Levamisole in Primary Breast Cancer

A Controlled Study in Conjunction with L-Phenylalanine Mustard

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Between September 1976 and May 1980, 135 patients with operable breast cancer and positive axillary nodes received l-phenylalanine mustard, adjunct to surgery, 0.15 mg/kg for five days, six weekly, and were randomised prospectively to levamisole 150 mg for three days, two weekly, or a placebo. Treatment was continued for two years or until evidence of treatment failure, whichever was the sooner. At 4½ years, for all patients, there was no significant difference between the two groups ($P = 0.09$), but in a subgroup of women ≤50 with 1–3 positive nodes, levamisole had a negative effect ($P = 0.05$). Although an analysis of the same age group, independent of the nodal status, did not reach significance, there was a trend in favor of placebo ($P = 0.08$) which was also apparent in premenopausal women ($P = 0.15$). In postmenopausal patients, however, and in those with more advanced disease with four or more positive nodes, although the results also failed to reach significance the trend in these subgroups favored levamisole. The results of this study suggest that levamisole has no place in the primary therapy of breast cancer in younger women and those with more favorable disease. The value of this agent in older patients and those with more advanced primary disease, remains unproven, but the favorable trends are in accord with a number of other studies with levamisole in metastatic breast and resectable lung cancer. Retrospective analysis confined to those women who received 75% or more of the total dose of l-phenylalanine mustard showed no evidence for a dose-responsive effect of adjuvant chemotherapy on the described pattern of results.

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LEVAMISOLE, a synthetic antihelmintic, active against most nematodes, has been widely and effectively used in veterinary science. In 1971, however, Renoux and Renoux[1] found that this agent also enhanced host defence mechanisms in that it augmented the protective effect of a brucella vaccine in mice while Verhaegen[2] showed that a three day course of levamisole could restore skin reactivity to PPD in patients with cancer. These observations stimulated intense interest, and a potential role for this agent in cancer therapy was heightened by the reports that levamisole therapy in mice could suppress the growth of injected sarcoma cells and reduce the number of lung metastases[3] and that in humans it would restore delayed hypersensitivity responses in those with anergy associated with old age and malignant disease.[4,5]

In 1975, although the mechanism of action remained unknown it was suggested that levamisole might have exciting possibilities but that further studies should be conducted as properly controlled clinical trials.[6]

In that same year the initial findings of the NSABP Trial using l-phenylalanine mustard (L-PAM), adjunct to surgery, showed an encouraging decrease in treatment failure in women with nodal positive primary breast cancer.[7]

Although the promise of this early report has not been sustained for all subgroups, in 1976, when the present trial was designed, it seemed appropriate to add L-PAM to a controlled trial of levamisole in a similar group of breast cancer patients.

Patients and Methods

Women ≤65, with operable breast cancer, T1a T2a together with some T3a tumours, with one or more positive axillary nodes, were considered eligible for inclu-

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sion in the study provided they met certain standard criteria for eligibility.[7] All patients received routine chest x-rays, a complete blood count and biochemical screen and a skeletal scintigram. In most cases the breast was removed by modified radical mastectomy with total axillary clearance but simple mastectomy with lower axillary dissection was an acceptable option.

Patient Entry and Drug Administration

One hundred and thirty-five patients were entered in the trial between September 1976 and May 1980. All patients received L-PAM, 0.15 mg/kg/day, orally for five days every six weeks and, on a randomised prospective double blind basis, levamisole 150 mg orally for three successive days each second week, or a placebo. The dosage of L-PAM was determined according to ideal weight and never exceeded 10 mg per day except for a few early patients in the trial. Treatment commenced between two and four weeks from surgery and was continued until there was evidence of treatment failure,[7] or for two years, whichever occurred first.

Standard dosage reduction criteria for hematologic side effects were employed. If Grade I toxicity occurred (leukocyte count 2.6–3.9 $\times 10^9$/L; platelets 75–99 $\times 10^9$/L) 50% of the calculated dose was given. With Grade II toxicity (leukocyte $\leq 2.5 \times 10^9$/L; platelets $< 75 \times 10^9$/L) L-PAM was discontinued. Levamisole/placebo was continued during Grade I toxicity but discontinued for Grade II.

Drug Compliance and Protocol Violations

Although 23 patients discontinued the drugs for reasons other than recurrence they have all been included in the statistical analysis. The various reasons for discontinuation are shown in Table 1. In most cases it was due to subjective toxicity, particularly to levamisole. Of 117 patients 69 received 75% or more of the total dose of L-PAM. 28 patients in this group were on levamisole and 41 on placebo. 48 patients received less than 75% of the total L-PAM dose; 29 on levamisole and 19 on placebo.

