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Adjuvant Immunotherapy by Levamisole in Resectable Lung Cancer: A Control Study*

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Abstract—*Since* 1976, *a double blind study has been conducted to assess the value of levamisole as adjuvant treatment to surgery for non-small cell carcinoma of the lung. Fifty-one patients were evaluable with a minimal follow-up period of* 1 yr. *No difference could be observed between the two groups in the duration of the survival and of the disease free survival.*

In cases of complete resection without any lymph node involvement, an increase of the free interval was observed. This was not statistically significant.

INTRODUCTION

LEVAMISOLE is believed to be an immunomodulating agent [1, 2] and has been reported to prolong disease free interval in patients with breast and lung cancer [3, 4]. For these reasons, a randomized trial was started in 1976 to assess the value of Levamisole as adjuvant therapy to surgery and irradiation for resectable non-small cell lung cancer.

MATERIALS AND METHODS

From 1976 to 1978, 73 patients were entered into this trial to assess in a double blind procedure the value of levamisole. They had to fulfil the following criteria: no history of other malignant disease, no prior treatment, squamous cell, large cell or adenocarcinoma of the lung resected without distant metastases detected by clinical examination, chest X-ray, bone, brain and liver scintigraphies, and, when indicated bone X-ray, peritoneoscopy with liver biopsies and computed axial tomography.

The local extent of the diesease was assessed on the operative specimen both by the pathologist and the surgeon according to the propositions of the American Joint Committee [5]. A stratification was made between the early stages (T_1, T_2, N_0) and the more advanced stages which include tumor extension outside the lung (T_3), lymph node involvement (N_1 and N_2) or microscopical evidence of residual tumor at the bronchial stump.

Three to four weeks after the surgical procedure, all patients received radiation therapy. A dose of 56 Gy was delivered to the mediastinum in 6 weeks. The target volume included the mediastinum from the sternal notch or the mediastinoscopy scar down to 5 cm under the carina. This treatment was carried out with one anterior field from a 35 MeV betatron and two posterior oblique fields with wedge filters from a telecobalt unit. The treatment was planned with a computed treatment planning system using the data of computed axial tomography of the chest. Care was taken to minimize the volume of pulmonary tissue irradiated and to decrease the dose delivered to the spinal cord. In presence of mediastinal lymph node involvement two

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opposite fields from a 35 MeV betatron were used.

Seventy-three patients were randomized after surgery to receive levamisole or the placebo in a double blind procedure. The drug or the placebo was started 1 month after the end of radiation therapy and was delivered for a period of 2 yr or until relapse with a dosage of 100 mg/m^2 *per os* twice a week (Fig. 1). Twenty-two patients were excluded from this analysis because of tumor progression before the administration of the drug or the placebo or refusal of any adjuvant treatment.

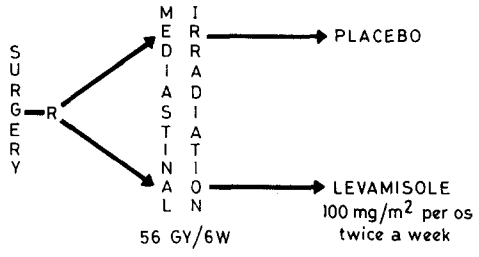

Fig. 1. Post-operative adjuvant levamisole trial in lung cancer. Non-small cell tumor.

The statistical analysis has been performed using the log-rank test for the duration of survival and of the disease free survival which was defined as the time until recurrence or death [6].

This series includes 51 evaluable patients: 24 for the placebo group and 27 for the levamisole group. Patients characteristics are summarized in Table 1. Both groups are quite similar in age, sex and tumor extension distribution. A slight but non-significant difference is observed for the histology and the surgical procedure.

