Cisplatin, Epirubicin, and Vindesine with or without Lonidamine in the Treatment of Inoperable Nonsmall Cell Lung Carcinoma

A Multicenter Randomized Clinical Trial

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BACKGROUND. Lonidamine (LND) is an indazol-carboxylic acid derivative that selectively inhibits the energy metabolism of neoplastic cells, and increases the permeability of cell membranes. In vitro studies have demonstrated that LND can potentiate the oncolytic activity of cytotoxic drugs and is able to reverse the acquired multidrug resistance of neoplastic cells. Some clinical trials have suggested a synergism of LND with alkylating agents, cisplatin, and anthracyclines in various solid tumors.

METHODS. From June 1990 to June 1993, 158 previously untreated patients with Stage IIIB and IV nonsmall cell lung cancer (NSCLC) were enrolled into a multicentric randomized trial to evaluate the addition of LND to a cisplatin-epirubicin-vindesine regimen. Eighty patients in the control arm (A) received cisplatin, 60 mg/m^2 intravenously (i.v.); epirubicin, 60 mg/m^2 i.v.; and vindesine, 3 mg/m^2 i.v. (PEV), on Day 1 every 4 weeks, whereas 78 patients in the experimental arm (B) received the same regimen with the addition of LND from 75 mg orally three times on Day 1 to 150 mg orally three times on Day 7+ until tumor progression occurred.

RESULTS. The experimental treatment achieved a significantly higher proportion of major responses in comparison with the control regimen (43% vs. 24%; $P = 0.02$). The addition of LND apparently potentiated the activity of this cytotoxic treatment, particularly in patients with metastatic disease (overall response rate, 39% vs. 17%). The median time to progression (5 vs. 8 months; $P = 0.0007$) and the median survival time (7.6 vs. 11 months; $P = 0.0013$) were also statistically improved in Arm B. The acute toxicity of the 2 treatments was low: only 6% of patients in Arm A and 4% of patients in Arm B had to withdraw from treatment due to Grade 4 World Health Organization toxicity. The main additional side effects related to the administration of LND were epigastralgia, myalgia, asthenia, and orchialgia. However, these symptoms were mild and controlled by the concomitant administration of low doses of steroids.

CONCLUSIONS. The mild acute toxicity of the PEV regimen and the acceptable and nonoverlapping additional side effects of LND render our experimental therapy worthy of consideration for the management of NSCLC patients with poor performance status or low tolerance to more aggressive therapeutic approaches. ***Cancer* 1996; 78:63–9.** © *1996 American Cancer Society.*

KEYWORDS: nonsmall cell lung carcinoma, lonidamine, cisplatin-epirubicin-vindesine regimen, toxicity.

Lung cancer represents the leading cause of cancer deaths in men and women in Western countries.[1,2] At present, the major contribution of histologic classification is the separation of small cell lung cancer (SCLC) from the other types (squamous, large cell, and adeno-

carcinoma) commonly termed nonsmall cell lung cancer (NSCLC). NSCLC accounts for about 75–80% of all lung cancers and can be surgically resected in only 30–40% of patients with limited disease.[3,4] The remaining patients, with locally advanced or metastatic disease (Stages IIIB and IV), are considered unresectable. For these patients, the role of chemotherapy has not yet been well defined and it is still in debate, especially considering the low survival rates obtained at 5 years, ranging from 10– to 15%.[3,5–8] Among the more than 50 cytotoxic agents fully evaluated in Phase II single agent trials, only a few (cisplatin, mitomycin C, ifosfamide, Vinca alkaloid derivatives, and high dose epirubicin) are able to induce objective response rates of about 15–20%.[9] Combination regimens containing cisplatin in association with vinka alkaloids or etoposide, with or without a third drug such as mitomycin C, yielded objective responses ranging from 25–50%.[10–13] Recently, Souquet et al.[14] have reviewed 7 randomized clinical trials performed in 700 patients with Stage IIIB and IV NSCLC comparing combination chemotherapies (4 of which included cisplatin) versus best supportive therapy. From this meta-analysis, a slight survival advantage during the first 6 months of treatment was found in patients treated with chemotherapy. However, the quality of life is not always fully evaluated in these patients.[15]