Protocol violations occurred in 14 patients (Table 2). There were two main reasons. Either commencement of trial drugs outside the four week period specified in the Protocol, or the presence of metastases, either missed at initial examination or found on skeletal scintigraphy.

Stratification

Patients were stratified by age; <50, ≥50; nodal status; 1–3 and ≥4 nodes positive, and menopausal status. Premenopausal patients included those women who were within 12 months of their last menstrual period. This stratification group also included those currently experiencing the menopause with the recent onset of irregular periods, hot flushes and dizzy spells. Postmenopausal patients included those women who had had a previous hysterectomy and were older than the age of 50.

TABLE 1. Adjuvant Alkeran and Levamisole/Placebo in Axillary Node Positive Breast Cancer: Discontinuation of Drugs for Reasons other than Recurrence

No.	Reason	Levamisole	Placebo
4	Levamisole toxicity	4	
4	Alkeran toxicity (1 death)	3	1
6	Surgeons request	5	1
8	Patients request	4	4
1	Death unrelated to carcinoma or therapy		1
23	Total	16	7

Patient Characteristics

Table 3 illustrates the distribution of 13 different patient characteristics between the levamisole and placebo groups. Statistical analysis showed them to be strictly comparable and this also applied for the subgroups stratified by the extent of nodal involvement.

Pathologic Examination

Although a number of pathologists contributed to this study the assessment of tumour grading was restricted to two senior staff members with a good degree of compliance. For the whole group of patients the average number of axillary nodes examined was 9.3.[1–23] In only 11 patients were <6 nodes examined.

Statistical Methods

The actuarial life table method has been used to estimate probability of remaining disease-free.[8] In Table 4 this is given at specified time intervals. The statistical significance of differences observed in exact failure times between levamisole and placebo groups has been assessed by the Wilcoxon Test as modified by Gehan[9] and by the logrank test.

TABLE 2. Protocol Violations

4	Commenced trial drugs 11–18 weeks after diagnosis.
3	Metastases at diagnosis.
2	Oophorectomy for gynaecological reasons while receiving trial drugs.
1	Withdrawn from trial by surgeon.
1	Carcinoma of the endometrium diagnosed at the same time as breast carcinoma.
2	Never commenced trial drugs.
14	Total

TABLE 3. Patient Characteristics: All Patients

	Levamisole		Placebo		Significance
	No.	%	No.	%	
Patients randomised	63		72		NS
Protocol violations	6		8		
Mean age (Range)	51.5 (29–65)*		50.5 (31–65)*		NS
≥50	32		38		NS
<50	25		26		NS
Premenopausal	22	39	27	42	NS
Intramenopausal	6	10	7	11	NS
Postmenopausal	29	51	30	47	NS
Mean possible time on study (Maximum = 4 yrs 6 mths)	3 y 1 m		2 y 8 m		
Mean commencement alkeran dose	9.3 mg		9.1 mg		
<4 involved nodes	35†	66	38	77	NS
≥4 involved nodes	18	34	11	24	NS
Grade 1 and 2	19†	68	23	74	NS
Grade 3	9	32	8	26	NS
Mean time from presentation of signs & symptoms to commencement of chemotherapy	6 m		3.4 m		
Stage					
T1	7		9		NS
T2	39		38		NS
T3	11		16 (1 unknown)		NS
Histologic features					
Infiltrating duct	52		63		NS
Infiltrating lobular	3		1		NS
Oestrogen receptors:					
+ve (≥9)	17†	59	16	50	NS
−ve (<9)	10	41	17	50	NS

* Numbers do not include women who are protocol violations.
† Values not obtained for all women on the study.
y: year; m: month.

Results

The results for all patients and for subgroups stratified by age, menopausal status, and nodal status, are shown in Table 4.

For all patients the percentage probability of remaining disease-free shows no difference between the two groups (Fig. 1). For women <50 and for the closely similar group of those who are pre and intra menopausal, the results are also not significant ($P = 0.09$; $P = 0.2$) but the trend in both cases favors placebo. In women <50 for example 76% of the placebo group were disease-free at 48 months compared to 49% on levamisole. Comparable figures for pre and intra menopausal women were 75% and 55%.

The extent of axillary node involvement has considerable prognostic significance. Patients with 1–3 nodes involved with tumor have a considerable survival advantage compared to those with four or more positive nodes.

