ORIGINAL RESEARCH

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A novel infusible botanically-derived drug, PG2, for cancer-related fatigue: A phase II double-blind, randomized placebo-controlled study

Abstract

Purpose: This study investigated the efficacy of the botanical-derived drug, PG2, a partially purified extract of *Astragalus membranaceus*, as a complementary and palliative medicine for managing cancer-related fatigue (CRF).

Methods: Patients with advanced cancer and moderate to severe CRF were randomized to receive either PG2 or a placebo (normal saline, NS) in the first treatment cycle (four weeks) in a double-blind manner; thereafter, on the next cycle (four weeks), all patients received open-label treatment with PG2.

Results: PG2 significantly improved CRF in the NS-primed group. In the first four week cycle, PG2 administration resulted in a greater fatigue-improvement response rate than seen with NS alone. In addition, approximately 82% of patients who reported an improvement of fatigue symptoms following the first cycle of PG2 experienced sustained benefits after administration of the second treatment cycle. Among patients treated with PG2 who did not report an improvement in symptoms throughout the first treatment cycle, approximately 71% showed significant improvement after the second treatment cycle. No major or irreversible toxicities were observed with PG2 treatment.

Conclusion: PG2 might be an effective and safe treatment for relieving CRF among advanced cancer patients.

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Cancer treatment is directed toward both curing and caring. In advanced cancer patients with poor disease control, palliative care to relieve symptoms causing suffering is crucial in holistic medicine management planning. Of the symptoms from which advanced cancer patients suffer, cancer-related fatigue (CRF) [1] is one of the most common and difficult-to-treat symptoms. Approximately 60 to 90% of advanced cancer patients report fatigue as their most frequent and debilitating symptom [2,3]. Fatigue can adversely affect psychosocial and physical functioning and noticeably decrease quality of life in cancer patients [4]. Current approaches for managing CRF are unsatisfactory [5] and the development of novel and effective treatments for improving CRF is urgently required.

Patients in need of improvement of cancer-related symptoms, including CRF, commonly use complementary and alternative medicine (CAM) by choice or because caregivers have recommended it. Traditional Chinese medicine (TCM), an important aspect of CAM, has been used for centuries. In TCM, *Astragalus membranaceus* is commonly used to treat the deficiency of *qi* (vital energy), which manifests as fatigue, diarrhea and lack of appetite [6]. Studies have shown that *Astragalus membranaceus*-based Chinese herbal remedies improve quality of life, alleviate chemotherapy toxicity, and boost immune functions in cancer patients [7-9]. PG2, extracted from *Astragalus*, has been developed as a novel CAM for cancer patients. Preclinical studies have shown that PG2 stimulates the secretion of hematopoietic growth factors from activated human peripheral blood mononuclear cells [10], enhances the proliferation and maturation of the progenitors of peripheral blood cells in mitomycin C-treated mice [11], and supports hematopoiesis in long-term bone marrow cultures [12]. In summary, PG2 is capable of stimulating immunity and hematopoiesis, and could play a role in the management of CRF.

In this study, a double-blind, randomized, placebo-controlled trial was conducted to examine the effects of PG2 infusion on CRF as a palliation in patients with advanced cancer.

Materials and Methods

Investigational drug

The investigational drug PG2 (PhytoHealth Corp., Taiwan) was extracted from *Astragalus membranaceus* as previously described [10-12]. PG2 is characterized as a mixture of polysaccharides prepared in sterile powder prior to use. For administration, each vial of 500 mg of PG2 was reconstituted with 10 ml normal saline and prepared by shaking thoroughly until completely dissolved. The dissolved solution was then injected

into normal saline (490 ml) and mixed well for intravenous (IV) infusion at a rate of 150 to 200 mL/h.

Patients

Inpatients and outpatients with advanced cancer who were undergoing standard palliative care at Mackay Memorial Hospital, a medical center hospital with a hospice education center in Taiwan, were recruited for the study. The inclusion criteria were as follows: patients had advanced cancer with a fatigue score of at least 4, based on the validated Taiwanese version of the Brief Fatigue Inventory-Taiwan (BFI-T) [13] and a life expectancy of at least three months. The BFI-T is a scale for measuring the severity of fatigue in cancer patients on a scale ranging from 0 to 10, with 0 indicating no fatigue and 10 indicating extreme fatigue. The BFI-T lists nine scenarios including present, usual and most severe episodes of fatigue over the last 24 h and their interference with general activity, mood, walking ability, normal work, interpersonal relations and enjoyment of life. The tabulated composite average score, as reported by the patient, represented the patient's global fatigue severity score (BFI-T score) [13-14]. Exclusion criteria were as follows: pregnancy or breastfeeding; a Karnofsky performance status (KPS) score of less than 30%; uncontrolled systemic diseases such as active infection, severe heart disease, hypertension, or diabetes mellitus; and use of any central nervous system stimulators or standard cancer chemotherapy within the previous 30 days. This clinical trial was reviewed and approved by the Institutional Review Board of Mackay Memorial Hospital.

