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Cancer immunotherapy with levamisole

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Abstract

Levamisole, an agent acting upon depressed cellular immunity, enhancing and normalizing it and consequently showing antitumor activity in the cancer-bearing body, was administered to patients with gastrointestinal cancer at a daily dose of 150 mg for three consecutive days every other week, starting as a rule, three days before operation. The patients were evaluated for survival. Of the 143 patients (66 with curative resection, 40 with noncurative resection and 37 without resection) who received levamisole therapy for one month or more, 57 survived postoperatively six months and of 44 treated 37 survived one year. In this study, 185 patients with gastrointestinal cancer were used for comparison purposes. The six-month survival rate was 100% (23/23) in the levamisole treated group and 95.3% (102/107) in the control group after curative resection (p greater than 0.5), 100% (23/23) and 90.5% (49/54) after noncurative resection (p less than 0.01), and 72.5% (8/11) and 33.3% (9/24), respectively, in non-resectable patients (p less than 0.01). The one-year survival rate was 100% (21/21) and 95.3% (102/107) after curative resection (p greater than 0.5), 77.8% (14/18) and 59.3% (32/54) after noncurative resection (0.05 less than p less than 0.1), and 40% (2/5) and 8.3% (2/24) in non-resectable patients (0.05 less than p than 0.1) in the levamisole group and in the control group, respectively. The difference in survival in survival rates between levamisole-treated and control groups was most prominent in the non-resectable patients followed by those undergoing noncurative resection and curative resection.

KEYWORDS: levamisole, gastrointestinal cancer, survival rate, immunotherapy

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CANCER IMMUNOTHERAPY WITH LEVAMISOLE

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Abstract. Levamisole, an agent acting upon depressed cellular immunity, enhancing and normalizing it and consequently showing anti-tumor activity in the cancer-bearing body, was administered to patients with gastrointestinal cancer at a daily dose of 150 mg for three consecutive days every other week, starting as a rule, three days before operation. The patients were evaluated for survival. Of the 143 patients (66 with curative resection, 40 with noncurative resection and 37 without resection) who received levamisole therapy for one month or more, 57 survived postoperatively six months and of 44 treated 37 survived one year. In this study, 185 patients with gastrointestinal cancer were used for comparison purposes. The six-month survival rate was 100% (23/23) in the levamisole treated group and 95.3% (102/107) in the control group after curative resection ($p > 0.5$), 100% (23/23) and 90.5% (49/54) after noncurative resection ($p < 0.01$), and 72.5% (8/11) and 33.3% (9/24), respectively, in non-resectable patients ($p < 0.01$). The one-year survival rate was 100% (21/21) and 95.3% (102/107) after curative resection ($p > 0.5$), 77.8% (14/18) and 59.3% (32/54) after noncurative resection ($0.05 < p < 0.1$), and 40% (2/5) and 8.3% (2/24) in non-resectable patients ($0.05 < p < 0.1$) in the levamisole group and in the control group, respectively. The difference in survival rates between levamisole-treated and control groups was most prominent in the non-resectable patients followed by those undergoing noncurative resection and curative resection.

Key words: levamisole, gastrointestinal cancer, survival rate, immunotherapy

Since Mathé *et al.* (1) used *Bacillus Calmette-Guerin* (BCG) in the treatment of leukemia, cancer immunotherapy with various immunostimulants has been practiced widely and the clinical results have been generally encouraging (2). We studied how cellular immunity of gastrointestinal cancer patients responded to levamisole which was considered, unlike classic immunostimulants, to selectively act upon depressed cellular immunity, activate and normalize it (3), and we reported the ability of levamisole to activate and normalize depressed cellular immunity (4, 5).

Patients, most of them suffering from gastrointestinal cancer, have been treated with levamisole at the dosages shown in Table 1, and the clinical course was observed for a year and a half at the longest, with the aim of obtaining

TABLE 1. CANCER IMMUNOTHERAPY WITH LEVAMISOLE

Chemical formula of levamisole: L-2, 3, 5, 6,-tetrahydro-6-phenylimidazo [2, 1-b] thiazole hydrochloride
Purpose for this study: Activity of cellular immunity and enhancement of antitumor activity in cancer patients by levamisole
Method of administration: 150 mg of levamisole daily for three consecutive days every other week (3 day's medication and 11 day's withdrawal)
Onset of treatment:
a) Three days before operation
b) After operation
c) Concurrently with anticancer therapy
Combination chemotherapy:
Mitomycin C: 5 courses of 4 mg twice a week
Futrafal: 600 to 800 mg/day
Examination:
Routine laboratory examination (hematological value, liver function, serum protein, etc.)
Immunological tests (lymphocyte blastformation rate against phytohemagglutinin, incidence of T- and B-cells, macrophage migration inhibition test, lymphocytotoxicity test, peripheral lymphocyte count, PPD reaction)

evidence of antitumor activity of levamisole. The treatment was started before operation in most cases. It is interesting to note that the difference in both six-month and one-year survival rates between treated and control groups has been more remarkable in more advanced cancer patients. This confirms our results from previous experiments (6).

