# Cisplatin–Cyclophosphamide–Mitomycin Combination Chemotherapy With Supportive Care Versus Supportive Care Alone for Treatment of Metastatic Non–Small-Cell Lung Cancer

*Giuseppe Cartei, Francesco Cartei, Aldo Cantone, Domenico Causarano, Giuseppe Genco, Arnaldo Tobaldin, Gaetano Interlandi, Tullio Giraldi**

***Background:*** **Patients with TNM stage IV non–small-cell lung cancer have short survival times. Previous controlled studies comparing chemotherapy and supportive care for the treatment of this type of cancer have not given consistent results, have included patients with different disease stages, and have rarely reported drug dose intensity.** ***Purpose:*** **The present trial was designed to assess the safety and the effect on survival of supportive care alone versus chemotherapy with cisplatin, cyclophosphamide, and mitomycin combined with appropriate supportive care in patients with stage IV non–small-cell lung cancer.** ***Methods:*** **Patients (n = 102) with stage IV non–small-cell lung cancer were randomly assigned to one of two treatment regimens. The combined modality group (52 patients) received supportive care along with cisplatin (75 mg/m$^2$), cyclophosphamide (400 mg/m$^2$), and mitomycin (10 mg/m$^2$) given intravenously at 3-week intervals. The supportive care group (50 patients) received supportive care alone. Randomization was stratified on the basis of histology (squamous versus nonsquamous cell carcinoma), performance status (Karnofsky), and weight loss (during the 6 months preceding randomization). The two groups were well matched for age and sex. Survival analysis was performed after the last patient died.** ***Results:*** **The median number of chemotherapy cycles was 3.5 per patient. Mean weekly delivered doses of drugs were as follows: cisplatin, 22.1 mg/m$^2$; cyclophosphamide, 118 mg/m$^2$; and mitomycin, 2.9 mg/m$^2$. Toxic effects due to chemotherapy were generally mild, but peripheral neuropathy and hematologic and renal toxic effects were observed. In the supportive care group, mean survival was 6.1 months (median, 4.0 months); six patients lived at least 12 months and two lived at least 18 months. In the combined modality group, mean survival was 11.3 months (median, 8.5 months); 20 patients lived at least 12 months, 13 lived at least 18 months, and five lived at least 24 months. Difference in survival was statistically significant ($P<.0001$). Survival was directly related to initial performance status in both groups ($P<.01$) and was significantly ($P<.01$) longer for patients with squamous cell carcinoma than for those with nonsquamous cell carcinoma.** ***Conclusions:*** **The combination of supportive care and cisplatin–cyclophosphamide–mitomycin therapy offers a survival advantage over supportive care alone in patients with advanced non–small-cell lung cancer.** ***Implications:*** **Metastatic non–small-cell lung cancer, generally considered to be unresponsive or marginally responsive to chemotherapy, can be treated with chemotherapy, with an expectation of prolonging patient survival. Although the results of the present study are encouraging, clinical research should continue to be directed toward developing more effective treatments for this disease. [J Natl Cancer Inst 85:794–800, 1993]**

Non–small-cell lung cancer is a common malignancy worldwide, and patients in whom this disease has metastasized to distant sites seem to receive little clinical benefit from current chemotherapy. Unselected patients with TNM stage IV (distant metastatic) non–small-cell lung cancer have median survival times of 4 months or less (*1-3*). Recent data from Eastern Cooperative Oncology Group (ECOG) studies including 1272 ambulatory patients with advanced non–small-cell lung cancer treated with combination chemotherapy including cisplatin show that median survival in patients on these studies ranges from 18 to 26 weeks (*4-7*). Among 893 patients on two of these ECOG studies, only 19% survived more than 1 year, and only 4% survived more than 2 years (*8*). Because of results such as these, the effectiveness of combination chemotherapy in patients with this disease is frequently questioned, with most oncologists remaining dubious of any positive effect of chemotherapy on patient survival.

Studies comparing chemotherapy and supportive care for the treatment of advanced non–small-cell lung cancer have yielded equivocal results. Two early controlled trials (*9,10*) using single agents or combination chemotherapy showed no

*See "Notes" section following "References."

survival advantage for patients treated with antineoplastics. Subsequently, Cormier et al. (*11*) reported a survival advantage for patients given chemotherapy compared with those receiving only supportive care, but that trial included very few patients.

