

Safety and efficacy of spleen aminopeptide oral lyophilized powder for improving quality of life and immune response in patients with advanced breast cancer: a multicenter, randomized, double-blind, placebo-controlled clinical trial

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Health-related quality of life (HRQoL) is an important consideration in managing patients. Spleen aminopeptide oral lyophilized powder (SAOLP) has been used to enhance cellular immunity in a patient. This multicenter, randomized, double-blind, placebo-controlled clinical trial was designed to evaluate the safety and efficacy of SAOLP for improving HRQoL in patients with breast cancer. Patients diagnosed with advanced breast cancer were included, and were administered SAOLP or placebo 4 mg qd for two cycles. The primary endpoint was improvement in HRQoL on day 42 measured by the EORTC QLQ-C30 and EORTC QLQ-BR23. Secondary endpoints included immunologic function, improvement in HRQoL on day 21 and 84, objective response rate, disease control rate, BMI and adverse events. On day 42, on the EORTC QLQ-C30 or EORTC QLQ-BR23, scores on the functional scales and QoL scale were significantly higher and scores on symptom scales were significantly lower in patients who received SAOLP compared to placebo ($P < 0.05$).

Introduction

In the United States (US), in 2020, there will be approximately 1 806 590 new cancer diagnoses and 606 520 cancer-related deaths [1]. On 1 January 2030, an estimated 22.1 million Americans will be living with a cancer history, an increase from the 16.9 million Americans who were living with a cancer history on 1 January 2019. In the US, in 2019, the most prevalent cancers among males included prostate (3 650 030), colon and rectum (776 120), and melanoma of the skin (684 470), and the most prevalent cancers among females included breast (3 861 520), uterine corpus (807 860), and colon and rectum (768 650). Among cancer survivors in the US in 2019, 56% received their diagnosis during the last decade, and 64% were aged ≥ 65 years [2]. Across all stages, survival rates were highest for prostate cancer (98%), melanoma of the skin

On day 84, the number of CD3, CD4 and CD8 cells were significantly higher in patients who received SAOLP. There were no significant differences in objective response rate, disease control rate or BMI. SAOLP may improve HRQoL and the immune response in patients with advanced breast cancer, represents a convenient and safe adjuvant therapy. *Anti-Cancer Drugs* 32: 1067–1075 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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(92%) and breast cancer (women) (90%) [1] During 2012–2016, the incidence of breast cancer in the US increased 0.3% per year, driven by an increased incidence of local stage and hormone receptor-positive disease [3].

Treatment for breast cancer includes surgery, radiotherapy and cytotoxic and endocrine drugs. Clinically, the goal of breast cancer treatment is to remove all visible cancer and manage the disease over the long term. Patient health-related quality of life (HRQoL), defined as the patient-perceived psychosocial, emotional and physical outcomes of medical intervention [4], is another important aspect of breast cancer treatment [5,6]. In particular, patient HRQoL should be considered when a treatment approach is unlikely to improve survival, as in some metastatic cancers. The American Society of Clinical Oncology, National Institutes of Health and the National Cancer Institute recommend that patients should only be exposed to treatments without evidence of survival benefits if they can reasonably expect an improvement in HRQoL. Accordingly,

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HRQoL evaluation is increasingly recognized as an important outcome measure in clinical trials [7].

Spleen aminopeptide oral lyophilized powder (SAOLP), which consists of peptides and nucleotides extracted from fresh pig spleen [8], has been used to enhance cellular immunity and immune homeostasis in pediatric patients with respiratory infection [9] or immune disorders [10,11], and in adult patients with hepatitis B [12]. In patients with gastrointestinal tumors, SAOLP administration was associated with improved HRQoL compared to placebo [13]. This multicenter, randomized, double-blind, placebo-controlled clinical trial was designed to evaluate the safety and efficacy of SAOLP for improving HRQoL and immune response during chemotherapy in Chinese patients with breast cancer.

Methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-arm clinical trial. Patients were randomized by the random number method to receive SAOLP or placebo, which were provided as matching white powders with a similar taste. Patients, physicians and nurses were blinded to the treatment allocation.

Study participants

Patients diagnosed with breast cancer based on biopsy or histology attending the Beijing Friendship hospital affiliated with Capital Medical University, Xiyuan Hospital, China Academy of Chinese medical sciences and Tianjin Medical University general hospital between August 2017 and June 2019 were eligible for this study.

Inclusion criteria were (1) Eastern Cooperative Oncology Group performance status of 0–2; (2) aged 18–75 years; (3) tumor stage IV, irrespective of whether the patient had undergone surgery; (4) maximum tumor diameter ≥ 10 mm on computed tomography (CT) and MRI; (5) adequate hematological, hepatic and renal function; and (6) expected overall survival of >3 months.

Exclusion criteria were (1) participated in another clinical trial in the past 3 months; (2) allergic to SAOLP or its constituents; (3) taking digitalis; or (4) psychopathic tendencies, pregnant or lactating.

Ethical issues

The trial was conducted according to the Declaration of Helsinki and the Ethical Guidelines for Clinical Research. The trial protocol was approved by an independent ethics committee at the Beijing Friendship Hospital. This trial was registered with the Chinese Clinical Trial Registry at <http://www.chictr.org.cn> (ChiCTR-IPR-17013733). All patients provided written informed consent to participate in the trial and authorized publication of this article.

Treatment

Breast cancer patients received standard therapy recommended by the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Patients were administered SAOLP or placebo (Fu Ketuo, Zhejiang Feng; State Medical Permit No. H20068132) 4 mg qd po. on the first day of chemotherapy for two cycles. SAOLP was manufactured according to the Standard for Quality Management of Chinese Medicinal Materials (GAP) (2002).

Patients who were intolerant to SAOLP or showed SAOLP-related or chemotherapy-related toxicity or disease deterioration were transferred to the emergency department. Patients treated for <3 weeks were only included in the safety analyses.

