CANCER BIOTHERAPY & RADIOPHARMACEUTICALS
Volume 21, Number 1, 2006

Somatostatin, Retinoids, Melatonin, Vitamin D, Bromocriptine, and Cyclophosphamide in Advanced Non–Small-Cell Lung Cancer Patients with Low Performance Status

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ABSTRACT

Background: *The prognosis of low performance status (PS) patients with advanced non-small-cell-lung cancer (NSCLC) is dismal. In these patients, we have determined the survival, clinical benefits, and toxicity of a multidrug regimen, based on cyclophosphamide and biotherapeutical agents.* ***Methods:*** *Patients with a diagnosis of stage IIIB or stage IV NSCLC, no previous surgery or chemoradiotherapy, and an Eastern Cooperative Oncology Group (ECOG) PS equal to or greater than 2 received a daily combination of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide.* ***Results:*** *Twenty-eight (28) patients were enrolled. The median age was 64 years (range, 35–74). The PS was 2 and 3 in 78.6% and 21.4% of patients, respectively. The median overall survival (intent-to-treat analysis) was 12.9 months (range, 1.5–33.5 months), The overall survival rates at 1 and 2 years were 51.2% and 21.1%, respectively. The side-effects were very mild, mostly consisting of diarrhoea, nausea/vomiting, and drowsiness of grade 1–2. Most patients experienced an improvement of both respiratory (cough and dyspnoea) and general (pain, fatigue, and insomnia) symptoms.* ***Conclusions:*** *Low PS patients with advanced NSCLC may benefit from a combination of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide, in terms of survival and quality of life, with very low side-effects.*

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

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in Western countries.[1] Non-small-cell lung cancer (NSCLC), including the histological subtypes of squamous-, adeno-, and large-cell carcinomas, accounts for approximately 80% of lung tumors. According to International Staging System for Lung Cancer, advanced NSCLC generally correspond to patients with stage IIIB and stage IV disease.[2]

When managed by best supportive care, patients with advanced NSCLC have a median survival of 3–4 months, with a 1-year survival of approximately 15%.[3–5] Meta-analyses have shown that the addition of platinum-based chemotherapy produces a modest, but statistically significant, improvement in median survival, and offers a 10% to 15% improvement in 1-year survival, as compared to treatment with best supportive care alone. Thus, platinum-based chemotherapy

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is the standard recommended treatment for advanced NSCLC.[3–5]

For patients with advanced NSCLC, performance status (PS) has long been known to be one of the most important prognostic factors.[6,7] The clinical benefit achievable with platinum-based chemotherapy seems to be restricted to patients with a good PS (0–1 Eastern Cooperative Oncology Group (ECOG) scale). On the contrary, patients with a PS of at least 2 seem to have no survival benefit from platinum-based treatment.[8,9] Moreover, several clinical trials have shown that advanced NSCLC patients with a PS of at least 2 had a comparable survival rate with either platinum-based or platinum-free chemotherapy. Compared to the former, the latter regimen, also showed a less severe toxicity profile.[10,11]

For patients with a PS of at least 2, no treatment is widely accepted as the standard, and several treatment options are available: best supportive care without chemotherapy; single-agent chemotherapy; nonplatinum-based combination chemotherapy; and platinum-based combination chemotherapy. It is evident that novel antitumoral approaches with low toxicity profiles, capable of giving clinical benefits, are urgently required for advanced NSCLC patients with a low PS.

In recent years, numerous biological agents that inhibit specific processes in tumor cells have undergone clinical evaluation.[12] Moreover, biological strategies capable of counteracting chemotherapy-induced damage of the immune system could potentially increase the survival time in lung cancer patients treated by chemotherapy. A similar antitumoral strategy was reported by Di Bella et al., who employed a single chemiotherapeutic agent, cyclophosphamide, together with biological compounds, such as somatostatin, retinoids, melatonin, vitamin D, and bromocriptine.[13] Recently, it has been shown that the association of cyclophosphamide, somatostatin, bromocriptin, retinoids, melatonin, and adrenocorticotrophic hormone (ACTH) is well tolerated and effective in the treatment of low-grade, advanced non-Hodgkin's lymphoma.[14] The rationale for this pharmacological association can be summarized as follows: firstly, the release of both growth hormone (GH) and prolactin (PRL), two hormones involved in neoplastic growth, is inhibited by somatostatin and bromocriptine, respectively[15]; secondly, retinoids, such as vitamin A and its analogs, regulate cell growth, differentiation, and immune function[16]; thirdly, melatonin is endowed with immunostimulant properties.[17] Moreover, each of the proposed biotherapeutical agents have specific antitumoral effects.

