Levamisole as an Adjuvant to Chemotherapy in Extensive Bronchogenic Carcinoma

A Veterans Administration Lung Cancer Group Study

STEPHEN DAVIS, MD,* WILLIAM MIETLOWSKI, PHD,† JAY J. ROHWEDDER, MD,‡ JOHN P. GRIFFIN, MD,§ AND AMIR A. NESHAT, MD‖

A randomized trial of 381 patients with extensive lung cancer compared immunochemotherapy with levamisole (150 mg/m² orally three times a week), cyclophosphamide (700 mg/m² IV every three weeks) and CCNU (70 mg/m² orally every six weeks) with the same chemotherapy without levamisole. When disease progressed, doxorubicin hydrochloride or doxorubicin hydrochloride plus levamisole was used. Hematologic toxicity required reduction of the levamisole dosage to 2.5 mg/kg (100 mg/m²) three times a week, every other week. When corrections are made for all variables, levamisole itself had a negative influence on survival. Patients given 150 mg/m² had a shorter median time to treatment failure ($P = 0.02$), lower response rate ($P = 0.02$), more toxicity ($P = 0.08$), and shorter median survival ($P = 0.08$). Patients with 10% or greater weight loss had significantly shorter survival ($P = 0.006$). The regimen with the reduced dosage of levamisole also was more toxic ($P = 0.05$) but otherwise did not differ from the control regimen. The cause of the adverse effect of levamisole is unknown. It did not occur because of an excess of toxic deaths or because smaller doses of cytotoxic drugs were given to patients treated with levamisole. Neither the initial lymphocyte count nor the Candida skin test reactions had a significant effect on the study endpoints when correction was made for dominant prognostic factors such as the initial performance status and weight loss.

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THE DISMAL PROGNOSIS for patients with extensive lung cancer may be partially explained by tumor-induced suppression of cell-mediated host defense mechanisms. In addition, attempts at chemotherapy further suppress immune competence and may thereby contribute to the "collapse-of-the-host" phenomenon frequent among these patients.

Levamisole, an orally administered antihelminthic drug considered an immunoreconstituting agent rather than an immune stimulant[1,2] has produced mixed results when used in patients with bronchogenic carcinoma initially treated by surgery.[2–4] The drug benefitted some patients with advanced breast cancer[5] and it restored tumor-specific and nonspecific immunity among patients with a variety of advanced solid tumors.[6–9] Tumor size has been considered critical to immunotherapy because maximum reduction in tumor bulk by surgery or radiotherapy usually has been a prerequisite for success; however, there is some evidence that patients with a large tumor burden and metastases may respond.[4,10,11]

The Veterans Administration Lung Group (VALG) studied levamisole as an adjuvant to cyclophosphamide plus CCNU and to doxorubicin hydrochloride in patients with advanced inoperable lung cancer. The trial was randomized and prospective.

Methods

Patients and Treatments

Participating hospitals considered every male veteran with primary cancer of the lung who had been seen between June 1977 and August 1978, for inclusion in the study. Eligible patients were those with: (1) histologic or cytologic proof of bronchogenic carcinoma; (2) extensive disease: extrathoracic metastases and/or involvement of contralateral lung, contralateral hilar lymph nodes, ipsilateral or contralateral cervical lymph nodes, noncontiguous involvement of the chest wall, or

From the Veterans Administration Medical Centers at *East Orange, New Jersey, ‡Ann Arbor, Michigan, §Memphis, Tennessee, and ‖Asheville, North Carolina; and †Frontier Science and Technology Research Foundation, Amherst, New York.

Address for correspondence: Stephen Davis, MD, Chief, Oncology/Hematology, VA Medical Center, East Orange, NJ 07019.

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a recurring exudative pleural effusion with or without demonstrable malignant cells; (3) objective evidence of local or distant progressive disease after prior surgery or irradiation; and (4) an initial Karnofsky performance status of 40 or more. Each patient gave informed consent.