Outcome measures

Patients' baseline characteristics were recorded before chemotherapy. The primary endpoint was the improvement in patient HRQoL on day 42. Secondary endpoints included immunologic function (CD3, CD4, CD8), improvement in patient HRQoL on day 21 and 84, objective response rate (ORR), disease control rate (DCR), BMI and adverse events.

EORTC QLQ-C30

The official Croatian translation of the European Organisation for Research and Treatment of Cancer (EORTC) [14] QLQ-C30 was used to assess cancer-specific HRQoL during the previous week [17]. The EORTC QLQ-C30 was administered on day 21, day 42 and day 84.

The EORTC QLQ-C30 consists of 30 questions, including five functional scales, nine symptom scales, and a global health status/quality of life scale (GHS/QoL). Responses to 28 questions are assessed on a 4-point Likert-type scale ('1='not at all', 2='a little', 3='quite a bit' and 4='very much'). Responses to two questions are assessed on a 7-point scale Likert-type scale ranging from 1='very poor' to 7='excellent'.

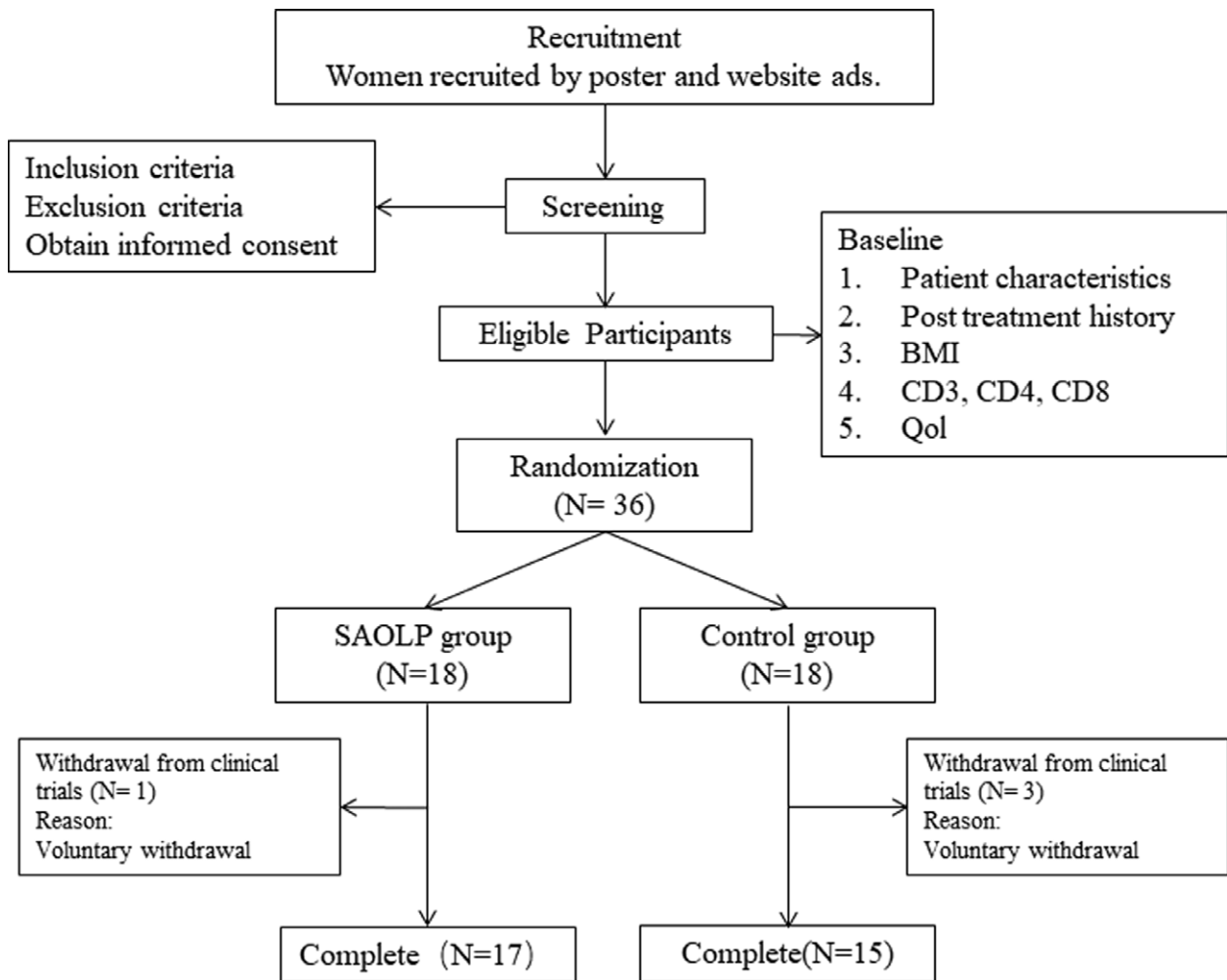
Baseline EORTC QLQ-C30, EORTC QLQ-BR23 and immune response

The EORTC QLQ-BR23 was used with the EORTC QLQ-C30 to assess breast cancer-specific HRQoL during the previous week, except for the sexual items, which were during the past 4 weeks. The EORTC QLQ-BR23 was administered on day 21, day 42 and day 84.

The EORTC QLQ-BR23 consists of 23 questions, including four functional scales and four symptom scales. Responses to questions are assessed on a 4-point Likert-type scale.

Data were collected through face-to-face interviews and review of patients' medical charts. Researchers collecting data were provided two days of training and

Fig. 1



Flow chart showing patient selection.