In 1984, we began the present study, a randomized trial of combination chemotherapy and supportive care versus supportive care alone for the treatment of stage IV non–small-cell lung cancer. The combination of cisplatin, cyclophosphamide, and mitomycin was chosen after our earlier phase II trial indicated good patient tolerance of this regimen (unpublished data).

While the present trial was under way, other researchers published reports on the effect of combination chemotherapy versus supportive care in patients with this disease. Rapp et al. (*12*) randomly assigned 142 patients to receive supportive care, cisplatin–vindesine therapy, or cisplatin–cyclophosphamide–doxorubicin therapy. Median survival of patients on the supportive care arm was 3.97 months, versus 5.76 months for those given cisplatin–cyclophosphamide–doxorubicin and 7.61 months for those given cisplatin–vindesine. Both chemotherapy combinations yielded a statistically significant ($P$ = .05 to .01) survival advantage (*12*). Ganz et al. (*13*), who randomly assigned 48 patients with advanced or metastatic non–small-cell lung cancer to receive supportive care or supportive care plus cisplatin and vinblastine, observed no statistically significant difference in patient survival. Cellerino et al. (*14,15*) randomly assigned 123 patients (115 fully evaluable) to receive chemotherapy with cyclophosphamide, epirubicin, and cisplatin alternating every 4 weeks with methotrexate, etoposide, and lomustine (58 patients) or supportive care (57 patients). No survival difference was observed. Woods et al. (*16*) gave 188 assessable patients either supportive care or vindesine and cisplatin. Eleven percent of the patients in the supportive care arm and 28% of those in the chemotherapy arm had distant metastases; median survival was 17 and 27 weeks for patients receiving supportive care and chemotherapy, respectively ($P$ = .33).

The present trial was designed to assess the safety and the effect on survival of supportive care versus a regimen of supportive care combined with cisplatin, cyclophosphamide, and mitomycin in patients with stage IV non–small-cell lung cancer. Cost of therapy and quality of life were not assessed in the present study, although the supportive care—with an emphasis on analgesics—was chosen with an eye toward optimum patient health and comfort.

## Patients and Methods

### Patients

The planned number of patients for the study was 100, and recruitment was stopped at 102. Patient eligibility requirements included age 75 years or less, geographic accessibility, histologically confirmed non–small-cell lung cancer without possibility of curative surgery or radiotherapy, former TNM stage III M1 disease (*17*) [equivalent to current TNM stage IV (*2*)], absence of brain metastasis, no previous chemotherapy, measurable or evaluable disease, Karnofsky performance status of 50 or more, white blood cell count greater than $4.0 \times 10^9$/L (4000/μL), platelet count greater than $100 \times 10^9$/L (100000/μL), creatinine clearance of 0.6 μmol/min (65 mg/min) or greater with 24-hour urine collection, and serum bilirubin level less than 35 μmol/L (2.0 mg/dL). Exclusion criteria included uncontrolled hypertension or angina pectoris, central nervous system stroke within the previous 3 months, arterial Burger disease, and a second primary tumor other than nonmelanoma cutaneous cancer. Informed consent was obtained according to contemporaneous Italian regulations.

In addition to physical examination, the staging of disease included bronchoscopy (if possible, with biopsy); total-abdomen examination with ultrasound; total-body 99mTc radionuclide bone scan; 99mTc radionuclide brain scan; and, beginning in 1985, abdominal, pelvic, and brain computed tomography. When necessary for diagnosis, lung or liver biopsy was performed; when bone scan indicated suspicious pathology, x-ray tomography of bone segments was performed.

Patients were then randomly assigned to receive combination chemotherapy with supportive care or supportive care alone; identical supportive care was planned for both groups. Randomization was stratified on the basis of histology (squamous versus nonsquamous cell carcinoma), Karnofsky performance status (100%-80%, 70%-50%), and weight loss (none or 10% or more over the last 6 months). Patient characteristics are listed in Table 1.