In particular, it has been demonstrated that specific somatostatin receptors may be expressed by lung tumors,[18] and, moreover, somatostatin and its analogs inhibit tumoral angiogenesis indirectly by inhibition of growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).[19] As a result, treatment with somatostatin analogs results in significant growth inhibition of both somatostatin receptor (SSTR)-positive and SSTR-negative lung tumors *in vivo*.[18]

On the other hand, retinoids are capable of inhibiting growth and inducing apoptosis in a variety of tumor cell lines.[20] As far as the role of retinoids in lung cancer treatment is concerned, a moderate activity of 13-*cis*-retinoic acid (13cRA) or all-*trans* retinoic acid (ATRA), as single agents, has been reported in a small series of mostly pretreated patients with advanced lung cancer. More encouraging findings derive from combination studies, in which retinoids, especially ATRA, are added to either alpha-interferon or chemotherapy and radiotherapy.[20]

The usefulness of melatonin as a new agent for antineoplastic treatment in humans is finally being recognized.[21,22] The antitumor mechanisms of melatonin include antiproliferative activity, immunostimulatory effects on host anticancer defenses, and antioxidant properties.[23] In non-small-cell lung cancer patients, the concomitant administration of melatonin may improve the efficacy of chemotherapy in terms of both survival and quality of life.[24]

Vitamin D compounds are potent antiproliferative agents in a wide variety of malignant cell types, including lung cancer. Their antineoplastic effects are associated with an increase in G0/G1 arrest, induction of apoptosis and differentiation, and modulation of growth factor expression.[25] In particular, calcitriol (1α,25-dihydroxyvitamin D_3), the active metabolite of vitamin D, potentiates the antitumor effects of many cytotoxic agents and inhibits motility and invasiveness of tumor cells, as well as the formation of new blood vessels.[26]

The aim of this study was to evaluate the survival, the clinical benefits, and toxicity of a combined regimen, based on somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide in chemotherapy-naïve patients

with advanced NSCLC and a low performance status (ECOG PS of at least 2).

MATERIALS AND METHODS

Patient Selection

Eligible patients were required to have histologically or cytologically documented advanced NSCLC of stage IIIB or IV. All patients were required to have an ECOG PS of at least 2. No prior chemotherapy, surgery, or thoracic radiotherapy was permitted for eligibility. Other eligibility criteria included: age of at least 18 years and bidimensionally measurable or assessable disease. Written, informed consent was obtained from each patient before they entered the study.

Treatment

The medical treatment included a combination of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide. Somatostatin was administered subcutaneously at a dose ranging from 1 to 3 mg/day within 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, two 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, two 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 received this combined regimen every day without interruption, for an indefinite period, unless unacceptable toxicity occurred.

Patient Evaluation

Baseline evaluation included medical history and physical examination, electrocardiogram, chest X-rays, thorax computed-tomography scan, and ultrasonography of the upper abdomen. Laboratory investigations included complete blood counts, urinalysis, and renal and liver function tests. Other imaging modalities, such as bone scintigraphy and magnetic resonance imaging, were performed according to specific clinical indications. All baseline imaging procedures were performed within 1 month before study entry. 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. Regular follow-up was performed every 2–3 months.

