

Clinical Trial of GFE on Cancer Patients

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Clinical Corroboration Group of GFE

On the basis of preclinical studies required by SFDA (China), clinical trial of GFE capsule on cancer patients was carried out in 1995.

The clinical trial program and assessment criteria of therapeutic effect were as followed 《The Guidance for Clinical Study of New Chinese Drug》 and 《The Guidance for Clinical Study of Immune Drug》 by sFDA (China). Zhejiang Cancer Hospital and other four local hospitals participated in the program. The clinical and laboratory data from 157 patients (107 treated and 50 control) were collected and evaluated.

(1) Criteria for selection and rejection of cases

① Cases selection: All patients were diagnosed as malignant cancer with pathology, X-ray and / or specific laboratory test. According to Traditional Chinese Medicine practice criteria of insufficiency of the spleen-qi (脾气虚) or insufficiency of the spleen-yang (脾阳虚) were also made. Insufficiency of spleen-yang is a syndrome marked by dyspepsia, abdominal distention, borborygmus, and lienteric diarrhea. Insufficiency of spleen-qi is a morbid condition marked by hypo-function of the spleen and cold syndrome.

② Patients with the following were rejected: (a) complicated with hepatic stasis and insufficiency of spleen; (b) with age under 18 or over 65 years old; (c) complicated with severe primary cardiovascular, liver or kidney diseases; (d) with psychosis; (e) interruption of drug taking, deleted laboratory data.

③ The patients were divided randomly into treated group or control group. The general status of the patients were in table 1.

(2) Treatment schedule and dose: All patients received chemotherapy or radiotherapy simultaneously or alternately and stopped to take any other drug. The patients in treated group took 4 GFE capsules (0.4 g each) 1 h before meal, three times a day. The treatment course lasted 28 days.

(3) Criteria for evaluation of curative effect:

① (Chinese Medicine) evaluation criteria for patients with insufficiency of spleen qi

Clinical cure: major and minor symptoms disappeared

Markedly effective: score drop $\geq 2/3$

Effective: score drop $= 2/3 \sim 1/3$

No effect: score drop $< 1/3$

② Evaluation criteria for clinical cure

Cure: symptoms disappear, signs essentially absent, laboratory index recovery, especially the immune index become normal and sustain 1 year.

Markedly effective: symptoms essentially absent, physical signs and immune function index essentially normal.

No effect: fluctuation of symptoms, signs and laboratory index ; immune function index without difference when compare with the control group.

Aggravation: symptoms, signs and laboratory index aggravate, more serious than the control, especially the immune function index.

(4) Result of cure effect:

① **Hematology:** Hb, RBC, WBC and platelet counts in treated group markedly increased after 1 course treatment, and highly significant when compared with the control group (table 3).

② **Tongue proper, tongue coating, and pulse profile** in treated group markedly improved after treatment, and little improvement in the control group (table 4, 5).

③ **Immune function:** As shown in table 5, the key immune cell for anticancer—NK cells increased or markedly increased in 86.4% treated patients. The CD4/CD4 ratio in 79.4% treated patients markedly increased or increased. Both parameters were improved than the control group. These reasonably explained and supported the anticancer therapeutic effect in treated patients.

④ **Dialectical cure:** The total curative effect of patients with spleen-qi xu (脾气虚) subgroup and those with spleen-yang xu (脾阳虚) subgroup were 86.2% and 83.7%

respectively; the two subgroups in the control were 60.9% and 48.2% respectively. There were highly significant between treated and control group ($P < 0.001$).

⑤ **Liver, kidney and heart function** of all treated patients were not affected by GFE.

All clinical findings in treated patients demonstrated that GFE exerted “yiqi jianpi” (益气健脾), “buxu fuzheng” (补虚扶正) and “puyi effect” (补益作用). The enhancement of immune cells revealed GFE’S anticancer effect in patients treated and coincided with the results from our animal experiments. The clinical data also confirmed the safety of GFE to cancer patients.

Conclusion: Maitake hot water extract (GFE) is a good supplementary Traditional Chinese Medicine for various cancer patients.

Table 1 General status of cancer patients

	Treated group	Control group
Number of patients	107	50
Male	74	34
Female	33	16
Age of patients with		
Solid cancer	53.7±14.5	50.4±15.6
Cancer of hemopoietic system	42.3±21.5	43.7±19.5
Diagnosis by Traditional Chinese Medicine criteria:		
Patients with <u>Insufficiency of the spleen-qi</u> [△] (脾气虚)	58	23
Patients with <u>Insufficiency of the spleen-yang</u> [◆] (脾阳虚)	49	27
Diagnosis by modern medicine criteria:		
Lung cancer	20	5
Gastric cancer	25	15
Liver cancer	40	24
Blood cancer	17	6
Others	5	0
CURATIVE EFFECT (%)	85**	54

△ According to the criteria in Chinese Traditional Medicine it is a syndrome marked by dyspepsia, abdominal distention, borborygmus, and lienteric diarrhea.

