A Double-Blind, Randomized, Placebo-Controlled Trial of *Panax Ginseng* for Cancer-Related Fatigue in Patients With Advanced Cancer

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Abstract

Background: Despite the high frequency, severity, and effects of cancer-related fatigue (CRF) on the quality of life (QoL) of patients with cancer, limited treatment options are available. The primary objective of this study was to compare the effects of oral *Panax ginseng* extract (PG) and placebo on CRF. Secondary objectives were to determine the effects of PG on QoL, mood, and function. **Methods:** In this randomized, double-blind, placebo-controlled study, patients with CRF ≥4/10 on the Edmonton Symptom Assessment System (ESAS) were eligible. Based on a pilot study, we randomized patients to receive either 400 mg of standardized PG twice daily or a matching placebo for 28 days. The primary end point was change in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale from baseline to day 29. **Results:** Of 127 patients, 112 (88.2%) were evaluable. The mean (SD) FACIT-F subscale scores at baseline, day 15, and day 29 were 22.4 (10.1), 29.9 (10.6), and 30.1 (11.6) for PG (P<.001), and 24.0 (9.4), 30.0 (10.1), and 30.4 (11.5) for placebo (P<.001). Mean (SD) improvement in the FACIT-F subscale at day 29 was not significantly different in the PG than in the placebo group (7.5 [12.7] vs 6.5 [9.9]; P=.67). QoL, anxiety, depression, symptoms, and functional scores were not significantly different between the PG and placebo groups. Improvement in the FACIT-F subscale correlated with baseline scores (P=.0005), Hospital Anxiety and Depression Scale results (P=.032), and sex (P=.023). There were fewer any-grade toxicities in the PG versus placebo group (28/63 vs 33/64; P=.024). **Conclusions:** Both PG and placebo result in significant improvement in CRF. PG was not significantly superior to placebo after 4 weeks of treatment. There is no justification to recommend the use of PG for CRF. Further studies are needed. **Trial Registration:** ClinicalTrials.gov identifier: NCT01375114.

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Background

Cancer-related fatigue (CRF) is the most common symptom in patients with cancer.[1,2] Despite the high frequency, severity, and effects of CRF on quality of life (QoL), limited treatment options are available.[1,3] Prior pharmacologic studies for CRF in patients with cancer have shown mixed results.[1,4,5] *Panax ginseng* extract (PG) is widely used in the United States and other countries, including Korea and China,[6,7] under the belief that it will improve overall QoL, including energy and vitality, particularly during times of fatigue or stress.[8–10] PG has been found to have direct action on the central nervous system (CNS), including cognition, sleep disturbance, depression, pain, and the ability to modulate inflammatory cytokines.[9,11–17] Despite its frequent use, there are no well-powered, placebo-controlled trials using validated CRF outcome measures to investigate the effects of PG in patients with cancer.[18] A prospective, open-label, pilot study by our group in 30 patients with CRF (≥4/10 measured by the Edmonton Symptom Assessment System [ESAS]) found that 400 mg twice daily of oral PG (prepared from *Panax ginseng* C.A. Meyer root) for 30 days was safe and well tolerated, with good adherence and no major toxicity.[19] There was significant improvement of Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale scores (mean difference [SD], 14.2 (17.4); *P*=.0006). Further, there was a significant mean (SD) improvement in ESAS feeling of well-being score from 4.67 (2.04) to 3.50 (2.34) (*P*=.01374) and ESAS appetite score from 4.29 (2.79) to 2.96 (2.46) (*P*=.001).

The primary objective of the current study was to examine the effects of oral PG at 400 mg twice daily compared with placebo on CRF as determined by FACIT-F subscale at the end of 4 weeks. Secondary objectives were to determine the effects of PG on QoL domains (FACIT-F), mood (Hospital Anxiety and Depression Scale [HADS]), patient-reported treatment benefit (Global Symptom Evaluation [GSE]), and physical function as measured by both the 6-minute walk test (6MWT) and hand grip strength (HGS; via Jamar hydraulic hand dynamometer [Lafayette Instrument, Lafayette, IN]). We also determined the side effects and tolerability of PG in these patients.