Table 1. Patient characteristics

	Levamisole	Placebo
No. of patients	27	24
Age (yr) mean	56	55
range	(49–70)	(41–72)
Sex	23 M/4F	23 M/1F
Cell type		
Squamous cell	18	20
Glandular cell	8	4
Large cell	1	—
Operation		
Pneumectomy	4	7
Lobectomy	23	17
Tumor extension		
$T_1T_2N_0$	12	11
T_3N_0	1	4
N_1	6 (15)	1 (13)
N_2	6	5
Residual disease	2	3

RESULTS

The report is based on 51 patients evaluable with a minimal follow-up period of at least 1 yr. No difference could be observed between the treated group and the control group in term of duration of survival or disease free survival ($P=0.49$) (Fig. 2). Considering the early stages (T_1 and T_2N_0), a trend was observed in favor of levamisole only for the duration of the disease free survival, however this difference does not reach a statistically significant level ($P=0.24$) (Fig. 3). For the more advanced stages, the duration of survival or disease free survival is similar for patients treated with levamisole or the placebo (Fig. 4).

Objective tumor recurrence has been documented in 26 cases; 3 patients died of unknown reason without evidence of recurrent disease. Local relapses occurred in three cases (two in the levamisole group and one in the placebo group); most failures resulted from distant metastases (11 and 12 cases respectively for control and treated group; Table 2).

The most common side effects were due to gastro-intestinal problems: nausea, gastritis. One patient presented a severe but reversible leucopenia with an increase in cold agglutinines and leucocytes antibody titer. Drug administration has been discontinued in 7 patients: 5 in the levamisole group and 2 in the control group (Table 3).

DISCUSSION

Although the number of patients is small, levamisole was not found to represent an effective adjuvant therapy after postoperative irradiation for lung cancer. The only difference between the 2 groups was a non-significant increase of the free survival observed for tumor classified as T_1 and T_2 without lymph node involvement.

Several studies using BCG as adjuvant immunotherapy have showed some benefit in term of recurrence rate, duration of the disease free survival or survival for stage I tumors (T_1N_0, T_2N_0 and T_1N_1) [7–9].

This supports the necessity of a careful staging procedure in any adjuvant treatment study.

To date, two large studies have been conducted to assess the value of levamisole [10, 11]. In both, the drug was administered in the same schedule for three days before the surgery. Their results are controversial: in the work of Amery *et al.* [10], an increase in the

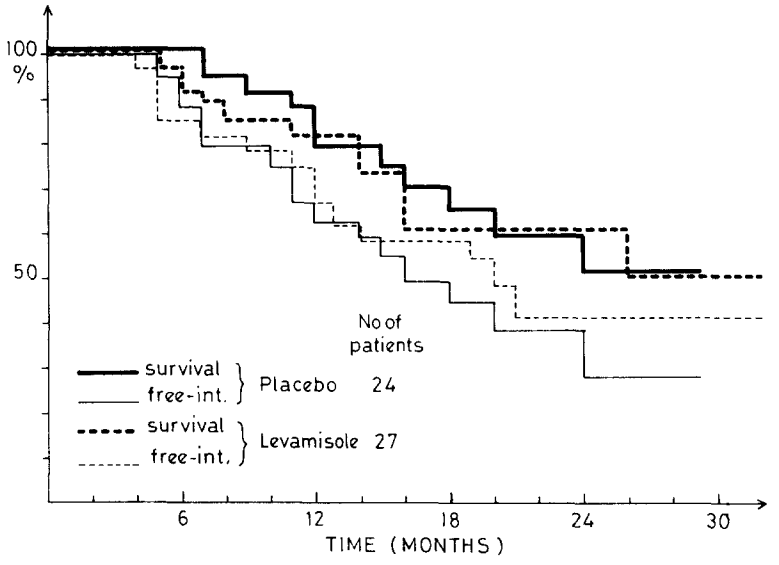

Fig. 2. Duration of survival and disease free survival related to drug administration.