In this trial, analysis of such subgroups shows no significant difference between patients on levamisole compared to those on placebo, but in those with less aggressive disease, where only 1–3 nodes are involved, the trend favors placebo, whereas in more advanced disease the trend favors levamisole.

Figure 2 shows the probability of remaining disease free in the subgroup of women <50 with 1–3 nodes. There were 18 patients in each treatment arm and at four years the difference between the two groups in favor of placebo is significant ($P = 0.04$–0.05 Wilcoxon; Logrank $0.01 < P < 0.05$). When the analysis is done by menopausal status rather than age, however, although the P value in favor of placebo is significant by Wilcoxon ($P = 0.04$) for pre and intra menopausal women with 1–3 nodes, it is not significant by logrank ($0.05 < P < 0.1$).

TABLE 4. Life Table Summaries of Percentage Probability Disease-Free Postmastectomy

		Patients followed	Months postmastectomy 6	12	18	24	30	36	42	S level
All patients	L	57	98	80	74	66	61	58	55	0.9
	Pl	64	94	86	75	64	64	58	58	
<50 yrs	L	25	96	76	68	55	55	49	49	0.09
	Pl	26	100	96	83	76	76	76	76	
≥50 yrs	L	32	100	84	81	77	68	68	61	0.2
	Pl	38	89	78	70	58	58	48	48	
Pre & intra-menopausal	L	28	96	75	71	60	60	55	55	0.2
	Pl	34	97	94	80	75	75	75	75	
Postmeno-pausal	L	29	100	86	78	73	62	62	53	0.2
	Pl	30	90	76	69	54	54	43	43	
<50 yrs 1–3 nodes +	L	18	100	78	66	54	54	54	54	0.05
	Pl	18	100	100	94	84	84	84	84	
≥50 yrs 1–3 nodes +	L	17	100	88	88	80	71	71	59	0.6
	Pl	20	95	85	75	64	64	64	64	
≥50 yrs ≥ nodes +	L	13	100	85	77	77	64	64	64	0.2
	Pl	7	69	69	69	46	46	23	23	
<50 yrs ≥4 nodes +	L	5	80	80	80	80	80	53	53	0.5
	Pl	4	100	75	50	50	50	50	50	
1–3 nodes +	L	35	100	82	76	65	61	61	55	0.3
	Pl	38	97	92	83	73	73	73	73	
≥4 nodes +	L	18	94	83	78	78	70	59	59	0.136
	Pl	11	81	71	59	42	42	21	21	
Oestrogen receptor +	L	17	100	82	76	76	69	69	49	0.5
	Pl	16	93	93	87	87	87	67	67	
Oestrogen receptor −ve	L	10	100	90	90	80	80	80	80	0.4
	Pl	17	100	88	70	58	58	58	58	

* S: Significance; L: Levamisole; Pl: placebo; +: Positive; −ve: Negative.

A significant difference between the levamisole and placebo treatment arms was not apparent in any of the other subgroups but in contrast to the results in younger women with 1–3 nodes the trends in older women with more advanced disease consistently favored levamisole.

Three further analyses were carried out excluding those patients who received less than 75% of the total dose of L-PAM. Forty-eight patients were in this category leaving 69 for analysis, 28 of whom were on levamisole and 41 on placebo. For all such patients, and for the subgroup ≥50 (16 levamisole; 26 placebo) this method of analysis had no significant influence on the results. For women <50, analysis confined to 24 patients receiving 75% or more of the dose of L-PAM not only confirmed the negative effect of levamisole in this age group but showed that the difference was now significant ($P = 0.03$).

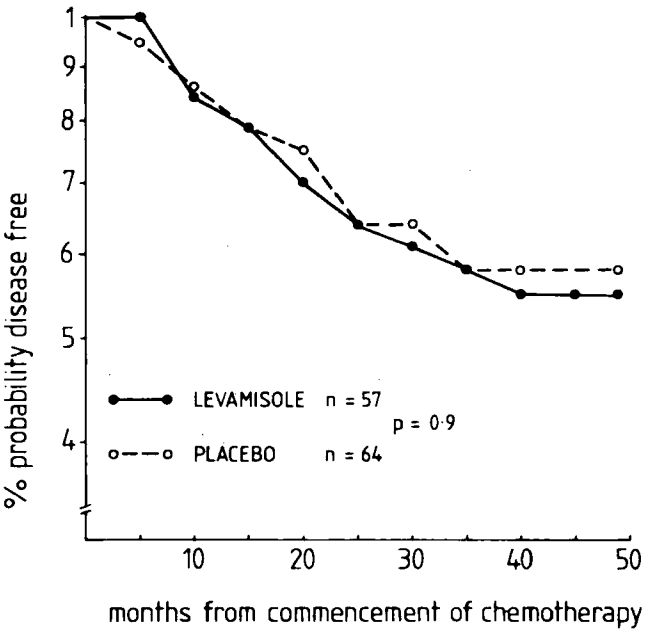

FIG. 1. Actuarial analysis of recurrence in axillary node positive breast cancer. All patients.