Study design

Patients who met the enrollment criteria and provided written informed consent were randomly assigned to one of two groups: the PG2 group or the placebo group. During the first cycle (4 weeks total), patients in the PG2-primed group received PG2 500 mg/day three times a week, and patients in the placebo-primed group received normal saline 500 ml three times a week. During the second cycle, all patients received open-label treatment with PG2. Because this was a double-blind study, the investigators, clinical research coordinator and participants remained blinded to the treatment assigned to the participants during the first cycle. The investigators assigned an authorized person to prepare PG2 or placebo injections in a locked room. This person also recorded the data and maintained the secrecy of treatment allocation. The study protocol is presented in Fig. 1.

FIGURE 1. Study flow chart

CRF Assessment

To evaluate the efficacy of study drug treatment, BFI-T (Supplemental Figure 1) was used to assess CRF before treatment (baseline) and at the end of the first, second and fourth week of each cycle. A fatigue-improvement responder was defined as a person with at least 10% improvement in the BFI-T score from the baseline score at any efficacy evaluation point [15]. A fatigue-improvement response rate (FIRR) was defined as the percentage of fatigue-improvement responders in a group at each timepoint. The purpose of this study was to compare the FIRR between the two study groups at the end of the first treatment cycle (that is, at the end of the fourth week) and the inter-cycle changes in the FIRR from the fourth week to the eighth week within each study group.

The randomized patients in this study who had no major protocol violations were evaluated. Major protocol violations

were defined as receiving any prohibited treatments during the study or receiving an incomplete during the first cycle, defined as receiving 10 doses or fewer of study drugs. Prohibited treatment included blood transfusion, surgery, immunomodulators, medroxyprogesterone, steroids and other herbal medicines. These treatments made patients ineligible for the study.

Safety evaluation

Adverse events were recorded as the onset of a new adverse effect or as an increase in the magnitude of existing adverse effects. Adverse events were tabulated and summarized using MedDRA (version 9.1). The patients' safety profiles included data on vital signs, results of physical examinations, and laboratory data. Data on vital signs were recorded during screening and on day of PG2 infusion. Physical examinations were conducted on the same days at each efficacy evaluation point.

FIGURE 2. Patient flow diagram

In the laboratory assessments performed during screening and at the end of each treatment cycle, hematological data, including hematocrit and hemoglobin values and red blood cell (RBC), platelet, white blood cell (WBC), and differential counts, were collected. A biochemical profile, including serum levels of alanine transaminase, aspartate transaminase, alkaline phosphatase, blood urea nitrogen, bilirubin, albumin, total protein, creatinine, C-reactive protein and pre-albumin, was also obtained. In addition, urine was evaluated for RBC and WBC counts, protein levels and pH.

Statistical analysis

The study was set up to include at least 30 evaluable patients from each study group for the efficacy analyses. In the primary analysis, the FIRR of the two study groups at the end of cycle 1 were compared using Pearson's chi-squared test or Fisher's exact test. Fisher's exact test was adopted if more than 20% of cells had an expected value of less than 5. If imbalances in the BFI-T score or other measurements were found at baseline, logistic regression was used to adjust these factors in the primary efficacy evaluation. At the end of cycle 2, the inter-cycle changes in the FIRR of the two study groups were evaluated using McNemar's test. Patients showing fatigue status changes from baseline were categorized into three BFI-T score levels according to the decreases in their scores, namely "Improvement of 20% or more," "Improvement of between 10 and 20%," and "Improvement of less than 10%." At the end of cycle 1, the distribution of changes in patients' fatigue statuses of the two groups categorized in this manner were compared. A chi-square test or Fisher's exact test was used to analyze the categorical data. Any missing data of BFI-T score changes from baseline were regarded as "Improvement of less than 10%," and the logistic regression method was used to adjust for withdrawal in efficacy evaluation. For drug-safety evaluation, the analyzed population included patients who were administered at least one dose of the study drugs (safety dataset). All laboratory variables and vital signs were tabulated. The chi-square or *t* test was used to examine differences among two groups at baseline and the end of each treatment cycle. A value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

