*CANCER BIOTHERAPY & RADIOPHARMACEUTICALS*
Volume 22, Number 1, 2007

DOI: 10.1089/cbr.2006.365

# Somatostatin, Retinoids, Melatonin, Vitamin D, Bromocriptine, and Cyclophosphamide in Chemotherapy-Pretreated Patients with Advanced Lung Adenocarcinoma and Low Performance Status

**Achille Norsa[1] and Vincenzo Martino[2]**
[1]Division of Thoracic Surgery, Ospedale Maggiore Azienda Ospedaliera, Verona, Italy
[2]Società Italiana di Bioterapia Oncologica Razionale, Bologna, Italy

*ABSTRACT*

***Background:*** *We previously reported on an improvement in survival and quality of life in chemotherapy-naïve patients with advanced non-small-cell lung cancer and low performance status (PS) treated with a combination of biotherapeutical agents and cyclophosphamide. In this study, we assessed the survival, clinical status, and toxicity of this multidrug regimen in chemotherapy-pretreated patients with advanced lung adenocarcinoma and low PS.* ***Methods:*** *Patients with stage IIIB or IV lung adenocarcinoma, who had progressed after prior standard chemotherapy, and with an Eastern Cooperative Oncology Group PS ≥2, received a daily combination of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide.* ***Results:*** *Twenty-three (23) patients were enrolled. The median age was 59 years (range, 42–75). The PS was 2 and 3 in 73.9% and 26.1% of patients, respectively. The median overall survival (intent-to-treat analysis) was 95 days (range, 19–214). The side-effects were mild, mostly consisting of diarrhea, nausea and vomiting, and drowsiness of Grade 1–2. There was an improvement in both respiratory and general symptoms, which was more evident in patients surviving more than 95 days.* ***Conclusions:*** *The combined regimen of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide is well tolerated and can improve disease-related symptoms in heavily pretreated patients with late-stage lung adenocarcinoma and poor PS.*

**Key words:** somatostatin, melatonin, vitamins, bromocriptine, cyclophosphamide, NSCLC, ECOG-PS

## INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer and is a leading cause of cancer-related death, with a 5-year survival of approximately 10%–15%.[1] The majority of NSCLC patients present with advanced-stage disease (stage IIIB or IV).[2] Currently, adenocarcinoma is the most common subtype of lung cancer, followed by squamous-cell carcinoma.[3] Among females, adenocarcinoma rates have always been higher than squamous-cell carcinoma rates in every area.[4] On the contrary, squamous-cell carcinoma rates exceeded adenocarcinoma rates among males in all areas in earlier years, but epidemiologic studies indicate that this trend is currently changing.[4,5]

***Address reprint requests to: Achille Norsa; Division of Thoracic Surgery; Ospedale Maggiore di Verona; Piazzale Stefani 1—37126 Verona, Italy; Tel.: +39-347-9346494 E-mail:*** **norsaachille@yahoo.it**

In advanced NSCLC, meta-analyses have demonstrated that platinum-based chemotherapy produced a modest, but statistically significant, survival benefit, palliation of symptoms, and improvement in the quality of life, when compared with the best supportive care.[6,7] These clinical benefits seem to be restricted to patients with a good performance status (PS): 0–1, according to the Eastern Cooperative Oncology Group (ECOG) scale.[8,9] Thus, first-line chemotherapy, especially when platinum-based, is the standard recommended treatment for patients with advanced NSCLC and a good PS. However, first-line responses are partial and short-lived. Typically, with current first-line platinum-based chemotherapy regimens, the response rate is approximately 25%, with a median survival of 7–10 months and a 1-year survival of approximately 35%.[10–12] The patients that will experience relapse or disease progression after first-line chemotherapy can be eligible for further second-line chemotherapy treatment. Recent studies using new drugs, such as docetaxel or gemcitabine, have demonstrated that second-line chemotherapy may be of value.[13,14] Also, in second-line chemotherapy trials, a PS of 0–1 was a good predictor of response.[15] Thus, for NSCLC patients who have progressive disease following chemotherapy and a PS $\geq$2, the prognosis is particularly poor; therefore, for these patients, effective, palliative, low-toxicity treatments are needed.