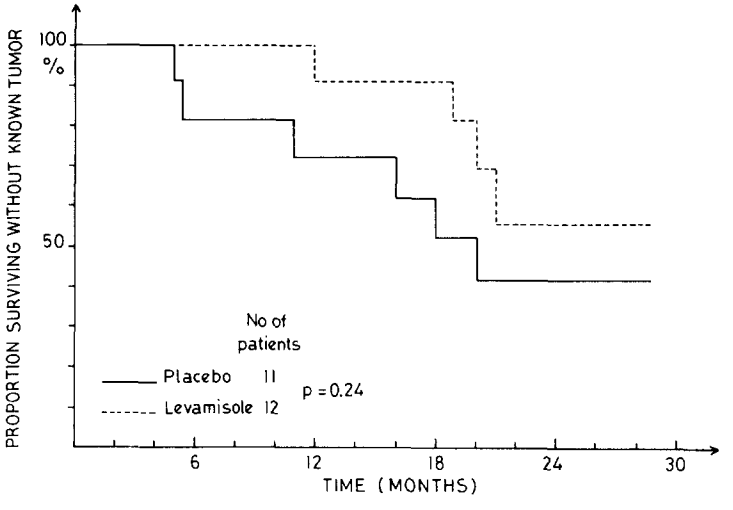

Fig. 3. Duration of the disease free survival for tumor classified T_1 or T_2N_0.

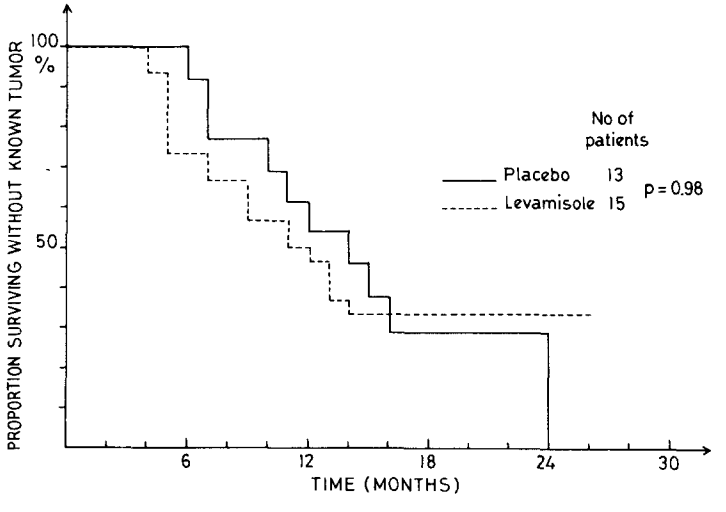

Fig. 4. Duration of the disease free survival for the more advanced stages.

Table 2. Postoperative adjuvant levamisole trial in lung cancer evolution according to treatment

	Levamisole		Placebo	
	$T_1T_2N_0$	Others	$T_1T_2N_0$	Others
Alive free of disease	8	5	5	3
Alive in relapse	2	1	4	2
Dead in cancer	2	9		6
Intercurrent			1	
Unknown reason			1	2
	12	15	11	13

Table 3. Postoperative adjuvant levamisole trial in lung cancer side effects of treatment

	Levamisole	Placebo
Rash	2	—
Nausea	1	2
Gastritis minor	1	—
major	2	—
Severe leucopenia	1	—

duration of the disease free survival and of survival was reported and correlated with a decrease in the frequency of distant metastases provided the patient received a dosage of at least 100 mg/m^2 twice a week. In contrast, in the trial of Anthony *et al.* [11] patients treated by levamisole presented a poorer survival than controls. The majority of deaths in the levamisole group resulted from an increase in postoperative death due to respiratory distress perhaps immunologically mediated. The results were however similar in both groups after excluding postoperative deaths. Both studies do not include a correlation of results with tumor stages. Moreover in three other studies, the addition of levamisole to BCG or *C. parvum* did not show any benefit in terms of survival or recurrence rate [12–14].

The differences between the studies using levamisole alone and ours were the use of postoperative radiation therapy and the start of the drug. Local relapses were seldom observed and most recurrences were due to distant metastases. Perhaps, the period of levamisole treatment was also not optimal and was too late in the course of this disease to show some benefit especially in presence of lymph node involvement.

The side effects of levamisole observed in our study required the administration of the drug to be discontinued in 5 out of 27 treated patients due to severe gastritis, rash or leucopenia. The neutropenia has been known to be related to leucocytotoxic agglutinating antibodies [15].

In conclusion in this study on a limited number of patients, levamisole administered at the recommended dosage was found ineffective as adjuvant therapy of non-small cell lung cancer treated by surgery and radiation.