Hematological Toxicity

Leukocyte Cells

The effect of L-PAM on the leukocyte count, with and without levamisole, is shown in Table 5. Excluding 12 protocol violations, the analysis was carried out on 117 patients over a 3½ year period.

The data confirms that the addition of levamisole has no effect on the frequency of Grade I toxicity. Grade II toxicity is uncommon, but all five patients were randomised to levamisole. Two of this group continued in the trial as the white count returned to normal but two other patients were withdrawn at their surgeons request. One patient died from the sequelae of overwhelming oropharyngeal sepsis despite appropriate withdrawal of therapy. Although prescribed a prophylactic broad spectrum antibiotic at a leukocyte count of 1.6×10^9/L she failed to comply and was admitted to hospital 48 hours later with severe pharyngeal sepsis which progressed to acute respiratory failure and cardiac arrest.

In 28% of the patients Grade I toxicity developed during the first four courses of therapy. The frequency increased to 45% between courses five and eight and then remained relatively stable until completion of treatment.

Platelets

Table 6 shows parallel data for the effect of L-PAM and levamisole on the platelet count. The frequency of Grade I toxicity is well below the level of effect on the leukocyte but thrombocytopenia has occurred more frequently in the placebo group. For Grade II toxicity, however, there is no difference between levamisole and placebo treated patients.

Subjective Toxicity

In June 1978 a questionnaire listing a number of possible side effects was completed by 66 women. Results are shown in Table 7. Other symptoms occurring more frequently in the levamisole group were skin rashes, diarrhoea, 'bone pain', swollen fingers and dizziness. Twelve women (nine levamisole, three placebo) discontinued adjuvant therapy for subjective reasons.

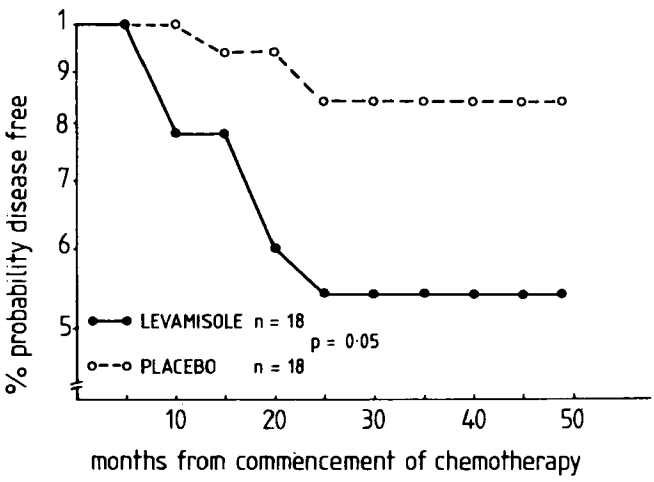

FIG. 2. Actuarial analysis of recurrence in axillary node positive breast cancer. Subgroup of women <50 years with four axillary nodes involved with tumor.

TABLE 5. Hematologic Toxicity

	Total		Placebo		Levamisole	
	No.	%	No.	%	No.	%
Leukocyte count						
Grade I ≥2.5; <4 × 10^9/L	72	62	36	50	36	50
Grade II <2.5 × 10^9/L	5	4	nil	—	5	100

TABLE 6. Hematologic Toxicity

	Total		Placebo		Levamisole	
Platelets	No.	%	No.	%	No.	%
Grade I						
≥75; <100 × 10^9/L	15	13	10	67	5	33
Grade II						
<75 × 10^9/L	10	9	5	50	5	50

Discussion

The precise mechanism of action of levamisole in its immunoregulatory role is still unresolved but there is suggestive evidence that it mimics the thymic hormone, thymopoietin[10] with the principal effect on the T-cell system and stimulation of phagocytosis.

The well recognized association of impaired immunity in advanced neoplastic disease[11,12] has long supported the hypothesis that an intact immune system is an important anticancer defence mechanism. Numerous clinical reports in the mid-1970's which attested to the bad prognostic implications of deficient immunity[13,14] strengthened the arguments for tumour immunotherapy and levamisole, a synthetic oral agent which restored immunity to normal, appeared to have advantages over the other immunostimulants such as vaccines and bacteriologic products.