Randomization was performed immediately before treatment, using a random-number table. The randomization achieved a good balance among stratified patient characteristics (*see* Table 1). Briefly, the Karnofsky performance status was the same (both mean and median) between the two groups. Patients with squamous cell tumor were almost identically distributed (25 of 50 in the supportive care group; 24 of 52 in the combined modality group), and those with adenocarcinoma and large-cell types were also fairly evenly distributed. Weight loss of 10% or more during the six months prior to randomization was observed in 21 patients—nine in the supportive care group and 12 in the combined modality group. The study population was predominantly (71.6%) male. Ages ranged from 39 to 73 years, with a median of 56.

### Supportive Care

Briefly, supportive care consisted of analgesics, an antitussive, relief of increased intracranial pressure, palliative radiotherapy, and treatment of infections and pleural effusions. For analgesia, patients were medicated on a regular cyclic schedule, instead of on an "as needed" basis. Treatment included the following: dicoflenac sodium (50-100 mg) every 24 hours, to be escalated up to every 18 or 12 or 6 hours, with or without lorazepam (1 mg, up to 2.5 mg, every 24 hours), if required. When the 24-hour dose of dicoflenac sodium reached 150 mg, cimetidine (200-400 mg), or beginning in 1985, ranitidine hydrochloride (150-300 mg), was given at 9:00 PM on that and subsequent days. Further steps in analgesia were cyclic daily intramuscular injections of pentazocine lactate (30 mg) or morphine hydrochloride (10 mg), or cyclic daily doses of buprenorphine hydrochloride (0.3-mg intramuscular injection or 0.2-mg sublingual tablet). Neuronal anesthesia by means of an epidural catheter was available when clinically indicated. Methylprednisolone (40-125 mg/day, given intravenously) was used for analgesia at 9:00 AM and also given by the epidural route (40 mg) if required. To relieve increased intracranial pressure, dexamethasone sodium phosphate was given, together with mannitol.

Therapy for pleural effusions included fluid drainage and local instillation of tetracycline (550-825 mg). Oral codeine salts were the antitussive of choice. For infections, ampicillin–cloxacillin or trimethoprim–sulphamethoxazole was the primary therapy. When required, palliative radiotherapy was given for painful osseous metastasis or impending bone fractures, for brain metastasis that developed after randomization, or for superior vena caval obstruction.

### Chemotherapeutic Regimen

When the present trial was devised, highly toxic chemotherapeutic regimens were excluded because of concern that more than modest toxicity could exert a deleterious effect on the quality of life of all patients and the length of survival of patients who did not respond to chemotherapy. The chemotherapeutic drugs were to be given on an outpatient basis, with

**Table 1.** Characteristics of 102 patients with stage IV non–small-cell lung cancer*

| Characteristic | Total | Treatment regimen: Supportive care alone | Treatment regimen: Cisplatin, cyclophosphamide, and mitomycin plus supportive care |
|---|---|---|---|
| Patients | 102 | 50 | 52 |
| Age, y (%) | | | |
| Range | 39-73 | 39-71 | 41-73 |
| Median | 56 | 57 | 56 |
| Mean | 56.6 | 56.7 | 56.5 |
| <50 | 14 (13.7) | 6 (12) | 8 (15.4) |
| 50-65 | 80 (78.4) | 40 (80) | 40 (76.9) |
| >65 | 8 (7.8) | 4 (8) | 4 (7.6) |
| Males | 73 | 36 | 37 |
| Females | 29 | 14 | 15 |
| Male-to-female ratio | 2.52 | 2.57 | 2.47 |
| Karnofsky performance status | | | |
| 100%-90% | 15 | 7 | 8 |
| 80%-70% | 35 | 18 | 17 |
| 60%-50% | 52 | 25 | 27 |
| Median, % | 60 | 60 | 60 |
| Mean, % | 66.5 | 66.6 | 66.5 |
| Weight loss ≥10% prior to randomization | 21 | 9 | 12 |
| Histologic type | | | |
| Squamous cell carcinoma | 49 | 25 | 24 |
| Adenocarcinoma | 36 | 17 | 19 |
| Large-cell cancer | 17 | 8 | 9 |

*Unless otherwise noted, values = No. of patients. Analysis of differences between the two groups did not reveal significant variation (Fisher's exact test, two-tailed).

