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Immunochemotherapy of gastric cancer with levamisole.

Hiroaki Miwa[*] Fumio Ono[†] Minoru Moriyama[‡]

Tsutomu Kobayashi[**] Tetsuhide Oka[††]

Kenji Nakamura[‡‡] Kunzo Orita[§]

[*]Okayama University,

[†]Okayama University,

[‡]Okayama University,

[**]Okayama University,

[††]Okayama University,

[‡‡]Okayama University,

[§]Okayama University,

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Hiroaki Miwa, Fumio Ono, Minoru Moriyama, Tsutomu Kobayashi, Tetsuhide Oka, Kenji Nakamura, and Kunzo Orita

Abstract

In 156 cases of gastric cancer, levamisole (LMS) was administered at a daily dose of 150 mg for three consecutive days every other week. The administration was started 3 days before operation. This medication was repeated for more than one month. The survival rate up to two years after surgery was studied. The survival rate was not affected in patients with Stage I and II gastric cancer, but in patients with Stage III, the difference in the survival rate between the LMS group and the control group was significantly higher than that in the control group (p less than 0.05). In patients with Stage IV, the survival rate in the LMS group was higher than that in the control group although the difference was not significant. In patients of Stage III and IV, the effect of LMS on the survival rate was highest in cases with curative resection (p less than 0.01). In cases with noncurative resection, the difference between the LMS group and the control group was greatest (24.4%) 12 months after surgery but not significant (p less than 0.5), and also in cases without resection the difference between the two groups was greatest (20.3%) 12 months after surgery but not significant (p less than 0.2).

KEYWORDS: levamisole, immunochemotherapy, gastric cancer, survival time.

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IMMUNOCHEMOTHERAPY OF GASTRIC CANCER WITH LEVAMISOLE

Hiroaki MIWA, Fumio ONO, Minoru MORIYAMA,
Tsutomu KOBAYASHI, Tetsuhide OKA,
Kenji NAKAMURA and Kunzo ORITA

Department of Surgery, Okayama University Medical School, Okayama 700, Japan (Director: Prof. K. Orita)

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Abstract. In 156 cases of gastric cancer, levamisole (LMS) was administered at a daily dose of 150 mg for three consecutive days every other week. The administration was started 3 days before operation. This medication was repeated for more than one month. The survival rate up to two years after surgery was studied. The survival rate was not affected in patients with Stage I and II gastric cancer, but in patients with Stage III, the difference in the survival rate between the LMS group and the control group was significantly higher than that in the control group ($p<0.05$). In patients with Stage IV, the survival rate in the LMS group was higher than that in the control group although the difference was not significant. In patients of Stage III and IV, the effect of LMS on the survival rate was highest in cases with curative resection ($p<0.01$). In cases with noncurative resection, the difference between the LMS group and the control group was greatest (24.4%) 12 months after surgery but not significant ($p<0.5$), and also in cases without resection the difference between the two groups was greatest (20.3%) 12 months after surgery but not significant ($p<0.2$).

Key words: levamisole, immunochemotherapy, gastric cancer, survival time.

The therapeutic results for gastric cancer have improved remarkably due to advances in surgical techniques but have reached a limit; moreover, radiotherapy has no effect against gastric cancer. On the other hand, chemotherapy has progressed but is not yet satisfactory as treatment of advanced gastric cancer in the end stage. Immunotherapy, therefore, has come on stage as another therapeutic method. Cancer immunotherapy does not have a long history; advance in cancer immunotherapy began with Mathè's study on the effect of Bacillus Calmette-Gùerin (BCG) in acute lymphoblastic leukemia (1), and only ten years have passed since then. Starting from this BCG immunotherapy, nonspecific cancer immunotherpay using immunostimulators has developed with good results.

Levamisole (LMS) (2) was developed originally as an anthelminthic against

Nematoda. Renoux *et al.* (3) first reported that LMS had antitumor effects. As a results of fundamental and clinical studies thereafter, LMS is now tested as an promising immunomodulator at many research institutes, being third to BCG and Corynebacterium parvum in the world (4).

