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Abstract

Cell-mediated immunity was studied in 23 cases of advanced gastrointestinal cancer. The patients received levamisole at 150 mg/day for three consecutive days each week for four weeks. In cases at the terminal stage of gastrointestinal cancer, the blastformation rate of peripheral blood lymphocytes against phytohemagglutinin (PHA) after the administration of levamisole showed a slight increase, but cases with blastformation rates over 40% increased markedly three or four weeks after the initial administration of levamisole. The peripheral blood lymphocyte count showed little change in these cases.

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REACTIVATING EFFECT OF LEVAMISOLE ON CELL-MEDIATED IMMUNITY IN GASTROINTESTINAL CANCER PATIENTS

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Abstract. Cell-mediated immunity was studied in 23 cases of advanced gastrointestinal cancer. The patients received levamisole at 150 mg/day for three consecutive days each week for four weeks. In cases at the terminal stage of gastrointestinal cancer, the blastformation rate of peripheral blood lymphocytes against phytohemagglutinin (PHA) after the administration of levamisole showed a slight increase, but cases with blastformation rates over 40% increased markedly three or four weeks after the initial administration of levamisole. The peripheral blood lymphocyte count showed little change in these cases.

Recently, the progress and prognosis of carcinoma in cancer patients have been investigated immunologically (1, 2). We have previously reported that cell-mediated immunity in gastrointestinal cancer patients reflected cancer progress, and that it was helpful in assessing the possibility of curative tumor resection and the prognosis (3-5).

Mathé *et al.* (6) used bacille Calmette Guérin (BCG) and demonstrated the efficiency of active immunotherapy of acute lymphoblastic leukemia in man for the first time. Bast *et al.* (7) reported the effectiveness of BCG immunotherapy for melanoma.

Various kinds of immunostimulants have been investigated for the purpose of cancer immunotherapy.

In the present study, we used levamisole, a kind of immunostimulant, for gastrointestinal cancer patients and found that levamisole was somewhat effective in activating cell-mediated immunity in cases of terminal stage of cancer patients.

MATERIALS AND METHODS

The study comprised 23 cases of advanced gastrointestinal cancer (three cases with curative resection, three of noncurative resection, and 17 of non-resectable and recurrent cases) who received levamisole for its antitumor effect and for the treatment of leukopenia following anticancer therapy.

Levamisole was administered orally in a dosage of 150 mg/day for three consecutive days a week for four weeks.

As a parameter of cell-mediated immunity, the blastformation rate was determined each week after levamisole administration. Peripheral lymphocyte counts were also performed.

The blastformation rate of peripheral blood lymphocytes against PHA was determined by the morphological procedure described previously (3-5).

RESULTS

In 23 cases given levamisole for four consecutive weeks, the blastformation rate was $48.8 \pm 17.0\%$ in the third week compared with $39.2 \pm 18.2\%$ before levamisole administration ($p=0.1$) and $47.4 \pm 14.4\%$ in the fourth week ($0.1 < p < 0.5$). This indicated a slight rise in the latter half of the month after levamisole administration (Fig. 1). Cases with blastformation rates over 40% comprised 47.6% of the entire group before levamisole administration, and increased to 80% of the group by four weeks after levamisole administration (Table 1). The peripheral blood lymphocyte count showed little variation throughout the course of levamisole administration (Fig. 1).

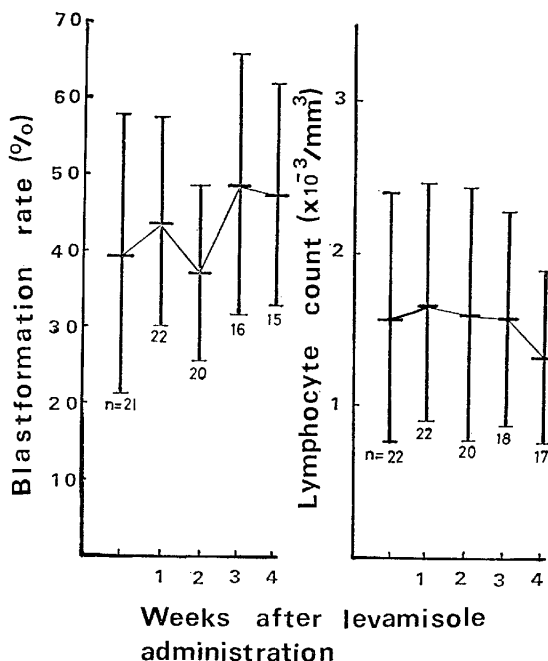


Fig. 1. Blastformation rate and lymphocyte count after administration of levamisole. Twenty-three cases received levamisole, p. o., 150mg/day three consecutive days in a week for four weeks. Data indicate mean $\pm$ S. D.