Patients were excluded if their disease was: (1) operable; (2) regionally limited and amenable to radiotherapy; (3) treated with prior chemotherapy; and (4) complicated by acute intercurrent infection, unstable cardiac disease, or another malignant tumor within five years.

Eligible patients entered the study when assigned a regimen by the Statistical Center using a stratified randomization scheme based upon institution, performance status, and weight loss during the previous six months. The two regimens were: (1) cyclophosphamide (700 mg/m^2 intravenously every three weeks) plus CCNU (70 mg/m^2 orally every six weeks); and (2) regimen (1) plus levamisole (150 mg/m^2 orally three times a week).

Patients whose disease showed progression after 12 weeks of treatment with the initial regimen were crossed over to a new regimen as follows: those first given cyclophosphamide and CCNU then received doxorubicin hydrochloride (60 mg/m^2 intravenously every three weeks, total dose 480 mg/m^2); those first given cyclophosphamide, CCNU, and levamisole then received doxorubicin hydrochloride plus levamisole. In March 1978, the levamisole dose was reduced to 2.5 mg/kg (100 mg/m^2) orally three times a week, every other week because more toxicity was found among patients receiving levamisole.

Toxicity was reported on a six-point scale: none, mild, moderate, severe, life-threatening, and lethal. All drugs were withheld if the leukocyte count was below 4000/mm^3 or the platelet count was less than 100,000/mm^3 at the scheduled time of drug administration. These values were then monitored weekly and when the minimum counts were exceeded, treatment was resumed. Antibiotics, transfusions, dexamethasone for brain metastases, and other supportive measures were given as needed.

Partial tumor response was defined as a 50% reduction in the product of the two largest perpendicular tumor diameters in patients with measurable disease, and a significant decrease (close to complete regression) in the size of an evaluable abnormality. Complete response was defined as disappearance of all measurable and evaluable disease.

Thirty-two of the 446 randomized patients (7%) were judged ineligible or cancelled participation. Another 7% were excluded from the analysis because of missing data forms. This report concerns the 381 cases that could be analyzed, of which 132 received the initial and 61 the reduced dosage of levamisole. The control regimen was given to 188 patients.

Statistical Methods

The treatments were evaluated in terms of survival, time to treatment failure, tumor response, and toxicity. Time to treatment failure was measured from randomization to objective tumor progression or death. A secondary endpoint was the correlation of survival and time to failure with the initial total lymphocyte count and skin test reaction using glycerinated Candida antigen. Initial lymphocyte counts were available for 316 (83%) of the cases. Skin tests were done in 166 (44%). The large number without skin tests was due, in part, to difficulty in obtaining glycerinated Candida antigen at the time the study was initiated.

Dosage data were analyzed to determine the effect of levamisole on the dosage and schedule of the chemotherapy. The unit of analysis was the drug dose per idealized cycle of drug administration. The formulae were written so that delays or interruptions in therapy without decrease in dosage were still recorded as a decrease in dose per cycle. The influence of treatment, duration of treatment, surface area, institution, and initial performance status on chemotherapy dosage was then studied. The data were analyzed using a multiple linear regression model in which insignificant variables are deleted in a stepdown manner.[12] Stanley has reviewed the contribution of all variables to survival in VALG studies.[26]

The analysis of survival and time to treatment failure was done using Cox's proportional hazards regression model, which takes into account important factors such as initial performance status, weight loss, cell type, prior surgery or radiotherapy, age, hepatomegaly, bone or scalene lymph node involvement, initial lymphocyte counts, and Candida skin tests.[13] "Not reported" was treated as a separate category for lymphocyte counts and skin tests because the missing data were substantial.