After 91 patients were screened, 90 advanced cancer patients were enrolled and randomized to either the PG2-primed group (45 patients) or the placebo-primed group (45 patients). Before the first dosage administration, 6.7% of patients ($n = 6$)

TABLE 1. Patient characteristics in both PG2- and placebo-primed groups

Characteristics	PG2-primed Group (n = 35)	Placebo-primed Group (n = 30)	P value
Cancer Type			
Female Breast	10 (29%)	8 (27%)	0.316†
Gynecological	2 (6%)	3 (10%)	
Gastrointestinal	4 (11%)	1 (3%)	
Head and Neck	6 (17%)	7 (23%)	
Respiratory	3 (9%)	4 (13%)	
Male Reproductive	4 (11%)	0 (0%)	
Other	6 (17%)	7 (23%)	
Gender (Male, Female)			
Male	14 (40%)	11 (37%)	0.783‡
Female	21 (60%)	19 (63%)	
Age, years			
Mean (SD)	64.00 (15.65)	56.90 (11.89)	0.046†
Primary cancer			
No	31 (89%)	26 (87%)	0.816‡
Yes	4 (11%)	4 (13%)	
Recurrence			
No	27 (77%)	22 (73%)	0.722‡
Yes	8 (23%)	8 (27%)	
Distant metastasis			
No	11 (31%)	10 (33%)	0.870‡
Yes	24 (69%)	20 (67%)	
Body weight loss in 6 months prior to this study			
<5%	31 (89%)	26 (87%)	0.816‡
>5%	4 (11%)	4 (13%)	
Karnofsky Performance Score			
Mean (SD)	66.86 (11.05)	69.33 (10.81)	0.366‡
Median	70.00	70.00	
§Baseline BFI-T Score			
Mean (SD)	5.34 (2.03)	6.04 (1.48)	0.119‡

SD: Standard deviation

† Two-sample *t*-test

‡ Fisher's Exact test

§ Baseline Brief Fatigue Inventory-Taiwan (BFI-T) Score: The evaluated time point was on the first study drug treatment day before study drug administration.

dropped out of the study: 1.1% of patients ($n = 1$) were unable to adequately communicate, 1.1% of patients ($n = 1$) died, and 4.4% of patients ($n = 4$) withdrew consent. By the end of the first cycle, 4.4% of patients ($n = 4$) withdrew consent, 4.4% of patients ($n = 4$) died during the study, 3.3% of patients ($n = 3$) were unconscious and were thus unable to continue to participate in the study, and an additional 8.9% of patients ($n = 8$) were excluded from the study because of major protocol violations. During the second cycle, 2.2% of patients ($n = 2$) withdrew from the study, 2.2% of patients ($n = 2$) died, and 3.3% of patients withdrew because of disease progression ($n = 1$) or adverse events ($n = 2$). In summary, by the end of the first cycle (4 weeks), 72.2% of patients ($n = 65$) continued to participate in the study, and 64.4% of patients completed the full two-cycle study ($n = 58$) (Fig. 2).

All baseline demographic characteristics of those patients, including age, sex, cancer type, disease status, BFI-T score and KPS were comparable, with no statistically significant differences ($P > 0.05$). The participants were diagnosed with various types of cancer, including head and neck, respiratory, breast (female), gastrointestinal, gynecological and reproductive (male). In the PG2-primed group ($n = 35$), 10 patients (29%) had breast cancer, the most frequent cancer type in the group. Thirty-five participants were 64.0 years of age on average. The average Karnofsky performance score was 66.86, and the average BFI-T score was 5.34. Twenty-four patients (69%) had distant metastasis, 27 patients (77%) did not have recurrent disease, and only four patients (11%) had lost more than 5% of their body weight in the past six months. In the placebo-primed group ($n = 30$), eight patients had breast cancer, the most frequent cancer type in the group. Thirty participants were 56.9 years of age on average. The average Karnofsky per-

TABLE 2. Fatigue Improvement Response Rate (FIRR) at Each Efficacy Evaluation Timepoint

	PG2-primed group		Placebo-primed group		P value†
	FIRR	N of evaluable patients	FIRR	N of evaluable patients	
Cycle 1					
Week 1	57.14%	35	32.26%	31	0.043
Week 2	57.14%	35	36.67%	30	0.099
Week 4	60.00%	35	40.00%	30	0.108
Cycle 2					
Week 1	51.51%	33	57.14%	28	0.660
Week 2	52.94%	34	64.29%	28	0.368
Week 4	58.60%	31	66.67%	27	0.501