During the past three years, we have been studying the antitumor and cellular immunomodulating effects of LMS (5, 6) and have assessed the two-year survival rate of gastric cancer patients, which is useful for evaluation of the antitumor effect of this drug to a certain extent. Therefore, we report below the results of our study and discuss trends in cancer immunotherapy using LMS with reference to the literature.

SUBJECTS AND METHOD

Subject. The subjects of our study were patients with gastric cancer who were admitted, and underwent operation in our Department of Surgery. Of these patients, 156 cases who were admitted into our Hospital during the period from 1976 to 1979 served as the LMS group, and 212 cases who were admitted from 1971 to 1976 and received neither LMS nor other immunotherapies served as the control group (Table 1). Between these two groups, there was no difference in age distribution, surgical intervention or anticancer therapy. A follow-up study for two full years was made on 196 cases of the control group and 101 cases of the LMS group.

TABLE 1. NUMBER OF GASTRIC CANCER PATIENTS IN THE LEVAMISOLE AND CONTROL GROUPS

Gastric cancer	Curative resection		Noncurative resection		No resection		Total	
Stage	Control	LMS	Control	LMS	Control	LMS	Control	LMS
I	36	35	0	0	0	0	36	35
II	14	18	0	0	0	0	14	18
III	48	31	8	9	0	0	56	40
IV	24	12	51	40	31	11	106	63
Total	122	96	59	49	31	11	212	156

LMS: Levamisole

Method. LMS, 150 mg/day, was administered orally in three divided doses after each meal for three consecutive days from just before operation to at least 1800 mg as the total dose. The medication was resumed for 3 days followed by an 11-day withdrawal period, then continued for as long as possible, and for at least one month. To both groups, combined chemotherapy, mitomycin-C, 4 mg, was given intravenously twice a week after operation up to a total of 40 mg, and FT-207, 600-800 mg/day, more than 8,000 mg as the total dose, was given orally for as long as possible.

RESULTS

Survival rate classified by the stage of gastric cancer. Fig. 1 shows the results obtained for the two-year survival rate in 212 cases of the control group and 156 cases of the LMS group. There were no deaths in patients with Stage I, in either the control group or the LMS group up to 2 years after operation. Among patients with Stage II, one of the LMS group died 9 months after operation, but there was no difference in survival rates for the two groups. Among patients with Stage III, the survival rate 18 months after oepration was 75.5% in the control group and 92.6% in the LMS group, but the difference was not significant ($p<0.1$). After 24 months, the difference in survival rate between the groups was large enough to be significant ($p<0.05$). Among patients with Stage IV, tne survival rate in the LMS group was higher than that in the control group; however, thereafter, the difference between the groups was not significant throughout the 24 months studies.

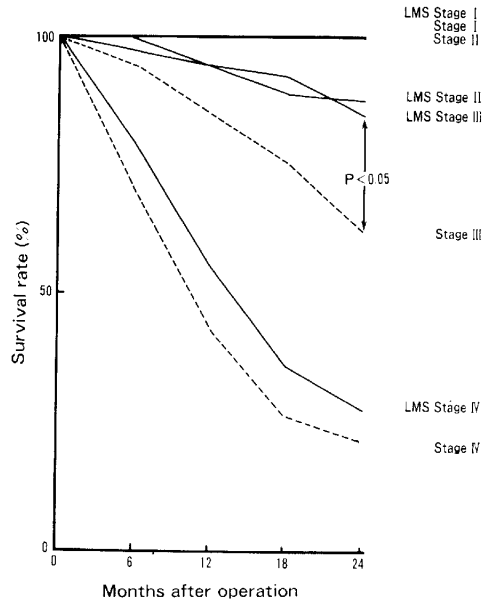

Fig. 1. Twenty-four month survival rates for patients with gastric cancer of operative curability for operation (Stage III and IV).
——: levamisole group, - - -: control group.

