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Full length article

# Efficacy and safety of Aiyu capsules for chemotherapy-induced leukopenia in cancer patients: A multi-center parallel-group randomized controlled trial

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ABSTRACT

*Objective:* This study aimed to assess the efficacy and safety of Aiyu capsules, a traditional Chinese medicine (TCM) formulation, in preventing and treating chemotherapy-induced leukopenia, as well as to evaluate their effects on patient-reported quality of life. The findings are intended to provide evidence supporting the adjunctive use of Aiyu capsules for the management of chemotherapy-associated bone marrow suppression.
*Methods:* In this multicenter, randomized controlled trial, 288 patients diagnosed with colorectal cancer, gastric cancer, lymphoma, or ovarian cancer were recruited from 20 centers, including Jiangxi Provincial People's Hospital, the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Shunde Hospital of Guangzhou University of Chinese Medicine, and the First Affiliated Hospital of Guangzhou University of Chinese Medicine, between May 2022 and February 2025. Participants were allocated in a 1:1 ratio to either the Aiyu

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capsules group or the control group using a stratified block dynamic randomization approach. Patients in the control group ($n = 144$) received standard chemotherapy and placebo therapy, whereas those in the Aiyu capsules group ($n = 144$) were administered oral Aiyu capsules beginning three days prior to chemotherapy initiation and continued for 21 consecutive days in conjunction with standard chemotherapy. Hematological parameters were monitored following chemotherapy and during the subsequent treatment cycle. Additional assessments included the utilization rate of granulocyte colony-stimulating factor (G-CSF), quality of life as measured by the Quality of Life Questionnaire-Core 30 (QLQ-C30), TCM syndrome scores, and the incidence and severity of adverse events (AEs) throughout the study period.

*Results:* Patients receiving Aiyu capsules demonstrated significantly greater improvements in quality of life and TCM syndrome scores compared with those receiving chemotherapy alone. At day 21, QLQ-C30 evaluations showed that the median change from baseline in the total score for items 1-28 was −2.50 in the Aiyu capsules group, compared with 0 in the control group ($p < 0.0001$), indicating a more pronounced enhancement in overall quality of life. Consistently, the median changes from baseline in global health status and overall quality of life scores were both 1 in the Aiyu capsules group and 0 in the control group ($p < 0.0001$). With regard to TCM-related outcomes, reductions in fatigue and palpitations at day 21 were significantly greater in the Aiyu capsules group ($p < 0.005$), and the decrease in total TCM syndrome scores was also more substantial (−2 vs. 0, $p = 0.0002$). The incidence of severe AEs was lower in the Aiyu capsules group than in the control group. Among all reported AEs, severe AEs accounted for 1.29% in the Aiyu capsules group versus 3.51% in the control group ($p < 0.005$). Similarly, grade 4 or higher AEs, as defined by Common Terminology Criteria for Adverse Event (CTCAE) criteria, occurred less frequently in the Aiyu capsules group (0.86% vs. 3.51%, $p < 0.005$).

*Conclusion:* When administered as an adjunct to standard chemotherapy in patients with colorectal cancer, gastric cancer, lymphoma, or ovarian cancer, Aiyu capsules were associated with meaningful improvements in quality of life and a reduction in the incidence of severe AEs, while maintaining a favorable safety profile.

## 1. Introduction

Malignancies continue to pose a significant global health burden. Chemotherapy remains a fundamental component of antitumor therapy and has been shown to substantially extend survival in patients with cancer. Nevertheless, chemotherapy-induced bone marrow suppression is among the most frequently encountered treatment-related toxicities.[1] This condition is typically characterized by declines in white blood cell (WBC) counts and hemoglobin concentrations.[2] The extent and persistence of these hematologic abnormalities are influenced by multiple factors, including the specific chemotherapeutic agents administered, dosage intensity, combination regimens, and individual patient characteristics.[3] Hematologic toxicity may increase susceptibility to infection and necessitate the administration of broad-spectrum antimicrobial therapy, thereby escalating healthcare costs and impairing patient quality of life.[4] In addition, bone marrow suppression often results in chemotherapy dose reductions or treatment delays, which may attenuate antitumor efficacy and adversely affect clinical outcomes.[5] Accordingly, effective strategies to prevent or alleviate chemotherapy-associated bone marrow suppression remain an important unmet need in contemporary oncology practice.