REFERENCES

1. D. Copeland, T. Stewart and J. Harris, Effect of levamisole (NSC-177023) on *in vitro* human lymphocyte transformation. *Cancer Chemother. Rep.* **58,** 167 (1974).
2. D. Tripodi, L. C. Parks and J. Brugmans, Drug induced restoration of cutaneous delayed hypersensitivity in anergic patients with cancer. *New Engl. J. Med.* **289,** 354 (1973).
3. Study Group for Bronchogenic Carcinoma, Immunopotentiation with levamisole in resectable bronchogenic carcinoma: a double blind controlled trial. *Brit. med. J.* **3,** 461 (1975).
4. A. F. Rojas, E. Mickiewicz, J. N. Feierstein, H. Glait and A. J. Olivari, Levamisole in advanced human breast cancer. *Lancet* **i,** 211 (1976).
5. American Joint Committee for Cancer Staging and End Results Reporting, Task Force on the Lung. *Manual for Classification of Cancer by Side*, p. 59. Chicago, Ill. (1977).
6. R. Peto, M. C. Pike, P. Armitage, N. E. Breslow, D. R. Cox, S. V. Howard, N. Mantel, K. McPherson, J. Peto and P. G. Smith, Design and analysis of randomized clinical trials requiring prolonged observations of each patients. II. Analysis and examples. *Brit. J. Med.* **35,** 1 (1977).
7. P. Pouillart, T. Palangie, M. Jouve and E. Garcia-Giralt, Systemic BCG in squamous cell lung cancer. In *Adjuvant Therapy of Cancer II* (Edited by S. E. Jones and S. E. Salmon) p. 553. Grune & Stratton, New York (1979).

8. M. F. McKneally, C. M. Maver, R. D. Alley, H. W. Kausel, T. M. Older, E. D. Foster and L. Lininger, Regional immunotherapy of lung cancer using intrapleural BCG: summary of four-year randomized study. In *Lung Cancer. Progress in Therapeutic Research* (Edited by F. Muggia and M. Rozencweig p. 471. New York, Raven Press (1979)
9. E. Perlin, R. K.. Oldham, J. L. Weese, W. Heim, J. Reid, M. Mills, C. Miller, J. Blom, D. Green, S. Bellinger, G. B. Cannon, I. Law, R. Connor and R. B. Herberman, Immunotherapy of carcinoma of the lung with intradermal BCG and allogenic tumor cells. *Int. J. Radiat. Oncol.* In press.
10. W. K. Amery, Final results of a multinuclear placebo-controlled levamisole study of resectable lung cancer. *Cancer Chemother. Rep.* **62,** 1677 (1978).
11. H. M. Anthony, A. J. Mearns, M. K. Mason, D. G. Scott, K. Moghissi, P. B. Deverall, Z. J. Rozycki and D. A. Watson, Levamisole and surgery in bronchial carcinoma: increase in deaths from cardiorespiratory failure. *Thorax* **34,** 4 (1979).
12. P. Wright, L. Hill, A. Peterson, R. Anderson, C. Bagley, I. Barnstein, T. Ivey, L. Johnson, E. Morgan, R. Ostenson and R. Pinkham, Adjuvant immunotherapy for lung cancer. In *Adjuvant Therapy of Cancer* II (Edited by S. E. Jones and S. E. Salmon) p. 545. Grune & Stratton, New York (1979).
13. E. C. Holmes and K. P. Ramming, Immunotherapy of lung cancer using levamisole and intralesional BCG. (In *Lung Cancer. Progress in Therapeutic Research.* (Edited by F. Muggia and M. Rozencweig) p. 483. Raven Press, New York (1979).
14. R. M. Fox, R. L. Woods, M. H. Tattersall and A. Basten, A randomized study of adjuvant immunotherapy with Levamisole and C. Parvum in operable non-small cell lung cancer. *Int. J. Radiat. Oncol.* In press.
15. M. Rosenthal, U. Trabert and W. Müller, Leucocytotoxic effect of levamisole. *Lancet* **i,** 369 (1976).