We hypothesized that patients who received PG would have greater average improvement in FACIT-F subscale scores from baseline to day 29 compared with those who received placebo.

Methods

Patients

The University of Texas MD Anderson Cancer Center Institutional Review Board approved this study, and all patients provided written, informed consent to participate in this prospective trial (ClinicalTrials.org identifier: NCT01375114). Eligible patients were enrolled from outpatient oncology centers and supportive care clinics at MD Anderson Cancer Center.

Eligibility criteria were the same as for our prior pilot study.[19] Briefly, we included patients diagnosed with cancer and CRF with an average intensity of ≥4/10 on the ESAS (scale, 0–10) during the 24 hours before study enrollment. CRF also had to be present every day for most of the day for a minimum of 2 weeks. Other important eligibility criteria were normal cognition; no infections; hemoglobin level ≥8 g/L within 2 weeks of enrollment; ECOG performance status (PS) ≤2; no current uncontrolled pain or depressive symptoms; no history of psychiatric illness, such as major depression, obsessive compulsive disorder, or schizophrenia; no uncontrolled diabetes or treatment with anticoagulants or systemic steroids; no history of hepatitis A, B, or C; no significant history of uncontrolled[19] hypertension or symptomatic tachycardia; and no current use of the following medications: ginseng, methylphenidate, modafinil, phenobarbital, diphenylhydantoin, primidone, phenylbutazone, monoamine oxidase inhibitors, clonidine, and tricyclic antidepressants.

The rationale for including various tumor types is multifold. First, CRF is a syndrome that results from increased production of inflammatory cytokines and tumor byproducts irrespective of tumor types. This pathophysiology of CRF is more related to the interaction between cancer and the host rather than to any specific histology, as demonstrated by similar rates of frequency and severity of fatigue across patients with various tumor types.[20,21] Second, the frequency and severity of CRF in patients who have various tumor types are largely the same, as seen in clinical trials of methylphenidate,[22] donepezil,[23] fish oil,[24] and dexamethasone[25] in the treatment of CRF. Third, by including patients with various tu-

mor types, we will obtain a more representative distribution in terms of age, sex, and behavior than we would in a study of patients with a single tumor type.

Intervention

In this double-blind, randomized, placebo-controlled trial, patients took 400 mg of PG capsules twice daily or a matching placebo (an inactive excipient methylcellulose) twice daily. The matching placebo was compounded by the same investigational pharmacy as the study drug. The placebo was prepared as colored capsules for similar appearance and we included an inactive excipient methylcellulose as an ingredient for the placebo. Timing of administration was specified as every morning and every afternoon before 3:00 PM for 28 days.

PG, which is commercially available, was supplied by Indena S.p.A. (Milan, Italy). It was prepared from *Panax ginseng* C.A. Meyer root (drug extract ratio 1:3–5) and standardized[26] to contain ≥7.0% of ginsenosides and malonyl ginsenosides (≥0.9% Rg_1 ≤1.4%; ≥1.7% Rb_1 ≤3.0%). The manufacturing percentage range (mean ± standard error of the mean) of ginsenosides was 12% ± 3%. The extract was prepared through hydroalcoholic extraction (EtOH 70%). Certificate of analysis (CofA) using high-performance liquid chromatography identification was obtained for each batch to ensure standardized contents of ginsenosides, pH, alcohol content, loss on drying, and total residual organic solvents. The CofA also complied with the standards of no heavy metals and no microbials, assessed based on microbial counts, total combined yeasts/molds, and presence of bile-tolerant gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, aflatoxins, and pesticides. The same process was used in studies involving animal models[27] and in our preliminary study using PG, which was found to be beneficial in reducing CRF.[19]

The decision to use an oral dose of PG at 400 mg twice daily for a duration of 4 weeks was based on the successful results of our preliminary study examining the safety and efficacy of PG in significantly improving CRF.[19] Our dosage of PG at 400 mg twice daily, containing ≥7.0% of ginsenosides and malonyl ginsenosides, is higher compared with that used in other clinical studies and monographs from the WHO and German Commission E,[8,28–42] which used PG for symptoms in patients without cancer. In these various studies, the dose ranged from 40 to 800 mg of ginseng extract.[19]

Outcomes

Demographic information was recorded at baseline (at randomization and before treatment), and included age, sex, race, religion, marital status, education, occupation, cancer stage, cancer type, and ECOG PS.