Lonidamine (LND) is an indazol-3-carboxylic acid derivative that has been found to interfere selectively with the energy metabolism of neoplastic cells as it inhibits mitochondrial hexokinase, which is normally absent in differentiated cells.[16] Furthermore, it can modify the lipid structure of cell membranes, increasing their permeability.[16–18] In preclinical in vitro and in vivo studies, LND increased the killing of cells induced by radiation, hyperthermia, and several antineoplastic drugs, such as cyclophosphamide, melphalan, carmustine, teniposide, mitomycin C, cisplatin, doxorubicin, and epirubicin.[19–28]

LND can be orally administered to humans, is rapidly absorbed by the gastrointestinal tract, and its plasma level has a half-life of about 12 hours. It is manufactured as 150-mg tablets. The specific side effects of LND are asthenia, myalgia, epigastralgia, orchialgia in men, conjunctivitis, and photophobia, which are usually mild and disappear after discontinuation of the drug.[29] It does not produce myelotoxicity, cardiotoxicity, or nephrotoxicity and thus has no overlapping toxicity with other cytotoxic agents.[21,29–30] Based on the above findings, we decided to evaluate the potentiating effect of LND on a combination of cisplatin, epirubicin, and vindesine that showed promising results in a previous Phase II trial conducted by our group.[31]

MATERIALS AND METHODS

From June 1990 to June 1993, a series of 158 consecutive patients were enrolled in a multicentric randomized study performed in 6 medical oncology or pneumology departments in the same geographic area of southern Italy. Baseline eligibility criteria included a histologically or cytologically proven diagnosis of NSCLC (with the exclusion of part oat cell mixed histology)[32] of Stage IIIB or IV, according to the TNM classification;[33] bidimensionally measurable indicator lesions not previously treated with chemotherapy; age $\leq$ 75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2; life expectancy $\leq$ 3 months; hemoglobin level of $\geq$ 11 g/dL, leukocyte count of $\geq$ 4000/mm^3, platelet count of $\geq$ 100,000/mm^3; and normal liver and renal function tests. A history of prior malignant neoplasm, recent myocardial infarction, or the presence of severe cardiac arrhythmia, serious concomitant medical illness, or brain metastases were considered exclusion criteria. Patients who had received previous surgical or radiation treatment were included in the study provided that the recurrent disease was pathologically documented and at least 4 weeks had elapsed since previous treatment was completed. All patients gave their informed consent to participate in this trial, which was approved by the Ethical Committee for Biomedical Research of the National Tumor Institute of Naples.

Patients were stratified for participating center, stage of disease (IIIB vs. IV), and PS (0–1 vs. 2), and randomly allocated to receive either cisplatin, 60 mg/m^2 intravenously (i.v.), epirubicin, 60 mg/m^2 i.v.; and vindesine, 3 mg/m^2 i.v. (PEV) on Day 1 every 28 days for a maximum of 6 courses (PEV – Arm A), or the same regimen as above plus LND orally 3 times a day at a total dose of 225 mg (75 mg + 75 mg + 75 mg) on Days 1 and 2; 300 mg (150 mg + 75 mg + 75 mg) on Days 3 and 4; 375 mg (150 mg + 150 mg + 75 mg) on Days 5 and 6; and 450 mg (150 mg + 150 mg + 150 mg) from Day 7 onward (PEV + LND – Arm B). Prehydration with 2 liters of saline solution to induce forced diuresis was administered in all patients, and the prophylactic antiemetic treatment was the same in both treatment arms. Low doses of steroids were administered to patients reporting myalgia or testicular pain possibly related to LND administration. Dose reductions or treatment delays were made on the basis of evaluated toxicities (according to the World Health Organization (WHO) scoring system)[34] before each chemotherapy course. In cases of incomplete bone marrow recovery, dosages of drugs were reduced as follows: 50% of the planned dose of epirubicin and vindesine, and 75% of the planned dose of cisplatin were given in the presence of a leukocyte count of 3000–3900/mm^3 or a platelet count of 75,000–