Aiyu capsules are a compound traditional Chinese medicine (TCM) formulation consisting of cremastra appendiculata, solanum lyratum, epimedium brevicornum, sophora flavescens, angelica sinensis, atractylodes macrocephala, and panax ginseng. From the perspective of TCM theory, cremastra appendiculata and solanum lyratum are used for their heat-clearing, detoxifying, blood-stasis-resolving, and mass-dissipating properties, whereas angelica sinensis, atractylodes macrocephala, panax ginseng, and epimedium brevicornum are traditionally employed to replenish qi and blood, reinforce kidney function, and restore vital essence[6–9]. Through the combined actions of these components, the formulation is believed to exert synergistic effects related to detoxification, resolution of pathological masses, and reinforcement of qi and blood.

As a Chinese patent medicine, Aiyu capsules have been proposed as an adjunctive therapy for chemotherapy-induced bone marrow suppression, with potential benefits including improvement in quality of life, preservation of hematopoietic function, and enhancement of overall antitumor treatment efficacy.[10] On the basis of this therapeutic rationale, the present investigation was designed as a multicenter, randomized, double-blind clinical trial conducted across 20 centers, including Jiangxi Provincial People's Hospital, the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, and the First Affiliated Hospital of Guangzhou University of Chinese Medicine. The study aimed to evaluate the efficacy of Aiyu capsules in the prevention and management of chemotherapy-induced bone marrow suppression among patients with colorectal cancer, gastric cancer, lymphoma, and ovarian cancer.

## 2. Materials and methods

### 2.1. Study population

This multicenter study enrolled 288 patients diagnosed with colorectal cancer, gastric cancer, lymphoma, or ovarian cancer who received treatment at 20 centers, including Jiangxi Provincial People's Hospital, the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Shunde Hospital of Guangzhou University of Chinese Medicine, and the First Affiliated Hospital of Guangzhou University of Chinese Medicine, among other hospitals, between May 2022 and February 2025. A predefined sample size of 72 patients was allocated to each cancer type, using a 1:1 assignment ratio, yielding a total study population of 288 patients across the four malignancies. In the control arm, the mean patient age was 60.43 ± 9.43 years, with equal representation of gastric cancer, lymphoma, colorectal cancer, and ovarian cancer (36 cases each). Patients in the Aiyu capsules group had a mean age of 57.44 ± 9.65 years and an identical distribution of cancer types. Baseline demographic and clinical variables were comparable between the two groups, with no statistically significant differences observed ($p > 0.05$), indicating baseline balance.

Eligible participants were required to meet the following criteria: (1) age 18–70 years, inclusive, regardless of sex; (2) histologically confirmed stage III or IV gastric cancer, colorectal cancer, ovarian cancer, or lymphoma, with a planned course of chemotherapy and normal baseline WBC counts; (3) an anticipated survival duration of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; and (4) eligibility for standard chemotherapy regimens, defined as XELOX for gastric and colorectal cancer, a platinum-based regimen combined with paclitaxel for ovarian cancer, and CHOP for lymphoma. Patients were excluded if they met any of the following conditions: (1) presence of another primary malignancy; (2) underlying primary hematologic disease; (3) confirmed central nervous system metastases or clinical suspicion thereof; (4) prior history of bone marrow or stem cell transplantation; (5) uncontrolled infection at enrollment or receipt of systemic anti-infective therapy

within 72 h before randomization; (6) severe hepatic or renal impairment; (7) clinically significant cardiac disease; (8) severe diabetes mellitus; (9) active hepatitis B or C infection or seropositivity for human immunodeficiency virus; (10) a documented history of allergic disorders, hypersensitivity, or known allergy to any study medication or its components; (11) participation in another investigational drug study within 4 weeks prior to enrollment; or (12) any other condition judged by the investigators to render the patient unsuitable for inclusion. All participants provided written informed consent before study entry. The study protocol was reviewed and approved by the Medical Ethics Committee of Jiangxi Provincial People's Hospital (Approval No. 2021ky061, dated June 24, 2021; and Approval No. Kehui [2022] 12, dated November 15, 2022).

### 2.2. Treatment

Chemotherapy protocols: Participants assigned to the control group underwent standard chemotherapy in accordance with established treatment protocols. In the Aiyu capsules group, standard chemotherapy was supplemented with oral Aiyu capsules (Guizhou Yibai Nuzi Pharmaceutical Co., Ltd.; National Drug Approval No. Z20025336; dosage form: 0.35 g per capsule). Administration of Aiyu capsules commenced three days prior to the initiation of chemotherapy and continued for a total duration of 21 days. The prescribed regimen consisted of three capsules per dose, administered three times daily. Throughout the treatment period, chemotherapy was delivered concurrently following standard regimen specifications.

