Benefits of adjuvant treatment with the Pingxiao capsule in patients with early breast cancer: A single-center retrospective cohort study

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Received January 19, 2024; Accepted May 22, 2024

DOI: 10.3892/ol.2024.14499

Abstract. Early breast cancer (EBC) is cancer that has not spread beyond the breast or the axillary lymph nodes. The present retrospective cohort study investigated the efficacy and safety of the Pingxiao capsule (PXC), which contains a formula of traditional Chinese herbs, as adjuvant therapy in patients with EBC in a single Chinese academic medical center. Patients with EBC who had received surgery and chemotherapy were analyzed and divided into the PXC and non-PXC groups. Disease-free survival (DFS) time, overall survival (OS) time, demographic characteristics and adverse events were examined. Kaplan-Meier survival curves were used to compare the differences in DFS and OS. A total of 371 participants with a median age of 54 years were included in this study. The median DFS time of all patients was 101 months. The overall DFS rate was 72.1% in the PXC group compared with 63.6% in the non-PXC group. For women with hormone receptor-negative tumors, the DFS rate in the PXC group was significantly higher than that in the non-PXC group, irrespective of node status. Adjuvant treatment with PXC for ≥3 months was associated with significantly longer median DFS time compared with that in the non-PXC group. In addition, the incidence of neutropenia rated to be grade 2 or higher was significantly lower in the PXC group compared with that in the control group, and a markedly, but non-significantly, lower prevalence of nausea was observed in PXC group (0 vs. 4.1%). In conclusion, PXC as an adjuvant therapy along with chemotherapy is associated with prolonged DFS times in patients with EBC when compared with chemotherapy alone. The therapeutic value of combined PXC and systemic chemotherapy should be further elucidated by rigorous prospective clinical trials.

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Key words: Pingxiao capsules, chemotherapy, breast cancer, disease-free survival, adverse event

Introduction

Breast cancer is the most commonly diagnosed cancer in women and the leading cause of cancer death, followed by lung and colorectal cancer (1). Decades of research have shown that breast cancer is a complex and heterogeneous disease. Clinical outcomes of breast cancer have substantially improved over the years with significant advances in treatment options. The latest developments in adjuvant therapies, particularly immunotherapy and antibody-drug conjugates, have demonstrated improved survival rates in patients with breast cancer. However, their therapeutic effects are known to be transient, and development of drug resistance in some patients limits its further use. Breast cancer remains a major contributor to mortality and morbidity (2). Therefore, it is necessary to continue efforts to identify novel adjuvant treatment strategies to optimize survival and quality of life for patients with breast cancer. Traditional Chinese herbs (TCHs) have demonstrated unique potential as they have shown efficacy in breast cancer treatment while boasting a significantly more favorable side effect profile compared with standard radiotherapy and chemotherapy. The mechanisms of action for TCHs is not yet fully elucidated but has been associated with the inhibition of cancer growth, the reduction of metastasis and invasion, the promotion of cancer cell apoptosis and the enhancement of the immune response (3). The Pingxiao capsule (PXC) contains a well-known TCH formula that has been widely used by Chinese patients as an alternative medicine adjunct in the treatment of cancer (4). The typical PXC formula consists of a mixture of *Strychnos nux-vomica* L., *Curcuma wenyujin* Y. H., *Agrimonia pilosa* Ledeb., *Toxicodendron vernicifluum*, *Trogopterus* dung, alumen, potassium nitrate (saltpeter) and *Citrus aurantium* L. (5).

Of these ingredients, *Curcuma wenyujin*, which contains curcumin, has been identified to have anti-tumor and anti-inflammatory effects (3).

Early breast cancer (EBC) is cancer is found only in the breast or nearby lymph nodes and has not spread to other parts of the body. The present retrospective cohort study was conducted in patients with operable EBC who were treated at a university affiliated academic hospital in order to investigate the clinical efficacy of PXC as a novel adjuvant agent and its potential to alleviate the side effects of systemic chemotherapy.

Patients and methods

Data source. A chart review was retrospectively performed on 371 patients who underwent surgery for EBC in the Department of Breast Surgery of the First Hospital of China Medical University (CMU; Shenyang, China) between August 2011 and March 2016.

Patient selection. Inclusion criteria used were as follows: i) Patients with an established diagnosis of EBC, defined as histological diagnosis of operable stage I to stage III invasive ductal carcinoma with achievement of an R_0 resection; ii) patients aged between 18 and 75 years; and iii) patients who underwent standard surgical treatment and adjuvant chemotherapy. All patients included in the study received at least one of the following: Chemotherapy, radiotherapy, endocrine therapy and/or anti-human epidermal growth factor receptor 2 (HER2) therapy, according to the NCCN guidelines (6,7). This included those with N0 cancer, who received chemotherapy due to high-risk factors such as an estrogen receptor (ER) expression level of <50% and/or a Ki67 level ≥30%. PXC used by the study population was manufactured by Xi'an Charoen Pokphand Pharmaceutical, Co., Ltd., (batch no. 1712140), which is the sole manufacturer and distributor of PXC. Patients were divided into the PXC group (patients who received PXC treatment) and the non-PXC group (patients who did not receive PXC) per chart review.

