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Abstract

Three types of traditional Chinese herb medicine were used to treat 98 patients with advanced esophageal squamous cell carcinoma prior to surgical treatment. Forty-two patients with the same diagnosis were treated with these herbs plus cyclophosphamide (endoxan). One hundred similar patients received surgical treatment without herbs or endoxan treatment as controls. Histologic examinations of surgical specimens were made on all of these patients. Stromal lymphoid-cell infiltration and cancer tissue degeneration were more prominent in Menispernum dehuricum DC- or Chelidonium majus L-treated patients, and were less clear in patients treated with herbs plus endoxan and the controls. The antitumor action of herbs is thought to be brought about by the activation of an immunological rejection mechanism. Herbs plus endoxan may result in the masking of the immunological response of hosts without obviously damaging cancer tissues.

KEYWORDS: esophageal cancer, Chinese herbs, histopathology, immunological response

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Efficacy of Traditional Chinese Herbs on Squamous Cell Carcinoma of the Esophagus : Histopathologic Analysis of 240 Cases

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Three types of traditional Chinese herb medicine were used to treat 98 patients with advanced esophageal squamous cell carcinoma prior to surgical treatment. Forty-two patients with the same diagnosis were treated with these herbs plus cyclophosphamide (endoxan). One hundred similar patients received surgical treatment without herbs or endoxan treatment as controls. Histologic examinations of surgical specimens were made on all of these patients. Stromal lymphoid-cell infiltration and cancer tissue degeneration were more prominent in *Menispernum dehuricum DC*- or *Chelidonium majus L*-treated patients, and were less clear in patients treated with herbs plus endoxan and the controls. The antitumor action of herbs is thought to be brought about by the activation of an immunological rejection mechanism. Herbs plus endoxan may result in the masking of the immunological response of hosts without obviously damaging cancer tissues.

Key words : **esophageal cancer, Chinese herbs, histopathology, immunological response**

Chinese herbs have had a favorable therapeutic effect on malignant tumors by "strengthening resistance and dispelling pathogenicity". Moreover, combination therapy with Western pharmaceuticals has resulted in improved survival rates (1-5). The antitumor activity of some herbs has been clearly demonstrated *in vitro* and *in vivo* (6, 7). However, the mechanism and histologic changes induced by herb treatment have not clearly been elucidated. We made a histopathological comparison of 140 patients with esophageal squamous cell carcinoma treated preoperatively with only herbs *(Menispernum dehuricum DC, Chelidonium majus L* or *Camptothecinum)* or herbs in combination with endoxan, and of 100 controls with no preoperative treatment.