100,000/mm^3, whereas therapy was delayed for 1 week in the presence of a leukocyte count of < 3000/mm^3 or platelet count of < 75,000/mm^3. In cases of serum creatinine raised > 25% of the upper normal limit, cisplatin was reduced to 50%; for serum creatine > 30% and/or bilirubin > 2 times the upper normal limit, chemotherapy was interrupted until recovery. The daily LND administration was reduced to 75 mg three times daily if Grade 1–2 WHO toxicity occurred, whereas it was temporarily discontinued in the case of Grade 3 toxicity, in which case the planned dose was gradually resumed in 7–10 days after cessation of symptoms.

Physical examination and laboratory assessments, chest X-ray and computed tomography (CT) scans of the lung and mediastinum, fiberoptic broncoscopy, isotopic bone scan, liver ultrasonography or CT scan, and brain CT scan (if central nervous system metastasis was suspected) were performed at baseline and after 3 and 6 courses to evaluate the response to therapy, which was classified according to WHO criteria.[35] The tests were subsequently repeated every 3 months.

Patients showing no change after the third cycle of therapy or progressive disease at any time during therapy, as well as patients suffering Grade 4 toxicity, received no further chemotherapy, but only supportive care. Radiotherapy was administered when required as palliative treatment for bone metastases, but irradiated sites were excluded from response evaluation.

The BMDP package (Statistical Software, Los Angeles, CA) was used for statistical analysis.[36] The overall response rate and the activity in subsets of patients of the two arms of the trial were compared using the chi-square or Fisher's exact test, respectively. The time to progression and survival curves were generated with the Kaplan–Meier method[37] using data from all patients entered into the study, and were compared using the Mantel–Cox and Wilcoxon tests.

RESULTS

One hundred and fifty-eight eligible patients (80 patients in Arm A and 78 in Arm B) entered this study. The main characteristics of the patients are presented in Table 1. The two arms were well balanced with respect to sex, age, PS, histology, stage of disease, and previous treatment. Greater than 80% of patients in both arms had Stage IV disease and a similar number of patients had multiple metastatic sites.

In Arm A, 309 cycles were administered, with a median number of 3.5 courses per patient (range, 1–6 courses); 21 courses (7%) were reduced, whereas 49 (16%) were delayed. In Arm B, the total number of administered cycles was 392, with a median number of 5 courses per patient (range, 1–6 courses). In 16 courses (4%) a dose reduction was applied, and in 42 courses (11%) a 1-week delay was required. The average relative dose intensity for all cytotoxic drugs was 92% in Arm A and 87% in Arm B (P = not significant). The daily dose of LND for patients in Arm B ranged from 225 to 450 mg; the median length of administration was 40 weeks (range, 4–125 weeks); 67 patients (86%) received the planned dose of LND without any reduction or discontinuation.

Only 150 patients were reassessed for response because 8 patients (5 in Arm A and 3 in Arm B) had an early discontinuation of treatment due to toxicity (Table 2)

In Arm A (PEV), 2 complete and 16 partial responses were observed among the 75 evaluated patients, for an overall activity rate of 24%; 32 patients showed stable disease and 25 progressed during therapy. In Arm B (PEV + LND), 3 complete and 29 partial responses were recorded among the 75 evaluated patients, giving an overall activity rate of 42%; 26 patients were classified as having stable disease and 17 with disease progression. The difference between overall

TABLE 1
Main Characteristics of Patients Enrolled in the Two Arms of the Trial

Characteristics	Arm A (PEV)	Arm B (PEV + LND)
Eligible	80	78
Males/females	77/3	74/4
Age in years		
Median	62	62
Range	45–75	46–75
Performance status		
0–1	53	50
2	27	28
Histology		
Squamous cell carcinoma	60	63
Adenocarcinoma	16	13
Large cell carcinoma	4	2
Prior treatment		
None	76	75
Radiotherapy	2	2
Surgery	2	1
Stage of disease		
IIIB	11	8
IV	65	67
Local relapse	4	3
Metastatic sites		
Lung	14	15
Liver	11	13
Bone	11	9
Skin	8	7
Lymph nodes	7	6
Adrenal	0	1
Multiple sites	14	16

PEV: cisplatin, epirubicin, and vindesine; LND: Ionidamine.