A research nurse supervised the completion of symptom assessment tools, including the FACIT-F, ESAS, and HADS, at baseline, day 15, and day 29. The GSE questionnaire was assessed on day 29. FACIT-F subscale is a QoL instrument commonly used in cancer clinical trials.[43] It consists of 27 general QoL questions divided into 4 domains (physical, social, emotional, and functional) and has a 13-item fatigue subscale; the latter of which was the primary outcome of our study. Using the subscale, patients rate the intensity of their fatigue and its related symptoms on a scale of 0 to 4. The total score ranges between 0 and 52, with higher scores denoting less fatigue. Test–retest reliability coefficients for the fatigue subscale range from 0.84 to 0.90. The FACT-F subscale has also demonstrated strong internal consistency (α, 0.93–0.95).[37] The FACIT-F subscale was used as the primary outcome measure because it is the most widely used, validated tool for assessing treatment response in CRF trials.[44–47]

The ESAS evaluates 10 commonly experienced symptoms, including pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, sleep disturbance, and impaired feelings of well-being. The severity of each symptom was rated on a numerical scale of 0 to 10 (0 = no symptom, 10 = worst possible severity). The ESAS is both valid and reliable in patients with cancer.[48] The ESAS fatigue item was used to identify patients with clinically significant fatigue and as a secondary outcome measure for our study.

Patients' depression and anxiety were assessed using HADS. This 14-item assessment instrument has been validated in a number of clinical situations and has been widely used in patients with cancer.[49]

In the GSE, patients were asked rate their CRF (eg, worse, about the same, or better) after treatment with the study medication. If their response was "better," they were asked to rate how much better (eg, hardly any better at all, a little better, somewhat

better, moderately better, a good deal better, a great deal better, a very great deal better).[50]

A research nurse supervised the completion of 2 objective measurements, the 6MWT and HGS, at baseline and day 29. The 6MWT was used to assess physical function, and has been recommended by the American Thoracic Society as an objective measure of functional capacity.[51] HGS was used to measure the maximum isometric strength of the hand and forearm muscles.[52]

Toxicity and safety was assessed by the research nurse using the NCI's CTCAE, version 4.0 (CTCAE v4.0). Questionnaire and medication review occurred at baseline (before treatment initiation); treatment days 8, 15, and 29; and 1 month after the study medication was stopped.

Statistical Analysis

The primary objective was to determine whether the average improvement in CRF from baseline to day 29 in patients who received PG was greater than in those who received placebo as measured by FACIT-F subscale scores. The primary end point, therefore, was the change in these scores from baseline to day 29. Differences in group means of the sample showed a normal distribution and were therefore analyzed using the 2-sample *t* test. Using similar methods, we analyzed differences between groups in scores at baseline and on days 15 and 29 for FACIT-F, HADS, ESAS symptoms, ESAS symptom distress scores, 6MWT, and HGS.

Our sample size estimation for this study was based on previous fatigue treatment trials.[53–55] Assuming a standard deviation of 5.8 in difference scores, with at least 50 evaluable patients per group, we planned to detect differences as small as 3.3 or larger with a 2-sided significance level of 0.05 and 80% power. To account for a dropout rate of 20% based on prior trials, we planned to recruit 64 patients into each group, for a total of 128 patients.

Baseline patient characteristics between the PG and placebo groups were compared using the chi-square test (or Fisher exact test for variables with expected cell frequencies ≤5). The number of patients experiencing adverse events (AEs) was compared between groups using the chi-square test; multiple linear model analysis was used in ad hoc analysis to determine the factors associated with FACIT-F subscale score improvement with PG. We analyzed all data at each time point (symptoms and AEs) for all patients who received at least one dose of study medication. All results reported in this study are based on 2-sided tests. The normality assumption was tested using the Shapiro-Wilk W statistic.[56] A *P* value ≤0.05 was considered statistically significant.