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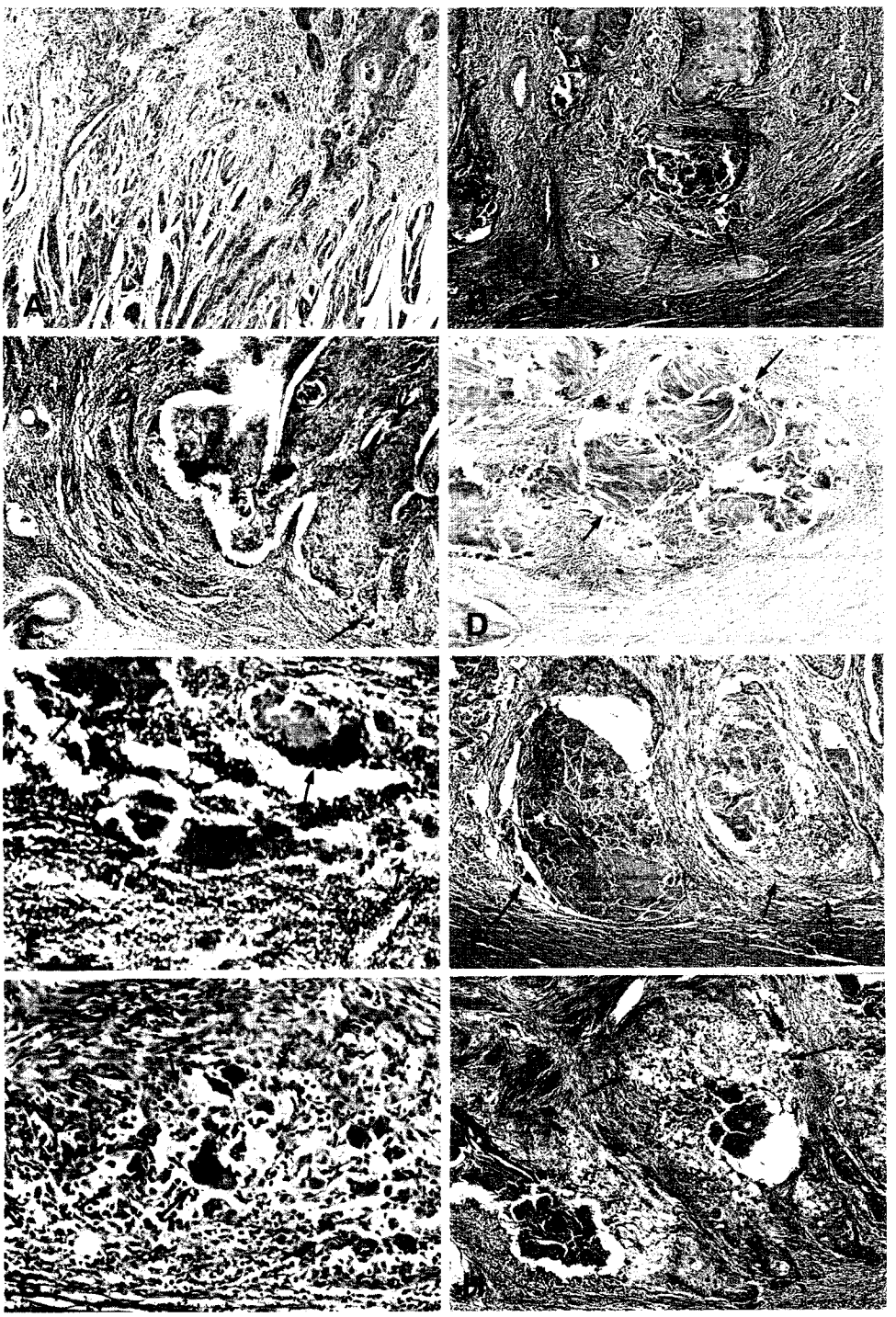
Materials and Methods

Patients. All patients, 162 males and 78 females, 53 ± 5 years of age, had esophageal squamous carcinoma in the advanced stage. They were treated at the Forth Affiliated Hospital of the Hebei Medical College. Treatment of cancer patients with Chinese herbs has been made possible thanks to vast and traditional experiences in the People's Republic of China, and no serious side effects have hitherto been reported. This work has been undertaken with the approval of the President and Director of the Hebei Medical College. The patients were divided into three groups : Group A, consisting of 98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patients treated preoperatively with only Chinese herbs, group B, consisting of 42 patients treated with herbs plus endoxan, and group C, 100 patients who underwent no pre-operation treatment (controls).

Menispernum dehuricum DC group (50 patients). The herb was boiled in water at a concentration of 1 : 4, precipitated with ethyl alcohol for 24 h, distilled to a solution of 1 : 1 ratio and ampouled for injection. A dose of 0.2 g/kg body weight was injected intramuscularly, twice a day for 20 days. Totoal doses were about 400 to 480 g.

Chelidonium majus L group (30 patients). The herb was extracted into a 50% solution with boiling water. A 30 ml dose (equivalent to 30 g of rough herbs) was given orally twice a day for two weeks.

Camptothecinum group (18 patients). The herb medicine was obtained from the Tenth Pharmaceutical Factory (Shanghai, China), and was dissolved in 10 ml of physiological saline. It was injected intravenously daily for two weeks at 0.5 mg/kg body weight. The intravenous injection of *Camptothecinum* is known to produce no side effects. The total dose administered was 300 to 360 mg per patient.

Combination therapy groups. Twenty-five patients received *Camptothecinum* with endoxan, and 17 patients received *Chelidonium majus L* with endoxan. They received the same herb dose as the herb only groups. Endoxan (200 mg) was given intravenously every other day for two weeks.

Histological preparation. Surgery was undertaken 3 to 5 days after the last treatment, and resected esophageal tissues and regional lymph nodes were examined. Tissues were fixed with 10% formalin and embedded in paraffin. Total-length sections were made through the central part of the cancer and stained with hematoxylin-eosin and elastica van Gieson.