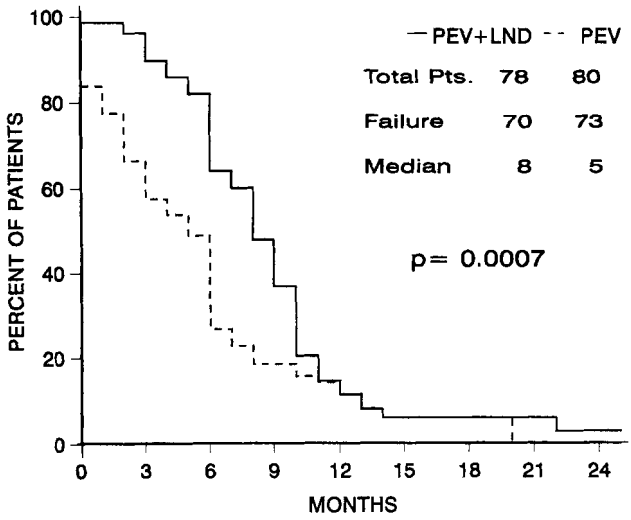

FIGURE 1. Progression free survival curves.

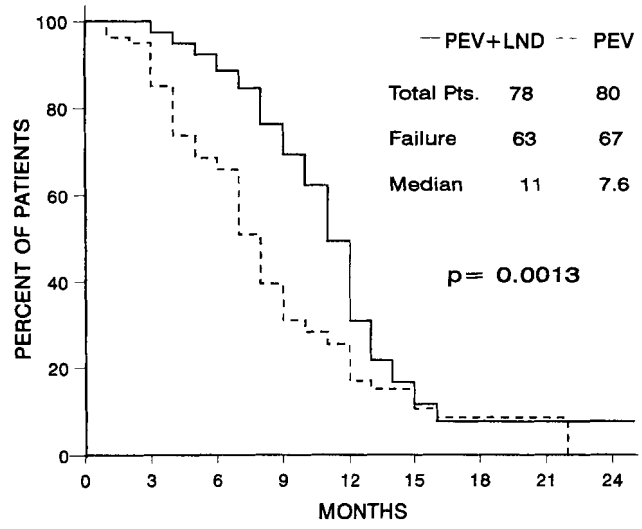

FIGURE 2. Overall survival curves.

response rates in the two arms, with regard to either the eligible or the evaluated patients, was statistically significant ($P < 0.02$ in both analyses). No difference in activity in the two arms was observed in Stage IIIB patients: five responses were observed in 11 patients in Arm A compared with six responses in eight patients in Arm B. On the contrary, a significantly higher proportion of patients with Stage IV disease showed a major response in Arm B (26 of 67 patients vs. 11 of 65 patients; $P = 0.009$), and the difference in response rates was even more evident in patients with multiple metastatic sites (8 of 16 patients vs. 2 of 14 patients; $P = 0.04$). Furthermore, it is worth mentioning that 3 responses (including 1 complete response) were reported among the 13 patients with liver metastasis in Arm B, compared with no response observed in the 11 patients with liver involvement in Arm A. The median duration of response was 8.2 months (range, 2–22 months) in Arm A, and 6.9 months (range, 2–20 months) in Arm B (P = not significant).

At the time of this analysis (June 1994), 143 of 158 patients had progressed and 130 had died. As shown in Figure 1, the median time to progression was significantly longer in patients treated with PEV + LND than in patients treated with PEV alone (8 vs. 5 months; $P = 0.0007$). Similarly, the median survival time observed in patients treated with PEV + LND was significantly longer compared with that observed in patients treated with PEV (11 vs. 7.6 months; $P = 0.0013$), and the 1-year probabilities of survival in the 2 arms were 31% and 17%, respectively (Fig. 2).