Treatment. The present study adjusted for confounders using the principle of restriction and matching. Subjects in the two cohorts (PXC vs. non-PXC) were matched in terms of age, tumor stage, axillary metastasis, hormonal receptor status, HER2 status and molecular subtypes to eliminate potential confounding factors. In addition, only those who had received PXC treatment within 1 year of diagnosis and had received standard dosing of PXC (4-8 capsules, three times a day for >1 month, for a maximum of 6 months; the dosage of each capsule is 230 milligrams) were included. Patients must also have completed any indicated standard treatment in addition to surgery (i.e. chemotherapy, radiotherapy, endocrine therapy accordingly) before PXC treatment, and those who did not comply with standard treatments were excluded from the study. Disease-free survival (DFS) was defined as the time from the date of surgery to either tumor recurrence or death due to any cause, and overall survival (OS) was defined as the interval between the date of surgery and the date of patient death or the last follow-up visit.

The study protocol was reviewed by the CMU Ethics Committee Institutional Review Board (approval no. 2020 NO.203). Approval was granted prior to the commencement of the study and the requirement for written consent was waived.

Adverse events (AEs) after chemotherapy. All subjects underwent chemotherapy. A total of 105 patients were treated with a docetaxel + anthracyclines + cyclophosphamide (TEC or EC-T) regimen, 12 patients were treated with an anthracyclines + cyclophosphamide (EC) regimen, 88 patients were treated with a docetaxel + cyclophosphamide (TC) regimen, 20 patients were treated with a docetaxel + platinum (DP) regimen, 121 patients were treated with an anthracyclines + cyclophosphamide + docetaxel + herceptin (EC-TH) regimen, 14 patients were treated with a 5-fluorouracil + anthracyclines + cyclophosphamide (CEF) regimen and 11 patients were treated with a CEF-T regimen. For all patients, treatments were initiated within 6 weeks of surgery according to NCCN. In addition, for patients with ER+ expression ≥10%, regardless of PR expression, endocrine therapy should be completed for 5 years. Data for AEs was obtained through chart review of routine documentation. All patients with breast cancer were routinely followed up in the Outpatient Clinic immediately before starting chemotherapy and all patients underwent routine laboratory tests. Patients were also followed up at an interval of 14 days after starting chemotherapy and then at the end of the first treatment cycle, 21 days after starting chemotherapy, during which they were admitted for observation. AEs were documented for every cycle of treatment by phone or during follow-up visits using the Common Terminology Criteria for Adverse Events version 4.0 (8). Treatment was either suspended or terminated for patients with AEs that were of grade 2 or higher during chemotherapy, and the period for which the agent was administered at the prescribed dose (not including the period when the dose was reduced) was recorded. Incidence of AEs, and the completion rate of the first cycle of chemotherapy at the prescribed dose were tabulated.

Statistical analysis. The primary objective of the present study was to assess the efficacy and survival benefit of PXC-based adjuvant therapy, and if this was significant, to identify prognostic factors for its use. Participant demographics and characteristic such as age, tumor stage, axillary metastasis status, hormonal receptor status, HER2 status and molecular subtypes were reviewed and tabulated. Descriptive statistics were reported as proportions and medians. Frequencies of tumor characteristics and response rates were compared using the χ^2 test or Fisher's exact test. DFS and OS were demonstrated using the Kaplan-Meier survival curve. The log-rank test was used to compare two or more survival curves, and Cox's proportional hazards regression models were used to analyze the independent predictors for recurrence. Survival duration was calculated starting from the time of surgery. $P \leq 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS 12.0 for Windows (SPSS Inc.).

Results

Patient characteristics. A total of 371 patients (age range, 27-65 years; median age, 50) met the inclusion criteria and

Table I. Demographics and baseline characteristics.

Parameters	PXC, n (%)	Non-PXC, n (%)	χ^2/Fisher's exact test value	P-value
Sex				
Female	154 (100)	217 (100)		
Age, years (%)				
≤50	87 (56)	107 (49)	1.864	0.172
>50	67 (44)	110 (51)		
Tumor stage			6.795	0.075
T1	35 (23)	41 (19)		
T2	103 (67)	154 (71)		
T3	9 (6)	20 (9)		
T4	7 (5)	2 (1)		
Axillary metastasis			3.994	0.259
N0	88 (57)	119 (55)		
N1	40 (26)	44 (20)		
N2	21 (14)	43 (20)		
N3	5 (3)	11 (5)		
Hormonal receptor			1.603	0.206
Positive	121 (79)	158 (73)		
Negative	33 (21)	59 (27)		
HER2			0.414	0.520
Positive	49 (32)	76 (35)		
Negative	105 (68)	141 (65)		
Molecular subtype			2.316	0.509
Luminal A	28 (18)	36 (17)		
Luminal B	93 (60)	122 (56)		
HER2-positive	13 (8)	18 (8)		
Triple-negative	20 (13)	41 (19)		