Histological examinations. Observations were focused on the characteristics and degree of degenerative changes in cancer parenchyma, especially the marginal areas of infiltration, and stromal lymphoid cell responses around the carcinoma. Morphology of the regional lymph nodes, *i. e.*, the degree of follicular hyperplasia (FH) and sinus histiocytosis (SH), was also examined. FH and SH were graded according to Black *et al.* (8).

Classification of degenerated cancer parenchyma. Degenerative changes in cancer specimens were classified into the following four grades.

No degeneration. Cords and strands of cancer tissue freely infiltrated to the esophageal wall without any degenerative changes (Fig. 1-A). Necrotic areas in the center of cancer nests were excluded, because they were considered to be secondary to a poor blood supply or to arise spontaneously parallel with cancer growth.

Slight degeneration. Degenerative changes, such as cytoplasmic swelling and nuclear pyknosis, were scattered in marginal areas of cancer nests, and were usually very mild.

Moderate degeneration. Approximately 50% or less of cancer cells in marginal areas of cancer nests were degenerative (Figs. 1-B and 1-C).

Severe degeneration. Over 50% of the marginal cell nests were degenerative forming a ragged margin (Figs. 1-D and 1-E).

Lymphoid-cell infiltration around cancer tissue. Lymphoid-cell infiltration was classified into the following four grades.

No infiltration. Lymphoid cells were only occasionally present around the marginal areas of cancer tissue (Fig. 1-A).

Slight infiltration. A small number of lymphoid cells were scattered around the marginal areas of cancer nests.

Moderate infiltration. Lymphoid cells infiltrated moderately and were sometimes aggregated locally.

Severe infiltration. A large number of lymphoid cells formed a band-like pattern around cancer nests (Fig. 1-B).

Fig. 1 Histopathological changes observed in carcinoma. Hematoxylin-eosin stain. A. Marginal cancer strands infiltrating freely into the muscle layer without degenerative changes. Mild lymphoid-cell response is seen. Control group. Patient died within one year of the operation. × 40. B. Moderate degeneration of marginal cancer strands (arrows) and vigorous lymphoid-cell response. Control group. Patient survived for over 10 years. × 40. C. Moderate degeneration of marginal cancer strands (arrows) and massive lymphoid-cell infiltration. *Chelidonium majus L*- treated group. Patient survived for over 5 years. × 100. D. Amorphous massive necrotic areas in cancer strands (arrows), with massive lymphoid-cell infiltration. *Chelidonium majus L*- treated group. Patient survived for over 10 years. × 40. E. High power magnification of Fig. 1-D showing necrotized cancer cells (arrows) adjacent to massively infiltrated lymphoid cells. × 200. F. Severe degeneration of the marginal portion of cancer strands (arrows) adjacent to a barrier-like lymphoid-cell infiltration. *Menispernum*-treated group. Patient survived for over 10 years. × 100. G. High power magnification of Fig. 1-F showing degenerated cancer cells (arrows) intermingled with lymphoid cells. × 200. H. High-grade degeneration of marginal cancer strands, showing vacuolation of cancer cells (arrows). *Camptothecinum* plus endoxan-treated group. Patient survived for over 3 years. × 100.

Results

Fifty percent of group C had no degenerative changes in cancer parenchyma (Table 1) with very mild lymphoid-cell infiltration (Fig. 1-A). Groups A and B showed moderate or severe degenerative changes. Vigorous lymphoid-cell infiltration was occasionally encountered in group C (Fig. 1-B) and frequently seen in groups A and B (Figs. 1-C to 1-H).

Cancer cell degeneration was statistically significant in patients who received *Menispernum dehuricum DC* and *Chelidonium majus L* with or without endoxan (groups A and B), in comparison with group C (Table 1) (9). The percentage of severe degeneration was highest in the *Chelidonium majus L* plus endoxan group (17.6 %), but the combined percentage of moderate and severe degeneration was higher in the herb groups, especially in the *Chelidonium majus L* group (53.3%) than in *Chelidonium majus L* plus endoxan group (35.2%). *Camptothecinum* with or without endoxan had no significant effect (Table 1).