All 158 eligible patients were evaluated for toxicity. No toxic deaths were reported. As mentioned earlier, five patients discontinued chemotherapy because of Grade 4 toxicity (renal toxicity, two patients; leukopenia, neurotoxicity, and cardiotoxicity, 1 patient each) in Arm A, and three patients (renal toxicity, vomiting, and sepsis, 1 patient each) in Arm B. As reported in Table 3, acute hematologic toxicity was quite mild and similar in the two arms of the trial. Table 4 reports nonhematologic toxicity. The chemotherapy-related side effects also occurred equally in the two groups of patients. The most frequent symptoms most likely related to LND administration were gastralgia and myalgia, which affected 22% and 19% of patients, respectively, whereas 9% of males complained of testicular pain. Only 8 patients (10%) had a temporary discontinuation of LND administration due to myalgia (4 patients), orchialgia (3 patients), or epigastralgia (1 patient).

TABLE 2
Responses Reported in the Two Arms of the Trial

Responses	Arm A (PEV)	Arm B (PEV + LND)
Complete responses	2	3
Partial responses	16	29
Stable disease	32	26
Progressive disease	25	17
Early withdrawal for toxicity	5	3
Total eligible	80	78

PEV: cisplatin, epirubicin, and vindesine; LND: lonidamine.

DISCUSSION

Chemotherapy is one of the major treatment modalities for malignant tumors, and it is the only one capable of affecting disseminated disease. Unfortunately,

TABLE 3
Worst Acute Hematologic Toxicity in Treated Patients

	WHO grade			
Toxicity	1	2	3	4
Leukocytes				
Arm A (PEV)	12	5	3	1
Arm B (PEV + LND)	11	7	5	0
Hemoglobin				
Arm A (PEV)	15	8	6	0
Arm B (PEV + LND)	13	7	6	1
Platelets				
Arm A (PEV)	2	1	1	0
Arm B (PEV + LND)	2	2	2	0

WHO: World Health Organization; PEV: cisplatin, epirubicin, and vindesine; LND: lonidamine.

TABLE 4
Worst Acute Nonhematologic Toxicity Reported in Treated Patients

	WHO grade			
Toxicity	1	2	3	4
Nausea/vomiting				
Arm A (PEV)	16	12	6	0
Arm B (PEV + LND)	18	18	8	1
Mucositis				
Arm A (PEV)	7	2	1	0
Arm B (PEV + LND)	8	2	3	0
Renal				
Arm A (PEV)	4	2	0	2
Arm B (PEV + LND)	6	2	0	1
Hair loss				
Arm A (PEV)	0	26	54	0
Arm B (PEV + LND)	0	8	70	0
Cardiac				
Arm A (PEV)	0	0	0	1
Arm B (PEV + LND)	0	0	0	0
Neurologic				
Arm A (PEV)	0	0	0	1
Arm B (PEV + LND)	0	0	0	0
Gastric disturbance[a]				
Arm A (PEV)	4	4	2	1
Arm B (PEV + LND)	8	5	4	0
Myalgia[a]				
Arm A (PEV)	1	0	0	0
Arm B (PEV + LND)	8	3	4	0
Asthenia[a]				
Arm A (PEV)	3	1	0	0
Arm B (PEV + LND)	2	4	2	0
Testicular pain[a]				
Arm A (PEV)	0	0	0	0
Arm B (PEV + LND)	2	1	3	0
Headache[a]				
Arm A (PEV)	0	0	0	0
Arm B (PEV + LND)	2	1	1	0
Conjunctivitis[a]				
Arm A (PEV)	0	0	0	0
Arm B (PEV + LND)	1	1	0	0

WHO: World Health Organization; PEV: cisplatin, epirubicin, and vindesine; LND: lonidamine.
[a] Possibly related to lonidamine administration.