were included in this study. Patients were followed up from 22 to 137 months, with the median follow-up time being 101 months. During the follow-up period, 122 patients (32.9%) experienced recurrence and 73 patients (19.7%) died. There were 154 patients (41.5%) in the PXC treatment group and 217 (58.5%) in the non-PXC group. Of those in the PXC group, 62 (16.7% of total) patients received treatment for 1 month, and 92 (24.8% of total) patients received treatment for ≥3 months, with an overall range of treatment duration of 1-6 months.

Subjects in the two cohorts (PXC vs. non-PXC) were similar in terms of age (P=0.172), tumor stage (P=0.075), axillary metastasis (P=0.259), hormonal receptor status (P=0.206), HER2 status (P=0.520) and molecular subtype (P=0.509), as demonstrated in Table I. Most patients had tumor ER^+ expression ≥10% (79% in PXC group, 73% in non-PXC group) and >70% of patients in each group had PR^+ tumors. Of the patients in the PXC group with ER^+ tumors, 100% patients received endocrine therapy when ER^+ expression ≥10%, and of the patients in the non-PXC group with ER^+ tumors, 96% received endocrine therapy. Most $HER2^+$ patients (98.0% of patients in the PXC group and 96.1% of patients in the non-PXC group) received anti-HER2 therapy. All cases of TNBC received 6-8 cycles of chemotherapy with TEC, EC-T or DP regimens (data not shown).

Efficacy analysis. At the conclusion of the study period, the overall DFS rate was 72.1% in the PXC group compared with 63.6% in the non-PXC group. However, Kaplan-Meier analysis showed no significant difference between the DFS rates of the PXC and non-PXC groups (P=0.098; Fig. 1A). In addition, OS was not significantly different between the PXC and non-PXC groups (P=0.557; Fig. 1B).

Subgroup analyses were performed to assess the effects of the administration duration of PXC, with subjects divided into groups who have received 1-3 months of PXC therapy and those with ≥3 months of PXC therapy, both of which were compared with the non-PXC group (Fig. 2). The results showed that the DFS rates were significantly higher in the PXC group with at least 3 months of treatment compared with those in the non-PXC group (76.1 vs. 63.6%, respectively; P=0.043 Fig. 2A). However, such a difference was not observed for OS (P=0.258 Fig. 2B). There was no significant difference in DFS (P=0.703) or OS (P=0.707) between those who used PXC for 1-3 months and those who did not use PXC (Fig. 2C and D).

Subgroup analysis was conducted between those who took PXC for ≥3 months and those who did not. In patients with hormone ER-negative tumors, the DFS rate in the PXC group (90.9%) was significantly higher than that in the non-PXC

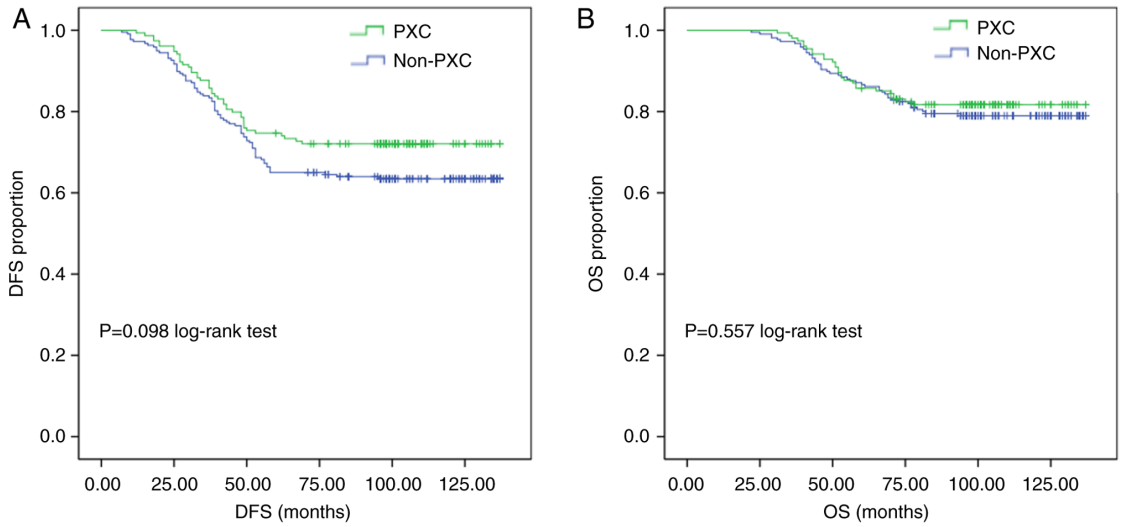

Figure 1. Kaplan-Meier curve of DFS and OS in patients with early breast cancer (irrespective of nodal status) treated with or without PXC. (A) DFS and (B) OS curve for the PXC and non-PXC groups. DFS, disease-free survival; OS, overall survival; PXC, Pingxiao capsule.