### 2.3. Outcomes

(1) Clinical efficacy: Fasting venous blood samples (5 mL) were obtained from patients in both groups before and after treatment. Of the collected samples, 2 mL was analyzed using an automated hematology analyzer to evaluate routine hematologic parameters as well as hepatic and renal function indicators. (2) Safety and tolerability: During the study period, all laboratory test abnormalities, changes in vital signs, electrocardiographic findings, and physical examination results, including body weight and ECOG performance status scores, were recorded. Patient-reported quality of life was assessed using the Quality of Life Questionnaire-Core 30 (QLQ-C30); TCM syndrome scores were documented; and the occurrence of adverse events (AEs) and serious AEs was monitored and recorded.

### 2.4. Statistical analysis

All statistical analyses were conducted using SAS software version 9.4. Data processing, statistical computation, and report generation were completed through customized SAS macro programming. Dichotomous and unordered categorical variables were summarized as frequencies and percentages and analyzed using the chi-square test. Ordinal variables were compared between groups using the Wilcoxon rank-sum test. Continuous variables were expressed as mean ± standard deviation and analyzed using independent-samples *t* tests. For variables that did not conform to a normal distribution, data were presented as medians with interquartile ranges, and between-group comparisons were performed using the Wilcoxon rank-sum test. A two-sided *P* value of less than 0.05 was considered indicative of statistical significance.

## 3. Results

### 3.1. Patient characteristics

This multicenter study involved 20 centers and enrolled a total of 288 patients, comprising 142 males and 145 females; one participant was lost to follow-up. The mean age of patients was 57.44 years in the Aiyu capsules group and 60.43 years in the control group. Overall, baseline demographic characteristics were well balanced between the two groups (Tables 1, 2). Although a statistically significant difference in age was observed, the magnitude of this difference was not considered clinically relevant. Baseline evaluations, including routine hematologic tests, blood biochemical parameters, routine urine and stool examinations, and electrocardiographic assessments, showed no significant differences between groups, indicating baseline comparability.

### 3.2. Bone marrow suppression

Changes in WBC counts over time among participants in the full analysis set (FAS) are illustrated in Fig. 1. The distributions of WBC counts during the treatment period, as analyzed in the FAS and presented in Tables 3 to 5, did not differ significantly between the two groups.

Further analyses based on both the FAS and the per-protocol set (PPS) were performed to assess the extent of chemotherapy-induced leukopenia and the incidence of grade 2 or higher leukopenia. These analyses demonstrated no statistically significant differences between two groups (Tables 6 to 12).

Trends in hemoglobin levels throughout the study period are shown in Table 13. Compared with the control group, the Aiyu capsules group exhibited smaller decreases in grade 2 and grade 3 hemoglobin levels, with a more pronounced reduction in the number of grade 2 cases. However, owing to the limited number of events, these between-group differences did not reach statistical significance.

### 3.3. Quality of life and TCM syndromes

Between-group comparisons of quality of life outcomes and TCM syndrome scores during the treatment period are summarized below (Tables 14, 15). Patients receiving Aiyu capsules experienced significantly greater improvements in quality of life measures and TCM syndrome scores than those in the control group ($p < 0.05$).

### 3.4. Safety analysis

#### 3.4.1. AEs

The overall incidence of AEs reported during the study period was comparable between the two groups, with no statistically significant differences observed (Tables 16, 17).

Notably, the occurrence of severe AEs was lower in the Aiyu capsules group than in the control group (Table 18). Among all reported AEs, severe AEs accounted for 1.29% in the Aiyu capsules group compared with 3.51% in the control group ($p < 0.005$). When AEs were further classified according to the Common Terminology Criteria for Adverse Events (CTCAE), the proportion of grade 4 or higher events was 0.86% in the Aiyu capsules group versus 3.51% in the control group ($p < 0.005$) (Table 19). There are 2 cases of death occurred in the control group, one of them attributed to the progression of lymphoma, the other died of COVID-19, neither death was treatment-related death.