Survival rate classified by operative curability. As described in the preceding paragraph, the effect of LMS was significant among patients of advanced gastric cancer, so the survival rate of gastric cancer Stage III and IV was classified according to operative curability (Fig. 2).

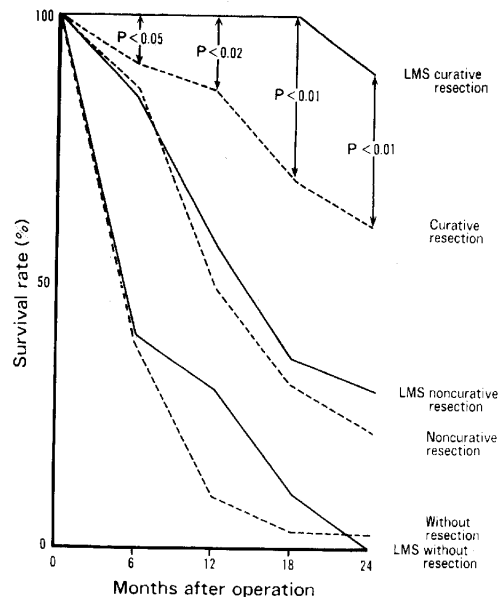

Fig. 2. Twenty-four month survival rates for patients with gastric cancer in different stages. ——: levamisole group, - - -: control group.

The breakdown of patients of control and LMS groups was as follows: Curative resection in 72 and 43 cases, non-curative resection in 59 and 49 cases, and no resection in 31 and 11 cases, respectively. Among patients with curative resection, the survival rate of the LMS group significantly exceeded that of the control group 6 months after operation ($p<0.05$). Afterwards, the difference between the groups increased and 24 months after operation, the LMS rate was 28.0% higher than the control ($p<0.01$). Among patients with non-curative resection, the difference in survival rate between the groups increased with lapse of time after operation and reached a maximum of 24.4% at 12 months, but this was not statistically significant ($p<0.5$). Among patients with no resection, death was observed in the LMS group 2 months later than in the control group, but up to 6 months after operation, the survival rate fell rapidly in both groups. Thereafter, the difference between the two groups gradually increased, and after 12 months, the survival rate of the LMS group exceeded by that of the control group by 20.3%. However, the lack of a significant difference was probably due to the small number of cases (p 0.2).

The increase in survival rate due to LMS was most remarkable in patients with somewhat advanced gastric cancer, especially in cases whose tumors, including the main lesion, could be resected as throughly as possible.

DISCUSSION

In the past ten years, cancer immunotherapies using immunostimulators have become popular. With progress of fundamental studies using experimental animals, these immunotherapies have come into clinical use sometimes with good results.

Cancer immunotherapy with LMS has been performed in the third greatest number of research institutes in the world (4). However, in spite of many fundamental studies, there are only a few reports referring to the clinical results of LMS. In particular, the effect of LMS on gastric cancer has been studies in detail only by our group (6).

As mentioned above, LMS influences cases with declining cellular immune status and works to improve the lower immune status (8), being different in this point from other immunostimulators. The result is that LMS is considered to have indirect antitumor and life-prolongation effects in the cancer host, whereas BCG works directly on cancer cells (9). The evaluation of LMS in cancer-bearing animals is, therefore, not always clear-cut; some researchers regard LMS as effective by itself (3, 10), others regard it as effective in combination with any anticancer therapy (11) or as noneffective (12), and still others have reported that LMS enhanced tumor development (13). However, these reports varied in detail such as species of experimental aninal, types of tumor, primary or metastatic tumor, slow-or rapidly-growing tumor, dose, commencement and duration of administration, combination use with various anticancer therapies or single use, and kind of drugs used in combination. Therefore, they are very difficult to evaluate.