MATERIALS AND METHODS

Levamisole was administered to a group of 143 patients admitted to our department mainly for gastrointestinal cancer (6, esophageal cancer; 72, gastric cancer; 27, colorectal cancer; 27, cancer of other organs). Sixty-six of them underwent curative resection 40 noncurative resection and 37 were not resectable (Table 2). Another group serving as control in this study included 185 patients

TABLE 2. PATIENTS RECEIVING LEVAMISOLE FOR ONE MONTH OR MORE

Site of cancer	Curative resection	Noncurative resection	Non-resection	Total
Esophagus	1(1)	0(0)	5(0)	6(1)
Stomach	40(7)	20(0)	12(1)	72(8)
Colorectum	20(5)	13(3)	8(3)	41(1)
Other	5(1)	7(0)	12(0)	24(1)
Total	66(14)	40(3)	37(4)	143(21)

(): Number of patients of over 70 years old

with gastrointestinal cancer admitted to our department during the period from 1971 to 1975 (107 had curative resection and 54 noncurative resection but 24 were not resectable). There was no noticeable difference between control and levamisole groups in regard to patient's age, surgical intervention and cancer chemotherapy combined.

A course of levamisole therapy, consisting of oral administration with a daily dose of 150 mg for three consecutive days followed by 11-day-withdrawal, was started, as a rule, three days before operation and repeated as much as possible. The 143 patients followed this course for at least one month and gave sufficient clinical data for evaluation.

RESULTS

Six-month survival rate. In the group receiving levamisole, those who survived six postoperative months were 57; 23 had curative resection, 23 had noncurative resection and 11 were not resectable. In the control group, there were 185 six-month survivals; 107 had curative resection, 54 had noncurative resection and 24 were not resectable.

After curative resection, the six-month survival rate was 100% (23 of 23 patients) in the levamisole group, while it was 95.3% (102 of 107 patients) in the control group. There was no significant difference in survival between these groups ($0.1 < p < 0.5$).

After noncurative resection, the survival rate was significantly higher in the levamisole group than in the control group at the $p < 0.01$ level, since it was 100% (23 of 23 patients) in the former and 90.7% (49 of 54 patients) in the latter.

In nonresectable cases, the survival rate was significantly higher in the levamisole group than in the control group at the $p < 0.01$ level, since it was 72.7% (8 of 11 patients) in the former and 37.5% (9 of 24 patients) in the latter. The difference in survival between the two groups was much more remarkable in nonresectable cases than in noncurative cases. It should be noted that no death occurred during the first five months after operation in levamisole treated patients.

The elevation of survival rate by levamisole was remarkable in advanced cancer patients (Fig. 1).

The average survival of the levamisole group and of the control group followed up for 6 months were 6 and 5.9 months after curative resection, 6 and 5.7 months after noncurative resection and 5.7 and 3.6 months in nonresectable patients, respectively.

One-year survival rate. Of the 143 patients who received levamisole, 44 were treated for one year and 37 survived, and in the control group of 185, 136 survived. A comparison was made between the survival rate of levamisole-

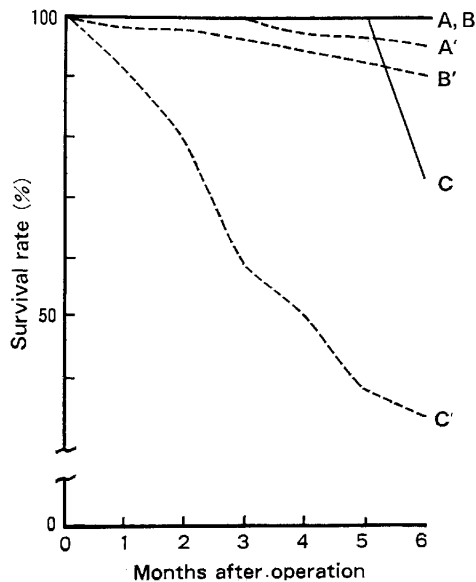


Fig. 1. Six-month Survival Ratios in Gastrointestinal Cancer. —, levamisole group; ----, control group; A, curative resection cases in levamisole group, (23/23), 100%; A': curative resection cases in control group, (102/107), 95.3% ($p > 0.5$); B: noncurative resection cases in levamisole group, (23/23), 100%; B': noncurative resection cases in control group, (49/54), 90.7% ($p < 0.01$); C: non-resection cases in levamisole group, (8/11), 72.7%; C': non-resection cases in control group, (9/24), 37.5% ($p < 0.01$).