†Chi-square test

FIGURE 3. Inter-cycle comparisons (from the fourth week to the eighth week within each study group) of the fatigue-improvement response rates (FIRR), analyzed by McNemar's test. There was no significant change in FIRR in the PG2-primed group but the observed increase in FIRR in the placebo-primed group was significant ($P=0.02$).

formance score was 69.33, and the average BFI-T score was 6.04. Twenty patients (67%) had distant metastasis, 22 patients (73%) did not have recurrent disease, and only four patients (13%) lost more than 5% of their body weight in the past six months (Table 1).

CRF Assessment

In the placebo-primed group, the FIRRs evaluated at the end of cycle 2 in this group increased significantly after PG2 administration ($P = 0.02$) relative to the value at the end of cycle 1 (Fig. 3). During cycle 1, the intergroup analysis showed that initial PG2 administration resulted in a significantly greater FIRR than NS infusion (FIRR 57% vs. 32% at week 1, $P = 0.043$). By weeks two and four, there were no significant differences between the two groups (Table 2). In laboratory tests, only the monocyte levels were significantly different after the 2-cycle treatment between the two groups ($P = 0.021$) (Table 3). Furthermore, although a 10% improvement in the BFI-T score was required to define a participant as a responder, 72% (15/21) of the 60% (21/35) of those who reported an improvement in fatigue symptoms in the PG2-primed group reported greater than 20% improvement at the end of cycle 1

(Fig. 4). In addition, approximately 82% of PG2 responders felt a sustained beneficial effect on CRF after the subsequent second-cycle administration. Furthermore, among the PG2 non-responders in the first cycle infusion, 71% of patients reported improvement after the second-cycle administration, indicating a possible positive role of prolonged administration for up to 8 weeks. After eight weeks of treatment, 17.6% of the patients in the PG2-primed group gained over 5% of their weight before the tests. None of the patients in the placebo-primed group gained over 5% of their weight before the tests. We further analyzed the BFI-T question 4 sub-questions to explore the influences of fatigue at different levels. Results show that at the end of cycle 1, the score of question 4b, which was related to emotional level, was 0.87 lower on average, which was the largest difference from the baseline. At the end of cycle 2, the largest improvement was in question 4c, which was used to evaluate walking ability. The reduction was 1.29 on average. This was followed by question 4b, with a reduction of 1.26 on average.

Toxicity Evaluation

No evident difference in the number and severity of adverse events between the PG2-primed and the placebo-primed groups was observed. None of the severe adverse events (SAE) was deemed to be causally related to PG2 treatment. The adverse events exclusively associated with PG2 administration were rashes (three cases), eczema (two cases), and pruritus (two

FIGURE 4. Distribution of changes in the Brief Fatigue Inventory-Taiwan (BFI-T) scores of the two study groups at the end of cycle 1 in comparison with baseline. Distribution of improvement between the two treatment groups was analyzed by Fisher's exact test, $p=0.25$.

cases) (Table 4). Most of these adverse events were minor, and all patients recovered without medical treatment in a short time. Additionally, the laboratory profiles, physical examination results and vital signs were similar between the two study groups.

TABLE 3. Changes in laboratory data after completion of two treatment cycles

	PG2-primed group		Placebo-primed group	
	Baseline	After 2 cycles	Baseline	After 2 cycles
WBC ($10^3/\mu\text{L}$)				
MEAN (SD)	5.52 (2.59)	5.85 (5.51)	6.55 (3.79)	5.4 (2.21)
Lymphocytes(%)				
MEAN (SD)	21.21 (8.53)	19.86 (10.11)	21.36 (12.24)	23.13 (11.40)
Basophils(%)				
MEAN (SD)	0.45 (0.75)	0.33 (0.33)	0.41 (0.40)	0.43 (0.27)
Eosinophils(%)				
MEAN (SD)	8.94 (36.50)	2.52 (3.34)	2.54 (2.11)	2.29 (1.78)
Monocytes(%)				
MEAN (SD)	8.57 (3.87)	7.62 (3.93)	7.12 (2.65)	5.70 (2.23) †
Neutrophils(%)				
MEAN (SD)	66.97 (8.54)	69.10 (9.85)	68.37 (13.81)	68.30 (12.53)
C-Reactive Protein				
MEAN (SD)	2.24 (2.93)	2.62 (3.72)	3.61 (6.39)	1.79 (2.31)