Amery *et al.* (14) summarized results obtained from experients on mice as follows: LMS is more effective against metastatic and slow-growing tumors than against primary and rapidly-growing ones, and its effective dose is between 2.5 and 10.0 mg/Kg. According to some reports on monotherapy, LMS has a narrow range of optimal doses. However, this is not always true, and LMS acts better in combination with antitumor agents.

The stage of cancer at which LMS was effective was assessed on the basis of clinical results. Rojas' results (15) on administration of LMS after radiotherapy to inoperable breast cancer of stage III (ULCC), Renoux's results (16) from administration to cancer patients making no response to any anticancer therapy, and our results from short-term administration to gastric cancar (6) and gastrointestinal cancer (8) suggest that LMS is effective against advanced cancer. However, the results of animal tests by Doller *et al.* (17) and us (18), indicate that LMS is not effective against cancer which has advanced beyond a certain degree. Our results (19) and Lichtenfeld's (20) proved that LMS was not effective in cases of gastric cancer in which main tumor could not be resected. These

results show the limitations of LMS therapy. Also in our follow-up study up to 2 years after operation, LMS was effective against gastric cancer of Stage IV, the most advanced stage, up to 18 months after operation although it was not effective thereafter. On the other hand, it was most effective in cases where the tumor could be resected as thoroughly as possible, even if at the end stage. These results are similar to the results of Amery *et al.* (21) in lung cancer, showing that the greater the diameter of resected tumor, the better the effect of LMS. In short, LMS produces better and more prolonged antitumor effects in cases where tumors can be more thoroughly resected.

In regard to the timing of administration of LMS, Rojas *et al.* (15) obtained good results from administration after radiotherapy in patients with breast cancer. Amery and Miwa (21, 8) start the administration of LMS before operation in order to prevent the decline of cellular immune status after operation. Symoens (23) recommends the use of LMS following cytoreductive therapy. In combination with chemotherapy, careful attention should be paid lest the effect of LMS be counteracted by the chemetherapy (24). This is true also of other immunostimulators such as BCG (25).

REFERENCES

1. Mathé, G., Amiel, J.L., Schwarzenberg, L., Scheneider, M., Cattan, A., Schelumberger, L., Hayat, M. and Vassal, F.: Active immunotherapy for acute lymphoblastic leukemia. *Lancet* **1**, 697-699, 1969.
2. Raeymaekers, A. H. M., Allewijin, F. T. N., Vandenberk, J., Demoen, P. A., Van Offenwert, T. T. T. and Janssen, P. A. J.: Nobel broadspectrum anthelmintics and related derivatives of 6-arylimidazo [2, 1-b] thiazole. *J. Med. Chem.* **9**, 545-551, 1966.
3. Renoux, G. and Renoux, M.: Levamisole inhibits and cures a solid malignant tumor and its pulmonary metastasis in mice. *Nature (New Biol.)* **240**, 217, 1972.
4. International Registry of Tumor Immunotherapy, Compendium of Tumor Immunotherapy Protocols, No. 7, International Cancer Research Data Bank-NIH, Bethesda, 1979.
5. Miwa, H., Kawai, T., Nakahara, H. and Orita, K.: Decrease in cell-mediated immunity by surgical intervention and its prevention by levamisole. *Int. J. Immunopharmacol.* **2**, 31-36, 1980.
6. Miwa, H. and Orita, K.: Immunochemotherapy of gastric cancer with levamisole. *Acta Med. Okayama* **32**, 363-367, 1978.
7. Japanese Research Society for Gastric Cancer: *The General Rules for the Gastric Cancer Study in Surgery and Pathology*, Kanahara Pub. Co. Ltd., Tokyo, 1979.
8. Miwa, H. and Orita, K.: Immunochemotherapy of gastrointestinal cancer patients with levamisole. *Acta Med. Okayama* **33**, 29-42, 1979.
9. Bast, R. C. Jr. and Bast, B. S.: Critical review of previously reported animal studies of tumor immunotherapy with nonspecific immunostimulants. *N. Y. Acad. Sci.* **27**, 69-93

duced remission of syngeneic murine leukemia by L-2, 3, 5, 6,-tetrahydro-6-phenylimidazo [2, 1, -b] thiazole hydrochloride. *Cancer Res.* **35**, 927-931, 1975.