cisplatin (75 mg/m$^2$), mitomycin (10 mg/m$^2$), and cyclophosphamide (400 mg/m$^2$) administered at 3-week intervals; our initial phase II trial had demonstrated this treatment schedule to be well tolerated. Cisplatin in 500 mL saline was given by intravenous infusion over a 90-minute period, preceded and followed by 500 mL of saline over a 60-minute period. Prehydration and posthydration included 40 mEq of KCl; when urinary loss of magnesium was observed, magnesium sulfate was added during hydration. Furosemide (40 mg, given intravenously) preceded cisplatin by 30 minutes. Cyclophosphamide and mitomycin were given as standard bolus intravenous injections at the end of posthydration.

To reduce emesis, metoclopramide (1 mg/kg, given intravenously) preceded and followed cisplatin. Because of some episodes of extrapyramidal side effects from metoclopramide, beginning in 1985 alizapride was preferred at a 100-mg oral dose before cisplatin infusion and 175 mg/m$^2$ in 100 mL saline given intravenously 20 minutes before and after cisplatin administration (*18*). Methylprednisolone (40 mg) was also given intravenously just before mitomycin.

A maximum of six cycles of chemotherapy was planned; treatment was stopped earlier if intolerable toxic effects, patient refusal, or disease progression was encountered. Chemotherapy was delayed until recovery from toxic effects in the event of the following: white blood cell count below 3900/μL, granulocyte count below 2500/μL, platelet count below 100000/μL, or serum creatinine level above 1.4 mg/dL. No dose reductions were allowed.

## Patient Follow-up

Patients were evaluated at least once every 3 weeks in both treatment arms for the first 6 months from the beginning of treatment, or up to the 6th cycle of chemotherapy, and every month thereafter.

If a patient was unable to attend the outpatient clinic and did not require or refused hospital admission, a member of the medical staff of the trial would seek out the patient's family physician, and together they would visit the patient. No patients were lost to follow-up, and all were included in the survival analysis.

## Evaluation of Toxic Effects

Because frequent blood counts in the supportive care group were unnecessary and to avoid excessive venipunctures in patients on chemotherapy, weekly hematological tests between cycles were not part of the protocol design. Tests were performed only before each chemotherapy cycle or once every 3 weeks in supportive care subjects. Testing consisted of complete blood counts; measurement of blood or serum levels of glucose, urea nitrogen, creatinine, uric acid, sodium, potassium, calcium, lactic dehydrogenase, gammaglutamyltranspeptidase, alanine and aspartate transaminase, alkaline phosphatase, total bilirubin, total proteins, albumin, blood osmolarity (Autoanalyzer SMAC 22, Technicon Corp., Tarrytown, N.Y.; or other autoanalyzers); and standard urinalyses. Creatinine clearance on 24-hour urinary collection was performed in selected cases. Evidence of hematologic, renal, liver, and gastrointestinal toxic effects, as well as hair loss, peripheral neuropathy, and infections, was carefully recorded and graded according to the criteria of Miller et al. (*19*). Complete physical examinations were routinely performed; electrocardiograms were done only when necessary.

## Response Criteria

The patients' survival, rather than the response rate of the measurable disease, was the primary end point of the present trial. However, classic criteria for measuring tumor response were followed (*19*). Treatment volumes irradiated during supportive care were excluded from consideration in evaluation of response to chemotherapy.

## Statistical Methods

Survival was calculated from the time of randomization to the time of death, using the Kaplan–Meier method. Analysis was performed only after the last patient died and included Fisher's exact test (two-tailed), analysis of variance, and Kaplan–Meier and logrank tests to analyze survival (Systat and Sygraph) (*20-22*). No interim analysis was performed.

## Results

### Supportive Care

Palliative radiotherapy was required for six patients in the supportive care group and for 10 patients in the combined modality group.

### Chemotherapy

A total of 200 chemotherapy cycles were given, ranging from one to eight per patient, with a mean of 3.85 and a median of 3.5. Five patients died within the 1st month of treatment and received only one cycle. These patients were considered to have had disease progression. At response evaluation before the third cycle, progression was present in an additional 19 patients (36.5%), stable disease in 15 (28.8%), and a partial response in 13 (25%).