Recently, we reported that a combination regimen of biotherapeutical agents (somatostatin, retinoids, melatonin, vitamin D, and bromocriptine) and cyclophosphamide was active in terms of both survival and quality of life for chemotherapy-naïve patients with advanced NSCLC and low PS.[16] It has been demonstrated that somatostatin and its analogs, retinoids, and vitamin D compounds, are capable of inhibiting growth and inducing apoptosis and differentiation in a wide variety of malignant cell types, including lung cancer.[17–19] Somatostatin and bromocriptine inhibit, respectively, the release of growth hormone (GH) and prolactin (PRL), two hormones involved in neoplastic growth.[20] Finally, melatonin is endowed with antiproliferative activity and immunostimolant and antioxidant properties.[21,22] Moreover, these biotherapeutical agents can potentiate the antitumor effects of many cytotoxic agents and inhibit the motility and invasiveness of tumor cells, as well as the formation of new blood vessels.[23–26]

The aim of this study was to evaluate the effects of a combined regimen based on somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide on survival, clinical status, and toxicity in patients with advanced adenocarcinoma of the lung and low PS, and who had previously been treated with standard chemotherapy regimens.

## MATERIALS AND METHODS

### Patient Selection

Eligibility criteria included pathologically confirmed adenocarcinoma of the lung, stage IIIB (with pleural effusion) or IV disease, age $\geq$18 years, and an ECOG performance status $\geq$2. Patients with brain metastases could be enrolled only if they were neurologically asymptomatic. All patients had to have experienced disease progression during or after first-line standard systemic chemotherapy. Prior radiotherapy was allowed, provided that it had been completed more than 2 weeks before enrollment. Patients who were pregnant, had other primary tumors, had serious peripheral neuropathy, or other significant medical conditions (e.g., uncontrolled diabetes) were not eligible. All patients signed a written, informed consent before the beginning of the treatment.

### Treatment

The treatment schedule consisted of a combination of somatostatin, retinoids, melatonin, vitamin D, from bromocriptine, and cyclophosphamide. Somatostatin was administered subcutaneously at a dose ranging from 1 to 3 mg/day every 8–10 hours using a syringe pump. The administration started at least 3 hours after dinner. Retinoids (ATRA, vitamin A palmitate, and beta-carotene at doses of 5 mg, 5000 Ul, and 20 mg/day, respectively, in 5 mL of vitamin E) were given orally, at 8 AM, before breakfast. Melatonin was administered orally at a dose of 20 mg/day, 2 times a day (10 mg at 2 PM and at 9 PM). Vitamin D (dihydrotachysterol) was given orally at a dose of 0.3 mg/day, at 8 AM before breakfast. Bromocriptine was administered orally at a dose of 2.5 mg/day, 2 times a day (1.25 mg at 2 PM and at 9 PM). Finally, cyclophosphamide was given orally every day at the dose of 50 mg (at 2 PM) or 100 mg (at 2 PM and at 9 PM), on the basis of the patient blood-cell count. Patients re-

ceived this combined regimen every day without interruption, for an indefinite period, unless unacceptable toxicity occurred.