Analysis of tumor response and toxicity was done using a linear logistic model that also allows for the factors listed.[14]

Results

Patients receiving levamisole in the initial 150 mg/m^2 dosage had shorter survival compared with those receiving chemotherapy alone, although the differences in survival, taking the study as a whole, did not quite reach statistical significance ($P = 0.084$). The survival curves for the treatments are shown in Figure 1. These data are similar to other VALG studies using similar poor-candidate patients.[24] Survival depended on the

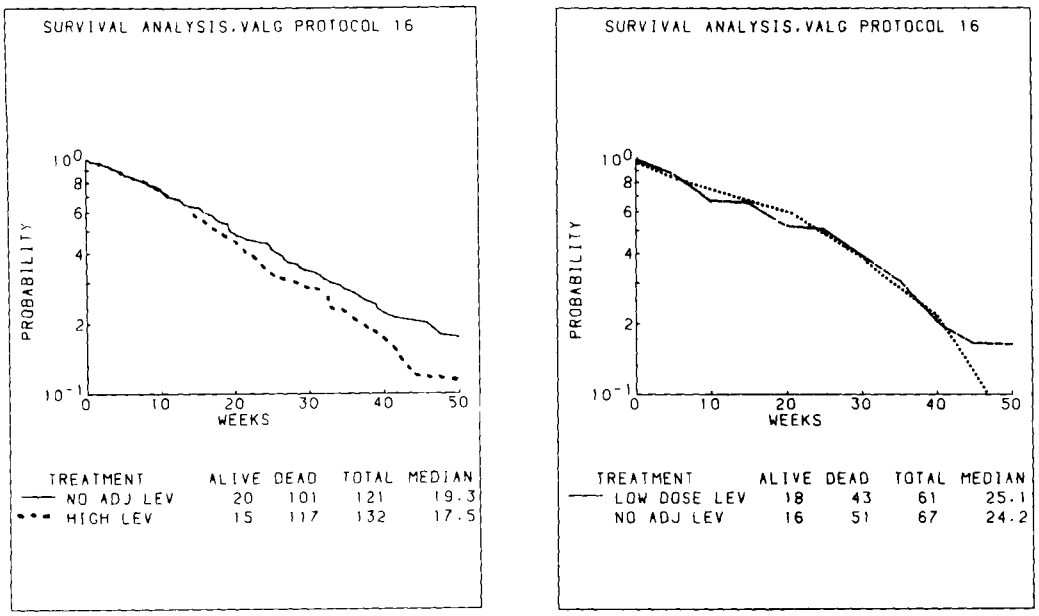

FIG. 1. Frame on left represents median survival of patients randomized to chemotherapy alone (no adj lev) and chemotherapy plus high-dose (150 mg/m^2) levamisole (high lev). Frame on right, those patients randomized from March 1978 to chemotherapy alone (no adj lev) and to chemotherapy plus low-dose (100 mg/m^2) levamisole (low-dose lev).

patient's weight loss in the six months before randomization; patients with more than 10% weight loss fared much worse if they received levamisole 150 mg/m^2. Their median survival was 12.5 weeks but that of the controls was 18.5 weeks (P = 0.006). In contrast, the survival of patients with weight loss of less than 10% given either dose of levamisole did not differ significantly from the control group. Taken individually, the important predictors of survival were initial performance status ($P < 0.001$), weight loss ($P < 0.001$), cell type ($P < 0.001$), age ($P = 0.005$), institution ($P = 0.005$), and hepatomegaly ($P = 0.006$).[15] That is, patients who survived longer had a high initial performance status, no evidence of weight loss or hepatomegaly and small-cell carcinoma. These prognostic variables have been described and discussed by VALG in a previous publication.[24]

The median time to treatment failure for the regimens is shown in Table 1. Levamisole 150 mg/m^2 and chemotherapy had an adverse effect on time to treatment failure compared with chemotherapy alone regardless of weight loss category or institution ($P = 0.022$). The median time to treatment failure for patients receiving levamisole 2.5 mg/kg (100 mg/m^2) was similar to patients in the control regimen. Most of the factors that predicted survival in the Cox Model[13] also were prognostic factors for the time to treatment failure: initial performance status ($P < 0.001$), weight loss ($P = 0.001$), hepatomegaly ($P = 0.001$), institution ($P = 0.004$), and cell type ($P = 0.074$).