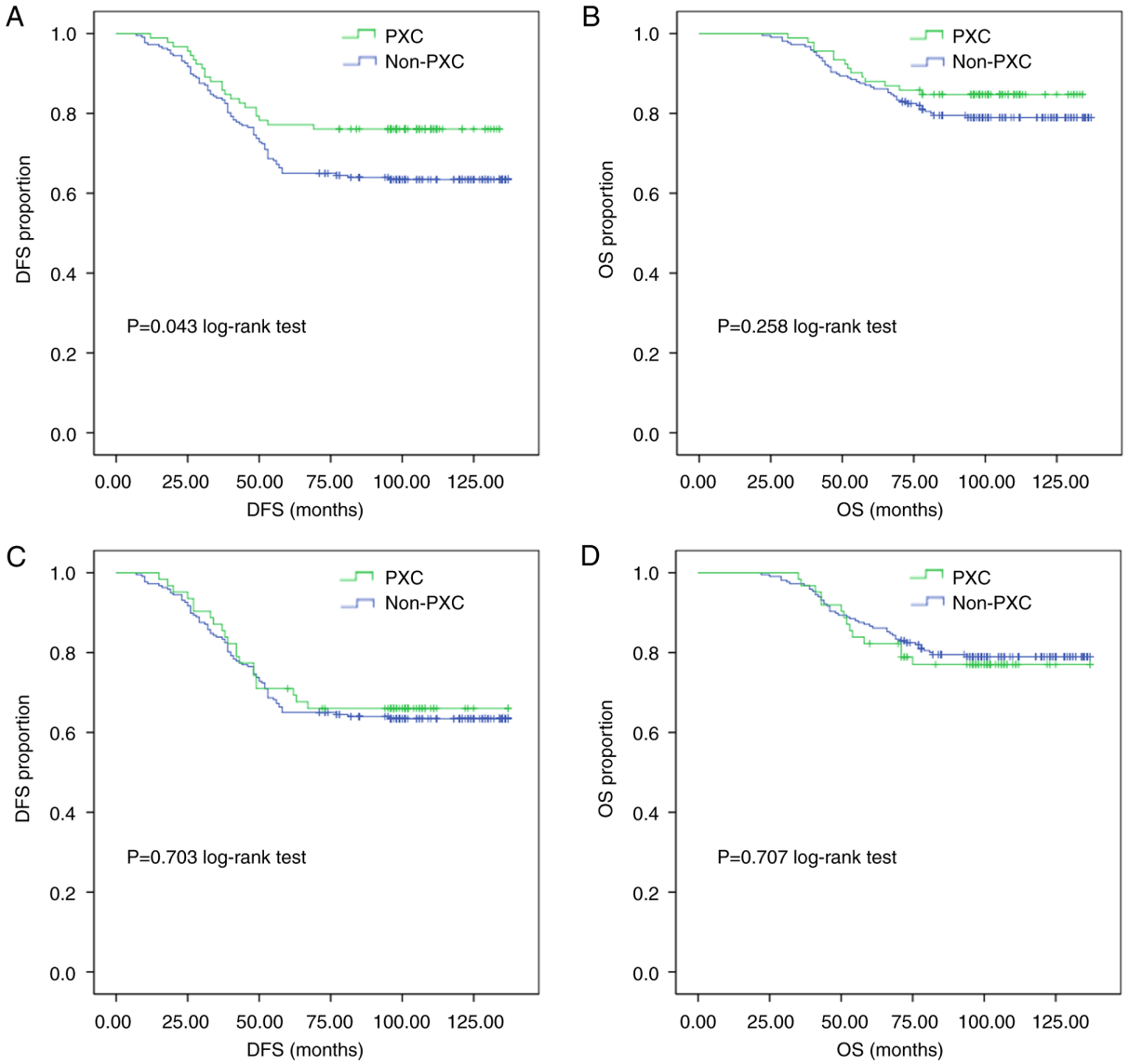

Figure 2. Kaplan-Meier curve of DFS and OS in patients with early breast cancer (irrespective of nodal status) treated with or without PXC. DFS and OS curves for the PXC and non-PXC groups according to treatment duration (1-<3 vs. ≥3 months). (A) DFS and (B) OS curves for the PXC ≥3 months and non-PXC groups. (C) DFS and (D) OS curves for the PXC 1-3 months and non-PXC groups. DFS, disease-free survival; OS, overall survival; PXC, Pingxiao capsule.