Calculation of dose intensity excluded the five patients who died before receiving the second cycle and the two patients who had more than six (i.e., eight) cycles. Consequently, 179 cycles were evaluated (from two to six per patient) over 4193 patient-days versus an ideal planned time of 3759 patient-days. The delay was mainly due to hematologic and/or renal toxic effects (*see below*). The intended weekly dose intensities for the chemotherapeutic regimen were as follows: cisplatin, 25.0 mg/m$^2$; cyclophosphamide, 133 mg/m$^2$; and mitomycin, 3.3 mg/m$^2$. The mean delivered dose intensities were 22.1, 117.9, and 2.9 mg/m$^2$ per week, respectively. The relative dose intensity (delivered dose/intended dose) was 0.88 for each drug.

### Toxic Effects

The cisplatin–cyclophosphamide–mitomycin regimen was relatively well tolerated. No deaths due to toxic effects were observed. Grade 2 nausea and vomiting was almost universal (190/200 cycles), but grade 3 vomiting requiring further antiemetic therapy was observed in only 18 cycles (9%). Three patients refused to continue therapy after the fourth cycle because of vomiting; another patient refused the second cycle but subsequently accepted two further cycles.

Peripheral neuropathy was observed in all patients who had at least three cycles of chemotherapy. After six cycles, this complication was grade 2 in six patients and grade 3 in two patients. All patients who had more than two cycles of chemotherapy experienced almost complete hair loss. Grade 2 stomatitis was present in 11 cycles, and grade 3 in three cycles. There was one episode of life-threatening sepsis; although this resolved with antibiotics, it precluded further therapy after the fourth cycle.

A grade 2 drop in hemoglobin levels was observed in 26 cycles (13%), and a grade 3 drop was observed in four cycles (2%). A grade 1 decrease in white blood cell and platelet counts caused a 1-week delay of chemotherapy in four patients. The overall delay due to hematologic toxic effects was 1 week in 32 cycles and 2 weeks in three cycles. Serum creatinine levels were above 1.5 mg/dL in four cycles and above 2.0 mg/dL in two cycles; in each case, normal levels were restored with hydration. In two patients, however, persistently elevated creatinine levels (grade 2) for at least 28 days following the fourth cycle precluded further therapy.

### Survival Analysis

Overall survival curves are shown in Fig. 1. Median survival was 4.0 months in the supportive care group and 8.5 months in the combined modality group ($P<.0001$). Survival longer than 12 months was observed in 20 patients (38.5%) in the combined modality group and six patients (12%) in the supportive care group (Table 2). Survival for both combined modality and supportive care groups was directly related to the initial performance status ($P<.01$). Median survival was 10.7 months for patients with squamous cell carcinoma versus 7.0 months for those with nonsquamous cell carcinoma (logrank test, $P<.01$). Improvement in survival due to chemotherapy was significantly ($P<.001$) maintained when patients were stratified for performance status: for patients with performance status less than 80, only 15% receiving supportive care and 56% receiving chemotherapy plus supportive care survived 6 months or longer; for patients with performance status of 80 or more, 92% receiving supportive care and 100% receiving chemotherapy plus supportive care survived 6 months or longer (Fig. 2).

## Discussion

Twenty years ago, there was no general agreement on how patients with inoperable non–small-cell lung cancer should