Table 1 Degree of cancer cell degeneration after treatment[a]

Group	Treatment (No. of cases)	Agent used	Cancer cell degeneration: no. of cases (%)				
			None	Slight	Moderate	Severe	Total
A	Chinese herbs only (98)	*Menispernum dehuricum DC***	9(18.0)	22(44.0)	14(28.0)	5(10.0)	50(100)
		*Chelidonium majus L***	5(16.7)	9(30.0)	13(43.3)	3(10.0)	30(100)
		Camptothecinum	4(22.2)	7(38.9)	5(27.8)	2(11.1)	18(100)
B	Chinese herbs + Endoxan (42)	*Chelidonium majus L* + Endoxan*	3(17.6)	8(47.1)	3(17.6)	3(17.6)	17(100)
		Camptothecinum + Endoxan	9(36.0)	8(32.0)	6(24.0)	2(8.0)	25(100)
C	Control (100)	None	50(50.0)	35(35.0)	12(12.0)	3(3.0)	100(100)

a: Modified and reproduced from reference 9 with permission of Okayama Igakkai Zasshi.
b: *, $p < 0.05$; **, $p < 0.01$.

Table 2 Grade of lymphoid cell response in peripheral areas of invading cancer cells after treatment[a]

Group	Treatment (No. of cases)	Agent used	Lymphoid cell response: no. of cases (%)				
			None	Slight	Moderate	Severe	Total
A	Chinese herbs only (98)	*Menispernum dehuricum DC***	0 (0)	15(30.0)	19(38.0)	16(32.0)	50(100)
		*Chelidonium majus L**	0 (0)	12(40.0)	11(36.7)	7(23.3)	30(100)
		*Camptothecinum***	1 (5.6)	8(44.4)	7(38.9)	2(11.1)	18(100)
B	Chinese herbs + Endoxan (42)	*Chelidonium majus L* + Endoxan	2(11.8)	5(29.4)	9(52.9)	1 (5.9)	17(100)
		Camptothecinum + Endoxan	4(16.0)	9(36.0)	12(48.0)	0 (0)	25(100)
C	Control (100)	None	12(12.0)	51(51.0)	30(30.0)	7 (7.0)	100(100)

a: Modified and reproduced from reference 9 with permission of Okayama Igakkai Zasshi.
b: *, $p < 0.05$; **, $p < 0.01$.

The lymphoid-cell response (Table 2) (9) was generally higher in patients treated with herbs only. Comparing with group C, marked lymphoid-cell infiltration was noted in the *Menispernum dehuricum DC* (32%), *Chelidonium majus L* (23.3%) and *Camptothecinum* groups than in the herb plus endoxan therapy groups. The growing fronts of cancer strands and cords were ragged due to cancer cell necroses and lymphoid-cell infiltration (Figs. 1-D and 1-E). In some areas, only keratotic cancer cells with pyknotic nuclei or amorphous keratinized material remained within densely infiltrated lymphoid-cell clusters (Figs. 1-F and 1-G). Foreign-body type giant cells were sometimes observed in such cases.

Table 3 summarizes the cases of FH and SH in the lymph nodes(9). FH was more frequent in groups A and B than in group C. FH in patients treated only with herbs (group A) was generally more marked than in the endoxan-combined therapy group (group B). However, there was little difference between the *Chelidonium majus L* group (81.3%) and its endoxan-combined therapy group (82.4%), although FH was more prominent than in group C. SH was also less frequent in the combined herb and endoxan groups.

Discussion

Clinical and experimental studies have shown Chinese herbs to have antitumor properties (1–7). Our histological study tends to confirm those earlier studies. Screening for antitumor components in plants and extraction of active components have been attempted in China, Japan and USA (6–8, 10–12). The effects of strong antitumor agents, such as plant alkaloids, have been known for some time. A number of Japanese workers (10–12) have noted that certain plant polysaccharides can raise the immunological capacity of hosts to reject the specific tumor antigen through immuno-potentiation, giving full play to the antitumor capacity of the host.