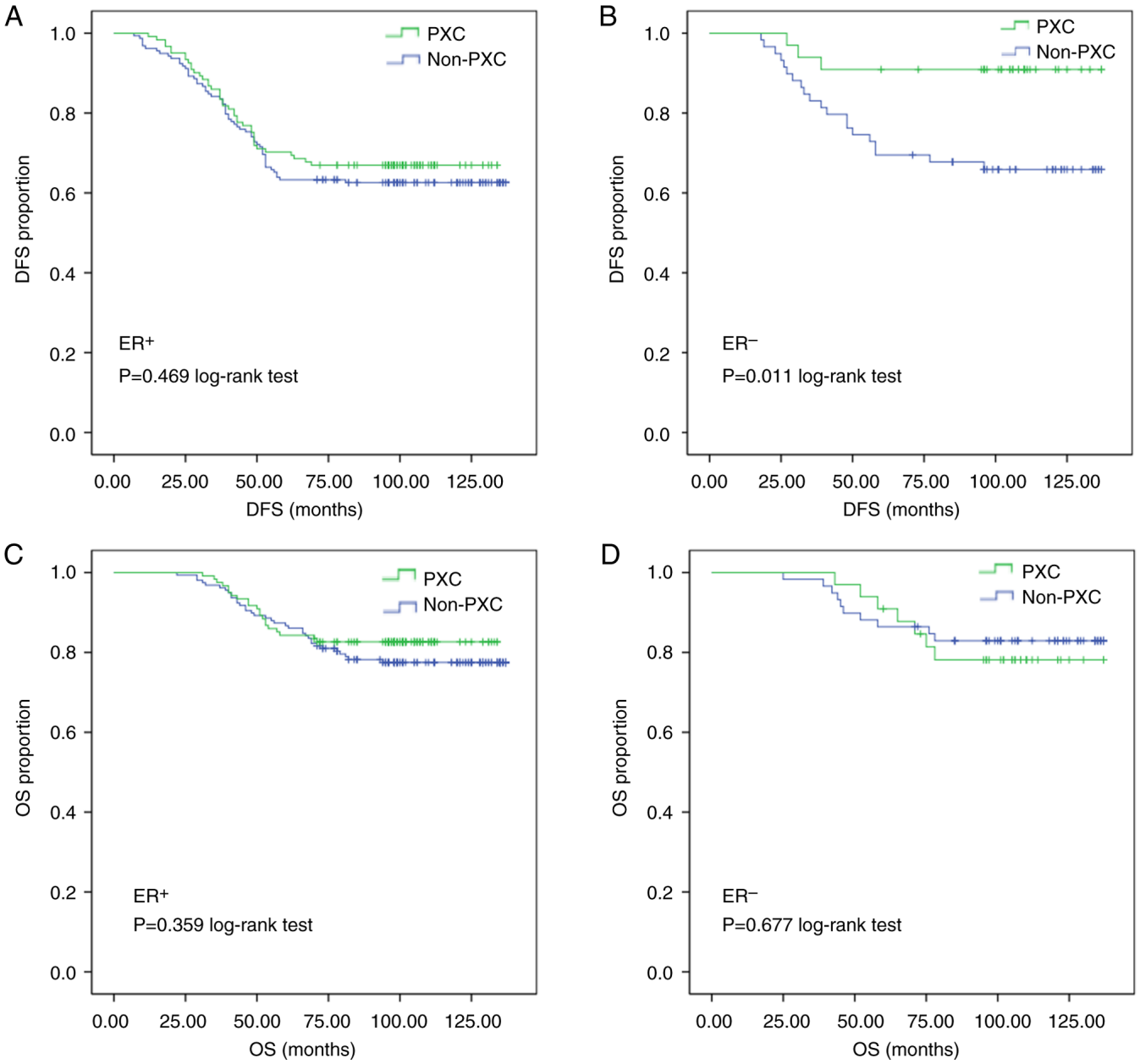

Figure 3. Kaplan-Meier curve of DFS and OS in patients with early breast cancer (irrespective of nodal status) with different ER statuses who were treated with or without PXC. DFS curve for the (A) ER$^+$ and (B) ER$^-$ PXC and non-PXC groups. OS curve for the (C) ER$^+$ and (D) ER$^-$ PXC and Non-PXC groups. DFS, disease-free survival; OS, overall survival; PXC, Pingxiao capsule; ER, estrogen receptor.

group (66.1%; P=0.011, Fig. 3B) regardless of node status; but there was no significant difference in DFS with PXC use in those with ER$^+$ tumors (P=0.469, Fig. 3A). As per HER2 status, there was no statistically significant difference in both DFS and OS between the PXC group and the non-PXC group (Fig. 4). In summary, DFS was significantly improved in patients with hormone receptor-negative tumors and in those with ≥3 months of treatment with PXC.

Prognostic factor analysis. Univariate and multivariate analyses for the risk of recurrence are summarized in Table II. Among the six variables in both univariate and multivariate analyses, three variables were identified to have prognostic significance: Tumor stage (P<0.001 and P=0.001, respectively), axillary metastasis (P<0.001 and P<0.001, respectively), and HER2 status (P=0.009 and P=0.018, respectively), all of which were associated with a higher risk of recurrence. By contrast, PXC use was associated with significantly lower risk of recurrence upon univariate analysis (P=0.046).