Table 1 Patients' baseline demographic and clinical characteristics

Characteristics		SAOLP group	Control group	Total	statistic(χ^2/t)	P value
Age	N (Nmiss)	18 (0)	18 (0)	36 (0)	3.07	0.004
	Mean (SD)	60.1 (7.5)	50.7 (10.7)	55.4 (10.3)		
	Median (Q1,Q3)	61.4 (54.2,65.1)	50.9 (43.4, 55.2)	54.3 (49.2,63.7)		
BMI	Min, Max	47.4, 73.7	34.6, 72.7	34.6, 73.7	-0.53	0.598
	N (Nmiss)	18 (0)	18 (0)	36 (0)		
	Mean (SD)	23.5 (2.9)	24.1 (2.9)	23.8 (2.9)		
ECOG	Median (Q1,Q3)	23.6 (20.7,24.9)	23.8 (22.6,25.0)	23.8 (22.5,25.0)	0.83	0.411
	Min, Max	19.4, 30.1	19.2, 31.2	19.2, 31.2		
	N (Nmiss)	18 (0)	18 (0)	36 (0)		
First line	Mean (SD)	0.9 (0.4)	0.8 (0.4)	0.9 (0.4)	1.45	0.229
	Median (Q1,Q3)	1.0 (1.0,1.0)	1.0 (1.0,1.0)	1.0 (1.0,1.0)		
	Min, Max	1.0, 2.0	0.0, 1.0	0.0, 2.0		
First line	NO,%	16 (88.9)	12 (66.7)	28 (77.8)	1.45	0.229
	YES,%	2 (11.1)	6 (33.3)	8 (22.2)		

ECOG: Eastern Cooperative Oncology Group.

were continuously supervised by the principal investigator. A pre-test was performed on 20 patients to provide feedback on the EORTC QLQ-C30 and EORTC QLQ-BR23 and ensure they were applicable to the trial population.

Immunologic function

The number of CD3+, CD4+ and CD8+ T lymphocytes and the CD4+/CD8+ ratio were measured by flow cytometry to evaluate patients' immune response. A decrease in CD3+ T lymphocytes indicates severe suppression of

Table 2 Baseline EORTC QLQ-C30 scores

Indicators		SAOLP group	control group	total	statistic(t)	P value
PF (physical function)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.07	0.794
	Mean (SD)	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)		
	Median (Q1,Q3)	1.7 (1.6,1.8)	1.6 (1.6,2)	1.6 (1.6,1.8)		
	Min, Max	1.0, 2.6	1.2, 2.2	1.0, 2.6		
RF (role function)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.08	0.778
	Mean (SD)	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)		
	Median (Q1,Q3)	1.3 (1,2)	1.5 (1.0,2.0)	1.5 (1.0,2.0)		
	Min, Max	1.0,2.5	1.0,2.5	1.0,2.5		
EF (emotional functioning)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.25	0.617
	Mean (SD)	1.6 (0.6)	1.7 (0.5)	1.6 (0.6)		
	Median (Q1,Q3)	1.5 (1.0,2.3)	1.8 (1.3,2.3)	1.8 (1,2.3)		
	Min, Max	1, 2.8	1, 2.5	1.0, 2.8		
CF (cognitive function)	N(Nmiss)	18(0)	18(0)	36(0)	0.15	0.702
	Mean (SD)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)		
	Median (Q1,Q3)	1.5 (1.0,2.0)	1.5 (1.0,2.0)	1.5 (1.0,2.0)		
	Min, Max	1.0,2.5	1.0,2.5	1.0,2.5		
SF (social function)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.86	0.355
	Mean (SD)	2.2 (0.6)	2.1 (0.5)	2.1 (0.6)		
	Median (Q1,Q3)	2.0 (2.0,3.0)	2 (2.0,2.0)	2 (2.0,2.5)		
	Min, Max	1,3	1,3	1,3		
QL (quality)	N (Nmiss)	18 (0)	18 (0)	36 (0)	2.62	0.106
	Mean (SD)	3.9 (0.9)	4.3 (0.8)	4.1 (0.9)		
	Median (Q1,Q3)	4.0 (3.0,5.0)	4.0 (4.0,5.0)	4.0 (3.3,5.0)		
	Min, Max	2.5,5.0	3.0, 5.5	2.5, 5.5		
FA (fatigue)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.41	0.52
	Mean (SD)	1.9 (0.5)	1.8 (0.3)	1.8 (0.5)		
	Median (Q1,Q3)	1.8 (1.3,2.0)	1.7 (1.7,2.0)	1.7 (1.7,2.0)		
	Min, Max	1.0, 3.0	1.3, 2.3	1.0, 3.0		
NV (nausea and vomiting)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.92	0.339
	Mean (SD)	1.2 (0.3)	1.4 (0.6)	1.3 (0.5)		
	Median (Q1,Q3)	1.0 (1.0,1.5)	1.0 (1.0,2.0)	1.0 (1.0,1.5)		
	Min, Max	1.0, 2.0	1.0, 3.0	1.0, 3.0		
PA (pain)	N (Nmiss)	18 (0)	18 (0)	36 (0)	1	0.337
	Mean (SD)	1.9 (0.6)	1.7 (0.6)	1.8 (0.6)		
	Median (Q1,Q3)	1.5 (1.5,2.5)	1.5 (1.0,2.0)	1.5 (1.5,2.0)		
	Min, Max	1.0, 3.0	1.0, 3.0	1.0, 3.0		
DY (dyspnea)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.13	0.722
	Mean (SD)	1.7 (0.5)	1.5 (0.5)	1.6 (0.5)		
	Median (Q1,Q3)	2.0 (1.0,2.0)	1.5 (1.0,2.0)	2.0 (1.0,2.0)		
	Min, Max	1.0,2.0	1.0,2.0	1.0,2.0		
AP (appetite loss)	N (Nmiss)	18 (0)	18 (0)	36 (0)	2.99	0.084
	Mean (SD)	1.9 (0.5)	1.8 (0.5)	1.9 (0.5)		
	Median (Q1,Q3)	2.0 (2.0,2.0)	2.0 (2.0,2.0)	2.0 (2.0,2.0)		
	Min, Max	1.0,3.0	1.0,3.0	1.0,3.0		
CO (constipation)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.73	0.393
	Mean (SD)	1.7 (0.5)	1.4 (0.6)	1.5 (0.6)		
	Median (Q1,Q3)	2.0 (1.0,2.0)	1.0 (1.0,2.0)	1.5 (1.0,2.0)		
	Min, Max	1.0,2.0	1.0,3.0	1.0,3.0		
DI (diarrhea)	N (Nmiss)	18 (0)	18 (0)	36 (0)	3.43	0.064
	Mean (SD)	1.2 (0.4)	1.3 (0.6)	1.3 (0.5)		
	Median (Q1,Q3)	1.0 (1.0,1.0)	1.0 (1.0,2.0)	1 (1,1)		
	Min, Max	1.0,2.0	1.0,3.0	1.0,3.0		
FI (financial difficulties)	N (Nmiss)	18 (0)	18 (0)	36 (0)	2.0 (2.0,3.0)	1.0 (1.0,3.0)
	Mean (SD)	2.6 (0.5)	2.2 (0.6)	2.4 (0.6)		
	Median (Q1,Q3)	3.0 (2.0,3.0)	2.0 (2.0,3.0)	2.0 (2.0,3.0)		
	Min, Max	2.0,3.0	1.0,3.0	1.0,3.0		