### Patient Evaluation

Before the initiation of chemotherapy, patients were evaluated as follows: medical history, physical examination, evaluation of PS, complete blood-cell count with differential and platelet count, blood biochemistry, liver and kidney function tests, electrocardiogram, chest X-ray, and computed tomography scans of the chest, abdomen, and brain. Other imaging modalities, such as bone scintigraphy and magnetic resonance imaging, were performed only if clinically indicated. All baseline evaluations had to be performed before therapy initiation. Complete and differential blood counts and biochemical analysis was performed every 2 weeks to assess hematologic parameters and levels of alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, serum creatinine, electrolytes, magnesium, calcium, and protein. A regular follow-up was performed every 1-2 months, according to the clinical status of the patients. Overall survival was the primary endpoint of this phase II study. Survival was defined as the time elapsed from the starting date of the treatment to the date of death or last follow-up. Secondary endpoints included the assessment of quality of life and toxicity. Symptom improvement, including cough, dyspnea, and pain, were evaluated by medical history review at doctor–patient consultations. Toxicity was assessed in all patients according to World Health Organization (WHO) clinical criteria. Survival and clinical efficacy were both determined according to the intent-to-treat (ITT) principle. Descriptive statistics were reported as proportions and medians. Survival curves were calculated by the Kaplan-Meier method.

## RESULTS

Twenty-three (23) consecutive eligible patients (16 females and 7 males) were enrolled in the study, and the patient characteristics are shown in Table 1. The median age was 59 years (range, 42–75). Seventeen (17) patients (73.9%) had an ECOG PS of 2, and 6 patients (26.1%) had an ECOG PS of 3. Tumor node metastasis (TNM)

**Table 1.** Patient Characteristics

| *Characteristics* | *No. of patients* | *Percent* |
|---|---|---|
| Total patients | 23 | 100 |
| Gender | | |
| Male | 16 | 69.6 |
| Female | 7 | 30.4 |
| Performance status (ECOG) | | |
| 2 | 17 | 73.9 |
| 3 | 6 | 26.1 |
| TNM staging | | |
| IIIB | 2 | 8.7 |
| IV | 21 | 91.3 |
| Metastatic sites[a] | | |
| Bone | 10 | 43.5 |
| Brain | 7 | 30.4 |
| Lymph nodes | 4 | 17.4 |
| Controlateral lung | 3 | 13.0 |
| Liver | 3 | 13.0 |
| Other | 4 | 17.4 |
| Age, years | | |
| Median | 59 | |
| Range | (42–75) | |

ECOG, Eastern Cooperative Oncology Group; TNM, tumor node metastasis.
[a]Numbers reflect multiple sites for some patients.

stages were as follows: stage IIIB, 2 patients (8.7%), and stage IV, 21 patients (91.3 %). The most common sites of metastases were in the bone, brain, and lymph nodes.

All patients were evaluated for response. According to ITT analysis, the median overall survival was 95 days (range, 19–214) (Fig. 1).

An improvement in both respiratory and general symptoms was observed in approximately 50% of patients. The clinical benefits were observed especially in those patients with more than 95 days of survival. In the majority of these patients, cough and dyspnea as well as chest and general pain were improved. Other symptoms, such as hemoptysis, fatigue, and insomnia, were also ameliorated in most of these patients. On the contrary, in the patients with less than 95 days of survival, the clinical benefits were only modest or were absent.

All patients were evaluated for toxicity. No treatment-related deaths were observed. There was a very good tolerance of the combined regimen in patients with a PS of both 2 and 3. Moreover, most patients carried on with the treatment at home. The main episodes of toxicity related to the administered biotherapeutic regimen were referable to gastrointestinal symptoms (Table 2).

Thirty percent (30%) of the patients experienced Grade 1 (4 cases) or 2 (3 cases) diarrhea. Twenty-six percent (26%) of patients experienced Grade 1 (3 cases) or 2 (3 cases) nausea or vomiting. Twenty-two percent (22%) of patients (5 cases) had Grade 1 drowsiness. These mild side-effects did not require the interruption of treatment, but only a reduction of the dose of somatostatin employed and of the daily schedule of melatonin administration (i.e., the 20-mg/day dose was subdivided into 3 instead of 2 administrations).