TABLE 1. Median Time to Failure by Treatment

Treatment	Median time to failure (wk)
Cyclophosphamide plus CCNU	11.0
Cyclophosphamide plus CCNU plus Levamisole 150 mg/M^2	7.9*
Cyclophosphamide plus CCNU plus Levamisole 2.5 mg.kg (100 mg/M^2)	12.2

* $P = 0.022$.

The overall response rate for the study was 14% (51 of the 353 patients). Survival was highly correlated with tumor response, the median survival for responders being 40.4 weeks, that of nonresponders 17.1 weeks ($P = 0.001$).[15] Patients who received levamisole 150 mg/m^2 had a lower response rate than patients given the control regimen (13 of 132 or 10% vs. 22 of 121 or 18%, $P = 0.02$).[14] There was no difference in response rate among patients receiving cyclophosphamide, CCNU, and the reduced dose of levamisole and those given cyclophosphamide and CCNU alone ($P = 0.536$). Similarly, the frequency with which tumors of different cell type responded was not dependent upon regimen. Small-cell carcinomas responded to treatment more frequently, as would be expected. Although our chemotherapy regimen might now be considered inferior for small-cell carcinomas, for extensive disease patients no one chemotherapy regimen appears to offer a survival advantage.[25]

Seventy patients were registered to receive cross-over therapy. Four had inevaluable disease. Four responses (5.7%) were reported. The response rates for the treatments are: Period I (150 mg/m^2 levamisole): Adriamycin, 0/22; Adriamycin + levamisole, 4/24 (16.7%); for Period II (100 mg/m^2 levamisole): Adriamycin, 0/13; Adriamycin + levamisole, 0/7. The response rates by cell type are: squamous, 1/15 (6.7%), small-cell, 1/

TABLE 2. Toxicity by Regimen

	Cyclophosphamide, CCNU		Cyclophosphamide, CCNU, levamisole, 150 mg/M²		Cyclophosphamide, CCNU, levamisole, 2.5 mg/kg (100 mg/M²)	
	Severe and life-threatening (%)	Lethal (%)	Severe and life-threatening (%)	Lethal (%)	Severe and life-threatening (%)	Lethal (%)
Hematologic*	35 (19)	0	41 (31)	3 (2)	21 (34)	0
Infection	2 (1)	3 (2)	6 (5)	3 (2)†	0	0
Vomiting	3 (2)	0	7 (5)	0	2 (3)	0
Other	3 (2)	0	3 (2)	0	0	0
Total	43 (23)	3 (2)	57 (43)	6 (2)	23 (38)	0

* This category includes granulocytopenia, thrombocytopenia and anemia.

† Those with lethal hematologic toxicity (granulocytopenia) died from infection.

17 (5.9%); adenocarcinoma, 1/14 (7.1%); large-cell 1/11 (9.1%), and other types, 0.4. Survival from crossover date was similar for both arms and both periods.

Toxicity was reported on a six-point scale: (1) none, (2) mild, (3) moderate, (4) severe, (5) life-threatening, (6) lethal. Table 2 shows that most important toxicity was hematologic. Leukopenia was responsible for 27 of the 62 (44%) severe or life-threatening hematologic reactions in patients given either levamisole dosage. Three leukopenic patients died with infections in the control regimen as did three who received the larger levamisole dosage. An analysis of toxicity among patients entered during the high- and the low-dose periods showed that patients given levamisole had a greater frequency of severe or life-threatening toxicity. The evidence bordered on statistical significance ($P = 0.08$ for the larger dose and $P = 0.05$ for the lower dose). Analysis of hematologic toxicity alone gave a similar result ($P = 0.09$ for the larger dose of levamisole and $P = 0.08$ for the smaller dose). The initial absolute lymphocyte count was an important predictive factor for toxicity. Patients with low counts experienced more toxicity regardless of regimen. No apparent reason for this correlation is noted. No neurologic, cardiac, or renal toxicity was noted in the study.