12. Johnson, R.K., Houchens, D.P., Gaston, M.R. and Golden, A.: Effect of levamisole (NSC-177023) in experimental tumor system. *Cancer Chemother. Rep.* (Part 1.) **59**, 697-705, 1975.
13. Fidler, I. J. and Spitler, L.E.: Effect of levamisole on *in vitro* and *in vivo* murine host response to syngeneic transplantable tumor. *J. Natl. Cancer Inst.* **55**, 1107-1112, 1975.
14. Amery, W.K., Spreafico, F., Rojas, A.F., Denissen, E. and Chirigos, M.A.: Adjuvant treatment with levamisole in cancer. A review of experimental and clinical data. *Cancer Treat. Rev.* **4**, 167-194, 1977.
15. Rojas, A.F., Feierstein, J.N., Mickiewicz, E., Glait, H. and Olivari, A.J.: Levamizole in advanced human breat cancer. *Lancet* **1**, 211-215, 1976.
16. Renoux, G. and Renoux, M.: Levamisole therapy in advanced cancer patients, A prognostic test? In *Control of Neoplasia by Modulation of the Immune System*, ed. M.A. Chirigos, Raven Press, New York, pp. 235-237, 1977.
17. Doller, E.W. and Rapp, F.: Effect of levamisole on metastasis by herpesvirus-transformed cells. In *Control of Neoplasia by Modulation of the Immune System*, ed. M.A. Chirigos, Raven Press, New York, pp. 97-106, 1977.
18. Orita, K., Miwa, H., Kawai, T., Nakahara, H., Hashimoto, M., Ohe, S. and Konaga, E.: Immunotherapy with levamisole. *Jpn. J. Cancer Clin.* **24**, 469-476, 1978 (in Japanese).
19. Miwa, H., Moriyasu, F., Kawai, T., Hamazaki, K., Nakahara, H., Tanaka, N. and Orita, K.: Effect of gastrectomy and immunotherapy with levamisole on gastric cancer Stage IV. *Jpn. J. Gastroenterol. Surg.* **12**, 303-307, 1979 (in Japanese).
20. Lichtenfeld, J.L.: Levamisole in patients with nonresectable bronchogenic carcinoma. In *Control of Neoplasia by Modulation of the Immune Sysetm*. ed. M.A. Chirigos, Raven Press, New York, pp. 135-145, 1977.
21. Study Group for Bronchogenic Carcinoma: Immunopotentiation with levamisole in resectable bronchogenic carcinoma. A double blind controlled trial. *Br. Med. J.* **3**, 461-464, 1975.
22. Amery, W.K.: Double-blind placebo-controlled clinical trial of levamisole in resectable bronchogenic carcinoma, In *Control of Neoplasia by Modulation of the Immune System*, ed. M.A. Chirigos, Raven Press, New York, pp. 197-203, 1977.
23. Symoens, J.: Levamisole, an antianergic chemotherapeutic agent. An overview. In *Control of Neoplasia by Modulation of the Immune System*, ed. M.A. Chirigos, Raven Press, New York, pp. 1-12, 1977.
24. Wood, W.A., Fliegelman, M.J. and Chirigos, M.A.: Effect of levamisole (NSC 177023) on DNA synthesis by lymphocytes from immunosuppressed C57BL mice. *Cancer Chemother. Rep.* (Part 1), **59**, 531-536, 1975.
25. Person, J.W., Person, G.R., Gibson, W.T.: Combined chemoimmunostimulation therapy against murine leukemia. *Cancer Res.* **32**, 904-907, 1972.