cellular immune function. CD4 and CD8 are two important T lymphocyte subsets. A decrease in CD4+ T lymphocytes indicates a decrease in lymphocyte function and B cell antibody production. A decrease in the CD4+/CD8+ ratio reflects a reduction in the health of the immune system.

Evaluation of tumor response

CT was performed 4 weeks before study initiation and 9 weeks after the end of treatment to evaluate tumor size and status. Response rates were assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). ORR was defined as the percentage of patients who had a complete response and

partial response. DCR was defined as the percentage of patients who had a complete response, partial response, and stable disease.

Adverse events

Adverse events were reported based on the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Sample size was determined according to previous observations using the same primary outcome measure. Fifteen participants per arm were required to detect a treatment effect with 80% power and a two-sided significance level of 5% on the physical functioning score on the EORTC

Table 3 Baseline EORTC QLQ-BR23 scores

Indicators		SAOLP group	Control group	Total	Statistic(t)	P value
BRBI (body image)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.19	0.666
	Mean (SD)	1.9 (0.6)	2 (0.5)	1.9 (0.5)		
	Median (Q1,Q3)	1 (3.3,0)	1 (3,0)	2 (1.6,2)		
	Min, Max	1, 3.3	1, 3	1,3.3		
BRSFF (sexual functioning)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.98	0.323
	Mean (SD)	1.6 (0.5)	1.4 (0.5)	1.5 (0.5)		
	Median (Q1,Q3)	1 (2,0)	1 (2,0)	1 (1,2)		
	Min, Max	1, 2	1, 2	1, 2		
BRSEE (sexual enjoyment)	N (Nmiss)	11 (7)	8 (10)	36 (0)	0.73	0.394
	Mean (SD)	1.9 (0.3)	2 (0)	1.9 (0.2)		
	Median (Q1,Q3)	1 (2,0)	2 (2,0)	2 (2,2)		
	Min, Max	1, 2	2, 2	1, 2		
BRFU (future perspective)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.03	0.871
	Mean (SD)	2.5 (0.6)	2.5 (0.5)	2.5 (0.6)		
	Median (Q1,Q3)	2 (4,0)	2 (3,0)	2 (2,3)		
	Min, Max	2, 4	2, 3	2, 4		
BRST (systemic therapy side effects)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.41	0.521
	Mean (SD)	1.6 (0.3)	1.5 (0.3)	1.6 (0.3)		
	Median (Q1,Q3)	1.1 (2.3,0)	1 (2.1,0)	1.5 (1.3,1.9)		
	Min, Max	1.1, 2.3	1, 2.1	1, 2.3		
BRBS (breast symptoms)	N (Nmiss)	18 (0)	18 (0)	36 (0)	0.19	0.662
	Mean (SD)	1.6 (0.4)	1.6(0.4)	1.6 (0.4)		
	Median (Q1,Q3)	1 (2,0)	1 (2.3,0)	1.6 (1.3,2)		
	Min, Max	1, 2	1, 2.3	1, 2.3		
BRAS (arm symptoms)	N (Nmiss)	11 (7)	9 (9)	20 (16)	0.2	0.657
	Mean (SD)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)		
	Median (Q1,Q3)	1 (2.7,0)	1 (2.3,0)	1.7 (1.3,2)		
	Min, Max	1, 2.7	1, 2.3	1, 2.7		
BRHL (upset by hair loss)	N (Nmiss)	14 (4)	11(7)	27 (9)	0.14	0.705
	Mean (SD)	2 (0.6)	1.9 (0.5)	2 (0.5)		
	Median (Q1,Q3)	1 (3,0)	1(3,0)	2 (2,2)		
	Min, Max	1, 3	1, 3	1, 3		

Table 4 Baseline immune response

Indicators		SAOLP	Placebo	Total	Statistic(t)	P value
CD3	N (Nmiss)	18 (0)	18 (0)	36(0)	0.53	0.597
	Mean (SD)	68.6 (10.4)	66.9 (9.5)	67.8 (9.9)		
	Median (Q1,Q3)	66.6 (59.4,76.3)	63.8 (59.4,77.2)	65.5 (59.4,76.7)		
	Min, Max	57.6, 89.7	54.4, 84.3	54.4, 89.7		
CD4	N (Nmiss)	18 (0)	18 (0)	36 (0)	1.19	0.244
	Mean (SD)	37.3 (8.3)	34.5 (5.7)	35.9 (7.2)		
	Median (Q1,Q3)	34.4 (32.4,43.6)	34.4 (30.2,39.6)	34.4 (30.7,39.8)		
	Min, Max	28.7, 63.0	26.9, 44.2	26.9, 63.0		
CD8	N (Nmiss)	18 (0)	18 (0)	36(0)	-1.49	0.145
	Mean (SD)	25.4 (9.9)	29.8 (8.0)	27.6 (9.1)		
	Median (Q1,Q3)	24.2 (20.1,28.9)	29.8 (22.3,36.5)	26.1 (20.3,35.8)		
	Min, Max	10.9, 50.5	18.4, 43.6	10.9 (50.5)		

QLQ-C30 and EORTC QLQ-BR23. Accounting for a 15% withdrawal and dropout rate, 36 subjects, 18 per arm, were needed to ensure statistically significant results.