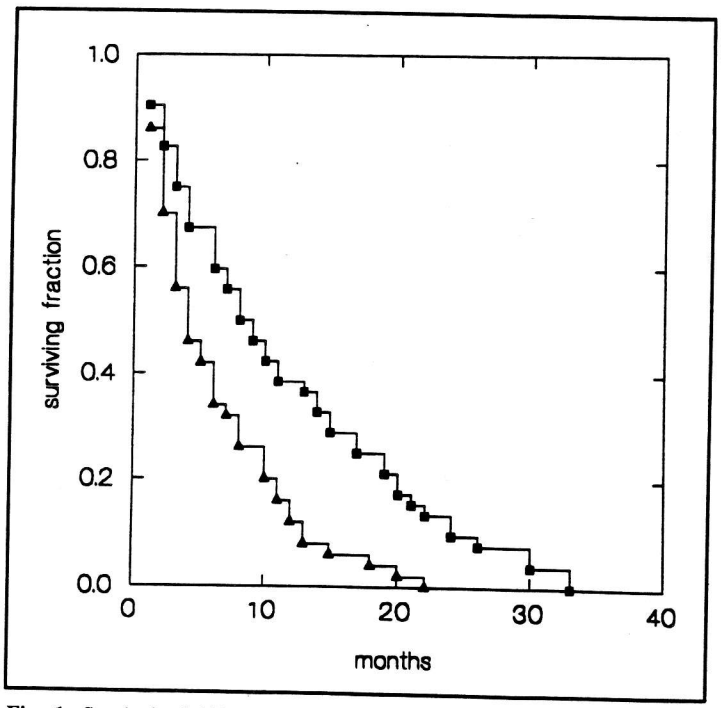


**Fig. 1.** Survival of 102 patients with stage IV non–small-cell lung cancer randomly assigned to receive supportive care (triangles) or supportive care plus cisplatin, cyclophosphamide, and mitomycin (squares). Difference in survival is statistically significant (Kaplan–Meier estimate, logrank test, $P<.0001$).

**Table 2.** Survival of patients with non–small-cell lung cancer receiving chemotherapy plus supportive care (n = 52) or supportive care alone (n = 50)

| | Survival, mo* | |
|---|---|---|
| | Supportive care group | Chemotherapy + supportive care group |
| Range | 1-22 | 1-33 |
| Median | 4.0 | 8.5 |
| Mean† | 6.12 | 11.33 |
| Survival, No. of patients (%) | | |
| ≥6 mo | 17 (34.0) | 35 (67.3) |
| ≥12 mo | 6 (12.0) | 20 (38.5) |
| ≥18 mo | 2 (4.0) | 13 (25.0) |
| ≥24 mo | 0 | 5 (9.61) |

*Kapan–Meier estimate.
†Logrank test, $P<.0001$.

be treated, or even if they should be treated at all if they were asymptomatic (*9*,*10*). Because survival was poor after treatment with either radiotherapy or chemotherapy and because the treatments themselves caused varying degrees of toxic effects, it was argued that these patients should only be treated palliatively. Durrant et al. (*9*) designed a trial in which patients with inoperable non–small-cell carcinoma of the bronchus confined to the thoracic cavity were randomly assigned to one of four treatment arms: supportive care only (with irradiation as needed if symptoms developed), chest irradiation, chemotherapy with mechlorethamine (nitrogen mustard), or irradiation and chemotherapy combined. The mean survival of the four groups ranged from 8.3 to 8.8 months, with no significant difference among groups. No pathologic diagnosis was available in 16%-25% of the patients (*9*), and some cases of small-cell cancer might have been included in that trial.

The study by Durrant et al. (*9*) opened the avenue for randomized investigations on the usefulness of therapies other than surgery in the treatment of advanced bronchial carcinoma. It also highlighted the importance of quality-of-life considerations in addition to the assessment of disease regression rates.

Subsequently, another randomized study (*10*) was conducted where no immediate treatment was compared with single- or multiple-agent chemotherapy in patients with inoperable lung carcinoma. The drugs used were procarbazine and a combination of mechlorethamine, vinblastine, procarbazine, and prednisolone. Median survival was as follows: with no immediate treatment, 220 days ($P<.05$); with procarbazine, 190 days; and with combination chemotherapy, 75 days. No difference in survival was observed among groups at 1 year (*10*).

Cormier et al. (*11*) observed a statistically better survival in patients treated with methotrexate, doxorubicin, cyclophosphamide, and lomustine. However, their study involved only 39 patients who had heterogeneous stages of disease.