The addition of levamisole did not significantly alter the amounts of chemotherapy the patients received.

The frequencies of severe or life-threatening toxicity were not significantly different after the 70 patients with progressive disease of 12 weeks were crossed over to doxorubicin or doxorubicin hydrochloride plus levamisole. In this period there were three lethal complications, two with thrombocytopenia and one with leukopenia.

In the analysis of survival and time to treatment failure, the key prognostic factors were the initial performance status, weight loss, and cell type (see above). Analyses were done to see if thse prognostic factors correlated with the initial lymphocyte counts and skin tests. Indeed, ambulatory patients with a good initial performance status did tend to have positive skin tests more often than nonambulatory patients ($P = 0.01$); however, weight loss and cell type were not related to skin-test reaction. None of the three key prognostic factors correlated with the initial lymphocyte count. Furthermore, when the important prognostic variables for survival and time to treatment failure were taken into account in the Cox Model,[13] neither initial skin test reaction nor the initial lymphocyte count had a statistically significant influence on survival regardless of the dose of levamisole.

Discussion

It is reasonable to suggest that immunotherapy in humans should follow maximum reduction of tumor burden. Tumor regressions have been seen, however, when 12 of 39 patients (31%) with advanced metastatic cancers were given Corynebacterium parvum in two independent investigations.[10,11] This success, discouraging results with conventional chemotherapy, and a report that levamisole prolonged life in patients with large tumors but still resectable lung cancer[2] prompted this Veterans Administration Lung Group (VALG) study.

Levamisole augments the impaired nonspecific markers of cellular immunity found in many lung cancer patients. These have been reviewed in detail.[2,4,6,9,16] They include decreased skin reactivity to tuberculin and other microbial antigens, depressed sensitization to dinitrochlorobenzene (DNCB), reduced numbers of circulating T-lymphocytes, lower absolute lymphocyte counts, and diminished lymphocyte reactivity to mitogen stimulation. Specific immunity against antigens on the surface of tumor cells also is bolstered by levamisole.[6] Liebler has summarized the conflicting results of studies that tried to use these tests to predict operability or survival in patients with lung cancer.[16] How levamisole produces immunoreconstitution is not clear, but

some data suggest it alters the levels of intracellular cyclic AMP and cyclic GMP in a way that augments the number and function of lymphocytes and macrophages.[17] Levamisole and thymosin appear to reconstitute the markers presently used to quantitate cellular immunity to normal. They do not stimulate them above normal. In contrast, Corynebacterium parvum and Bacillus Calmette Guerin (BCG) act as true immune stimulants, increasing cellular immunity above normal levels.[1]

Because levamisole alone has no antineoplastic effect it has been used as an adjuvant to surgery in lung cancer, malignant melanoma, and bowel cancer, to irradiation in breast cancer, and to chemotherapy in leukemia.[2,18] In controlled studies uncontested improvement in survival has been reported only among breast cancer patients.[5] Levamisole prolonged survival in a preliminary report of resectable bronchogenic carcinoma.[2] Unhappily, a larger randomized trial with 318 operable patients found that those given levamisole had poorer survival because more died with unexplained cardiorespiratory failure.[3,19]

The present VALG study is the first large trial in which levamisole was used in patients with cancer too advanced for surgery or irradiation. Analyses were done when 290 of the 381 patients (76%) had died. Patients given 150 mg/m^2 of levamisole as an adjuvant to double-drug chemotherapy for advanced lung cancer had a shorter time to treatment failure and a lower response rate than the control group. There also was evidence that these patients had worse survival than the control group given chemotherapy alone. Patients with more than 10% weight loss had substantially worse survival when given levamisole. The adverse effect of levamisole was not explained by an excess of toxic deaths. Analyses also showed that it was not caused by an alteration of the dosage of cytoreductive chemotherapy given.