Continuous data are reported as mean, SD, median, minimum and maximum. Categorical variables are reported as number of cases and percentage. Standardized EORTC QLQ-C30 and EORTC QLQ-BR23 scores were calculated according to the following formulae: (1) for functional items, standardized score=[1 - (crude score-1)/range] × 100; 2) for general health and symptomatic items, standardized score=[(crude score - 1) × range] × 100. Thus, for functional and general health items, a higher standardized score indicated better patient HRQoL. In contrast, for symptomatic items, a higher standardized score indicated worse patient HRQoL. Standardized EORTC QLQ-C30 and EORTC QLQ- BR23 scores on day 21, day 42 and day 84 for patients treated with

chemotherapy and SAOLP or placebo were compared with the two-sample independent *t* test. Statistical analyses were performed with SPSS v20.0 (IBM SPSS Inc., Chicago, Illinois, USA) using a two-sided analysis. *P* < 0.05 was considered statistically significant.

Results

Patient characteristics

This study included 36 patients with breast cancer diagnosed based on biopsy or histology. All patients had stage IV ductal adenocarcinoma of the breast. Thirty patients underwent surgery, 28 patients received preoperative first-line chemotherapy, 16 patients received endocrine treatment and 10 patients received radiotherapy.

Eighteen patients each were randomized to receive SAOLP or placebo. Four patients were lost to follow-up and did not have data relevant to the primary outcome

Table 5 EORTC QLQ-C30 scores on day 21, day 48 and day 84

Indicators		Placebo	SAOLP	Statistic(t)	P value	Placebo	SAOLP	Statistic(t)	P value	Placebo	SAOLP	Statistic(t)	P value
		(day 21)	(day 21)	(day 21)	(day 21)	(day 42)	(day 42)	(day 42)	(day 42)	(day 84)	(day 84)	(day84)	(day 84)
PF (physical function)	N (Nmiss)	17 (1)	17 (1)	1.21	0.235	17 (1)	15 (3)	6.95	<0.001	17 (1)	15 (3)	7.75	<0.001
	Mean (SE)	78.4(2.0)	74.9(2.1)			83.1(2.1)	58.7(2.9)			84.7(1.9)	57.3(3.1)		
RF (role function)	N (Nmiss)	17 (1)	17 (1)	1.6	0.119	17 (1)	15 (3)	4.12	<0.001	17 (1)	15 (3)	8.36	<0.001
	Mean (SE)	82.4 (5.0)	71.6 (4.5)			87.3 (4.2)	58.9 (5.6)			90.2 (3.5)	48.9 (7.0)		
EF (emotional functioning)	N (Nmiss)	17 (1)	17 (1)	0.93	0.362	17 (1)	15 (3)	6.47	<0.001	17 (1)	15 (3)	6.76	<0.001
	Mean (SE)	82.4 (4.1)	76.5 (4.9)			93.6 (2.4)	60.6 (4.7)			94.6 (2.1)	60.0 (4.9)		
CF (cognitive function)	N (Nmiss)	17 (1)	17 (1)	1.94	0.061	17 (1)	15 (3)	2.94	0.006	17 (1)	15 (3)	6.19	<0.001
	Mean (SE)	83.3 (3.2)	74.5 (3.2)			92.2 (3.2)	76.7 (4.2)			92.2 (2.9)	63.3 (3.7)		
SF (social function)	N (Nmiss)	17 (1)	17 (1)	1.71	0.096	17 (1)	15 (3)	5.6	<0.001	17 (1)	15 (3)	6.42	<0.001
	Mean (SE)	68.6 (4.7)	58.8 (3.2)			79.4 (3.7)	46.7 (4.7)			80.4 (3.6)	40.0 (5.3)		
QL (quality)	N (Nmiss)	17 (1)	17 (1)	2.56	0.015	17 (1)	15 (3)	10.53	<0.001	17 (1)	15 (3)	13.59	<0.001
	Mean (SE)	60.8 (2.7)	50.0 (3.2)			78.9 (2.4)	37.2 (3.2)			81.4 (1.5)	32.8 (3.4)		
FA (fatigue)	N (Nmiss)	17 (1)	17 (1)	-1.21	0.233	17 (1)	15 (3)	-6.72	<0.001	17 (1)	15 (3)	-8.52	<0.001
	Mean (SE)	26.1 (3.9)	32.0 (2.8)			13.1 (3.0)	51.1 (4.9)			9.8 (2.3)	62.2 (6.0)		
NV (nausea and vomiting)	N (Nmiss)	17 (1)	17 (1)	-1.37	0.18	17 (1)	15 (3)	-1.92	0.064	17 (1)	15 (3)	-2.47	0.019
	Mean (SE)	6.9 (2.9)	13.7 (4.1)			4.9 (2.8)	15.6 (5.0)			4.9 (2.4)	16.7 (4.3)		
PA (pain)	N (Nmiss)	17 (1)	17 (1)	-0.32	0.754	17 (1)	15 (3)	-2.3	0.029	17 (1)	15 (3)	-3.39	0.002
	Mean (SE)	21.6(4.7)	23.5(4.1)			14.7(3.7)	30.0(5.7)			11.8(4.0)	34.4(5.5)		
DY (dyspnea)	N (Nmiss)	17 (1)	17 (1)	-0.68	0.28	17 (1)	15 (3)	-2.67	0.012	17 (1)	15 (3)	-3.68	0.001
	Mean (SE)	17.6 (4.2)	21.6 (4.0)			9.8 (3.8)	24.4 (3.9)			5.9 (4.3)	26.7 (3.6)		
AP (appetite loss)	N (Nmiss)	17 (1)	17 (1)	-0.65	0.518	17 (1)	15 (3)	-2.91	0.007	17 (1)	15 (3)	-2.23	0.033
	Mean (SE)	25.5 (4.5)	29.4 (3.9)			13.7 (4.1)	28.9 (3.0)			19.6 (4.1)	33.3 (4.6)		
CO (constipation)	N (Nmiss)	17 (1)	17 (1)	0.34	0.734	17 (1)	15 (3)	-1.4	0.171	17 (1)	15 (3)	-2.3	0.029
	Mean (SE)	13.7 (4.1)	17.8 (4.0)			5.9 (3.2)	13.3 (4.4)			3.9 (2.7)	15.6 (4.4)		
DI (diarrhea)	N (Nmiss)	17 (1)	17 (1)	-0.79	0.434	17 (1)	15 (3)	-2.05	0.049	17 (1)	15 (3)	-2.61	0.014
	Mean (SE)	5.9 (3.2)	9.8 (3.8)			2.0 (2.0)	11.1 (4.2)			0 (0)	13.3 (5.4)		
FI (financial difficulties)	N (Nmiss)	17 (1)	17 (1)	0.3	0.765	17 (1)	15 (3)	-2.06	0.048	17 (1)	15 (3)	-4.67	<0.001
	Mean (SE)	49.0 (4.2)	47.1 (5.0)			41.2 (3.5)	57.8 (7.6)			35.3 (4.5)	71.1 (6.4)		