Rapp et al. (*12*) observed that chemotherapy with cisplatin–vindesine or cisplatin–cyclophosphamide–doxorubicin produces a statistically greater survival, compared with supportive care alone. In the former regimen, cisplatin was given at 120 mg/m$^2$, and vindesine at 3 mg/m$^2$. In the latter regimen, doxorubicin and cyclophosphamide, at relatively low doses (40 and 400 mg/m$^2$, respectively), were added to cisplatin (40 mg/m$^2$). This study also made an analysis of drug dose intensity. The actual administered dose

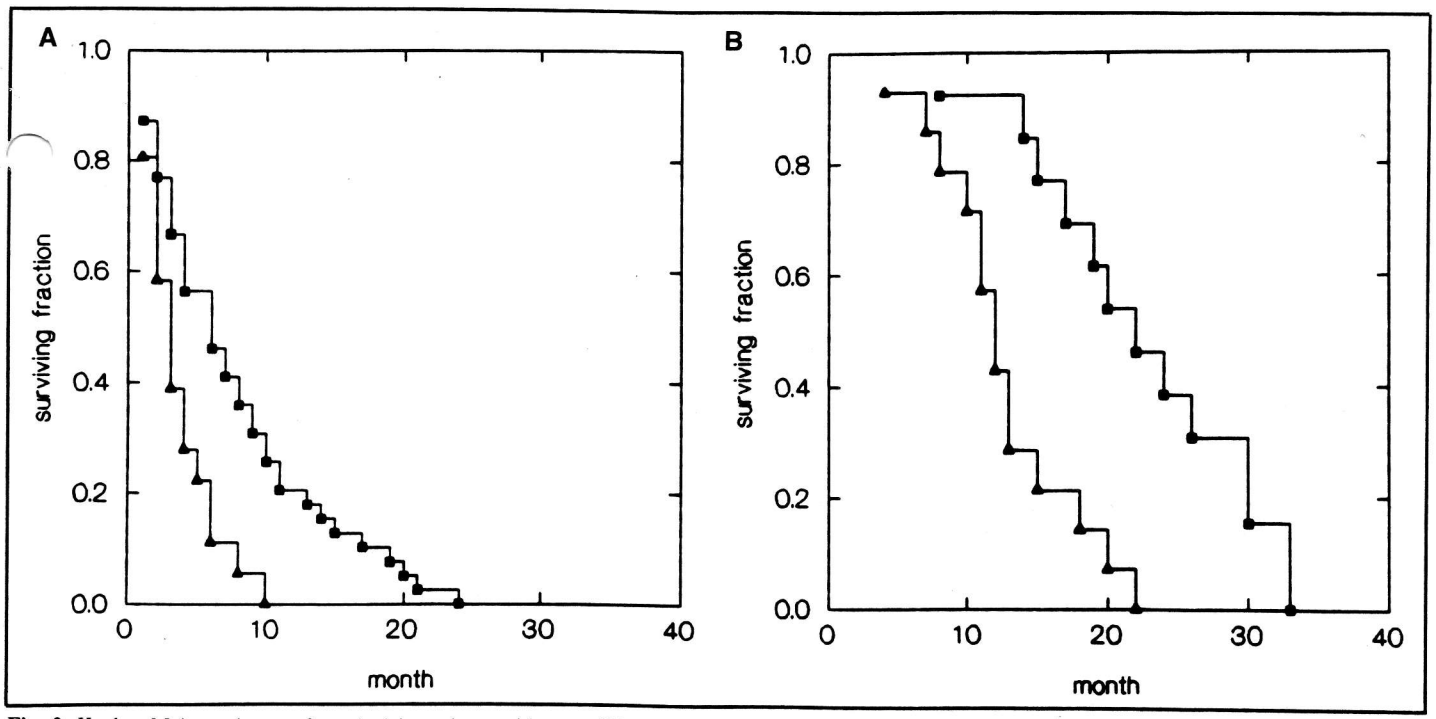


**Fig. 2.** Kaplan–Meier estimate of survival in patients with stage IV non–small-cell lung cancer grouped according to Karnofsky performance status. Patients with performance status less than 80 (A). Patients with performance status of 80 or more (B). Triangles = supportive care; squares = supportive care plus cisplatin, cyclophosphamide, and mitomycin. Differences are significant for any stratification (logrank test, $P<.001$).

of cisplatin was substantially higher in the cisplatin–vindesine arm (dose intensity, 17.4 mg/m$^2$ per week) than in the other chemotherapy arm. Patients receiving cisplatin and vindesine had a longer median survival than those receiving cisplatin, cyclophosphamide, and doxorubicin.

Quoix et al. (*23*) observed a statistical improvement in the survival of patients treated with cisplatin and vindesine, compared with supportive care alone, although there were only 43 patients in the study.