The 150 mg/m^2 (3.4 mg/kg) dose of levamisole used three days each week in our study is similar to the 2.5 mg/kg given three days every other week to patients in other studies with resectable lung cancer. Slightly larger doses were used initially in our study because the beneficial effects in earlier work with surgical patients appeared confined to those who received at least 2.5 mg/kg each treatment day.[2] The dosage was also somewhat larger than the 150 mg/day given with benefit to patients with advanced breast cancer, but it was less than the 300–600 mg per day proposed for future patients with breast cancer.[5]

The side effects of levamisole, usually reversible, should not be minimized. Gastrointestinal upset, lethargy, weakness, and debilitation caused by levamisole may be under-reported when mild to moderate. Parkinson and co-workers found these side effects severe enough to stop treatment in one-fifth of the patients given 2.5 mg/kg for two days each week.[20] In this study there was some evidence that patients receiving adjuvant levamisole in either dosage had a greater frequency of severe or life-threatening toxicity. Hematologic toxicity caused us to reduce the initial 150 mg/m^2 dosage. Leukopenia, the most common limiting toxicity, was encountered by other investigators.[21,22] It has been ascribed to levamisole-dependent leukoagglutinins. It was not practical to study such antibodies in this cooperative study, and it is unknown whether they represent an adverse reaction common to any immunologic therapy. Likewise, the incidence and importance of antiheart antibody and drug-induced vasculitus found in patients treated with levamisole in earlier studies is unknown.[3,19] Although reproducible enhancement of tumor growth caused by levamisole has been reported only in allogeneic animal models,[2] Lichtenfeld saw three patients whose lung cancer appeared to progress after large doses of levamisole.[21] Our patients given levamisole had a shorter median time to treatment failure and a lower response rate than those given cyclophosphamide and CCNU alone, but no acceleration of tumor growth was recognized.

This work provides some explanation for the disparate results of studies that sought to relate tests of cellular immune competence to prognosis in lung cancer.[16] Initial performance status is the dominant prognostic factor for survival in inoperable lung cancer.[23] Extent of disease and recent weight loss rank second and third. They, too, have great strength relative to other patient characteristics. Age, tumor histology, and institution appear to be influential when considered alone, but hold little sway once correction is made for these three. Studies of immune competence have stratified patients to correct for extent of disease, but little or no allowance has been made for the main strength of performance status and weight loss. We did demonstrate a relationship between the initial performance status and the Candida skin test results. The stern influence of weight loss was not reflected in the skin tests. It is not surprising, then, that skin tests did not correlate with survival. Moreover, there was no significant correlation between the initial lymphocyte count and the cardinal predictors of survival in extensive-disease patients: performance status, weight loss, and tumor histology. Patients treated with levamisole whose negative skin tests and low lymphocyte counts suggested immunocompromise showed neither enhanced survival nor longer time to relapse. This clear failure of immunotherapy in the patients with extensive disease who would seem most likely to benefit is less disheartening if the number and importance of nonimmunologic factors that bear on their survival is appreciated.

These results support the majority experience that patients with cancer too advanced for surgery or irradiation are poor candidates for immunotherapy with levamisole.

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APPENDIX

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Pathology panel: East Orange, New Jersey, Oscar Auerbach, MD and Charles Carrington, MD; and West Haven, Connecticut, Raymond Yesner, MD.

Statisticians: William Mietlowski, PhD, Marvin Zelen, PhD, and Ken Stanley, PhD, Frontier Science and Technology Research Foundation, Amherst, New York. Typing and editorial assistance; Harriet Jacobs, VAMC, East Orange, N. J.