## 4. Discussion

Within the theoretical framework of TCM, malignant tumors are generally categorized under the concepts of zhengjia and jiju, and their pathogenesis is attributed to a complex interaction of qi stagnation, blood stasis, phlegm-damp accumulation, and pathogenic toxins.[11] The

**Table 1**
Baseline distribution of sex and ethnicity of study participants.

| Characteristic | Category | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| Sex | Male<br>Female | 70 (48.61)<br>74 (51.39) | 72 (50.35)<br>71 (49.65) | 0.09 | 0.7683 |

**Table 2**
Baseline distribution of age, height, and body weight of study participants.

| Variable | Statistic | Aiyu capsules group | Control group | Statistic | *P* value |
|---|---|---|---|---|---|
| Age, year | *n* (missing) | 144 (0) | 142 (2) | | |
| | Mean ± SD | 57.44 ± 9.65 | 60.43 ± 9.43 | −2.65 | 0.0085 |
| | 95% CI | 55.85, 59.03 | 58.86, 61.99 | | |
| | Median (Q1, Q3) | 58.52 (51.83, 64.13) | 61.69 (55.12, 67.48) | | |

SD, standard deviation; CI, confidence interval.

formulation of Aiyu capsules reflects these principles. *Angelica sinensis* and panax ginseng are incorporated to replenish blood and reinforce qi, thereby facilitating the smooth circulation of blood.[12] Epimedium brevicornum is used to warm and tonify kidney yang, while cremastra appendiculata, sophora flavescens, solanum lyratum, and atractylodes macrocephala function to clear heat and toxins, support qi replenishment, and strengthen spleen function.[9,13,14] Through the synergistic effects of these components, the formulation is intended to enhance acquired qi and blood production and to ameliorate chemotherapy-associated qi and blood deficiency.[12] In this study, no statistically significant differences were identified between the Aiyu capsules and control groups in terms of the extent, frequency, or duration of chemotherapy-induced leukopenia, nor in the rate of G-CSF use during the subsequent chemotherapy cycle. Nevertheless, reductions in hemoglobin levels of grades 2 and 3 were less pronounced in the Aiyu capsules group than in the control group. Moreover, patients receiving Aiyu capsules exhibited significantly greater improvements in quality of life and TCM syndrome scores. The incidence of moderate to severe AEs was also significantly lower in the Aiyu capsules group. Collectively, these findings indicate that adjunctive administration of Aiyu capsules alongside chemotherapy may contribute to improved post-treatment quality of life and symptom relief, reduce treatment-related AEs, and demonstrate an acceptable safety profile in patients with malignant tumors. The potential mechanism underlying these effects may be related to the role of Aiyu capsules as a TCM preparation capable of correcting syndromes characterized by concurrent deficiencies of qi and blood and enhancing host immune function.

**Table 3**
Distribution of white blood cell counts during the treatment period in the full analysis set.

| Time point | Statistic | Aiyu capsules group | Control group | Statistic | *P* value |
|---|---|---|---|---|---|
| Day 3 | *n* (missing) | 117 (27) | 121 (23) | | |
| | Mean ± SD | 5.96 ± 2.55 | 6.65 ± 4.28 | −1.51 | 0.1326 |
| | 95% CI | 5.49, 6.42 | 5.88, 7.42 | | |
| | Median (Q1, Q3) | 5.44 (3.90, 7.58) | 5.70 (4.15, 8.09) | | |
| Day 7 | *n* (missing) | 115 (29) | 102 (42) | | |
| | Mean ± SD | 4.90 ± 2.60 | 5.41 ± 4.65 | −1.02 | 0.3086 |
| | 95% CI | 4.42, 5.38 | 4.50, 6.32 | | |
| | Median (Q1, Q3) | 4.42 (3.20, 6.03) | 5.12 (3.60, 6.30) | | |
| Day 14 | *n* (missing) | 102 (42) | 83 (61) | | |
| | Mean ± SD | 4.97 ± 4.55 | 4.95 ± 3.77 | 0.03 | 0.9734 |
| | 95% CI | 4.08, 5.86 | 4.12, 5.77 | | |
| | Median (Q1, Q3) | 3.93 (2.79, 5.93) | 4.31 (3.09, 5.99) | | |
| Day 21 | *n* (missing) | 136 (8) | 132 (12) | | |
| | Mean ± SD | 5.27 ± 3.27 | 5.11 ± 2.30 | 0.45 | 0.6521 |
| | 95% CI | 4.71, 5.82 | 4.72, 5.51 | | |
| | Median (Q1, Q3) | 4.34 (3.63, 5.71) | 4.67 (3.67, 5.85) | | |

SD, standard deviation; CI, confidence interval; Q1, first quartile; Q3, third quartile.