Results

A total of 112 patients were evaluable; 56 received PG and 56 received placebo. Figure 1 shows the details of a CONSORT diagram including patient enrollment, randomization, follow-up, and patients in analysis. Adherence to study medication was assessed by the percentage of prescribed pills taken during the study period. Pill count was assessed using a pill diary completed by the study patients. Of the 127 patients who participated in the study, 112 (88.2%) had an adherence rate of 100%; 15 (11.8%) had an adherence rate ranging from 2 (3.4%) to 42(72.4%) pills. There was no significant difference in the adherence rates between the PG and placebo groups (*P*=.81).

No significant group differences were seen in baseline characteristics except cancer type (Table 1). There were also no significant group differences in baseline FACIT, ESAS, HADS, 6MWT, and HGS scores. Of 112 patients, 110 (98.2%) had advanced cancer. There was significant improvement in mean change of the FACIT-F subscale (Figure 2) and ESAS fatigue scores in the PG and placebo groups at days 15 and 29. The mean (SD) FACIT-F subscale scores at baseline, day 15, and day 29, respectively, were 22.4 (10.1), 29.9 (10.6), and 30.1 (11.6) for PG (*P*<.001) and 24.0 (9.4), 30.0 (10.1), and 30.4 (11.5) for placebo (*P*<.001). Mean (SD) improvement in the FACIT-F subscale at day 29 (primary outcome) was not significantly different in the PG and placebo groups (7.5 [12.7] vs 6.5 [9.9], respectively; *P*=.67). Clinically meaningful improvement in change for the FACIT-F subscale was seen in 35 of 63 patients (55.5%) in the PG group versus 35 of 64 (54.6%) in the placebo group (*P*>.2). Mean (SD) improvements in the ESAS fatigue item, FACIT-F, HADS, ESAS, 6MWT, and HGS scores at day 29 were not significantly different in the PG and placebo groups (Table 2), and the frequency of GSE score of "better" was not significantly different between the groups (PG group, 21/54 [39%] vs placebo, 20/53 [38%]; *P*=.93).

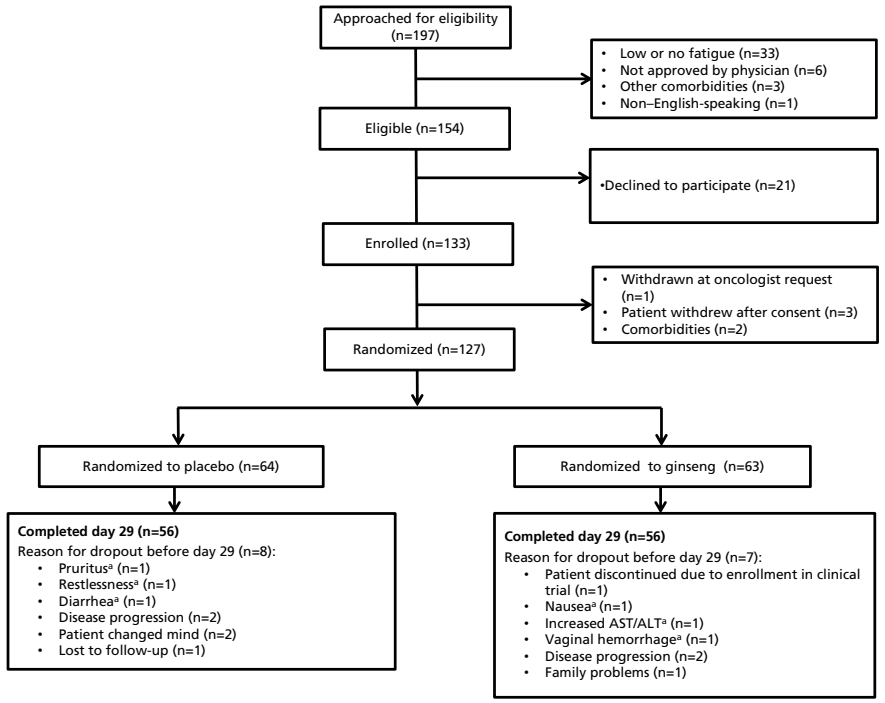


Figure 1. CONSORT diagram.
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.
[a]Unrelated to study drug.