The primary endpoint of this phase II study was to evaluate the overall survival that was measured from the first day of treatment to the date of death or last follow-up. Secondary objectives were assessement of quality of life and toxicity. Symptom improvement, including cough, dyspnoea, and pain were evaluated by medical history review at doctor-patient consultations. Toxic effects were assessed accord-

Table 1. Patient Characteristics

Characteristics	*No. of patients*	*%*
Total patients	28	100
Gender		
Male	19	67.9
Female	9	32.1
Performance status (ECOG)		
2	22	78.6
3	6	21.4
TNM staging		
IIIB	6	21.4
IV	22	78.6
Histologic type		
Adenocarcinoma	16	57.1
Squamous	8	28.6
Large cell	4	14.3
Metastatic sites[a]		
Lymph nodes	7	29.2
Brain	6	21.4
Bone	5	17.9
Controlateral lung	4	14.3
Pleura	2	7.1
Adrenal gland	2	7.1
Liver	2	7.1
Other	6	21.4
Age, years		
Median	64	
Range	(35–74)	

ECOG, Eastern Cooperative Oncology Group; T, primary tumor; N, regional lymph nodes; M, distant metastasis.

[a]Numbers reflect multiple sites for some patients.

ing to criteria developed by the World Health Organization (WHO).

Clinical efficacy was analyzed according to an intent-to-treat (ITT) analysis. Descriptive statistics were reported as proportions and medians. Survival curves were calculated by the Kaplan-Meier method.

RESULTS

Between May 1995 and February 2002, 28 consecutive eligible patients (19 males and 9 females) were enrolled in the study. Patient characteristics are listed in Table 1. The median age was 64 years (range; 35–74 years). Sixteen (16) patients (57.1%) had adenocarcinoma, 8 patients (28.6%) had squamous-cell carcinoma, and 4 patients (14.3%) had large-cell carcinoma. Twenty-two (22) patients (78.6%) had an ECOG PS of 2, and 6 patients (21.4%) had an ECOG PS of 3. Primary tumor, regional lymph nodes, and distant metastasis (TNM) stages were as follows: stage IIIB 6 patients (21.4%) and stage IV 22 patients (78.6 %). The most common sites of metastases were in the lymph nodes, brain, bone, and controlateral lung.

All patients were valuable for response. According to ITT analysis, the median overall survival was 12.9 months (range, 1.5–33.5 months; Fig. 1). The survival rates at 1 and 2 years were 51.2% (95% CI, 31.0–68.2) and 21.1% (95% CI, 7.0–40.2), respectively (Fig. 1). There was improvement in both respiratory and general symptoms. Cough and dyspnoea improved in 80% and 70% of patients, respectively. Chest and general pain improved in the majority of patients, with a reduction of analgesic consumption. Other symptoms, such as haemoptysis, fatigue, and insomnia, were also ameliorated in most patients.

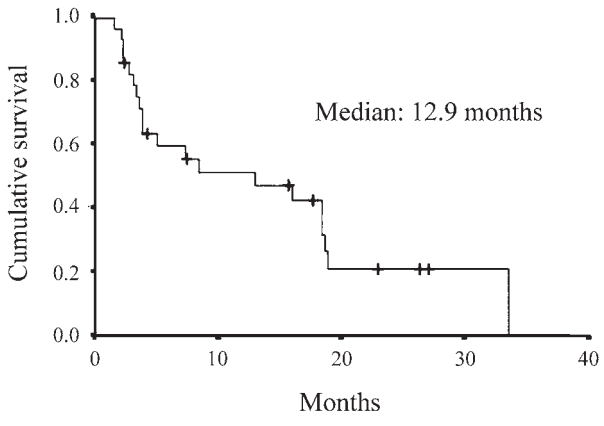

Figure 1. Overall survival curve. Events 20 (71.4%); censored 8 (28.6%; indicated by "+").

Table 2. Toxicity According to WHO Criteria

	No. of patients (%)	
Adverse event	*Grade 1 (%)*	*Grade 2 (%)*
Gastrointestinal		
Nausea/vomiting	4 (14.3)	2 (7.1)
Diarrhoea	7 (25.0)	3 (10.7)
Neurological		
Drowsiness	6 (21.4)	—

WHO, World Health Organization.