Although extensive experimental data in tumor bearing animal models tended to support the value of levamisole therapy[15,16] Amery and his colleagues,[17] reviewing the role of levamisole in experimental and clinical cancer, cautioned against the extrapolation of animal cancer models to human cancer and emphasised the need for validation by controlled clinical investigation. A number of such studies have now been reported.

TABLE 7. Subjective Toxicity

	Levamisole (n = 36)*		Placebo (n = 30)*		Significance
	No.	%	No.	%	χ^2
Nausea	16	44	5	17	$P = 0.02$
Depression/irritability	14	39	4	13	$P = 0.02$
Peculiar taste in mouth	10	28	1	3	$P = 0.008$
Tiredness	15	42	4	13	$P = 0.01$

* Number of patients interviewed.

In resectable lung cancer, a depressing disease which has proved unresponsive to adjuvant chemotherapy,[18] the effect of levamisole used alone in an adjuvant setting, has proved somewhat disappointing.[19] One study, however, attributed such failure to inadequate dose levels as in one subgroup of patients, weighing less than 70 kg, levamisole prolonged both the disease-free interval and survival.[20]

Levamisole has also been intensely studied as adjunctive therapy in advanced breast cancer. In 1976 a group from Buenos Aires[21] reported significant prolongation of the median disease-free interval and survival in a levamisole treated group compared to controls. These patients were all advanced Stage III tumours rendered clinically disease-free by radiotherapy but in a number of other studies, in patients with disseminated breast cancer, the value of levamisole has been assessed as an adjuvant in combination with cyclic chemotherapy. One report[22] failed to show an advantage for levamisole but in two other well designed randomised double-blind studies levamisole in combination with triple agent chemotherapy, including Adriamycin, was associated, not only with an increase in the response rate but also with significant improvement in survival.[23,24]

The current trial has examined the effect of levamisole in a different group of breast cancer patients with operable, but nodal positive disease, all of whom received l-phenylalanine mustard in a dose schedule similar to that of the original NSABP study. This NSABP Trial has not, however, substantiated its earlier promise and at four years beneficial results are essentially confined to premenopausal women and limited improvement of the disease-free interval.[25]

The L-PAM treated control group in this present study show a similar pattern of advantage for premenopausal women but with the addition of levamisole it is this subgroup in particular which shows a disconcerting negative trend which, for women <50 with 1–3 positive nodes reaches significance ($P = 0.05$).

It is generally accepted that the involvement of four or more axillary nodes with tumor is a reliable index of wide spread micro-metastatic disease and poor prognosis. In this subgroup, however, the addition of levamisole to single agent chemotherapy with L-PAM is clearly associated with a beneficial affect on the disease-free interval. Although not statistically significant the trends are consistent for women with four or more involved axillary nodes in both age groups. The subgroup <50 is of particular interest because the addition of levamisole has negated the significant improvement in the disease-free interval enjoyed by such women in the NSABP Trial. It should be emphasised, however, that

these results, although of interest and potential importance, should be interpreted with some caution. The trial is limited to a relatively small number of patients from a single centre and the statistical significance of small variations in response can therefore be misleading.

The Danish Breast Cancer Group[26] recently reported that adjuvant treatment with levamisole is associated with an increased recurrence rate but significant differences in trial design and analysis make comparison difficult. In the Danish Trial, for example, in which levamisole was used alone, a surprisingly high percentage of patients had their treatment discontinued within six months because of side effects. At one year a statistically significant difference in the recurrence rate between levamisole treated and control patients was only achieved by including such a subgroup in the premenopausal arm and excluding such patients in the postmenopausal analysis.

The strikingly high incidence of hematological toxicity reported by the Danish group; 15% of premenopausal and 20% of postmenopausal patients, was not apparent in our own study where the addition of levamisole to L-PAM had no effect on the frequency of Grade I toxicity for either leukocyte or platelets. The reason for this difference is uncertain although the dose level of levamisole in the Danish Trial 25 mg/kg for two days each week exceeded our own protocol dose by approximately 200 mg each two weeks and this difference may be significant.

Although the statistical validity is arguable, recent retrospective analysis of the role of the dose level of chemotherapy in the Milan Study[27] has shown a clear dose-response effect suggesting that clinical benefit is dependent upon full dose administration. In the current study, however, analysis confined to those patients who received 75% or more of the dose of L-PAM served only to reinforce the negative effect of levamisole in women <50 and had no significant influence on the results in other subgroups.

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