In a study involving only 48 patients, Ganz et al. (*13*) compared supportive care to combination chemotherapy with vinblastine (6 mg/m$^2$) and cisplatin (120 mg/m$^2$) every 4 weeks for two cycles and every 6 weeks thereafter. Patients on chemotherapy had a slightly longer median survival (20.4 weeks versus 13.6 weeks), although the increase was not statistically significant.

Moreover, Kaasa et al. (*24*) observed no survival benefit with cisplatin and etoposide chemotherapy compared with supportive care alone in 87 patients.

The largest of these randomized trials (188 patients), Woods et al. (*16*) observed no statistical improvement in patients with stage IIIb or IV (*2*) non–small-cell lung cancer when treated with cisplatin and vindesine compared with supportive care alone. However, patients without distant metastases (stage IIIb) treated with chemotherapy had longer survival ($P$ = .075). In contrast to the treatment policy of Rapp et al. (*12*), these authors discontinued chemotherapy in patients with stable disease.

Cellerino et al. (*14,15*) evaluated 115 patients, 46 stage III and 69 stage IV patients, using alternating chemotherapy regimens of cyclophosphamide–epirubicin–cisplatin and methotrexate–etoposide–lomustine versus supportive care. Cisplatin was planned at a dose of 10 mg/m$^2$ per week, i.e., approximately half the dose intensity of cisplatin used by Rapp et al. (*12*) or by us in the present study. Twelve (20.7%) of 58 patients experienced partial remission and 31 (53.4%) achieved stable disease in the chemotherapy group. No statistically significant difference in survival was observed in the study, although an advantage for chemotherapy was observed in some subsets of patients.

Thus, only three randomized studies, two previously published in detail (*11,12*) and one preliminary report (*23*), indicate that chemotherapy is associated with a statistically significant advantage in survival compared with supportive care alone in patients with advanced non–small-cell lung cancer. Interpretation of these data is complicated by various factors, including small sample size, inadequate chemotherapeutic doses, unbalanced distribution of patients, and loss of significant numbers of patients to follow-up.

The present study, which included a balanced and adequate number of patients, indicates that metastatic non–small-cell lung cancer, generally considered to be unresponsive or only marginally responsive to chemotherapy, can be treated with cisplatin, cyclophosphamide, and mitomycin chemotherapy, with a statistically significant though modest increase in patient survival compared with supportive care alone. A specific assessment of quality of life or cost of therapy was not performed in this study. However, chemotherapy was generally well tolerated by the patients, and only three of them refused continued therapy because of vomiting. Supportive care was given to allow an optimal quality of life, and great attention was paid to nutrition and analgesic therapy.

Although our results are encouraging, the present combination chemotherapy should not be considered standard since all patients eventually died. The search for more effective chemotherapy for this disease should continue.

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## Notes

*Affiliations of authors:* G. Cartei, Division of Medical Oncology and Cancer Center, Udine, Italy.
F. Cartei, Division and Institute of Radiology and Radiotherapy, General Hospital and University of Pisa, Italy.
A. Cantone, Division of Internal Medicine, General Hospital, Bassano del Grappa (VI), Italy.
D. Causarano, Division of Internal Medicine, General Hospital, Marostica (VI), Italy.
G. Genco, Medical Day Hospital, Geriatric Hospital, Padova, Italy.
A. Tobaldin, Division of Internal Medicine, General Hospital, Rovigo, Italy.
G. Interlandi, Surgical Division, General Hospital, San Bonifacio (VR), Italy.
T. Giraldi, Section of Pharmacology, Department of Biomedical Sciences and Technologies, University of Udine, Italy.
*Correspondence to:* Prof. G. Cartei, Divisione di Oncologia Medica e Centro di Prevenzione dei Tumori, USL7, 33100 Udine, Italy.
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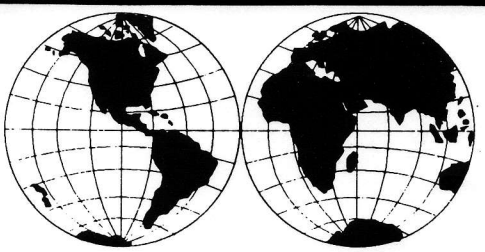

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