days; ④ Non-compliant or unable to assess condition; ⑤ Pregnancy/lactation.

(4) Intervention:

Treatment Group: Wenyang Tongbi Granules (10 g/bag, 2 bags daily) + Placebo Mecobalamin (1 capsule, tid).

Control Group: Placebo Wenyang Tongbi Granules (5% original formula content, 10 g/bag, 2 bags daily) + Mecobalamin (1 capsule, tid).

Duration: 42 consecutive days.

(5) Primary Outcome Measure:

Overall Response Rate (ORR): Assessed per NCI-CTCAE v5.0.

Complete Response (CR):Reduction to Grade 1.

Partial Response (PR):Decrease ≥1 grade.

No Change (NC):No improvement.

Progressive Disease (PD):Increase ≥1 grade.

Formula:ORR = (Number of CR + PR) / Total number × 100%.

(6) Secondary Outcome Measures:

Time to significant relief of limb paresthesia.

Improvement rate of EORTC QLQ-CIPN20 scores:（Post−Pre）/Pre×100%.

Remission rate of neuropathic pain (DN4):（Post−Pre）/Pre×100%.

Reduction rate of TCM syndrome scores: （Post−Pre）/Pre×100%.

Numbness distribution and symptom severity (novel scale, Patent App: 202511273259.8).

Improvement rate of ECOG performance status: （Post−Pre）/Pre×100%.

Changes in serum neurofilament light chain (NEFL).

Changes in serum interleukin-6 (IL-6).

Changes in serum nerve growth factor (NGF).

(7) Safety Assessments:

Physical examination, vital signs, labs (CBC, urinalysis, LFTs, RFTs), 12-lead ECG. Adverse Events (AEs) graded per NCI-CTCAE v5.0.

3. Statistical Analysis & Quality Control

Data will be analyzed using SPSS 26.0 (two-sided tests, $P<0.05$ significant).Categorical variables(e.g., ORR, safety indicators) will be described as frequencies/percentages, compared using Chi-square or Fisher’s exact test.

Continuous variables (e.g., CIPN20 scores, DN4, TCM scores, KPS) will be tested for normality (Shapiro-Wilk). Normally distributed data presented as Mean ± SD (t-test/ANOVA); non-normal data as Median (IQR) (Mann-Whitney U/Kruskal-Wallis). Data Cleaning:Standardized definitions for dropouts/terminations. Primary analysis uses Intention-to-Treat (ITT); sensitivity analysis uses Per-Protocol (PP). Missing data handled via Multiple

Imputation.Consistency Checks:Inter-rater reliability for CIPN grading (Kappa ≥0.75) and TCM syndrome differentiation (ICC ≥0.8). Independent blinded adjudication for 20% of outcomes.

4. Adverse Event (AE) Management

Definition:Any untoward medical occurrence in a subject, irrespective of causal relationship to the study drug.

Grading:Per NCI-CTCAE v5.0 (Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Death).

Causality Assessment:Determined by temporal relationship, known adverse reactions, dechallenge/rechallenge, and alternative explanations (Classified as Certain, Probable, Possible, Unlikely, Unrelated).

Serious Adverse Events (SAEs):Immediate reporting to IRB/Sponsor within 24 hours. Fatal/life-threatening SAEs reported to NMPA within 15 days. Follow-up until resolution.

5. Ethics & Compliance

This protocol complies with the Declaration of Helsinkiand Chinese GCP regulations. Approved by the Institutional Review Board (IRB) of the National Cancer Center. Subject privacy protected via anonymization. All signed informed consent forms and source documents retained for 5 years post-study.