In a multiple linear model analysis, improvement in the FACIT-F subscale score from day 0 to 29 was significantly correlated with baseline FACIT-F subscale score (P=.0005), HADS score (P=.032), and male sex (P=.023), such that higher fatigue, depression, and male sex were associated with greater improvement in CRF. Age, race, marital status, employment status, education, primary site, ECOG PS, or baseline HADS anxiety were not associated with change in CRF. There were fewer any-grade toxicities in the PG versus placebo group (28/63 vs 33/64, respectively; P=.024; Table 3). Table 4 summarizes the type of grade 3 to 5 AEs in both groups.

Discussion

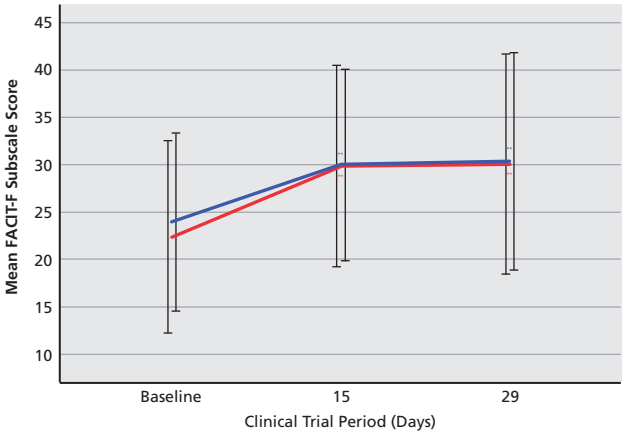
Our study is the first randomized, double-blind, placebo-controlled control study to successfully evaluate the effects of PG on CRF using validated tools. In this study, we found that PG intake was associated with a significant reduction in the severity of CRF in patients with advanced cancer (Figure 2). However, PG was not significantly better than placebo in improving CRF at day 29 as measured by the FACIT-F subscale. We also found that PG did not significantly improve QoL, anxiety, depression, cancer-related symptoms, patient-reported benefit of treatment on CRF, and physical function scores compared with placebo according to FACIT-F, HADS, ESAS, GSE, 6MWT, and HGS, respectively. There were, however, significantly fewer AEs in the PG group than the placebo group.

Our results confirm the data from our preliminary study that the use of PG is safe and tolerable. Although well tolerated at the current dose of 400 mg twice daily, PG use is not recommended for CRF treatment in the clinical setting, because its effect was no different from that of placebo. In contrast to other pharmaceutical and nutraceutical randomized controlled trials to treat CRF, which have been negative, the use of PG in our study was found to be safe in patients with cancer and was associated with clinically meaningful benefit in >55% of patients.[57] The study had a strong placebo response, which is common in fatigue studies and a major barrier for the study of new interventions.[58] The exact reason for placebo response in our study is unclear. However, the history of PG use to improve overall QoL, including energy and vitality, may have resulted in a high expectation of benefit.[18,59,60] Strategies to