TABLE 1. PERCENT OF CASES OVER 40% IN BLASTFORMATION RATE AFTER ADMINISTRATION OF LEVAMISOLE 4 CONSECUTIVE WEEKS

Weeks after levamisole administration	Number of cases	Percent of cases
0	10/21*	47.6
1	19/22	63.6
2	8/20	40.0
3	11/16	68.8
4	12/15	80.0

* Number of cases over 40% in blastformation rate/number of cases examined.

A comparison of the results before levamisole administration with those after levamisole administration showed that the blastformation rate rose slightly in the first and the third weeks but dropped in the second and the fourth weeks after levamisole administration (Table 2).

TABLE 2. PERCENT OF CASES SHOWING HIGHER VALUES AFTER LEVAMISOLE ADMINISTRATION THAN VALUES BEFORE THE ADMINISTRATION

Examination	Weeks after levamisole administration			
	1	2	3	4
Blastformation rate	(12/20)* 60.0	(6/18) 33.3	(9/16) 56.3	(7/15) 46.7%
Lymphocyte count	(12/21) 57.1	(11/19) 57.9	(14/17) 82.4	(6/16) 37.5%

* Number of cases showing higher values after levamisole administration than values before the administration/number of cases examined.

Peripheral blood lymphocyte counts after the start of levamisole administration in each individual rose until, and mostly during, the third week, but decreased in the fourth week (Table 2).

DISCUSSION

The interest around the world in nonspecific and specific immunotherapy as an adjunct to cancer therapy has been focused on using BCG. Recently, levamisole has also been used for its activation of cell-mediated immunity and for its antitumor effect.

Renoux and Renoux (8) showed that levamisole activates cell-mediated immunity *in vivo*. Since then, there have been several reports of the *in vitro* or *in vivo* activation of cell-mediated immunity by, and the antitumor effect of, levamisole (9-13).

Levamisole, chemically L-2, 3, 5, 6,-tetrahydro-6-phenyl-imidazo [2, 1-b] thiazole hydrochloride, is an isomer of tetramisole. Levamisole acts as a stimu-

lant in those patients who have decreased cell-mediated immunity. This immunostimulation consists of four processes: 1. increase of the peripheral blood lymphocyte count, 2. stimulation of T lymphocytes, 3. increase of reactivity to dinitrochlorobenzene (DNCB) or purified protein derivatives (PPD) 4. anti-tumor effect resulting from the above 1. to 3. processes. Contradictory reports have appeared of the effect of levamisole on the peripheral lymphocyte count. Chan *et al.* reported a definite increase in the peripheral lymphocyte count due to levamisole (14), while Levo *et al.* contended that it did not increase the lymphocyte count but increased the percentage of active T lymphocytes (10). The effect of levamisole on the stimulation of T lymphocytes was an increased blastformation rate when lymphocytes were cultured with mitogen or antigen *in vitro* (11).

Various workers have shown that, when peripheral blood lymphocytes were cultured with both levamisole and PHA, Pockeed mitogen (PWM), or the lymphocytes of another person, the blastformation rate increased (11, 12). However, this only occurred with certain concentrations of levamisole (11) and did not occur without mitogen. In our results, the peak effect of levamisole (increased blastformation rate against PHA) was in the third week after levamisole administration. The value, however, was only significant at the $p=0.1$ level.

The administration of levamisole was associated with an increase in delayed hypersensitivity in cancer patients. Levo *et al.* (15) reported that the administration of levamisole to patients with Hodgkin's disease resulted in the conversion of their skin tests from negative to positive. Rojas *et al.* (16) also reported that when the skin reactions to DNCB and PPD were compared in two groups of before levamisole treatment and after 20 months of follow-up, levamisole treatment was associated with an increase in positive DNCB tests, candida tests and PPD tests compared with pretreatment in the same group. Similar results have been reported by Tripodi *et al.* (13) and Verhaegen *et al.* (9).

In animal tumors, as well as in some human neoplasms, levamisole may lead to antitumor effects (16, 17).

The administration of levamisole clinically is not uniform, but many authors use the drug in a dose of 150 mg/day for three consecutive days a week, continued every other week. There is as yet no report giving levamisole 150 mg/day for three consecutive days a week for four weeks.

There is no major toxicity attributable to levamisole. In our study, two patients complained of urticaria and one patient complained of nausea. These side effects disappeared soon after withdrawal of levamisole.

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