Although a trend toward reduced myelosuppression was observed, the lack of statistical significance in WBC count recovery and G-CSF utilization may be attributed to several factors. Specifically, the profound myelosuppressive effects of the standard chemotherapy regimens may require an observation period longer than the 21-day treatment cycle for the Aiyu capsules to demonstrate full hematologic reversal. Additionally, future studies exploring dose optimization of Aiyu capsules or alternative timing for blood sampling may better capture its

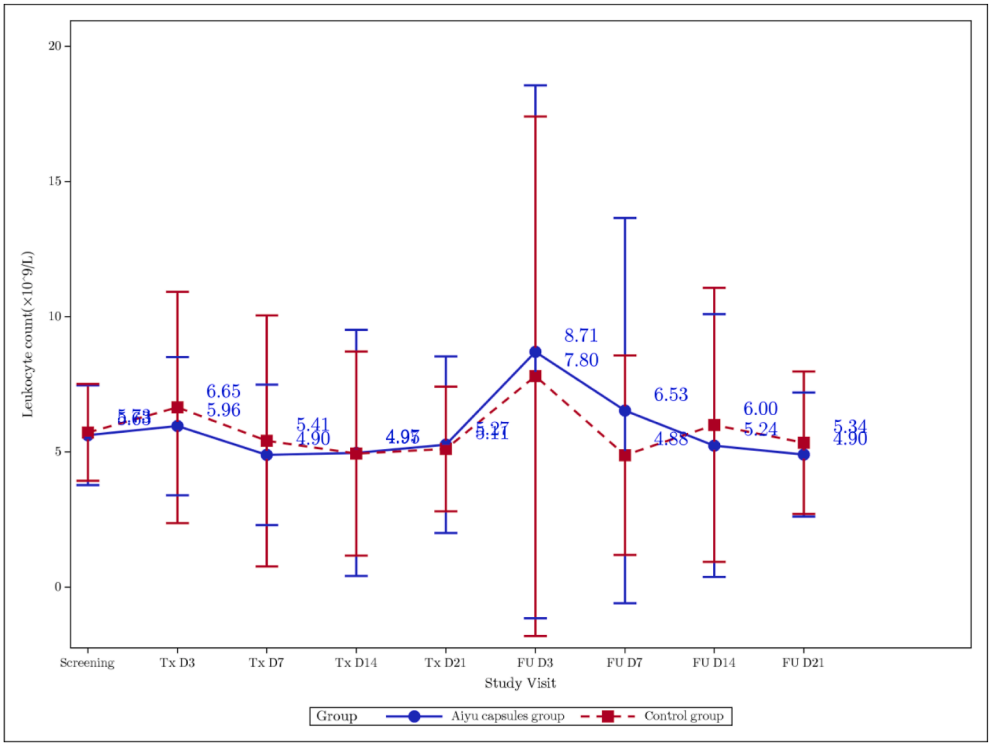



**Fig. 1.** Trends in white blood cell counts across different study visits in the full analysis set.

**Table 4**
Between-group distribution of the clinical significance of white blood cell counts during the treatment period in the full analysis set.

| Time point | Clinical significance | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| Day 3 | Normal | 89 (76.07) | 87 (71.90) | 3.79 | 0.1503 |
| | Abnormal without clinical significance | 10 (8.55) | 20 (16.53) | | |
| | Abnormal with clinical significance | 18 (15.38) | 14 (11.57) | | |
| Day 7 | Normal | 70 (60.87) | 75 (73.53) | - | 0.1461 |
| | Abnormal without clinical significance | 5 (4.35) | 3 (2.94) | | |
| | Abnormal with clinical significance | 40 (34.78) | 24 (23.53) | | |
| Day 14 | Normal | 49 (48.04) | 48 (57.83) | 1.80 | 0.4065 |
| | Abnormal without clinical significance | 10 (9.80) | 6 (7.23) | | |
| | Abnormal with clinical significance | 43 (42.16) | 29 (34.94) | | |
| Day 21 | Normal | 100 (73.53) | 100 (75.76) | 2.11 | 0.3483 |
| | Abnormal without clinical significance | 7 (5.15) | 11 (8.33) | | |
| | Abnormal with clinical significance | 29 (21.32) | 21 (15.91) | | |

**Table 5**
Between-group comparison of the incidence of white blood cell decreased during the treatment period in the full analysis set.

| Time point | White blood cell status | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| Day 3 | Normal | 89 (76.07) | 87 (71.90) | 13686.50 | 0.4664 |
| | Decreased | 28 (23.93) | 34 (28.10) | | |
| Day 7 | Normal | 58 (49.15) | 62 (54.39) | 12929.00 | 0.4276 |
| | Decreased | 60 (50.85) | 52 (45.61) | | |
| Day 14 | Normal | 31 (26.72) | 38 (36.89) | 10722.50 | 0.1084 |
| | Decreased | 85 (73.28) | 65 (63.11) | | |
| Day 21 | Normal | 44 (32.12) | 58 (42.65) | 17651.00 | 0.0739 |
| | Decreased | 93 (67.88) | 78 (57.35) | | |

hematopoietic benefits.