Table 6 EORTC QLQ-BR23 scores on day 21, day 48 and day 84

Indicators		SAOLP	Placebo	Statistic(t)	P value	SAOLP	Placebo	Statistic(t)	P value	SAOLP	Placebo	Statistic(t)	P value
		(day 21)	(day 21)	(day 21)	(day 21)	(day 42)	(day 42)	(day 42)	(day 42)	(day 84)	(day 84)	(day84)	(day 84)
BRBI (body image)	N (Nmiss)	17 (1)	17 (1)	2.1	0.044	17 (1)	15 (3)	6.98	<0.001	17 (1)	15 (3)	7.08	<0.001
	Mean (SE)	77.9 (4.3)	64.2 (4.9)			83.8 (4.0)	45.0 (3.8)			85.8 (3.3)	46.7 (4.6)		
BRSFF (sexual functioning)	N (Nmiss)	17 (1)	17 (1)	-1.02	0.315	17 (1)	15 (3)	-1.37	0.181	17 (1)	15 (3)	-1.37	0.181
	Mean (SE)	82.4 (4.2)	88.2 (4.0)			83.3 (4.0)	91.1 (3.9)			83.3 (4.0)	91.1 (3.9)		
BRSEE (sexual enjoyment)	N (Nmiss)	10 (8)	6 (12)	0.76	0.458	10 (8)	10 (8)	-1.9	0.074	11 (7)	10 (8)	-1.53	0.144
	Mean (SE)	70.0 (3.3)	66.7 (0)			73.3 (4.4)	86.7 (5.4)			75.8 (4.7)	86.7 (5.4)		
BRFU (future perspective)	N (Nmiss)	17 (1)	17 (1)	2.58	0.015	17 (1)	15 (3)	4.36	<0.001	17 (1)	15 (3)	6.14	<0.001
	Mean (SE)	58.8 (3.5)	45.1 (4.0)			66.7 (5.0)	35.6 (5.1)			68.6 (4.5)	22.2 (6.2)		
BRST (systemic therapy side effects)	N (Nmiss)	17 (1)	17 (1)	-0.47	0.641	17 (1)	15 (3)	-2.92	0.007	17 (1)	15 (3)	-4	<0.001
	Mean (SE)	18.2 (2.3)	19.9 (2.7)			12.6 (3.0)	25.1 (3.0)			11.5 (2.3)	26.7 (3.0)		
BRBS (breast symptoms)	N (Nmiss)	17 (1)	17 (1)	-0.42	0.675	16 (2)	15 (3)	-4.07	<0.001	17 (1)	15 (3)	-5.21	<0.001
	Mean (SE)	19.6 (2.7)	21.6 (3.8)			12.0 (2.7)	30.6 (3.7)			8.3 (2.3)	30.0 (3.6)		
BRAS (arm symptoms)	N (Nmiss)	17 (1)	17 (1)	-0.68	0.502	17 (1)	15 (3)	-1.98	0.057	17 (1)	15 (3)	-2.72	0.011
	Mean (SE)	17.6 (2.7)	20.3 (2.7)			15.7 (2.5)	23.7 (3.2)			14.4 (2.3)	25.2 (3.3)		
BRHL (upset by hair loss)	N (Nmiss)	12 (6)	12 (6)	-0.69	0.496	8 (10)	10 (8)	-1.56	0.138	11 (7)	11 (7)	-1.78	0.091
	Mean (SE)	33.3 (7.1)	38.9 (3.7)			29.2 (11.7)	50.0 (7.5)			24.2 (9.1)	42.4 (4.7)		

measure; therefore, data from 32 patients were included in the final analysis (Fig. 1).

The demographic and baseline characteristics of the included patients are summarized in Table 1. Patients had a median age of 55.4 years (range 49.2–63.7). 22.2% of patients received first-line chemotherapy, and 77.8% of patients received second- or later-line chemotherapy.

EORTC QLQ-BR23

There were no significant differences in baseline EORTC QLQ-C30 (Table 2), EORTC QLQ-BR23 (Table 3) or immune response in patients who received SAOLP or placebo (Table 4).