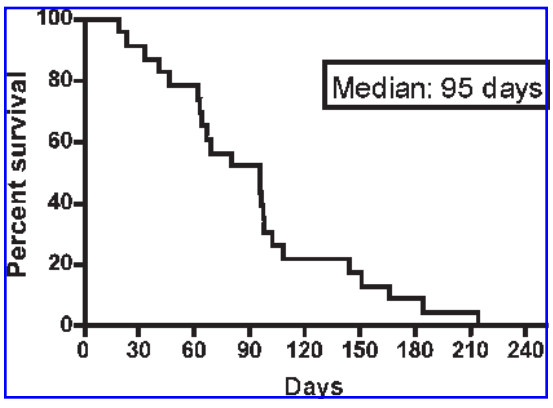


**Figure 1.** Overall survival curve.

**Table 2.** Toxicity According to WHO Criteria

| | *No. of patients (%)* | |
|---|---|---|
| *Adverse event* | *Grade 1 (%)* | *Grade 2 (%)* |
| Gastrointestinal | | |
| Nausea/vomiting | 3 (13.0) | 3 (13.0) |
| Diarrhea | 4 (17.4) | 3 (13.0) |
| Neurological | | |
| Drowsiness | 5 (21.7) | — |

WHO, World Health Organization.

## DISCUSSION

This paper reports that chemotherapy-pretreated patients, with advanced adenocarcinoma of the lung and a poor PS, treated with a combination of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide, had a median overall survival of 95 days, with very modest toxic effects. There was also an improvement in both respiratory and general symptoms associated with length of survival.

Patients with progressive NSCLC, who were unresponsive to previous chemotherapy, have an extremely poor prognosis and are often symptomatic, with specific pulmonary symptoms (e.g., cough, dyspnea, and hemotypsis) and general symptoms (e.g., fatigue, pain, and insomnia) that can cause extreme distress. The patient population in this study was heavily pretreated, symptomatic, and with a PS of 2 or 3. In these patients, a key therapeutic scope was to palliate disease-related symptoms without compromising the overall quality of life. In this study, approximately 50% of patients experienced an improvement in both pulmonary and general symptoms, with an association between symptom improvement and length of survival.

Previously, we reported that in chemotherapy-naïve patients with advanced NSCLC and a poor PS, the same biotherapeutical regimen yelded a median overall survival of 12.9 months with 1- and 2-year survival rates of 51.2% and 21.1%, respectively. The difference in median overall survival between chemotherapy-naïve and chemotherapy-pretreated patients—12.9 versus 3.2

months (95 days), respectively—indicates that the activity of this biotherapeutic regimen may be influenced by previous standard chemotherapy regimens. This result was also reported in a series of patients with low-grade non-Hodgkin's lymphomas. Also in this case, the activity of the employed biotherapeutic regimen (somatostatin, retinoids, melatonin, vitamin D, bromocriptine, ACTH, and cyclophosphamide) depended on the type of previous therapy.[27]

With respect to safety, drug-related adverse events were mild or moderate (Grades 1 or 2) and consisted mainly of gastrointestinal signs and drowsiness. There was no adverse events of Grades 3 or 4. Moreover, this biotherapeutical combination was not associated with common conventional chemotherapy adverse events, such as neutropenia, thrombocytopenia, or peripheral neuropathy. Finally, the majority of patients carried on with treatment at home. Thus, the favorable safety profile of the biotherapeutical regimen, demonstrated in this case series, concurs with the results of previous studies.[16,27]

## CONCLUSIONS

In conclusion, the results from this series of patients show that the combined regimen of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide is well tolerated and can be effective at improving disease-related symptoms in heavily pretreated patients with late-stage lung adenocarcinoma and poor PS. In this subset of patients, the use of biological compounds with low toxicity, such as those analyzed in this study, or other under investigation, such as gefitinib (an epidermal growth factor receptor inhibitor),[28] can be therapeutically helpful. Consistently, recent advances in tumor biology point to combination therapies of biological compounds with conventional chemotherapy or radiotherapy as a device to maximize antitumoral effects and the overall quality of life.[29]