SD: Standard deviation

† Two-sample *t*-test

Discussion

To our knowledge, this was the first randomized trial to evaluate the efficacy of *Astragalus membranaceus* in CRF of advanced cancer patients by using a double-blind design with both placebo-controlled and self-controlled groups. A four-week treatment cycle was used because of our clinical practices: cancer patients generally return for visits every four weeks when not undergoing any special treatment. The two-cycle design allowed patients treated with placebo the opportunity to be treated with PG2 to obtain any benefits; however, only the data from the first treatment cycle can be used to compare the efficacy of PG2 with the placebo, due to the study's double-blind, randomized and placebo-controlled design. Additionally, because there were two cycles for the PG2-primed group, exploring the cumulative effect of PG2 was possible. Our results show that PG2 administration is safe and effective and can achieve fatigue improvement in advanced cancer patients when used over an eight-week interval. The difference in the FIRR between the two groups was significant during the first week of the first cycle, but no significant difference was seen in subsequent weeks. This may be attributed to the small number of participants enrolled in the study. Conversely, the FIRRs in the placebo-primed group increased significantly after PG2 treatment during the second cycle (Figure 3). This difference in FIRRs was the most convincing and consistent finding in our study, and suggests that PG2 may improve CRF in advanced cancer patients.

In cancer patients, fatigue and depression might coexist and show considerable overlap of symptoms [5,15,16]. The common pharmacological interventions for CRF include psychostimulants and corticosteroids. Psychostimulants show great promise in the alleviation of CRF through the psychiatric approach [15,17]; however, these compounds are associated with a high risk of abuse and have adverse effects, including irritability, anorexia, insomnia, fluctuations in mood, nausea and heart beat irregularities [5,14,16-18]. Glucocorticoids have been used in CRF treatment to relieve physical symptoms; however, recent studies show that short-term glucocorticoid administration improves CRF, whereas long-term use causes detrimental side effects such as muscle wastage [5,19].

Chinese patients with advanced cancer frequently resort to TCM for general symptom relief [20]. *Astragalus*, with a long history of usage in TCM, has demonstrated a wide range of immunopotentiating effects [21,22], has proven to stimulate cell-mediated immune mechanisms, and has effects on cardiovascular and neuroendocrine systems. It is also effective as an adjunct cancer therapy to prolong survival, increase tumor response, decrease chemotherapy toxicity, and improve quality of

TABLE 4. Summary of Adverse Events

	PG2-primed group	Placebo-primed group
All AEs (from Screening)		
Number of AEs	226	195
AEs in severity		
“Mild”	91 (40.27%)	69 (35.38%)
“Moderate”	121 (53.54%)	109 (55.90%)
“Severe”	14 (6.19%)	17 (8.72%)
Patients with AEs	41 (93.18%)	40 (100.00%)
Patients with SAEs	8 (18.18%)	9 (22.50%)
Patients discontinued due to AE	2 (4.55%)	1 (2.50%)
Patients with treatment-related AEs	8 (18.18%)	8 (20.00%)
Cycle 1		
Number of AEs	128	114
AEs in severity		
“Mild”	52 (40.63%)	39 (34.21%)
“Moderate”	69 (53.91%)	66 (57.89%)
“Severe”	7 (5.47%)	9 (7.89%)
Patients with AEs	36 (81.82%)	35 (87.50%)
Patients with SAEs	3 (6.82%)	7 (17.50%)
Patients discontinued due to AE	1 (2.27%)	1 (2.50%)
Patients with treatment-related AEs	5 (11.36%)	5 (12.50%)
Cycle 2		
Number of AEs	83	75
AEs in severity		
“Mild”	34 (40.96%)	29 (38.67%)
“Moderate”	44 (53.01%)	38 (50.67%)
“Severe”	5 (6.02%)	8 (10.67%)
Patients with AEs	28 (70.00%)	28 (80.00%)
Patients with SAEs	5 (12.50%)	3 (8.57%)
Patients discontinued due to AE	2 (5.00%)	1 (2.86%)
Patients with treatment-related AEs	3 (7.50%)	5 (14.29%)

† Analysis population: all patients who were administered at least one dose of study drugs.

