

Effects of Spinal-Z in Patients with Gastroesophageal Cancer

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Key Words

Gastroesophageal cancers, Adenocarcinoma, Squamous cell carcinoma, Peganum harmala, Dracocephalum kotschyi Boiss, Spinal-Z

Abstract

Objective: The purpose of this study was to investigate the efficacy and safety of spinal-Z, derived from Peganum harmala seeds and Dracocephalum Kotschyi Boiss leaves, in patients with esophageal and stomach adenocarcinoma, and squamous cell carcinoma of the esophagus.

Methods: Sixty-one patients with malignancies of the upper gastrointestinal tract were randomly assigned to one of two groups (treatment or control) in a double-blind fashion. Six capsules of Spinal-Z were prescribed to the patients with the regimen of 600 mg/m²/day, and placebo to the control group, for six months.

Results: There were no significant differences between the two groups with regard to age, sex, duration of cancer, type of cancer and family history of cancer. There were significant differences in abdominal pain, heartburn, constipation and vomiting between the two

groups, following spinal-Z therapy. Evaluation of drug side effects showed no difference in cough or other respiratory symptoms, itching, headache or dizziness between the two groups, both before and after treatment.

Conclusion: This study indicates that Spinal-Z is safe and efficacious in the management of patients with upper gastrointestinal tract cancers.

1. Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide, with especially high mortality rates in Asia, Europe and South America (1). Because the prognosis for GC is poor and it is often diagnosed at a locally advanced or metastatic stage, the treatment remains challenging. In advanced and metastatic stages, the disease does not respond well to conventional treatments. Chemotherapy, radiotherapy, and surgery, the most common treatments modalities, are either poorly effective (2), and/ or have significant and severe side effects (3). Therefore, there are efforts to discover new therapeutic agents with low toxicity and fewer side effects.

It has been shown that neoplasms in the digestive organ are mostly due to modifications in dietary habits and natural plants and herbal remedies have been reported to have anti-cancer properties (4-11). There-

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fore, the use of easily accessible and inexpensive natural products and herbal drugs may have important therapeutic potential. Herbal drugs include plants, herbal complexes, or even a combination of plants, which have been used for thousands of years prior to the invention of chemical agents.

Spinal-Z is a methanolic compound, from the dried seeds of *Peganum* (*Peganum harmala*) and *Dracocephalum Kotschy* Boiss leaves (12). Spinal-Z has cytotoxic, anti-inflammatory, analgesic, anti-bacterial and anti-virus effects (12).

The purpose of this study was to investigate the efficacy and safety of spinal-Z in patients with gastroesophageal adenocarcinoma and squamous cell carcinoma of the esophagus.

2. Materials and Methods

Subjects. This study was designed as a randomized, double-blind placebo-controlled trial and conducted at the Oncology Clinic of the Baqiyatallah Hospital, Tehran, Iran. Included in the study were 61 male and female subjects aged 25 to 75 years with histologically documented gastroesophageal cancer. Exclusion criteria were a history of hypersensitivity to herbal preparations, intolerance to chemotherapy, uncontrolled disease symptoms and the occurrence of severe adverse events during treatment.

The enrolled subjects were randomized to receive either Spinal-Z (600 mg/m²/day) (group T; n = 37) or placebo (group C; n = 24) for a period of 6 months. Placebo capsules contained starch and were matched in color and size to Spinal-Z capsules. All patients were under treatment with standard chemotherapy regimens appropriate for their respective cancer, and the chemotherapy regimens were maintained throughout the trial. The following chemotherapeutic agents were employed: 5-fluorouracil, uracil, and cisplatin. Patients were visited every two weeks and asked about their compliance and the regularity of consumption of the study medication, as well as any adverse effects. A board-certified oncologist visited patients at baseline and at the conclusion of the treatment period. The study was approved by the Ethics Committee of the Baqiyatallah University of Medical Sciences, and all participants gave written informed consent.

Biochemical analyses. Fasting blood samples were collected at baseline and at the end of the trial. Collected samples were centrifuged for 10 min to obtain serum. Serum samples were kept at - 80 °C until analysis. Biochemical parameters assessed in each sample were absolute neutrophil count, blood uric acid, serum creatinine, blood urea nitrogen, hemoglobin, hematocrit, platelets, white blood cells count, creatine phosphokinase, alanine transaminase and aspartate transaminase. Measurements were conducted using commercial enzyme immunoassay kits.

Statistical analysis. Statistical analyses were performed using the SPSS software version 17 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean \pm SD or number (%). Within-group comparisons were performed using a paired samples t-test (in the case of normal distribution

of data) or Wilcoxon signed-ranks test (in the case of non-normal distribution of data). Between-group comparisons were made using independent samples t-test (in the case of normal distribution of data) or Mann-Whitney U-test (in the case of non-normal distribution of data). Categorical variables were compared using the chi-square test. Correlations of the evaluated parameters during the study were assessed using Pearson's (in the case of normal distribution of data) or Spearman's rank (in the case of non-normal distribution of data) correlation coefficients.

3. Results

Demographic data

The total number of males and females was 37 (60.7%) (T: 23, C:14) and 24 (39.3%) (T:14, C:10), respectively. There was no significant difference between the two groups in terms of gender (P=0.79).

Forty-four patients (78.6%) had gastric adenocarcinoma, while 3 (5.4%) had esophageal adenocarcinoma and nine patients (16.1%) had esophageal squamous cell carcinoma. There was no significant difference (P=0.94) between treatment and control groups with regards to cancer type. Approximately, 50 patients (82%) had a family history of cancer. One of them (1.6%) had a family history of esophageal cancer. Four patients (6.6%) had a family history of gastric cancer, and six patients (9.8%) had a history of other cancer types. There was no significant difference between the treatment and control groups in terms of family history of cancer (P=0.81) (Table 1).

Only 18 patients (30%) had a history of radiotherapy, while 42 patients (70%) had no history of radiation therapy (Table 1). There was no difference between the treatment and control groups in terms of a history of radiotherapy (P=0.39). The average age in the female and male subjects was 59.79 \pm 10.06 and 63.39 \pm 10.41 years, respectively. There was no difference between the two genders regarding age (P=0.09).

Laboratory measurements before and after the trial

The average hemoglobin (Hb) level in the drug treatment group was significantly increased from 11.59 \pm 1.41 milligrams (mg)/ deciliter (dl) to 12.15 \pm 1.48 mg/dl after spinal-Z (P<0.01). Similarly, the mean of Hb in the placebo group was significantly (P=0.04) increased from 11.26 \pm 1.42 mg/dl to 11.71 \pm 1.08 mg/dl after treatment. The mean of Hb before and after treatment did not show a difference between the treatment and control groups (P=0.44). The mean (Hct) in the drug group before and after treatment was 36.48% \pm 4.84% and 37.70% \pm 4.83%, respectively (P=0.01). The mean Hct was also significantly increased (P=0.02) from 34.92% \pm 3.57 % before treatment to 36.18% \pm 2.47% after treatment in the placebo group. The average for Hct before and after treatment did not show a difference between the treatment and control groups (P=0.67) (Table 2).

The average white blood cell (WBC) count in the drug group was unchanged before (7.02 \pm 2.58 mg/dl) and af-

Table 1 Demographic data of each patient group

Categorical Variables	Level	Drug (N=37)		Placebo (N=24)		Total (N=61)		P value
		N	%	N	%	N	%	
		Sex	Male	23	62.2%	14	58.3%	
	Female	14	37.8%	10	41.7%	24	39.3%	
Cancer Family History	No	30	81.1%	20	83.3%	50	82.0%	0.816
	Esophagus	1	2.7%	0	.0%	1	1.6%	
	Stomach	2	5.4%	2	8.3%	4	6.6%	
	Other part	4	10.8%	2	8.3%	6	9.8%	
Underling Disease	No	22	61.1%	18	75.0%	40	66.7%	0.181
	Hypertension	5	13.9%	1	4.2%	6	10.0%	
	Diabetes	5	13.9%	1	4.2%	6	10.0%	
	Hypertension & diabetes	2	5.6%	0	.0%	2	3.3%	
	Other	2	5.6%	4	16.7%	6	10.0%	
Cancer Type	Esophageal squamous cell carcinoma	6	17.1%	3	14.3%	9	16.1%	0.945
	Esophageal adenocarcinoma	2	5.7%	1	4.8%	3	5.4%	
	stomach adenocarcinoma	27	77.1%	17	81.0%	44	78.6%	
Radiotherapy History	Yes	9	25.0%	9	37.5%	18	30.0%	0.391
	No	27	75.0%	15	62.5%	42	70.0%	

Table 2 Laboratory criteria before and after treatment in two groups

Variables	Group	Before		After		diff	P value	P value
		Mean	SD	Mean	SD			
Hgb	Drug	11.59	1.41	12.15	1.48	.56	.006	0.448
	Placebo	11.26	1.42	11.71	1.08	.45	.042	
Hct	Drug	36.48	4.84	37.70	4.83	1.22	.010	0.670
	Placebo	34.92	3.57	36.18	2.47	1.25	.027	
WBC	Drug	7.02	2.58	6.44	2.23	-.58	.074	0.611
	Placebo	7.20	2.51	6.76	1.56	-.43	.422	
Pit	Drug	220.80	52.88	216.06	51.83	-4.73	.593	0.691
	Placebo	264.27	129.04	247.00	88.65	-17.27	.301	
MCV	Drug	85.52	5.68	84.34	6.16	-1.17	.268	0.495
	Placebo	81.54	8.62	80.60	7.45	-.94	.380	
Neutrophil	Drug	59.68	12.53	61.07	12.64	1.39	.419	0.828
	Placebo	60.44	10.55	62.26	13.04	1.82	.468	
Basophil	Drug	1.42	1.96	2.09	1.81	.66	.151	0.541
	Placebo	1.46	1.63	2.42	1.51	.95	.035	
Lymphocyte	Drug	32.62	14.30	31.09	13.04	-1.53	.485	0.235
	Placebo	32.37	12.98	38.08	27.46	5.71	.423	
BUN	Drug	21.7	10.11	20.90	10.07	-.80	.424	0.170
	Placebo	18.58	7.55	20.37	6.85	1.78	.104	
Cr	Drug	1.03	.36	1.04	.24	.005	.915	0.313
	Placebo	.90	.29	.91	.30	.008	.903	
Uric Acid	Drug	4.66	1.05	4.66	.74	.003	.986	0.678
	Placebo	4.80	.80	4.78	.58	-.017	.920	
ALT	Drug	31.05	30.08	30.43	26.73	-.61	.778	0.617
	Placebo	17.91	7.21	20.88	8.72	2.97	.112	
AST	Drug	27.86	24.41	26.4	19.73	-1.46	.327	0.715
	Placebo	20.35	7.82	21.53	5.12	1.17	.292	
ALP	Drug	319.36	377.60	277.86	220.19	19.50	.336	0.462
	Placebo	194.11	51.54	195.47	45.84	1.35	.660	

Table 3 Gastrointestinal complaints in both groups before and after treatment

Group	Variables	Before		after		diff	P value	P value
		N	%	N	%			
Abdominal Pain (Positive)	Drug	13	43.3%	4	13.3%	-30%	0.004	0.084
	Placebo	8	50.0%	4	25.0%	-25%	0.219	
Anorexia (Positive)	Drug	19	63.3%	3	10%	-53.3%	<0.001	0.863
	Placebo	8	50.0%	2	12.5%	-37.5%	0.109	
Heart Burn (Positive)	Drug	14	46.7%	10	33.3%	-13.4%	0.388	0.028
	Placebo	8	50.0%	7	43.8%	-6.2%	0.999	
Constipation (Positive)	Drug	8	26.7%	1	3.3%	-23.4%	0.016	<0.001
	Placebo	4	25.0%	4	25.0%	0%	0.999	
Nausea (Positive)	Drug	11	36.7%	5	16.7%	-20%	0.070	0.045
	Placebo	4	25.0%	1	6.3%	-18.7%	0.375	
Vomiting (Positive)	Drug	7	23.3%	3	10.0%	-13.3%	0.289	0.261
	Placebo	3	18.8%	3	18.8%	0%	0.999	

ter treatment (6.44 ± 2.33 mg/dl) ($P=0.07$). The mean WBC count was also unchanged before (7.20 ± 2.51 mg/dl) and after treatment (6.76 ± 1.56 mg/dl) ($P=0.42$), and there was no difference in mean WBC count between the treatment and control groups ($P=0.61$). No hepatic enzyme changes were seen (ALT, AST and ALP) between spinal-Z and placebo treatment ($P>0.05$). Laboratory data are presented in Table 2. There were no significant differences between the treatment and control groups before and after treatment for any other laboratory parameters.

Investigation of gastrointestinal complaints

In the treatment group, 13 patients (43.3%) complained of abdominal pain before treatment, and this significantly decreased to 4 patients (13.3%) after treatment ($P=0.004$). In the placebo group, 8 patients (50%) complained of abdominal pain before treatment, and this decreased to 4 patients (25%) after treatment, but this was not significant ($P=0.21$). However, there was no difference regarding abdominal pain between the treatment and control groups before and after treatment ($P=0.08$) (Table 3).

19 patients (63.3%) in group T had complained about anorexia prior to treatment. After the trial, the number of patients with this complaint decreased to three (10%) ($P<0.001$). In the placebo group, 8 patients (50%) complained about anorexia before treatment and whilst this

fell to 2 patients (12.5%) after treatment, this difference was not significant ($P=0.1$). The between-group comparison of anorexia showed no difference ($P=0.86$) (Table 3). In the patients receiving Spinal-Z, 14 patients (46.7%) reported heartburn and 8 patients (26.7%) reported constipation before treatment that decreased to 10 patients (33.3%) reporting heartburn and only one patient (3.3%) reporting constipation after treatment ($P=0.38$ and $P=0.01$, respectively). In the placebo group, 8 patients (50%) reported heartburn and 4 patients (25%) reported constipation before treatment that did not differ after 6 months ($P=0.99$, $P=0.99$, respectively). Overall, there was a significant difference in terms of heartburn and constipation between the treatment and control groups before and after treatment ($P=0.02$ and $P<0.001$) (Table 3).

In the treatment group, 11 subjects (36.7%) and seven subjects (23.3%) had complained of nausea and vomiting, respectively, before the treatment, but this did not differ after treatment (five patients (16.7%) and three patients (10%), $P=0.07$, $P=0.28$, respectively) In the placebo group, 4 cases (25%) and 3 cases (18.8%) complained of nausea and vomiting, respectively, before the start of the trial, but this did not differ after treatment (one patient (6.3%) and three patients (10%), $P=0.37$, $P=0.99$, respectively). Overall, there was a significant difference in terms of nausea between the treatment and control groups before and after the treatment ($P=0.04$) but not for vomiting ($P=0.26$) (Table 3).

Table 4 Evaluation of drug side effects in both groups before and after treatment

Group	Variables	Before		After		diff	P value	P value
		N	%	N	%			
Cough (Positive)	Drug	12	40%	1	3.3%	- 36.7%	0.001	0.167
	Placebo	2	12.5%	2	12.5%	0%	0.999	
Respiratory (Positive)	Drug	8	27.6%	1	3.4%	- 24.2%	0.016	0.998
	Placebo	4	25.0%	1	6.3%	- 18.7%	0.250	
Muscle weakness (Positive)	Drug	16	55.2%	5	17.2%	-38%	0.001	0.032
	Placebo	7	43.8%	4	25.0%	- 18.8%	0.275	
Itching (Positive)	Drug	4	13.8%	1	3.4%	- 10.4%	0.375	0.999
	Placebo	1	6.3%	0	0%	- 6.3%	0.999	
Headache (Positive)	Drug	8	27.6%	1	3.4%	- 24.2%	0.016	0.999
	Placebo	3	18.8%	0	0%	- 18.8%	0.999	
Dizziness (Positive)	Drug	8	27.6%	0	0%	- 27.6%	<0.001	0.999
	Placebo	6	37.5%	0	0%	- 37.5%	<0.001	

Evaluation of drug side effects

Spinal-Z side effects evaluation showed a significant difference only regarding muscle weakness between two groups. Other side effects, including cough and respiratory symptoms, itching, headache and dizziness did not show any significant difference before and after treatment between groups T and C (Table 4).

4. Discussion

Stomach and esophageal cancers are two cancers of the gastrointestinal tract with a very poor prognosis (13). Gastric cancer is one of the leading causes of death with only a 5-20% survival rate (14). The 6-year and 10-year survival rate among patients with squamous cell carcinoma of the esophagus reported to be 39.5% and 12%, respectively (15). Recent findings have shown that of 1,000 Iranian people, 21 patients with cancer of the upper digestive tract die each year (16). These observations indicate the need for improved risk identification and earlier tumour detection facilitating early treatment strategies (15, 17). Different treatment regimens for esophagus and gastric cancer are well documented (18-27)

and include: Docetaxel, cisplatin, and fluorouracil (20-22); epirubicin, cisplatin, and fluorouracil (18); fluorouracil, leucovorin, and irinotecan(24); fluorouracil, leucovorin, and oxaliplatin (23); capecitabine and irinotecan (25); capecitabine and oxaliplatin (26). No single standard treatment regimen has been found to be superior for gastro-esophageal cancer (28).

In cases of gastric adenocarcinoma, surgical removal of all or part of the stomach is the only treatment that can cure the disease (29). In the advanced stages, symptom relief is the more critical issue. Radiotherapy or chemotherapy alone after surgery has no effect on survival rate, but simultaneous use of them is effective. The two main drugs in cancer chemotherapy are cisplatin and 5-FU that have a long track record of use (29, 30).

In our randomized double-blind study of Spinal Z versus placebo there was no difference in the patient demographics. The mean age of cancer in the female patients was lower than in the male patients, and could indicate an early diagnosis of cancer in females compared to males. The main symptomatic complaints of the study patients were dysphagia, abdominal pain, constipation, anorexia, and dyspepsia. For abdominal pain, anorexia, and constipation symptoms, there was a significant reduction in the Spinal Z group, whereas in patients who received placebo showed no symptomatic changes, suggesting the effectiveness of Spinal-Z in this patient cohort.

An improved therapeutic effect was shown in a clinical trial by Rezvani and colleagues by utilizing oxaliplatin instead of cisplatin and capecitabine instead of 5-FU in patients with advanced gastric cancer (31). Mean progression-free survival (PFS) was seven months and mean overall survival (OS) of patients was 10.6 months. The results of this study, in patients with inoperable and metastatic gastric cancer, demonstrated that a regimen consisting of EXE (Epirubicin, Xeloda, Eloxatin) once every three

weeks is effective and tolerable, and can be given on an outpatient basis (31).

Seilanian Toosi and colleagues evaluated chemotherapy and radiotherapy before surgery and after surgery in patients with esophageal squamous cell carcinoma (32). This retrospective cohort study, from 2000 to 2005 was performed on 75 patients with esophageal cancer. 42 patients received at least treatments of adjuvant chemotherapy containing Cisplatin and 5- fluorouracil. According to the results of this study, there was a complete response to therapy before surgery in 5 patients (7/6%) with a median follow-up of 13 months. Recurrence occurred in 21 patients (28%), including nine with local regional recurrence, nine with distant metastases, and three with local and distant recurrence occurring simultaneously. For all patients, three-year survival was 62.2%. The survival rate in patients who had received at least three cycles of chemotherapy compared to patients who received less than three cycles or received no chemotherapy did not differ ($P=0.09$). Patients with class I and II tumors had a significantly improved survival compared with the III class ($P=0.05$) (32).

In another study, Yazdanbod and colleagues evaluated Spinal-Z for the treatment of cancer of the upper gastrointestinal tract (33). This study was performed over nine months in seven patients. These patients were enrolled voluntarily at different intervals. After the start of treatment, during the first visit and at follow up checks, one patient showed raised liver enzymes (AST, ALT, and bilirubin). This patient died with a diagnosis of drug-induced hepatitis (hepatitis fulminant) though causality to spinal-Z was not shown; however, assessment of Spinal-Z side effects on the liver is therefore important and further research is necessary. One patient died at an early stage with a diagnosis of myocardial infarction (MI). In another patient, serial sonography showed a decrease in growth of metastatic tumors. In other patients, common side effects such as dizziness and nausea were reported (33).

In the study presented here, two plants, including *P. harmala* and *D. Kotschy*, were employed in the Spinal-Z preparation as palliative therapy in patients with esophageal squamous cell carcinoma and stomach adenocarcinoma, and to improve quality of life in these patients. No alteration in the blood cell count, liver, renal function tests and inflammatory profile was detected.

Alkaloids of harmala plants have multiple effects, including analgesic (34), anti-inflammatory (35) and cytotoxic (36), and inhibitory effects on the enzyme topoisomerase that induces programmed cell death and accelerates cancer cell death (37). These compounds also have antioxidant and anti-mutagenic effects (38, 39). The Spinal-Z capsule is a dried extract of harmala beans that has three alkaloids (harman, harmine, harmaline) plus leaves of *D. Kotschy* that contain the flavonoid xanthomicrol, which has anti-tumor properties and exerts its anti-tumor effect through inhibition of DNA isomerase (17). This flavonoid has also analgesic and sedative effects in cancer patients, exerted via blocking of the H2 receptor and inhibition of monoamine oxidase (MAO) (34, 40).

5. Conclusion

Results of this study indicated that spinal-Z was safe for use in the management of symptoms in patients with non-metastatic gastro-esophageal cancer. Further trials are warranted to investigate the impact and efficacy of this herbal preparation as an adjuvant therapy in patients with cancer.

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