◆ A morbid condition marked by hypo-function of the spleen and cold syndrome.

** P<0.01 compare with control group.

Table 2 Blood Hemoglobin level and RBC count in patients before and after treatment by GFE

Group	Hb (g/L)		RBC count ($\times 10^{12}/L$)		
	≥ 100 (%)	<100 (%)	≥ 3.50 (%)	<3.50 (%)	
Treatment	Before	30(33.33)*	60(66.67)	31(34.44)	59(65.56)
	After	69(76.67)	21(23.33)	73(81.11)	17(18.89)
Control	Before	10(22.73)	34(77.27)	11(25.00)	33(75.00)
	After	19(43.18)	25(56.82)	17(38.64)	27(61.36)
				P1	P2
				<0.010**	<0.001**
				>0.05	>0.05
				<0.001	<0.001
				>0.05	>0.05

χ^2 test: P1, compare with that before treatment; P2, compare with control. * Number and percentage of patients.

** Highly significant after treatment.

Table 3 Blood WBC count and platelet count in patients before and after treatment

Group	WBC ($\times 10^9/L$)		Platelets ($\times 10^{12}/L$)		
	≥ 100 (%)	<100 (%)	≥ 3.50 (%)	<3.50 (%)	
Treatment	Before	25(27.78)*	65(72.22)	21(23.33)	69(76.67)
	After	74(82.22)	16(17.78)	68(75.56)	22(22.44)
Control	Before	9(20.45)	35(79.55)	7(15.91)	37(84.09)
	After	18(40.91)	26(59.09)	9(20.45)	35(79.55)
				P1	P2
				<0.001**	<0.001**
				>0.05	>0.05
				<0.001	<0.001
				>0.05	>0.05

P1, compare with that before treatment; P2, compare with control. * Number and percentage of patients.

** Highly significant after treatment.

Table 4 Tongue and pulse profile of radial artery (舌和脉象) in patients before and after GFE treatment

Group	Tongue proper			Tongue coating and saliva			Pulse profile				
	Enlarging	Light color	Others	Thin and white	Thick and greasy	Decrease salivation n	Others	Taint pulse	Deep pulse	Others	
Treatment	Before	34(31.7) [△]	63(58.8)	10(9.3)	87(81.3)	10(9.3)	5(4.6)	5(4.6)	51(47.6)	50(46.7)	6(5.6)
	After	18(16.8)*	25(34.3)*	64(59.8)*	40(37.3)*	11(10.2)	4(3.7)	52(48.6)*	23(21.5)*	18(16.8)*	66(61.6)*
Control	Before	14(28.0)	14(28.0)	6(12.0)	41(82.0)	2(4.0)	2(4.0)	5(10.0)	23(46.0)	21(42.0)	6(12.0)
	After	8(16.0)	20(40.0)	22(44.0)	17(34.0)*	5(10.0)	3(6.0)	25(50.0)*	15(30.0)	13(26.0)*	22(44.0)*

△ Number and percentage (in bracket) of patient. * P<0.01, significant compare with that before treatment.

+ In Traditional Chinese Medicine the gross appearance of tongue and pulsation status of radial artery by palpation (舌和脉象) of patient are valuable parameters in assessing clinical picture. GFE treatment improved both tongue appearance and pulse profile.

Table 5 Effect of GFE on key immune cells of cancer patients

Parameters	Treatment group			Control group				
	Marked increase	Increase	No change	Total curative effect	Marked increase	Increase	No change	Total curative effect
NK cells number	29(28.1)	60(58.3)	14(13.6)	89(86.4)***	9(18.8)	15(31.2)	24(50.0)	24(50.0)
CD ₄ /CD ₈ ratio	33(32.4)	48(47.0)	21(20.6)	81(79.4)**	8(19.1)	14(33.3)	20(47.6)	22(52.4)

** P<0.01; *** P<0.001, compare with control. In brackets are percentage of patients.

CD₄ and CD₈ are antigens, the higher CD₄/CD₈ ratio reveals higher immune function

Toxicology and Adverse Reactions

Toxicology Study :

(1) Ames test revealed no mutagenicity; by contraries GFE exerted antimutagenicity to mutagens.

(2) Micronucleus test in mice revealed no mutagenicity; by contrasies GFE exerted antimutegenic effect.

The results of these two tests were reported exclusively in the world; these strongly support the counter action of GFE on muctagenic toxicity of anticancer drugs.

(3) GFE exerted no cytotoxicity on 3T3 cells in Nelson Procedure/

(4) Oral LD50 of GFE in rat > 10000 mg/kg. Rats fed with GFE 30 days didn't reveal any abnormal change.

Adverse reactions: No reported since 1995.

Interactions with drugs: Monitor blood glucose levels closely due to claims that maitake has hypoglycemic effects.

Interactions with food: No interactions are known to occur.

GFE is considered as GRAS (generally recognized as safe) by USFDA. In a word, GFE is a very safe traditional Chinese drug.