‡ AE: Adverse events

§ SAE: Severe Adverse events

life [8, 9, 23]. In a randomized controlled trial, the WBC, platelets and CD8 of the patients treated with *Astragalus* were reduced [8]. Compared with patients without *Astragalus*, the CD4/CD8 ratio, IgM, and IgG increased [8]. In some studies, *Astragalus* is believed to improve immune functions such as WBC and lymphocytes [8,24]. In numerous studies on immunology and cytokines, values of WBC, lymphocytes, CD4, and CD8 are considered to be related to fatigue [25,26]. The scientific evidence of its effectiveness was limited prior to our study because most studies are not double-blinded and placebo-controlled [7-9]. In this study, patients treated with PG2 reported a greater improvement in fatigue symptoms than with NS injection. Additionally, PG2 proved to be an effective enhancement of mood and thus enjoyment of life for patients. These results are valuable because fatigue and depression may coexist and show considerable overlap of symptoms in cancer patients [5,15,16]. To our knowledge, PG2 is the first fatigue modulator to relieve fatigue-related psychosocial distress. Moreover, the adverse events among patients receiving PG2 were not significantly different from those among patients receiving the placebo, proving minimal adverse risks related to PG2 application to patients.

The high placebo effect observed in this study has also been reported in previous studies on CRF [15,18,27]. Finding an appropriate placebo is often difficult, especially in clinical trials of Chinese herbal medicine [7], and numerous studies have demonstrated that different routes of placebo administration trigger different responses. Nevertheless, researchers believe that a placebo-controlled trial is essential to determine whether the findings are independent or caused by an extension of the placebo effect [5,15,17,18,28-30]. In future studies, the placebo-controlled group should be established as a baseline comparison to other non-controlled groups. For this study, we used intravenously administered normal saline (500 mg/day, three times per week) as the placebo during the first treatment cycle (FIRR, 29-40%). Although reports indicate that patients believe artificial nutrition (feeding through a nasogastric or gastrostomy tube, or total parenteral nutrition) to relieve their symptoms [26], no study has evaluated the effect of normal saline injection for CRF; therefore, future studies can also focus on this particular area.

During the initial enrollment of participants, a range of cancer diseases were included in the study. We observed that the application of PG2 among various cancer types yielded notable variances of CRF relief. In our study, most of the participants had breast cancer (18 participants) or head and neck cancer (13 participants). In the first treatment cycle, 70% (7/10) of the breast cancer patients who received PG2 treatment

were fatigue-improvement responders. This percentage was the highest among all the groups with different types of cancers. The second highest percentage was 67% (4/6) with the head and neck cancer patients. In addition, 8 patients in the control group were fatigue-improvement non-responders in the first cycle, but responders in the second cycle. Among them, five were breast cancer patients, comprising 62.5% of the breast cancer patients in the control group. This means that PG2 was helpful for breast cancer patients. In future studies, focusing on the specificity of cancer types or patient sex would be beneficial to determine the maximum effectiveness of PG2 on particular patients.

In future studies, an expansion of study cycles from two to additional cycles, possibly following patients' disease progressions until death, would be helpful. This could provide additional data to evaluate the consistency of PG2 effectiveness on CRF, even during patients' rapid final deterioration, thus potentially proving a greater potency of PG2 in patients with endstage cancer, even if the FIRR reflects only 10% improvement when compared to the enrollment baseline data.

The limitations of this study include a moderate dropout rate, rapid disease progression during treatment course, and moderate sample size, all of which could contribute to the only marginal improvement of FIRR. The rate of dropout might be because of the relative weakness of the enrolled participants, which compromised compliance with transporting patients to the hospital to receive drug infusions three times per week. Another limitation is the rapid disease progression and short life expectancy of far-advanced cancer patients, which leads to incomplete efficacy evaluation and withdrawal from the study. Ethical considerations suggest that expanding recruitment solely to reach a statistical difference may be inappropriate. Nevertheless, the efficacy of PG2 could be validated by a significant improvement of FIRR in the placebo-primed group before and after PG2 administration, although the compassionate design in cycle two is open-labeled.

Conclusion

PG2 could be an effective and safe palliative treatment for relieving fatigue in advanced cancer patients.

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Brief Fatigue Inventory

Throughout our lives, most of us have times when we feel very tired or fatigued.

Have you felt unusually tired or fatigued in the last week? Yes No

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0	1	2	3	4	5	6	7	8	9	10
No										As bad as
Fatigue										you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No										As bad as
Fatigue										you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No										As bad as
Fatigue										you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
B. Mood										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
C. Walking ability										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
D. Normal work (includes both work outside the home and daily chores)										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
E. Relations with other people										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
F. Enjoyment of life										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes