ONCOLOGY

Prospects of Using Phytoadaptogen in the Treatment of Diffuse Stomach Cancer

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The efficiency of treatment of diffuse stomach cancer can be improved by using a complex phytoadaptogen. In groups receiving phytoadaptogen, the level of tumor marker CA 19-9 decreased and the mean life span of patients increased by 2.5 times. The drug exhibited immunomodulating (including interferonogenic and adhesiogenic), antioxidant, and hormone-modulating effects.

Key Words: *stomach cancer; metastases; immunomodulating therapy; phytoadaptogen*

The development of pathogenetically-based methods for the treatment of diffuse stomach cancer (SC) remains a pressing problem. Combinations of surgical and chemotherapeutic methods are insufficiently effective [3]. Plant adaptogens, known as geroprotectors, attract special interest as drugs to be used for combined therapy of tumors. The use of geroprotectors in oncology is a promising trend, because a direct relationship between the incidence of tumors and rate of population aging was demonstrated [1,6].

Phytoadaptogens are characterized by complex effects. They are active immunomodulators inducing, among other things, production of IFN [5]. Phytoadaptogens are characterized by antistress activity: they reduce the levels of cortisol and adrenocorticotropic hormone during stress and stimulate recovery of the immune defense mechanisms [7]. Phytoadaptogens increase the levels of natural antidepressants (endorphines and dopamine) [11] and act as antioxidants [8]. Binding to the multiple drug resistance protein, they retain cytostatics in tumor cells, thus increasing the efficiency of chemotherapy in tumor patients [9]. Phytoadaptogens inhibit telomerase activity and induce tumor cell apoptosis [10]. They exhibit an antiangiogenic effect on the tumor [12]. The antitumor effects of adaptogens are also due to their adhesiogenic activity, and therefore, adaptogens, as differentiation inductors, reduce the rate of tumor cell proliferation and inhibit tumor growth. By regulating cell-cell adhesion in tissue, adaptogens mediate the increase in the expression on tumor cells of adhesion ligands for immunity effectors, thus promoting antiinflammatory stimulation. The latter fact causes tumor cell lysis by immune effectors reducing tumor "escape" from the immunological control [2].

We studied the possibility of improving the efficiency of combined therapy of patients with diffuse SC by using Phytomix-40 (PM-40), a complex adaptogen, containing ginseng, eleutherococcus, Rhodiola rosea, Echinopanax elatum, Schizandra, and other plants.

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MATERIALS AND METHODS

Eighty-two patients with diffuse SC (mean age 59 years) took part in the study. Group 1 (n=19; 23%) patients received PM-40 during combined treatment (surgery+polychemotherapy (PCT)+PM-40), including the preoperative period (7 days). Group 2 (control 1; n=20; 25%) received combined therapy (surgery+PCT). Group 3 (n=16; 20%) received surgical treatment and PM-40 courses before (7 days) and after surgery. Group 4 (control 2; n=27; 32%) received surgical treatment alone. A total of 77% patients presented with stage IV disease, 2.5% with stage IIIA, and 21.5% with stage IIIB. The groups were matched for gender, age, and tumor process dissemination. Polychemotherapy was carried out according to the standard routine ELF protocol (etoposide, leukovorin, fluorouracil). A course of PM-40 lasted for 1.5 months; the drug was taken in a dose of 15 ml+5 ml water 15-20 min before meals 3 times per day. The patients received 5-6 courses, on average. The drug dose was increased by 5 ml per day with each next course. Cortisol and tumor markers (CA 19-9 and carcinoembryonic antigen) were measured in the sera of SC patients by enzyme immunoassay. The immune status was evaluated by the immunofluorescent method. The production of IFN by induced leukocytes was tested *in vitro* by the common method. The content of IFN was expressed in activity units (U/ml). Leukocyte sensitivity to IFN preparations, IFN inductors, and PM-40 was evaluated by the priming test [4]. The levels of MDA and glutathione, activities of SOD, catalase, glutathione-S-transferase were measured by the common methods. The data were analyzed using Statistics software and ANOVA.

RESULTS

The level of spontaneous IFN-producing activity of leukocytes was low in SC patients (0.15±0.07 U/ml). Induction with ridostin, neovir, cycloferon, and amixin increased IFN production to 3 U/ml, which corresponded to 8-fold dilution of the preparation. Treatment with PM-40 increased this parameter to 5.5 U/ml, which can indicate high interferonogenic activity of

TABLE 1. Immune Status of Patients with Diffuse SC Treated by PM-40 ($M±m$)

Antigen	Normal level, %	Before surgery (n=27)	After surgery, 10 days (n=27)	After PCT, group 1 (n=14)	After surgery, 4-5 months; group 3 (n=15)
CD3	60-75	51.9±2.9	60.7±1.6 p_1=0.005	64.6±2.6 p_3=0.026	66.4±1.8 p_4=0.031
CD4	35-46	30.5±2.2	32.1±1.8 p_2=0.04; p_3=0.036	42.1±2.1 p_4<0.001	42.6±0.8
CD8	25-30	27.9±2.1	26.2±1.5	27.1±2.1	27.0±1.5 p_4=0.728
CD4/CD8	1.5-1.9	1.1±0.1	1.2±0.1	1.6±0.3 p_2<0.001; p_3<0.001	1.6±0.1 p_4=0.01
CD20	5-15	5.4±0.4	7.6±0.8 p_1=0.017	12.6±1.5 p_2=0.003; p_3<0.001	13.3±0.5 p_4<0.001
HLA-DR	7-15	8.1±0.8	8.7±0.8	11.5±1.1 p_2=0.050; p_3=0.027	12.4±0.9 p_4=0.011
CD16	10-20	10.5±0.9	12.2±1.2	20.4±2.0 p_2<0.001; p_3<0.001	20.2±0.9 p_4<0.001
CD11b	15-20	13.5±1.0	13.0±1.2	17.6±1.8 p_2=0.03; p_3=0.019	18.5±0.7 p_4=0.003
CD18	56-64	53.6±1.7	56.6±1.7	66.2±2.1 p_2=0.001; p_3=0.002	69.8±2.6 p_4=0.118
CD95	10-30	9.3±0.8	12.3±1.3	20.1±1.7 p_2<0.001; p_3=0.002	
CD25	0-5	1.4±0.4	2.3±0.4 p_1=0.010	4.0±0.7 p_2=0.04, p_3=0.004	

Note. p_1: significant differences before/after surgery; p_2: significant differences after surgery/after PCT; p_3: significant differences before surgery/after PCT; p_4: significant differences after surgery/4-5 months after PM-40 treatment.