EORTC QLQ-C30 on day 21, day 42 and day 84

On day 21, the score on the global health status/QoL scale was significantly higher in patients who received SAOLP compared to placebo. There were no significant differences in scores on the functional scales or the symptom scales. On day 42, scores on the five functional scales (physical, role, cognitive, emotional and social) and the global health status/QoL scale were significantly higher in patients who received SAOLP compared to placebo ($P < 0.05$). Scores on six of the symptom scales (fatigue, pain, dyspnea, loss of appetite, diarrhea and financial difficulties) were significantly lower in patients who received SAOLP compared to placebo ($P < 0.05$). On day 84, scores on the

Table 7 Immune response on day 21, day 48, and day 84

Indicators		SAOLP (day 21)	Placebo (day 21)	Statistic(t)	P value
CD3	N (Nmiss)	17 (1)	17 (1)	1.86	0.073
	Mean (SE)	70.5 (2.3)	64.4 (2.4)		
CD4	N (Nmiss)	17 (1)	17 (1)	2.05	0.049
	Mean (SE)	36.7 (1.4)	32.9 (1.1)		
CD8	N (Nmiss)	17 (1)	17 (1)	1.25	0.219
	Mean (SE)	30.1 (2.6)	25.9 (2.1)		
CD4/CD8	N (Nmiss)	17 (1)	17 (1)	0.15	0.879
	Mean (SE)	1.38 (0.14)	1.36 (0.08)		
Indicators		SAOLP (day 42)	Placebo (day 42)	Statistic(t)	P value
CD3	N (Nmiss)	17 (1)	14 (3)	10.47	<0.001
	Mean (SE)	76.1 (1.4)	59.0 (5.0)		
CD4	N (Nmiss)	17 (1)	14 (3)	6.12	<0.001
	Mean (SE)	39.2 (1.4)	29.0 (0.6)		
CD8	N (Nmiss)	17 (1)	14 (3)	5.52	<0.001
	Mean (SE)	34.6 (2.3)	20.5 (0.6)		
CD4/CD8	N (Nmiss)	17 (1)	14 (3)	-2.02	0.055
	Mean (SE)	1.22 (0.09)	1.43 (0.04)		
Indicators		SAOLP (day 84)	Placebo (day 84)	Statistic(t)	P value
CD3	N (Nmiss)	17 (1)	14 (4)	15.1	<0.001
	Mean (SE)	77.8 (1.2)	57.7 (0.4)		
CD4	N (Nmiss)	17 (1)	14 (4)	5.31	<0.001
	Mean (SE)	42.0 (1.5)	29.0 (2.2)		
CD8	N (Nmiss)	17 (1)	14 (4)	8.82	<0.001
	Mean (SE)	36.9 (1.8)	18.9 (0.3)		
CD4/CD8	N (Nmiss)	17 (1)	14 (4)	-2.58	0.015
	Mean (SE)	1.20 (0.07)	1.53 (0.11)		

Table 8 BMI on day 21, day 48 and day 84

Indicators		SAOLP	Placebo	Statistic(t)	P value
BMI_Day 21	N (Nmiss)	17 (1)	17 (1)	0.06	0.951
	Mean (SE)	23.7 (0.7)	23.6 (0.7)		
BMI_Day 42	N (Nmiss)	17 (1)	15 (3)	0.2	0.84
	Mean (SE)	23.4 (0.8)	23.2 (0.7)		
BMI_Day 84	N (Nmiss)	17 (1)	15 (3)	1.49	0.147
	Mean (SE)	23.6 (0.7)	22.2 (0.5)		

five functional scales (physical, role, cognitive, emotional and social) and the global health status/QoL scale were significantly higher in patients who received SAOLP compared to placebo ($P < 0.05$). Scores on the nine symptom scales (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea and financial difficulties) were significantly lower in patients who received SAOLP compared to placebo (Table 5).

EORTC QLQ-BR23 on day 21, day 42 and day 84

On day 21, scores on two of the functional scales (body image and future perspective) were significantly higher in patients who received SAOLP compared to placebo ($P < 0.05$). On day 42, scores on two of the functional scales (body image and future perspective) were significantly higher and scores on two of the symptom scales (systemic therapy side effects and breast symptoms) were significantly lower in patients who received SAOLP compared to placebo ($P < 0.05$). On day 84, scores on two of the functional scales (body image and future perspective) were significantly higher and scores on three of the symptom scales (systemic therapy side effects, breast symptoms and arm symptoms) were significantly lower in patients who received SAOLP compared to placebo ($P < 0.05$) (Table 6).

Immune response on day 21, day 42 and day 84

On day 21, there were no significant differences in the number of CD3, CD4 or CD8 cells or the CD4/CD8 ratio in patients who received SAOLP or placebo. On day 42, the number of CD3, CD4 and CD8 cells were significantly higher in patients who received SAOLP compared to placebo ($P < 0.05$). On day 84, the number of CD3, CD4 and CD8 cells and the CD4/CD8 ratio were significantly higher in patients who received SAOLP compared to placebo ($P < 0.05$) (Table 7).

Objective effective rate and disease control rate

ORR was 7.1% and 8.3% ($P = 1.000$) in patients who received SAOLP or placebo, respectively. DCR was 100 and 83.3% ($P = 0.203$) in patients who received SAOLP or placebo, respectively. There were no significant differences in ORR or DCR in patients who received SAOLP or placebo (Table 8).

BMI

On day 21, day 42 and day 84, BMI was higher in patients who received SAOLP compared to placebo, but the differences were NS.

Safety

Across all enrolled patients, 47.22% (17/36) of patients reported an adverse event. Most of the adverse events were Grade 1 or 2. Frequent nonhematological toxicities included nausea/vomiting, fatigue and proteinuria. Among patients who received SAOLP, 50% (9/18) of patients reported an adverse event. Among patients who received placebo, 44.4% (8/18) of patients reported an adverse event. No patients reported a serious drug-related adverse event. All adverse events were considered related to chemotherapy.

Discussion

This clinical trial was designed to evaluate the safety and efficacy of SAOLP for improving HRQoL and immune response during chemotherapy in Chinese patients with breast cancer. Breast cancer treatment involves a multimodal approach that includes chemotherapy [15]. Chemotherapy can significantly improve survival and quality of life compared to best supportive care in patients with breast cancer [16–18]. However, adverse effects of chemotherapy in patients with malignant tumors include fatigue, nausea and vomiting, bone marrow suppression, renal toxicity, neurotoxicity and cancer-related cognitive impairment [19]. Accordingly, most patients with breast cancer experience a decline in HRQoL due to tumor burden and treatment effects, such as loss of appetite, reduction in body mass and emotional instability. Improving the quality of life of patients with cancer is essential to decrease psychological distress and enhance coping [20,21]. Disease, such as malignant tumor, may weaken the immune system, which can have a direct effect on treatment outcomes and prognosis. Therapies that manipulate the immune system may achieve long-term cancer regression.