Table 1. Patient Demographics and Clinical Characteristics at Baseline

Characteristic	Placebo[a]	PG[b]	Total[c]	*P* Value
Median age (IQR), y	61.0 (53.3–66.8)	61.0 (54.0–67.0)	61.0 (54.0–67.0)	.76
Women, % (n)	37.5 (24)	46.0 (29)	41.7 (53)	.37
Race/Ethnicity, % (n)				.30
White	84.4 (54)	77.8 (49)	81.1 (103)	
African American	4.7 (3)	6.3 (4)	5.5 (7)	
Asian/Other	9.4 (6)	0 (0)	4.7 (6)	
Hispanic	1.6 (1)	15.9 (10)	8.7 (11)	
Median education (IQR), y	14.0 (12.0–16.0)	15.0 (13.0–16.0)	14.0 (12.0–16.0)	.48
Cancer diagnosis, % (n)				.01
Breast	10.9 (7)	23.8 (15)	17.3 (22)	
Gastrointestinal	0 (0)	6.3 (4)	3.1 (4)	
Genitourinary	73.4 (47)	49.2 (31)	61.4 (78)	
Gynecologic	1.6 (1)	0 (0)	0.8 (1)	
Thoracic	7.8 (5)	14.3 (9)	11.0 (14)	
Other[d]	6.3 (4)	6.3 (4)	6.3 (8)	
ECOG performance status, % (n)				.30
0	7.9 (5)	14.8 (9)	11.3 (14)	
1	74.6 (47)	62.3 (38)	68.5 (85)	
2	17.5 (11)	23.0 (14)	20.2 (25)	
Baseline Symptom and Muscle Function Scores				
Instrument	**Placebo,[a] mean (SD)**	**Ginseng,[b] mean (SD)**	**Total,[c] mean (SD)**	***P* Value[e]**
ESAS score				
Pain	2.4 (2.5)	2.9 (2.7)	2.7 (2.6)	.35
Fatigue	6.1 (1.7)	6.1 (1.9)	6.1 (1.8)	.81
Nausea	1.3 (2.1)	2.2 (2.8)	1.7 (2.5)	.056
Depression	1.3 (1.9)	1.7 (2.1)	1.5 (2.0)	.23
Anxiety	1.8 (2.0)	2.1 (2.5)	2.0 (2.3)	.54
Drowsiness	3.6 (2.5)	3.4 (2.8)	3.5 (2.7)	.66
Dyspnea	2.0 (2.2)	2.4 (2.4)	2.2 (2.3)	.32
Appetite	3.7 (2.4)	3.8 (2.6)	3.7 (2.5)	.73
Sleep	4.0 (2.6)	4.0 (2.7)	4.0 (2.6)	.89
Feeling of well-being	3.9 (2.3)	4.1 (2.4)	4.0 (2.4)	.60
Symptom distress	26.2 (10.2)	28.2 (15.2)	27.2 (12.9)	.37
HADS score				
Anxiety	5.7 (3.3)	6.2 (3.9)	5.9 (3.6)	.41
Depression	6.3 (3.1)	6.4 (3.6)	6.3 (3.4)	.93
FACIT score				
Fatigue subscale score	24.0 (9.4)	22.4 (10.0)	23.2 (9.7)	.36
Physical well-being	16.9 (5.1)	16.8 (5.7)	16.9 (5.4)	.89
Social/Family well-being	23.3 (4.6)	22.0 (5.5)	22.7 (5.1)	.14
Emotional well-being	18.3 (3.5)	17.7 (4.7)	18.0 (4.1)	.40
Functional well-being	16.8 (4.4)	16.1 (5.8)	16.5 (5.1)	.41
FACIT-F total score	99.4 (20.6)	95.0 (24.5)	97.2 (22.7)	.27
Hand grip strength, kg				
Right hand	28.3 (10.4)	29.4 (13.9)	28.8 (12.2)	.62
Left hand	26.6 (10.9)	27.4 (12.8)	27.0 (11.8)	.68
Total distance walked in 6 minutes, m	383.4 (99.9)	383.3 (105.2)	383.4 (102.0)	1.00

Abbreviations: ESAS, Edmonton Symptom Assessment System; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; PG, *Panax ginseng* extract.
[a]N=64.
[b]N=63.
[c]N=127.
[d]Other: melanoma (n=4), lymphoma (n=1), neuroendocrine carcinoma (n=2), and desmoplastic small cell round tumor (n=1).
[e]2 sample *t* test.



Day	PG Group Mean (SD)	Placebo Group Mean (SD)[a]
Baseline	22.4 (10.1)	24 (9.4)
15	29.9 (10.6)	30 (10.1)
29	30.1 (11.6)	30.4 (11.5)

Figure 2. Change in mean (SD) fatigue score (FACIT-F) for PG (red) and placebo (blue) groups.
Error bars indicate SDs of the groups.
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue subscale; PG, Panax ginseng extract.
[a]*P*<.001 for baseline and day 15 scores and for baseline and day 29 scores in both groups.

account for a placebo response include recruiting a larger number of patients and increasing study duration, both of which escalate study costs. Although longer study duration could potentially eliminate the placebo response, it is not always feasible due to the increased risk of attrition in patients with advanced cancer.[61] Therefore, potential future clinical trials might consider a placebo run-in before starting the study drug to eliminate placebo responders and allow for shorter studies.