The results of univariate and multivariate analysis for DFS are summarized in Table III. Among the six variables in the univariate analysis, tumor stage (P=0.002) and axillary metastasis (P<0.001) were identified to have prognostic significance. Multivariate analysis using Cox's proportional hazard model identified axillary metastasis (P<0.001) to be an independent prognostic factor for DFS.

AEs in patients receiving chemotherapy. The following incidences of AEs (only those rated grade 2 or higher were included) were observed in the non-PXC group and the PXC

Table II. Analysis of potential risk factors for recurrence.

	Univariate analysis		Multivariate analysis	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.197 (0.840-1.708)	0.320	1.081 (0.752-1.553)	0.674
Tumor stage	1.890 (1.458-2.449)	<0.001	1.644 (1.219-2.217)	0.001
Axillary metastasis	2.302 (1.929-2.746)	<0.001	2.155 (1.797-2.583)	<0.001
Hormonal receptor	1.159 (0.760-1.768)	0.492	0.976 (0.637-1.459)	0.910
HER2	1.613 (1.127-2.310)	0.009	1.548 (1.078-2.224)	0.018
PXC	0.853 (0.731-0.997)	0.046	0.918 (0.785-1.073)	0.284

HR, hazard ratio; CI, confidence interval; PXC, Pingxiao capsule; HER2, human epidermal growth factor receptor 2.

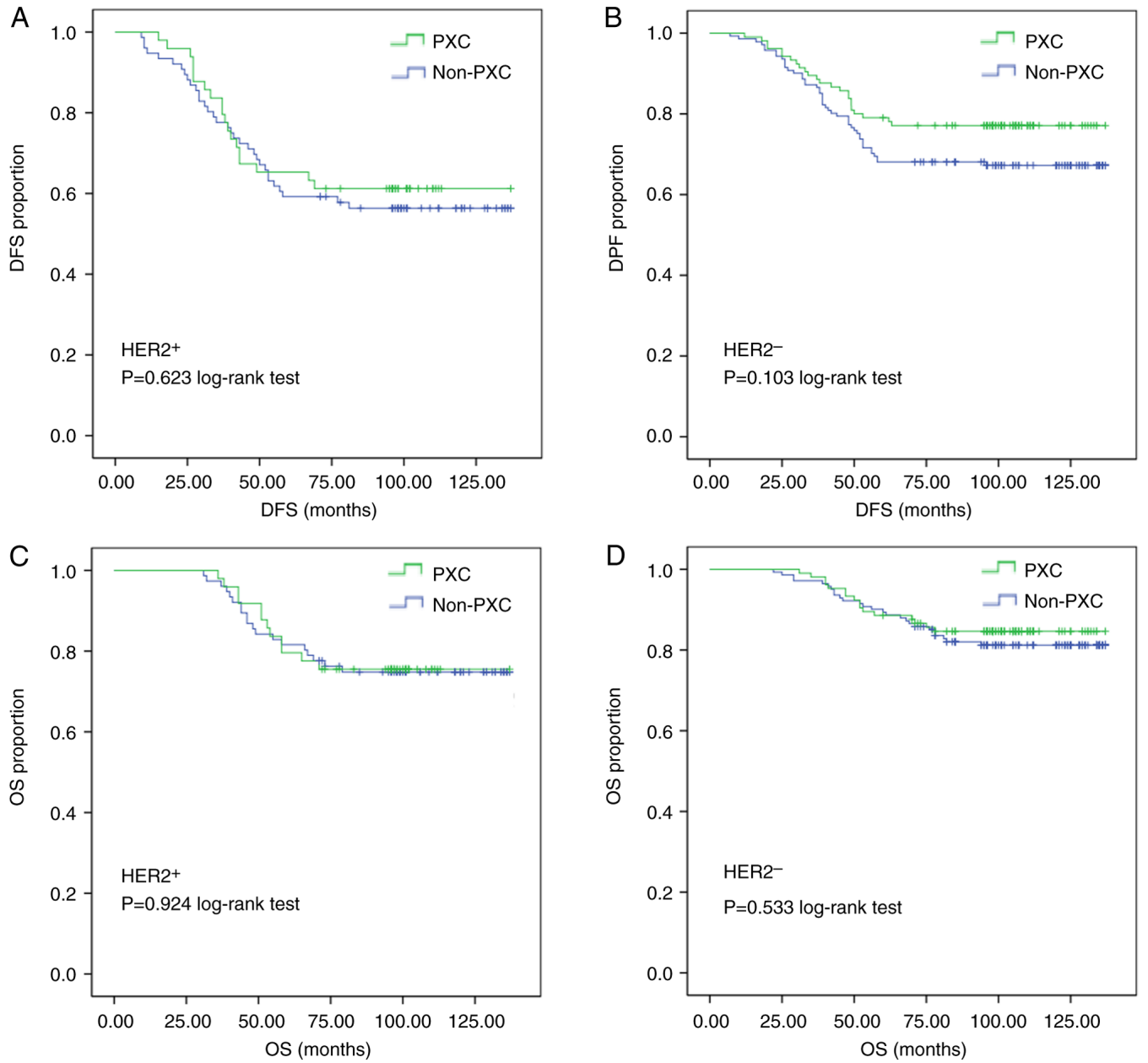

Figure 4. Kaplan-Meier curve of DFS and OS in patients with early breast cancer (irrespective of nodal status) with different HER2 statuses who were treated with or without PXC (≥3 months). DFS curves for the (A) $HER2^+$ and (B) $HER2^-$ PXC and non-PXC groups. OS curves for the (C) $HER2^+$ and (D) $HER2^-$ PXC and non-PXC groups. DFS, disease-free survival; OS, overall survival; PXC, Pingxiao capsule; HER2, human epidermal growth factor receptor 2.

Table III. Analysis of possible risk factors for survival.

	Univariate analysis		Multivariate analysis	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.197 (0.840-1.708)	0.320	1.049 (0.656-1.677)	0.842
Tumor stage	1.711 (1.225-2.389)	0.002	1.302 (0.870-1.950)	0.200
Axillary metastasis	3.180 (2.522-4.010)	0.000	3.045 (2.398-3.867)	0.000
Hormonal receptor	1.114 (0.647-1.916)	0.697	0.861 (0.495-1.497)	0.596
HER2	1.541 (0.968-2.451)	0.068	1.365 (0.852-2.187)	0.195
PXC	0.898 (0.739-1.091)	0.278	0.918 (0.785-1.073)	0.284

HR, hazard ratio; CI, confidence interval; PXC, Pingxiao capsule; HER2, human epidermal growth factor receptor 2.

Table IV. Chemotherapy-related adverse events (PXC ≥3 months).

	PXC ≥3 months		Non-PXC		
Graded groups	n	%	n	%	P-value
Anemia					0.409
0-1	89	96.7	204	94.0	
2-4	3	3.3	13	6.0	
Neutropenia					0.003
0-1	70	76.1	127	58.5	
2-4	22	23.9	90	41.5	
Nausea					0.062
0-1	92	100.0	208	95.9	
2	0	0	9	4.1	
Fatigue					0.388
0-1	84	91.3	204	94.0	
2	8	8.7	13	6.0	
Oral mucositis					>0.999
0-1	87	94.6	206	94.9	
2-3	5	5.4	11	5.1	
Diarrhea					0.289
0-1	91	98.9	209	96.3	
2-3	1	1.1	8	3.7	
Anorexia					0.409
0-1	89	96.7	204	94.0	
2-3	3	3.3	13	6.0	

PXC, Pingxiao capsule.

group with ≥3 months of treatment: 6.0 and 3.3% for anemia (P=0.322); 41.5 and 23.9% for neutropenia (P=0.003), 4.1 and 0.0% for nausea (P=0.062); 6.0 and 8.7% for fatigue (P=0.388), 5.1 and 5.4% for oral mucositis (P=0.894); 3.7 and 1.1% for diarrhea (P=0.214); and 6.0 and 3.3% for anorexia (P=0.322), as detailed in Table IV. The incidences of neutropenia (P=0.003) of grade 2 or higher were significantly lower in the PXC group than those in the control group. Compared with that in the non-PXC group, the incidence of nausea (≥ grade 2) in the PXC group was markedly reduced (4.1 vs. 0%), although it did not reach statistical significance (P=0.062; Fisher's exact test). Notably, all patients had no obvious side effects caused by PXC. These results suggest that PXC treatment may play a role in preventing neutropenia and alleviating nausea in patients with EBC receiving chemotherapy.

Discussion

Conventional and targeted therapies for breast cancer currently include a combination of cytotoxic chemotherapy drugs and pathway-selective small molecule inhibitors as adjuncts. However, these treatment options are typically associated with systemic toxicity, intrinsic or acquired therapeutic resistance, and the emergence of drug-resistant cancer stem cell populations. Traditional Chinese medicine is an alternative school of medicine that utilizes time-tested formulas of medicinal herbs, acupuncture and mind-body practices to promote holistic healing and its use dates back >3,000 years (9). In China, TCH use has been a part of conventional cancer treatment for >50 years (10). Yet, there remains a paucity of high-quality clinical trials on TCH regimens. This gap in knowledge can be attributable to the fact that TCH formulas are often complex, relying on a concoction of medicinal herbs that exert varying but synergistic effects. The benefit is its ability to deliver a multi-target, multi-media and multi-link system of therapeutics, although its active ingredients, toxicity and adverse reactions, are often difficult to elucidate. In recent years, several popular traditional Chinese medicine regimens have gained increasing recognition as safe adjuncts to cancer treatment, with little detectable systemic toxicity and adverse effects (11). Medicinal plants, such as *Tripterygium wilfordii*, have been reported to contain components that have the capability of directly initiating apoptosis, and *T. wilfordii* has been reported to induce apoptosis of cancer cells in hepatocellular carcinoma and lung cancer A549 cells (12). Similarly, PXC might be one popular formulation of TCH that also has components with antitumor effects documented in the literature (13).

The present study retrospectively analyzed patients with EBC to investigate the benefits of PXC as an adjunct to standard of care chemotherapy, endocrine therapy and anti-HER2 therapy. Among all the study subjects, the median DFS

time was 101 months, and the completion of adjuvant PXC therapy for ≥3 months was associated with an increase in DFS rate of 12.5%. In addition, an increase in DFS rate of 24.8% was observed in ER-negative patients associated with PXC use. These findings are in support of the existing body of evidence that Chinese herbal regimens may play an active role in targeting multiple functional signaling pathways in hyper-proliferative breast cancer (14,15), and are associated with the inhibition of cancer growth, the reduction of metastasis and invasion, the promotion of cancer cell apoptosis and the enhancement of immunity (16). Notably, curcumin, one of the bioactive components in PXC, has been reported to inhibit the proliferation and migration of cervical cancer cells, and cause the apoptosis of metastatic cells without affecting the normal epithelial cells (17). Curcumin is also able to reverse TGF-induced epithelial-mesenchymal transformation (EMT) in hepatocellular carcinoma by down regulating the expression of Snail (3). Distinct EMT transition states present different functions, with the hybrid EMT state presenting the highest metastatic potential (18).

Neutropenia and nausea are commonly reported toxicities associated with chemotherapy (19,20). Chemotherapy-induced neutropenia and nausea/vomiting are often ranked by patients as one of the most distressing and feared consequences of chemotherapy (21,22). In addition to its antitumor effects, TCH also has the advantages of a more favorable side-effect profile and lower systemic toxicity. Use of traditional Chinese herbal formulas has been reported to reduce the side effects of radiotherapy and chemotherapy, such as insomnia, depression and fatigue, which significantly improves the quality of life of patients with cancer (3). The present results are consistent with these findings, showing that TCH capsule combined with chemotherapy significantly improving the survival time and alleviating adverse events with similar TCH formula use to PXC (23,24).

Limitations of the present study include a relatively small sample size and recruitment restricted to a single institution. Although, to the best of our knowledge, the present study is first and largest study to date to specifically evaluate the role of PXC as an adjunct therapy in patients with EBC, the patient sample did not reveal significant benefits of PXC use in terms of OS, which is possibly attributable to the limited duration of PXC treatment and an insufficient length of follow-up. Despite these factors, the study remains of high generalizability among the Asian population of Chinese descent, given that the population in China is highly homogenous in ethnicity, with >90% being Han Chinese. As with other retrospective cohort studies, the present study is also inevitably subject to potential selection bias.

Side effects from PXC use itself are rare, but a non-specific mild drug rash, dizziness and diarrhea have been reported in the literature (5). Given its favorable side-effect profile and low level of systemic toxicity, adjuvant therapy with a PXC course of 5-10 years (as in current standard endocrine therapy) should be considered for more robust evaluation of its therapeutic effects and survival benefits. Side-effect profile assessment with long-term use would also be beneficial. Therefore, large-scale prospective cohort studies or randomized clinical trials with a longer duration of treatment and follow-up (5 to 10 years) would be crucial to further delineate the efficacy of PXC as an adjunctive therapy for EBC along with its long-term side-effect profile.

In conclusion, to the best of our knowledge, the present retrospective cohort study is the first to demonstrate significant improvement in DFS in patients who used PXC as an adjunct to their standard breast cancer treatment. This benefit was most notable in patients with hormone receptor-negative early breast cancer and when duration of use for PXC was ≥3 months. A well-designed, largescale prospective study with longer term PXC treatment duration may be beneficial to further elucidate the therapeutic effect of PXC as a potent adjuvant agent.

Acknowledgements

Not applicable.

Funding

This study was supported by grants from the Natural Science Foundation of Liaoning Province (grant no. 20180551215), the Key Research and Development Plan Guidance Project of Liaoning Province (grant no. 2019JH8/10300020) and the Key Project of China Health Promotion Foundation (grant no. CHPF-RXO180301).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SW and XZ conceived and designed the experiments. SW, LZ, HJ and XZ analyzed data. CZ and XZ interpreted data and drafted the manuscript. All authors read and approved the final manuscript. SW, CZ, LZ, HJ, and XZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was reviewed by the China Medical University Ethics Committee Institutional Review Board (Shenyang, China; approval no. 2020 NO. 203). Approval was granted prior to commencement of the study and the requirement for written consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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