In conclusion, the use of Aiyu capsules as an adjunct to chemotherapy appears to attenuate chemotherapy-induced physiological impairment, alleviate clinical symptoms, and decrease the incidence of AEs, while maintaining favorable safety. These findings support the potential clinical value of this combined therapeutic approach.

**Table 7**
Between-group comparison of the incidence of white blood cell decreased during chemotherapy.

| Analysis set | White blood cell decreased | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| FAS | Yes | 102 (70.83) | 84 (59.57) | 3.98 | 0.0459 |
| | No | 42 (29.17) | 57 (40.43) | | |
| PPS | Yes | 97 (71.32) | 75 (60.00) | 3.72 | 0.0539 |
| | No | 39 (28.68) | 50 (40.00) | | |

FAS, full analysis set; PPS, per-protocol set.

**Table 8**
Between-group comparison of the incidence of grade 2 or higher white blood cell decreased during chemotherapy.

| Analysis set | Grade $\geq$ 2 white blood cell decreased | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| FAS | Yes | 55 (38.19) | 41 (29.08) | 2.65 | 0.1035 |
| | No | 89 (61.81) | 100 (70.92) | | |
| PPS | Yes | 52 (38.24) | 37 (29.60) | 2.16 | 0.1415 |
| | No | 84 (61.76) | 88 (70.40) | | |

FAS, full analysis set; PPS, per-protocol set.

**Table 9**
Comparison of the frequency of white blood cell decreased during chemotherapy.

| Analysis set | Frequency of white blood cell decreased | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| FAS | 0 | 42 (29.17) | 60 (41.67) | 22115.00 | 0.0546 |
| | 1 | 48 (33.33) | 36 (25.00) | | |
| | 2 | 32 (22.22) | 34 (23.61) | | |
| | 3 | 13 (9.03) | 12 (8.33) | | |
| | 4 | 9 (6.25) | 2 (1.39) | | |
| PPS | 0 | 39 (28.68) | 53 (41.41) | 15858.50 | 0.0650 |
| | 1 | 46 (33.82) | 31 (24.22) | | |
| | 2 | 30 (22.06) | 33 (25.78) | | |
| | 3 | 13 (9.56) | 10 (7.81) | | |
| | 4 | 8 (5.88) | 1 (0.78) | | |

FAS, full analysis set; PPS, per-protocol set.

However, the present study is limited by a modest sample size, limited data availability, and a relatively short follow-up period. Future studies with larger cohorts, more comprehensive data collection, and extended follow-up are required to generate more robust evidence and to establish a stronger scientific and theoretical basis for the combined use of Aiyu capsules and chemotherapy in the management of malignant tumors.

**Table 6**
Between-group comparison of the magnitude of white blood cell decreased during chemotherapy.

| Analysis set | CTCAE grade | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| FAS | Normal | 42 (29.17) | 57 (40.43) | 18900.00 | 0.0590 |
| | Grade 1 | 47 (32.64) | 43 (30.50) | | |
| | Grade 2 | 36 (25.00) | 24 (17.02) | | |
| | Grade 3 | 17 (11.81) | 13 (9.22) | | |
| | Grade 4 | 2 (1.39) | 4 (2.84) | | |
| PPS | Normal | 39 (28.68) | 50 (40.00) | 15326.00 | 0.0735 |
| | Grade 1 | 45 (33.09) | 38 (30.40) | | |
| | Grade 2 | 34 (25.00) | 22 (17.60) | | |
| | Grade 3 | 16 (11.76) | 12 (9.60) | | |
| | Grade 4 | 2 (1.47) | 3 (2.40) | | |

*The magnitude of decrease refers to the CTCAE grade corresponding to the nadir value of white blood cell or neutrophil counts observed during chemotherapy.
CTCAE, Common Terminology Criteria for Adverse Events; FAS, full analysis set; PPS, per-protocol set.

**Table 10**
Comparison of the frequency of grade 2 or higher white blood cell decreased during chemotherapy.

| Analysis set | Frequency of grade ≥ 2 white blood cell decreased | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| FAS | 0 | 89 (61.81) | 103 (71.53) | 21854.50 | 0.0758 |
| | 1 | 38 (26.39) | 30 (20.83) | | |
| | 2 | 14 (9.72) | 8 (5.56) | | |
| | 3 | 2 (1.39) | 3 (2.08) | | |
| | 4 | 1 (0.69) | 0 (0.00) | | |
| PPS | 0 | 84 (61.76) | 91 (71.09) | 16059.50 | 0.0824 |
| | 1 | 36 (26.47) | 29 (22.66) | | |
| | 2 | 14 (10.29) | 7 (5.47) | | |
| | 3 | 1 (0.74) | 1 (0.78) | | |
| | 4 | 1 (0.74) | 0 (0.00) | | |

FAS, full analysis set; PPS, per-protocol set.

**Table 11**
Comparison of granulocyte colony-stimulating factor use during chemotherapy.

| Analysis set | G-CSF use | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| FAS | Yes | 30 (20.83) | 22 (15.28) | 1.50 | 0.2204 |
| | No | 114 (79.17) | 122 (84.72) | | |
| PPS | Yes | 28 (20.59) | 22 (17.19) | 0.50 | 0.4809 |
| | No | 108 (79.41) | 106 (82.81) | | |

G-CSF, granulocyte colony-stimulating factor; FAS, full analysis set; PPS, per-protocol set.

**Table 12**
Comparison of granulocyte colony-stimulating factor use across different time intervals in the full analysis set.

| Time interval | G-CSF use | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|---|
| 7 days before chemotherapy to day 3 of chemotherapy | Yes | 8 (5.56) | 5 (3.47) | 0.73 | 0.3945 |
| | No | 136 (94.44) | 139 (96.53) | | |
| Day 3 to day 7 of chemotherapy | Yes | 8 (5.56) | 4 (2.78) | 1.39 | 0.2382 |
| | No | 136 (94.44) | 140 (97.22) | | |
| Day 3 to day 14 of chemotherapy | Yes | 21 (14.58) | 16 (11.11) | 0.78 | 0.3786 |
| | No | 123 (85.42) | 128 (88.89) | | |

**Table 13**
Between-group comparison of the magnitude of hemoglobin decreased during chemotherapy.

| CTCAE grade | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|
| Grade 1 | 88 (70.40) | 67 (57.26) | 15142.50 | 0.0448 |
| Grade 2 | 29 (23.20) | 41 (35.04) | 1661.50 | 0.6810 |
| Grade 3 | 8 (6.40) | 9 (7.69) | | |

CTCAE, Common Terminology Criteria for Adverse Events.

**Table 14**
Change from baseline in QLQ-C30 quality of life scores at day 21 of treatment.

| Domain | Statistic | Aiyu capsules group | Control group | Statistic | *P* value |
|---|---|---|---|---|---|
| Items 1–28 total score | *n* (missing) | 136 (5) | 134 (7) | | |
| | Mean ± SD | −3.29 ± 7.75 | 0.31 ± 8.13 | | |
| | 95% CI | −4.61, −1.98 | −1.08, 1.70 | | |
| | Median (Q1, Q3) | −2.50 (−6.50, 0.00) | 0.00 (−3.00, 4.00) | 20708.50 | < 0.0001 |
| Global health status | *n* (missing) | 136 (5) | 134 (7) | | |
| | Mean ± SD | 0.62 ± 0.83 | 0.07 ± 1.09 | | |
| | 95% CI | 0.48, 0.76 | −0.11, 0.26 | | |
| | Median (Q1, Q3) | 1.00 (0.00, 1.00) | 0.00 (−1.00, 1.00) | 15214.00 | < 0.0001 |
| Overall quality of life | *n* (missing) | 136 (5) | 134 (7) | | |
| | Mean ± SD | 0.64 ± 0.80 | −0.01 ± 1.06 | | |
| | 95% CI | 0.50, 0.77 | −0.20, 0.17 | | |
| | Median (Q1, Q3) | 1.00 (0.00, 1.00) | 0.00 (−1.00, 1.00) | 14870.00 | < 0.0001 |

SD, standard deviation; CI, confidence interval.

**Table 15**
Change from baseline in traditional Chinese medicine symptom scores at day 21 of treatment.

| Symptom domain | Statistic | Aiyu capsules group | Control group | Statistic | *P* value |
|---|---|---|---|---|---|
| Fatigue | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.69 ± 1.63 | 0.06 ± 1.76 | | |
| | 95% CI | −0.97, −0.41 | −0.24, 0.36 | | |
| | Median (Q1, Q3) | 0.00 (−2.00, 0.00) | 0.00 (0.00, 2.00) | 19912.00 | < 0.0001 |
| Insomnia | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.35 ± 1.38 | −0.05 ± 1.30 | | |
| | 95% CI | −0.58, −0.11 | −0.27, 0.18 | | |
| | Median (Q1, Q3) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 18415.00 | 0.0985 |
| Palpitations | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.21 ± 0.99 | −0.02 ± 1.00 | | |
| | 95% CI | −0.38, −0.04 | −0.19, 0.16 | | |
| | Median (Q1, Q3) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 18466.00 | 0.0443 |
| Shortness of breath | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.12 ± 1.25 | 0.02 ± 0.97 | | |
| | 95% CI | −0.33, 0.09 | −0.15, 0.18 | | |
| | Median (Q1, Q3) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 18210.00 | 0.1453 |
| Pallor | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.18 ± 1.27 | −0.12 ± 1.13 | | |
| | 95% CI | −0.40, 0.04 | −0.32, 0.07 | | |
| | Median (Q1, Q3) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 17886.00 | 0.5204 |
| Dizziness | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.36 ± 1.20 | −0.14 ± 1.14 | | |
| | 95% CI | −0.57, −0.15 | −0.33, 0.06 | | |
| | Median (Q1, Q3) | 0.00 (−2.00, 0.00) | 0.00 (0.00, 0.00) | 18407.50 | 0.0961 |
| Poor appetite | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.44 ± 1.08 | −0.17 ± 1.29 | | |
| | 95% CI | −0.62, −0.25 | −0.39, 0.05 | | |
| | Median (Q1, Q3) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 18492.50 | 0.0642 |
| Abdominal distension | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.33 ± 1.13 | −0.12 ± 1.15 | | |
| | 95% CI | −0.53, −0.14 | −0.32, 0.08 | | |
| | Median (Q1, Q3) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 18450.00 | 0.0596 |
| Loose stools | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −0.15 ± 1.36 | −0.12 ± 1.07 | | |
| | 95% CI | −0.38, 0.08 | −0.31, 0.06 | | |
| | Median (Q1, Q3) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 17686.00 | 0.7441 |
| Total score | *n* (missing) | 133 (11) | 132 (12) | | |
| | Mean ± SD | −2.83 ± 6.40 | −0.65 ± 5.62 | | |
| | 95% CI | −3.92, −1.73 | −1.62, 0.32 | | |
| | Median (Q1, Q3) | −2.00 (−6.00, 0.00) | 0.00 (−4.00, 2.00) | 19873.50 | 0.0002 |

SD, standard deviation; CI, confidence interval.

**Table 16**
Between-group distribution of adverse events during the study period.

| Adverse events | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|
| Yes | 101 (70.14) | 100 (69.44) | 0.02 | 0.8979 |
| No | 43 (29.86) | 44 (30.56) | | |

**Table 17**
Between-group distribution of the highest CTCAE grade of adverse events.

| CTCAE grade | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|
| Normal | 43 (30.07) | 44 (30.56) | 20569.50 | 0.9742 |
| Grade 1 | 33 (23.08) | 33 (22.92) | | |
| Grade 2 | 42 (29.37) | 41 (28.47) | | |
| Grade 3 | 22 (15.38) | 20 (13.89) | | |
| Grade 4 | 3 (2.10) | 4 (2.78) | | |
| Grade 5 | 0 (0.00) | 2 (1.39) | | |

CTCAE, Common Terminology Criteria for Adverse Events.

**Table 18**
Between-group distribution of severe adverse events among reported adverse events.

| Adverse event severity | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|
| Severe | 6 (1.29) | 15 (3.51) | 4.76 | 0.0291 |
| Mild to moderate | 458 (98.71) | 412 (96.49) | | |

**Table 19**
Between-group distribution of severe adverse events according to CTCAE grading among reported adverse events.

| CTCAE grade category | Aiyu capsules group, *n* (%) | Control group, *n* (%) | Statistic | *P* value |
|---|---|---|---|---|
| Severe (grade 4–5) | 4 (0.86) | 15 (3.51) | 7.49 | 0.0062 |
| Mild to moderate (grade 1–3) | 460 (99.14) | 412 (96.49) | | |

CTCAE, Common Terminology Criteria for Adverse Events.

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## Data availability

The data are available within the Article or available from the authors upon request. Source data are provided with this paper.

## Declaration of competing interest

The authors declare no competing interests.

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