In our study, the frequency of grade 3 to 5 AEs (Table 4) was significantly less in the PG group (1.6%) compared with the placebo group (14%), suggesting the potential role of PG in modulating the toxicities of cancer and its treatments. Further studies are needed.

Barton et al[62] recently published a multicenter, double-blind, placebo-controlled, randomized control study for the treatment of CRF using a different ginseng preparation, *Panax quinquefolius*, also known as American or Wisconsin ginseng. However, there were several notable differences in the results be-

Table 2. Change in Symptom Scores at Days 15 and 29

	Day 29 From Baseline					Day 15 From Baseline				
	Ginseng (N=56)		Placebo (N=56)			Ginseng (N=52)		Placebo (N=54)		
Instrument	Mean	SD	Mean	SD	*P* Value	Mean	SD	Mean	SD	*P* Value
FACIT-F subscale	7.5	12.7	6.5	9.9	.67[a]	7.1	10.4	6.1	10.1	.62
FACIT physical well-being	2.8	5.3	2.1	5.1	.44	2.3	4.7	2.2	4.7	.98
FACIT social/family well-being	0.3	4.1	–0.5	3.6	.29	–0.1	4.9	–0.3	3.5	.77
FACIT emotional well-being	1.0	3.9	0.1	3.2	.17	1.0	4.0	1.3	2.9	.73
FACIT functional well-being	1.4	3.9	–0.1	4.2	.07	0.7	3.4	0.9	4.2	.75
FACIT-F total score	13.0	20.6	8.2	19.0	.20	11.2	18.4	10.1	17.8	.76
Mean ESAS score (SD)										
Pain	–0.6	2.0	–0.1	3.0	.34	–0.1	2.7	0	2.2	.93
Fatigue	–1.9	2.6	–2.1	2.6	.71	–1.5	2.4	–1.6	2.4	.72
Nausea	–0.8	2.4	–0.3	2.1	.29	–0.6	2.6	–0.4	2.0	.67
Depression	–0.3	2.2	0.1	2.2	.36	–0.3	1.6	–0.4	1.8	.90
Anxiety	1.3	3.2	1.3	3.7	.90	1.3	2.5	1.6	3.3	.61
Drowsiness	–0.9	3.1	–0.6	3.2	.56	–0.4	2.6	–0.7	2.5	.57
Shortness of breath	–0.7	2.0	0.0	2.5	.11	–0.5	2.3	–0.1	2.0	.27
Appetite	–0.4	3.2	–0.8	3.6	.52	–0.6	2.9	–0.6	2.9	.99
Sleep	-0.7	2.8	0.2	3.2	.10	–0.7	2.1	–0.5	2.3	.59
Feeling of well-being	–1.5	2.9	–0.6	3.3	.16	–1.3	2.5	–1.2	2.7	.84
Symptom distress	–7.6	15.3	–4.7	14.7	.32	–6.1	11.0	–5.8	10.9	.88
Mean HADS score (SD)										
HADS anxiety	–1.3	4.3	–0.8	2.8	.45	–1.2	3.7	–1.0	3.1	.77
HADS depression	–0.7	3.0	–0.9	2.6	.66	–0.6	2.4	–1.0	2.1	.43

Abbreviations: ESAS, Edmonton Symptom Assessment System; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HADS, Hospital Anxiety and Depression Scale.
[a]Primary outcome.

Table 3. Adverse Events in Placebo and Ginseng Groups

Maximum Grade	Placebo	Ginseng	*P* Value[a]
3–5	9	1	
1–2	24	27	.024
None	29	36	

[a]Chi-square test.

tween that study and ours. Barton et al's study found that CRF, as assessed by the Multidimensional Fatigue Symptom Inventory (MFSI) general scale, was not significantly better in the *P quinquefolius* group than the placebo group at the end of 4 weeks of treatment (primary end point). However, MFSI scores were significantly improved at the end of 8 weeks and in the subgroup of patients receiving chemotherapy at the end of 4 weeks.