SAOLP consists of polypeptides and nucleotides extracted from the pig spleen, which may enhance the body's cellular immunity, stimulate the release of a variety of immune molecules and promote antitumor immunity. SAOLP has potential to shorten the course of the disease and improve HRQoL in patients with immune dysfunction [22]. However, the effect of SAOLP during chemotherapy in patients with cancer is unclear. In one study [13], immunity and DCRs were improved in patients with gastrointestinal cancer ($n = 60$) treated with oxaliplatin and capecitabine combined with SAOLP compared to oxaliplatin and capecitabine combined with placebo. To the authors' knowledge, the present study is the first randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of SAOLP for improving HRQoL and immune response during chemotherapy in patients with breast cancer. Data suggest that SAOLP improved HRQoL and immune response in the study population. SAOLP was well tolerated as there were no significant differences in ORR, DCR or adverse events in patients receiving SAOLP compared to placebo.

There were several limitations to our study. First, the sample size was small. Second, SAOLP was only used during two cycles of chemotherapy. Larger, longer-term studies are required to confirm the safety and efficacy of SAOLP for improving HRQoL and immune response in patients with advanced cancer.

Conclusion

SAOLP in combination with chemotherapy may improve HRQoL and immune response in patients with advanced

cancer. SAOLP represents a convenient and safe adjuvant therapy.

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Conflicts of interest

There are no conflicts of interest.

References

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**:7–30.
- 2 Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; **69**:363–385.
- 3 DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**:438–451.
- 4 Sitlinger A, Zafar SY. Health-related quality of life: the impact on morbidity and mortality. *Surg Oncol Clin N Am* 2018; **27**:675–684.
- 5 Di Maio M, Perrone F. Quality of life in elderly patients with cancer. *Health Qual Life Outcomes* 2003; **1**:44.
- 6 Mahfouz MA, Almaghrabi MY. Quality of life for elderly breast cancer patients: a new regard. *Transl Cancer Res* 2020; **9**:S122–S125.
- 7 Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. *BMJ* 1998; **317**:771–775.
- 8 Shen XF, Zhou A, Huang Q. An analysis of spleen aminopeptide oral lyophilized powder in the treatment of children after tonsillectomy. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2017; **31**:1690–1692.
- 9 Tan TJ, Liu GY, Liao JY, Zeng GQ, Gan L, Shui-Lan LU, et al. The effect of spleen aminopeptide on treatment and prevention of pediatric repeated respiratory infection and its influence on T lymphocyte subset. *Med Recapitulate* 2015; **21**:2257–2258.
- 10 Wang W, Yu-Xue LI, Min HU. Efficacy of spleen aminopeptide combined with vitamin A and E in the treatment of children with recurrent respiratory tract infection and its immune function. *Clin Misdiagn Misther* 2019; **32**:21–24.
- 11 Boying DU, Gao J, Liu C, Weiwei MA, Qin X, Suwen XU. Observation of the curative effect of Yupingfeng granule and spleen aminopeptide in the children with pneumonia and syndrome of lung-spleen deficiency in recovery stage. *Modern J Integr Trad Chin Western Med* 2017; **26**:3883–3885.
- 12 Min M, Huaming S, Hua L. Effects of spleen aminopeptide oral lyophilized powder on immune function of patients with chronic hepatitis B. *Modern J Integr Trad Chinese Western Med* 2010; **19**:1953.
- 13 Liang XU, Ming-xing Z, Bang-wei CAO. Therapeutic efficacy of oral lyophilized powder splenic aminopeptide combined with platinum-containing chemotherapy in patients with gastrointestinal tumors. *Chin J Clin Oncol Rehabil* 2019; **26**:1043–1047.
- 14 Koller M, Aaronson NK, Blazeby J, Bottomley A, Dewolf L, Fayers P, et al.; EORTC Quality of Life Group. Translation procedures for standardised quality of life questionnaires: The European Organisation for Research and Treatment of Cancer (EORTC) approach. *Eur J Cancer* 2007; **43**:1810–1820.
- 15 Teraoka S, Sato E, Narui K, Yamada A, Fujita T, Yamada K, et al. Neoadjuvant chemotherapy with anthracycline-based regimen for BRCAness tumors in triple-negative breast cancer. *J Surg Res* 2020; **250**:143–147.
- 16 Prioli KM, Pizzi LT, Kash KM, Newberg AB, Morlino AM, Matthews MJ, Monti DA. Costs and effectiveness of mindfulness-based art therapy versus

- standard breast cancer support group for women with cancer. *Am Health Drug Benefits* 2017; **10**:288–295.
- 17 Freedman RA, Partridge AH. Emerging data and current challenges for young, old, obese, or male patients with breast cancer. *Clin Cancer Res* 2017; **23**:2647–2654.
 - 18 Hausmann J, Nestle-Kraemling C, Bölke E, Wollandt S, Speer V, Djepmo Njanang FJ, *et al.* Long-term quality of life after preoperative radiochemotherapy in patients with localized and locally advanced breast cancer. *Strahlenther Onkol* 2020; **196**:386–397.
 - 19 Campbell KL, Zdravec K, Bland KA, Chesley E, Wolf F, Janelins MC. The effect of exercise on cancer-related cognitive impairment and applications for physical therapy: systematic review of randomized controlled trials. *Phys Ther* 2020; **100**:523–542.
 - 20 Konieczny M, Cipora E, Sygit K, Fal A. Quality of life of women with breast cancer and socio-demographic factors. *Asian Pac J Cancer Prev* 2020; **21**:185–193.
 - 21 Mojgan F, Karimollah HT, Moslemi D. Analysis of quality of life in breast cancer survivors using structural equation modelling: the role of spirituality, social support and psychological well-being. *Int Health* 2020; **12**:354–363.
 - 22 Hua YC, Wang J. Process of splenic aminopeptide oral freeze-dried powder on patients with immune dysfunction. *Eval Anal Drug-Use Hosp China* 2019; **19**:644–646.