Tumor inhibiting effects of herbs, especially *Menispernum dehuricum DC* and *Chelidonium majus L*, appear secondary to enhancement of the host's antitumor defense mechanism, *i. e.*, activation of the rejection response of immunologically competent cells. Direct suppression appears insignificant. First, tumor cell degeneration of the herbal groups was quantitatively different compared with the control group (Table 1). Moreover, the morphological response to treatment only with herbs (Figs. 1-C to 1-G) was not as rapid and

Table 3 Follicular hyperplasia (FH) and sinus histiocytosis (SH) in lymph nodes after treatment[a,b]

Group	Treatment (No. of cases)	Agent used	No. of cases (%)		No. of cases (%)		Total[c]
			FH (%) (+~++)	FH (%) (−)	SH (%) (+~++)	SH (%) (−)	
A	Chinese herbs only (62)	*Menispernum dehuricum DC*	24(70.6)	10(29.4)	7(20.6)	27 (79.4)	34
		Chelidonium majus L	13(81.3)*	3(18.7)	4(25.0)	12 (75.0)	16
		Camptothecinum	8(66.7)	4(33.3)	2(16.7)	10 (83.3)	12
B	Chinese herbs + Endoxan (37)	*Chelidonium majus L* + Endoxan	14(82.4)*	3(17.6)	2(11.8)	15 (88.2)	17
		Camptothecinum + Endoxan	5(25.0)*	15(75.0)	0 (0)	20(100.0)	20
C	Control (70)	None	37(52.9)	33(47.1)	10(14.3)	60 (83.7)	70

a : Modified and reproduced from reference 9 with permission of Okayama Igakkai Zasshi.
b : +, mild ; ++, moderate to severe ; −, no response ; *, $p < 0.05$.
c : Lymph nodes of 62 of 98 cases in group A, 37 of 42 cases in group B and 70 of 100 cases in group C were examined.

vigorous as the vacuolation or liquifactive necrosis in response to endoxan (Fig. 1-H), 5-fluorouracil (5-Fu), colchicine or other conventional chemotherapeutic agents. This slow response has been described elsewhere (13).

Second, in the herbal groups, cell degeneration and stromal lymphoid-cell response were more marked than in the controls (group C) (Table 2). Xian previously reported (14) that even though the size of tumors was about the same, the growth pattern of cancer tissue, stromal lymphoid cell response and fibrous tissue proliferation varied considerably. This suggests a complicated interrelationship between invasive cancer and stromal host resistance even in controls (Figs. 1-A and 1-B). We have proposed patho-morphological stages in cancer : steady progressive, resistant accelerative, and non-resistant accelerative, and the prognostic value of these stages has been verified by follow-up data (15). Recently, this concept was supported by the finding that a close interrelationship exsists between the evolution and development of cancer and the immunologic status of hosts (16). Animal experiments have already established the killing capacity of immuno-competent T-lymphocytes against cancer cells (17). In herbally treated cases (Figs. 1-C to 1-G), we have recognized the co-existence of tumor degeneration and intensive lymphoid-cell infiltration appearing in "barricades", suggesting that the cause of tumor degeneration was due to enhanced cell-mediated immunologic response.

Third, an intensified degeneration of cancerous tissue was less common in the combined herb and endoxan groups, with a decreased response of lymphoid-cells surrounding the tumor mass, than in the herbal groups (Tables 1 and 2). This suggests that a small dose of a chemotherapeutic agent is insufficient to affect tumor cells directly but inhibits the cellular immunologic response of hosts, thus impairing immunologic function. Michell and De Conti (18) reported that a small dose of 5-Fu apparently inhibited the immunologic function of hosts. Lastly, higher SH and FH of non-metastatic lymph nodes were observed in the herbal groups than in the herb plus endoxan groups and the control group (Table 3). This finding indicates that Chinese herbs possess an enhancing function on the immunologic system. On the basis of our morphologic analyses, the antitumor properties of Chinese herbs appear to result mainly from the stimulation of the host's immunologic system. Various degrees of cancer tissue degeneration are indirectly induced by enhanced stromal lymphoid-cell response. Variations in the degree of degeneration are determined by the pre-operative state, *i.e.*, whether hosts were in immuno-depression (resistant accelerative) or in immuno-paralysis (non-resistant accelerative) (14).

A rational application of Chinese herbs to cancer-bearing patients may activate immunologic function, modulate the immunologic status and improve the inherent antitumor capacity of hosts. Therefore, our findings not only support the principle of "strengthening resistance and dispelling pathogenicity" (4, 5), upheld by traditional Chinese medicine, but also are in accord with contemporary tumor immunological therapy. Thus, we think that it is important to investigate the role of Chinese herbs in cancer therapy to obtain a more satisfactory result.

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