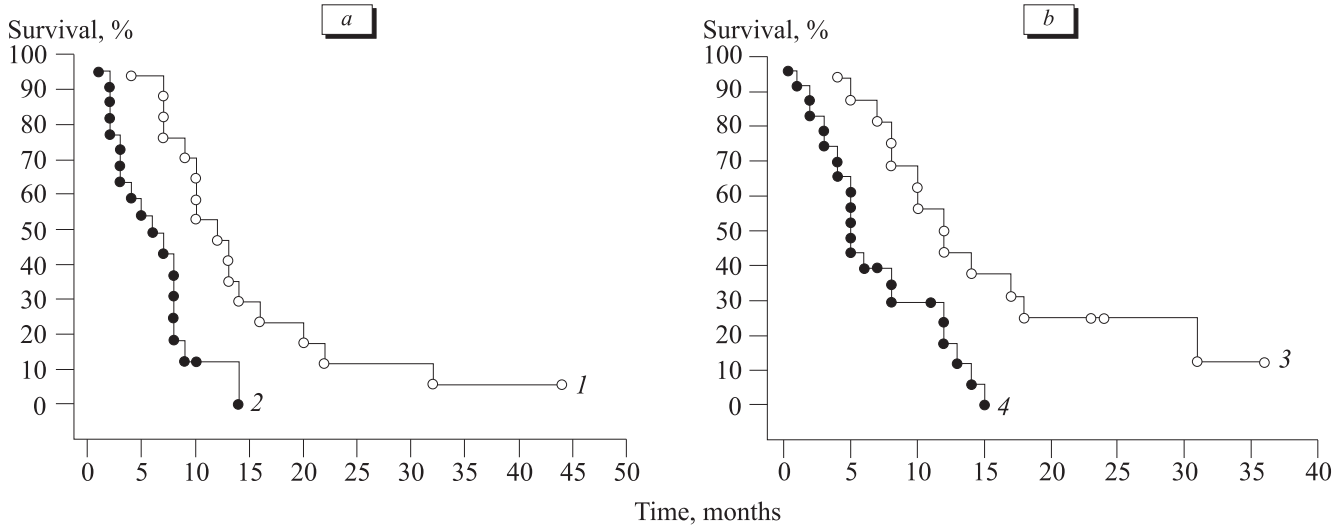

Fig. 1. Survival of patients with diffuse SC after combined treatment (*a*) and surgery (*b*). *1*) group 1; *2*) group 2; *3*) group 3; *4*) group 4.

the phytoadaptogen. The number of patients sensitive to IFN, IFN inductors, and PM-40 increased in the following series: reaferon (15%) → leukinferon (22%) → human leukocytic interferon (25%) → intron A (27%) → roferon A (35%) → gammaferon (31%) → ridostin (52%) → neovir (46%) → cycloferon (69%) → amixin (67%). On the other hand, 100% patients were sensitive to PM-40. This confirms its advantage in comparison with adaptoten monopreparations, to which selectively sensitivity of patients was demonstrated.

The phytoadaptogen normalized cellular and humoral immunity and natural resistance of patients with SC. It increased the expression of leukocytic integrins, which attests to activation of immunity effectors and can lead to stimulation of tumor cell lysis by these effectors (Table 1). The drug normalized the blood level of MDA in patients. The antistress effect of PM-40 manifested by reduced production (normalization) of cortisol. Serum concentration of CA 19-9 tumor-associated antigen decreased under the effect of PM-40 from 96.6±38.0 to 18.3±5.1 ng/ml (p_1=0.047). These values stabilized after PCT courses (16.2±6.1 ng/ml). The mean lifespan (MLS) in group 1 was 14.3 months, median survival 11 months; in group 2 the MLS was 5.4 months, with a median of 5.8 months; in group 3 the MLS was 15.1 months, with a median of 12 months; and in group 4 the MLS was 6.3 months with a median of 5 months (Fig. 1). Due to addition of PM-40 to combined therapy of SC patients it was possible to carry out more PCT courses: 1.7 times more PCT courses were carried out in group 1 compared to group 2. No positive shifts in immunological values were detected in control groups.

Prolongation of the lifespan of patients with diffuse SC and reduction of the level of CA 19-9 tumor marker after treatment with PM-40 were presumably mediated through stimulation of immunological (including the interferonogenic and adhesiogenic), endocrine, and antioxidant mechanisms of defense from the tumor and was due to possible normalizing effect of PM-40 on tumor cell differentiation and homeostasis. Complex pharmacological effects of the phytocomplex can be explained by the fact that many of its bioactive components are fat-soluble signal molecules capable of independent attacks at the plasma membrane multireceptor systems and stimulating the intracellular steroid receptors. This is due to the structural and functional relationships of many components (panaxosides, eleutherosides, aralosides, *etc.*) of the preparation to steroids, which, due to their structure, are characterized by high biological activity [5].

Correction of defense systems by complex phytoadaptogens opens prospects for the creation of immunobiological bases of nontoxic prevention and therapy of tumor diseases.

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