Minimal clinically important difference (MCID) helps us evaluate the clinical meaningfulness of any observed treatment or intervention-related differences using a validated instrument for fatigue. It is difficult to compare the effects of *P ginseng* and *P quinquefolius* on CRF, because different instruments were used to assess CRF in the Barton et al[62] study compared with ours. One alternate measure is to compare these studies using MCID. Both studies found clinically meaningful improvement of fatigue at the primary end point; however, Barton et al's study found lower placebo response, which was slightly below the threshold of MCID on the MFSI general scale.[63] In our study, the placebo response was more robust and exceeded the threshold of MCID (3.5) by 3 points on the FACIT-F subscale. The reasons for the different placebo response in these 2 studies are not known, and this requires further research.

Table 4. Summary of Adverse Events Experienced by Patients[a]

Adverse Event	Placebo (N=9)	Ginseng (N=1)
Allergic reaction	1	0
Appendicitis	1	0
Dyspnea	1	0
Fatigue	2	0
Hyperglycemia	1	0
Hypokalemia	1	0
Infections and infestations	0	1
Lung infection	1	0
Thrombotic thrombocytopenic purpura	1	0

[a]Maximum grade NCI Common Terminology Criteria for Adverse Events, version 4.0 criteria grade ≥3 (N=10).

One important difference in our study from that of Barton et al is a higher ginsenosides ratio of Rg_1 to Rb_1 in the PG preparation than in *P quinquefolius*.[64–66] Prior studies suggest that the higher contents of Rg_1 in *P ginseng* is associated with CNS stimulant action, whereas the Rb_1 contents of *P quinquefolius* are mainly calming to the CNS. Our study results did not suggest better antifatigue effects with a higher ginsenoside concentration compared with those of Barton et al.[62] However, the species of ginseng used to prepare the ginseng extract capsules by Barton et al was *P quinquefolius* compared with *P ginseng* used in our study. Further studies are needed to evaluate whether the antifatigue effects differ between *P ginseng* and *P quinquefolius*.

Lastly, our study enrolled mostly patients with advanced cancer (98.2%) compared with the Barton et al study, which enrolled those with early-stage cancer and cancer survivors. It is very likely that the mechanisms of CRF associated with advanced cancer differ from those of early cancer and cancer survivors due to the presence of tumor byproducts, increased inflammatory response, higher brain exposure to toxic effects of cancer therapy, higher frequency of cancer cachexia, and other CRF-related symptoms.[20,67–69] More research is needed to characterize the mechanistic differences in fatigue subtypes.

Our study has various strengths and limitations. In addition to being the first successfully completed randomized controlled trial of PG in patients with cancer using validated measures, the results also suggest PG feasibility and safety in advanced cancer. Our study results suggest a potential role of PG in managing toxicities due to its significant modulation of AEs with respect to placebo (Table 3). The main limitation of this study is that the effect of PG on CRF was measured for only 29 days. However, under ideal circumstances, treatments that act promptly are best for the management of an acute and debilitating condition such as CRF in the advanced cancer setting. Additionally, further studies are needed to understand the mediating mechanisms of action of PG on CRF, including the role of inflammatory cytokines.[70]

There are no pharmacokinetic studies of PG in patients with cancer that show the difference or similarity between the 800-mg daily dose and the 400-mg twice-daily dose. The use of an oral 400-mg twice-

daily dose (last dose before 3:00 PM) was intended to distribute the ginseng dose according to diurnal variation of CRF, and to avoid insomnia due its CNS action as a result of nighttime dosing.[71–76] However, further studies are needed to determine the ideal frequency of PG administration. Our sample size calculation for this study was based on a standard deviation of 5.8 on the FACIT-F subscale score in an exercise intervention study for CRF. The change in FACIT-F subscale score is the most commonly used primary outcome measure in CRF treatment trials. This includes pharmacologic CRF trials in advanced cancer by our group,[45–47] in addition to those used by other groups in CRF and treatment trials using exercise intervention.[77] However, it may be possible that the exercise interventions may have an effect on biobehavioral factors associated with CRF and are quite different from that for ginseng, and therefore further studies are necessary.

Conclusions

Our results show that oral PG at a dose of 400 mg twice daily and a matching placebo resulted in significant improvement in CRF with minimal side effects. However, PG was not significantly superior to placebo after 4 weeks of treatment for the management of CRF and other accompanying symptoms. Based on these findings, there is no justification to recommend PG for managing fatigue in patients with advanced cancer. Further studies are needed.

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