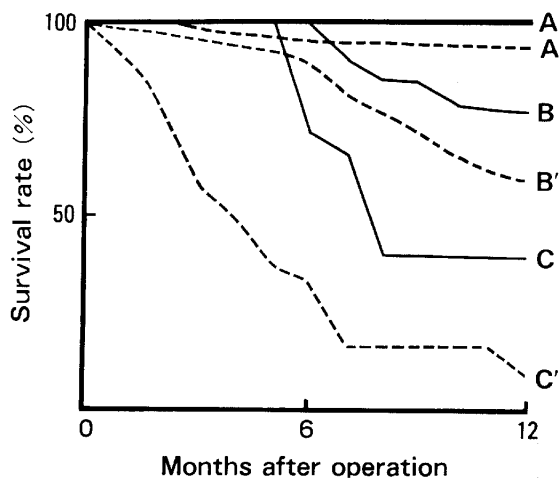


Fig. 2. One-year Survival Ratios in Gastrointestinal Cancer. Figure signatures are the same as Figure 1. A: (21/21), 100%; A': (102/107), 95.3% ($p > 0.5$); B: (14/18), 77.8%; B': (32/54), 59.3% ($0.05 < p < 0.1$); C: (2/5), 40.0%; C': (2/24), 8.3% ($0.05 < p < 0.1$).

treated patients and that of control patients. After curative resection, 21 patients receiving levamisole all survived one year, while 102 of 107 patients (95.3%) survived for one year in the control group ($p > 0.5$). After noncurative resection, the one-year survival rate was 77.8% (14 of 18 patients) in the levamisole group and 59.3% (32 of 54 patients) in the control group ($0.05 < p < 0.1$), while in nonresectable patients, 40% (2 of 5 patients) and 8.3% (2 of 24 patients) ($0.05 < p < 0.1$), respectively. The trend that levamisole was more effective in advanced and malignant patients was also seen in one-year survival rates. However, the small number of cases does not permit meaningful statistical examination (Fig. 2).

The average survival of the levamisole group and of the control group followed for one year were 12 and 11.6 months after curative resection, 10.9 and 9.9 months after noncurative resection and 8.2 and 4.8 months in nonresectable patients, respectively.

DISCUSSION

Renoux, G. and Renoux, M. first found that levamisole had antitumor properties and the ability to enhance cellular immunity (7, 8). A considerable number of publications regarding levamisole have followed them. As we have described elsewhere (4, 5), the ability of levamisole to enhance cellular immunity is characterized, unlike other immunostimulants, by its effect on depressed cellular immunity alone, enhancing and normalizing it.

The first report dealing with antitumor activity of levamisole in animals was that of Renoux, G. and Renoux, M. in which levamisole was proved to be effective against Lewis lung (3LL) tumor in mice (8). However, data on its effectiveness are controversial; against tumor, levamisole was effective when administered by itself (9), effective only when it was used in combination with anticancer agents (10), or ineffective (11). We started levamisole therapy in mice when spontaneous breast cancer became palpable. The therapy consisted of 10 subcutaneous doses of 1.15 mg/kg/day administered every other day. Cancer-bearing mice receiving physiological saline were used for comparison purposes. It was confirmed that levamisole had a remarkable antitumor activity and prolonged the length of survival time to a considerable extent; the mean survival was 30 ± 7 days in the control group and 50 ± 10 days in the treated group. Mice bearing transplanted with hepatoma MH 134 cells were injected with either 10 doses of levamisole 1.15 mg/kg/day dissolved in physiological saline or only physiological saline, every other day from 7 or 10 days after the tumor transplantation. The animals were evaluated for tumor growth and survival. Levamisole administered from 10 days after tumor transplantation was found to be most effective in depressing tumors and prolonging survival (6). This compares closely with our present findings that the antitumor activity of levamisole is more

remarkable in more advanced cancers.

Rojas, *et al.* (12) studied the effect of levamisole in patients with inoperable Stage III breast cancer who had been treated with radiotherapy alone. The patients were split into two groups, one assigned to levamisole at 150 mg/day for three consecutive days every other week and the other not. As a result, the levamisole-treated patients were protected from recurrence of cancer and benefited by a prolonged survival. Amery (13) performed a double-blind trial with levamisole on patients with operable bronchogenic cancer. The patients were allocated to receive levamisole 150 mg/kg or a placebo for three consecutive days every other week from three days before operation. Levamisole-treated patients had much longer disease-free interval and lower incidence of recurrence when compared to placebo-treated patients. He also noted that the larger the tumors were, the more remarkable the antitumor activity of levamisole was (14). Renoux, G. and Renoux, M. (15) recently reported on 56 patients with advanced solid tumor which was beyond the control of every available therapy. Fifteen of them were treated with levamisole and 25 were not. The length of survival time was remarkably increased in the former 15 patients. Devois (16) administered levamisole to patients with cancer of various types and obtained a high 25-month survival rate as compared to those who did not receive levamisole. According to Devois, 68% of the patients not receiving levamisole therapy were living after 12 months, but it was only after 20 months that the number surviving decreased to that percentage in levamisole-treated patients. Thus levamisole prolonged the survival time to a remarkable extent. He also followed up survival for 24 months in levamisole-treated and untreated patients who were in different stage of breast cancer. The increase in survival rate due to levamisole was most significant in Stage IV patients.

These reports are consistent with our results. But some authors disagree with us. Lichtenfeld *et al.* (17), for example, gave levamisole to 23 inoperable or recurrent lung cancer patients for 35 days but obtained neither prolongation of survival nor objective improvement.

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