chemotherapy usually has only limited activity for most solid tumors, including NSCLC. Even though chemotherapy is now recommended in the majority of cases of locally advanced or disseminated NSCLC, the response that can be obtained is affected by several variables, such as disease extension, PS of patients, and their previous treatment. However, these prognostic factors cannot completely explain the poor results usually obtained in this kind of tumor; it is a common observation that the administration of an effective cytotoxic treatment does not directly translate into prolonged survival of patients, and the low fraction of proliferating cells and an acquired resistance due to genetic or phenotypic transformations should also be taken into consideration.[38–39] In the continuous search for new approaches to circumvent this problem, LND has been shown to possess interesting pharmacologic properties. It has been suggested that LND potentiates the cytotoxic activity of other drugs by means of a double mechanism, i.e., inhibition of the energy metabolism of tumor cells and modification of the permeability of their membranes. In vitro studies have demonstrated the synergystic activity of LND combined with alkylating agents or anthracyclines. Furthermore, LND was able to reverse the acquired resistance of breast or ovarian cancer cell lines to anthracyclines and cisplatin; these findings have been subsequently confirmed in clinical trials.[25,26,41–45]

Our results seem to confirm that LND administered with cisplatin,[40] epirubicin, and vindesine may also enhance their activity against cell clones with intrinsic resistance to cytotoxic treatments. In our study, we used the PEV regimen as control treatment.[31] It was moderately active and well tolerated by our patients. Although the response rate to this treatment was not as high as reported with three other drug regimens,[8–13] the median progression free and survival times in our control arm were similar to those expected in a case series of NSCLC patients with mainly metastatic disease. The administration of LND in combination with this regimen in the experimental arm significantly increased the response and 1-year survival rates, and significantly prolonged freedom from progression and median survival. These results were obtained without worsening the expected side effects of the cytotoxic regimen and with additional toxicity that was usually mild and acceptable and that did not impair the tolerance of patients for the treatment. Furthermore, the addition of LND seemed particularly useful in Stage IV patients, and especially in those patients with widespread metastatic disease. The durations of responses were superimposable with those ob-

tained with PEV alone. However, the prolonged progression free intervals of patients in Arm B would suggest that they also benefitted from an improved quality of life. Unfortunately, this trial was not designed to address this issue, and so no definite conclusions can be drawn from our results.

Gatzemeier et al.[46] first reported the results of a 3-arm randomized trial in which 184 patients with advanced (mainly Stage IV) NSCLC received either LND alone (64 patients), a mitomycin plus vindesine regimen (60 patients), or a combination of both (60 patients). Although the patients treated with chemotherapy ± LND showed a higher response rate, and had a longer median survival than patients treated with LND alone, the combined treatment did not obtain a significantly better median survival time than chemotherapy (221 vs. 194 days). However, the authors reported a higher proportion of patients alive after 12 months (32% vs. 20%).[46] These figures were very close to those obtained in our trial.

Another randomized trial[47] recently evaluated the addition of LND to the MACC (methotrexate, doxorubicin, cyclophosphamide, and lomustine) regimen in 151 patients with advanced NSCLC. In this study, the overall response rate was 8% among patients who received MACC alone, and 16% in the group treated with MACC + LND. However, progression free survival (17 vs. 20 weeks) and overall survival (27 vs. 30 weeks) were not significantly different. These results may be explained by the low activity of the MACC regimen, a combination that does not include cisplatin. Although LND was also able to exert some synergism with the cytotoxic drugs employed in this study (doubling the overall response rate), the activity in the experimental arm was too low to significantly improve the overall and long term outcome of the whole patient population.

Conversely, a recently published meta-analysis[48] on the role of chemotherapy in advanced NSCLC stressed that the survival of patients was slightly improved only in trials using cisplatin-based regimens, whereas the meta-analysis of Souquet et al.[14] reported a significant reduction of mortality for chemotherapy-treated patients only during the first 6 months of follow-up and no difference afterward.

In our trial, the improvement in freedom from progression and survival also was evident in the first 6–12 months, whereas the plotted curves were superimposable at 18–24 months of follow-up. It remains debatable whether a survival gain of a few weeks is also clinically meaningful if it is not associated with the relief of symptoms and an acceptable quality of life. However, the mild acute toxicity of the PEV regimen, and the nonoverlapping side effects attributable to LND, render the treatment easily acceptable by almost all patients. Because it has not yet been demonstrated that "more is better" in all advanced NSCLC patients, the good tolerance and low toxicity profile of the combination therapy regimen we adopted should be worth considering in the management of those patients with poor PS or other contraindications to more aggressive treatments.

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