All patients were valuable for toxicity. No treatment-related death was observed. There was a very good tolerance of the combined regimen in patients with PS of both 2 and 3. Moreover, most patients carried on the treatment at home. The main episodes of toxicity were referable to gastrointestinal symptoms (Table 2). Thirty-six percent (36%) of the patients experienced grade 1 (7 cases) or grade 2 (3 cases) diarrhoea. Twenty-one percent (21%) of the patients experienced grade 1 (4 cases) or grade 2 (2 cases) nausea or vomiting. Twenty-one percent (21%) of the patients (6 cases) had grade 1 drowsiness. These mild side-effects did not require the interruption of the 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 three instead of two administrations).

DISCUSSION

This paper reports that chemotherapy-naïve patients with advanced NSCLC and a poor PS, treated with a combination of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide, had a median overall survival of 12.9 months with 1- and 2-year survival rates of 51.2% and 21.1%, respectively. There was also an improvement in both respiratory and general symptoms, whereas toxic effects were very modest.

Performance status is an important prognostic factor for survival in patients with advanced NSCLC.[6,7] Patients assessed as an ECOG PS of

at least 2 are considered to have a poor PS, and they may constitute up to 30%–40% of the population of newly diagnosed patients with lung cancer.[27] These patients experience a significantly impaired quality of life, with dyspnoea, pain, haemoptysis, fatigue, anorexia, and cachexia. Median overall survival of patients with a poor PS is always shorter than that of patients with a PS of 0–1. When managed by best supportive care, including palliative radiotherapy, corticosteroids, antibiotics, analgesics, antiemetics, and transfusion, patients with advanced NSCLC have a median survival of 2–3 months and 4–5 months in a PS of at least 2 or a PS of 0–1, respectively.[28,29] A worse PS is also characterized by lower response rates to chemotherapy. In 1960, patients, treated with cisplatin-based chemotherapy between 1981 and 1994, the median survival times were 9.4, 6.4, and 3.3 months in patients with a PS of 0, 1, and 2, respectively.[28] Similarly, in the ECOG 1994 trial, which compared four platinum combination regimens in 1155 patients, the median survival times were 10.8, 7.1, and 4.1 months, with a 1-year survival rate of 42%, 30%, and 19% in patients with a PS of 0, 1, and 2, respectively.[30] In recent years, to reduce the toxicity of platinum-containing regimens, several randomized trials of platinum-free chemotherapy have been carried out. For paclitaxel monotherapy, the median survival for patients with a PS of at least 2 was 4.1 months, compared with 2.9 months for best supportive care.[28] Vinorelbine monotherapy resulted in equivalent survival (median, 18 weeks) with less toxicity than the combination of vinorelbine with cisplatin in patients with a PS of at least 2.[9] For paclitaxel and gemcitabine combined therapy, the median survival for patients with a PS of at least 2 was 4.8 months, compared with 10.2 months for patients with a good PS.[31]

The primary aim of this study was to evaluate the efficacy, in terms of survival, of a novel therapeutic approach, based on a combination of biotherapeutical agents with cyclophosphamide. Compared with the aforementioned literature data, the results obtained seem to indicate the efficacy of this treatment in patients with advanced NSCLC and a poor PS. Moreover, the improvement of both respiratory and general symptoms also indicates an efficacy of the treatment in terms of quality of life.

One of the most significant findings in this study is the very mild toxicity observed in comparison with the toxicity caused by the commonly used chemotherapy regimens. The severe side-effects that characterize the platinum-containing or platinum-free regimens (including haematotoxicity, nephrotoxicity, and ototoxicity) can be often not acceptable for lung cancer patients with a poor PS. The novel regimen proposed in this study may, therefore, be a valid therapeutic alternative for this subtype of patients.

CONCLUSIONS

In conclusion, this study provides preliminary evidence that the combined regimen of somatostatin, retinoids, melatonin, vitamin D, bromocriptine, and cyclophosphamide is active in the treatment of chemotherapy-naïve patients with advanced NSCLC and a poor PS, in terms of both survival and quality of life, and presents very mild side-effects.

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