## REFERENCES


1. Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;2:533.
2. Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710.
3. Riquet M, Foucault C, Berna P, et al. Prognostic value of histology in resected lung cancer with emphasis on the relevance of the adenocarcinoma subtyping. *Ann Thorac Surg* 2006;81:1988.
4. Devesa SS, Bray F, Vizcaino AP, et al. International lung cancer trends by histologic type: Male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer* 2005;117:294.
5. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand, and Europe. *Lung Cancer* 2001;31:123.
6. The Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small-cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-Small-Cell Lung Cancer Collaborative Group. BMJ 1995;311:899.
7. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non-small-cell lung cancer: A meta-analysis. *Lancet* 1993;342:19.
8. Bunn PA, Jr. Chemotherapy for advanced non-small-cell lung cancer: Who, what, when, why? *J Clin Oncol* 2002;20:23S.
9. Soria JC, Brisgand D, Le Chevalier T. Do all patients with advanced non-small-cell lung cancer benefit from cisplatin-based combination therapy? *Ann Oncol* 2001;12:1667.
10. Kelly K, Crowley J, Bunn PA, Jr., et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: A Southwest Oncology Group trial. *J Clin Oncol* 2001; 19:3210.
11. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92.
12. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;20:4285.
13. Fossella FV, Lynch T, Shepherd FA. Second-line chemotherapy for NSCLC: Establishing a gold standard. *Lung Cancer* 2002;38(Suppl. 4):5.
14. Kosmas C, Tsavaris N, Mylonakis N, et al. An overview of current results with the gemcitabine and docetaxel combination as initial and salvage chemotherapy regimen in advanced non-small-cell lung cancer. *Crit Rev Oncol Hematol* 2003;45:265.
15. Shepherd FA, Dancey J, Ramlau R, et al. Prospective, randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095.
16. Norsa A, Martino V. Somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide in advanced non-small-cell lung cancer patients with low performance status. *Cancer Biother Radiopharm* 2006; 21:68.
17. O'Byrne KJ, Schally AV, Thomas A, et al. Somatostatin, its receptors and analogs, in lung cancer. *Chemotherapy* 2001;47(Suppl. 2):78.

18. Toma S, Raffo P, Isnardi L, et al. Retinoids in lung cancer chemoprevention and treatment. *Ann Oncol* 1999; 10(Suppl. 5):S95.
19. Banerjee P, Chatterjee M. Antiproliferative role of vitamin D and its analogs—a brief overview. *Mol Cell Biochem* 2003;253:247.
20. Colao A, Lombardi G. Growth-hormone and prolactin excess. *Lancet* 1998;352:1455.
21. Guerrero JM, Reiter RJ. Melatonin-immune system relationships. *Curr Top Med Chem* 2002;2:167.
22. Vijayalaxmi TCR, Jr, Reiter RJ, Herman TS. Melatonin: From basic research to cancer treatment clinics. *J Clin Oncol* 2002;20:2575.
23. Dasgupta P. Somatostatin analogues: Multiple roles in cellular proliferation, neoplasia, and angiogenesis. *Pharmacol Ther* 2004;102:61.
24. Karamouzis MV, Papavassiliou AG. Retinoid receptor cross-talk in respiratory epithelium cancer chemoprevention. *Trends Mol Med* 2005;11:10.
25. Trump DL, Hershberger PA, Bernardi RJ, et al. Antitumor activity of calcitriol: Preclinical and clinical studies. *J Steroid Biochem Mol Biol* 2004;89–90:519.
26. Lissoni P, Chilelli M, Villa S, et al. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: A randomized trial. *J Pineal Res* 2003;35:12.
27. Todisco M, Casaccia P, Rossi N. Cyclophosphamide plus somatostatin, bromocriptin, retinoids, melatonin, and ACTH in the treatment of low-grade non-Hodgkin's lymphomas at an advanced stage: Results of a phase II trial. *Cancer Biother Radiopharm* 2001;16:171.
28. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. *J Clin Oncol* 2005;23:3235.
29. Onn A, Tsuboi M, Thatcher N. Treatment of non-small-cell lung cancer: A perspective on the recent advances and the experience with gefitinib. *Br J Cancer* 2004; 91(Suppl 2):S11.