

A phase II study of paclitaxel in advanced bronchioloalveolar carcinoma (EORTC trial 08956)¹

Giorgio V. Scagliotti^{a,*}, Egbert Smit^b, Lionel Bosquee^c, Mary O' Brien^d, Andrea Ardizzoni^{e,1}, Peter Zatloukal^f, Wilfried Eberhardt^g, Maartje Smid-Geirnaerd^h, Hein G. de Bruinⁱ, Sonia Dussenne^j, Catherine Legrand^j, Giuseppe Giaccone^k,

on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group (LCG)

^a *University of Torino, Department of Clinical and Biological Sciences, S. Luigi Hospital, Regione Gonzole 10, Orbassano (Torino) 10043, Italy*

^b *Martini Ziekenhuis, Groningen, The Netherlands*

^c *Centre Hospitalier de la Citadelle, Liège, Belgium*

^d *Royal Marsden Hospital, Sutton, UK*

^e *Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*

^f *University Hospital Na Bulovce, Charles University and Postgraduate Medical School, Prague, Czech Republic*

^g *Universitaetsklinikum-Essen, Essen, Germany*

^h *Stichting Oosterschelde Ziekenhuizen, Goes, The Netherlands*

ⁱ *Daniel den Hoed Cancer Center of the Erasmus MC, Rotterdam, The Netherlands*

^j *EORTC Data Center, Brussels, Belgium*

^k *Vrije Universiteit Medisch Centrum, Amsterdam, The Netherlands*

Summary

Purpose: The incidence of bronchioloalveolar carcinoma (BAC) has risen steadily over the last decades along with the increasing frequency of adenocarcinomas. BAC is relatively resistant to commonly used chemotherapy regimens. A phase II study with single agent paclitaxel in patients with stages IIIB, IV or recurrent BAC was performed.

Experimental design: Patients with BAC with at least one target bidimensionally measurable lesion staged as unresectable stages IIIB, IV or recurrent disease, not previously irradiated; ECOG performance status 0-2; life expectancy greater than 3 months; age range between 18 and 75, received paclitaxel at a dose of 200mg/m² i.v. as 3 h continuous infusion on day 1 every 21 days. Treatment was continued until progression or up to a maximum of six cycles.

Results: Nineteen patients were eligible. Median number of cycles was 3 (range 0-6); 35% of patients received the planned six cycles of chemotherapy. One patient died of unrelated cause before the start of treatment. Both hematological and non-hematological toxicities were generally mild. Only one partial response (PR) was observed among the 18 eligible patients who started protocol treatment, with a response rate of 5.6% (95% CI: 0.1-27.3%). After an independent review, two PR were confirmed, for a response rate of 11.1% (95% CI: 1.4-34.7%); nine patients had stable disease (50.0%), three patients had progressive disease (11.1%) and four patients were not assessable (22.2%). Median survival was 8.6 months (95% CI: 5.8-14.5) and 1-year survival was 35.0% (95% CI: 14.1-55.8). Median progression free survival for all patients was 2.2 months (95% CI: 1.5-6.0). The study was terminated due to the low response rate.

Conclusions: Paclitaxel as single agent in stages IIIB-IV BAC was well tolerated and manageable but of limited efficacy. BAC should not be excluded from trials of new forms of chemotherapy.

Keywords: Non-small-cell lung cancer; Taxanes; Paclitaxel; Chemotherapy

¹ This publication was supported by grant numbers 5U10 CA11488-27 through 5U10 CA11488-34 from the National Cancer Institute (Bethesda, MD, USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

1. INTRODUCTION

Bronchioloalveolar carcinoma (BAC) is currently recognized to be a histological subtype of adenocarcinoma [1]. The incidence of BAC has risen steadily over the last decades along with the general increase in frequency of adenocarcinomas, reaching up to 24% of lung cancer cases in some clinical series [2]. BAC tends to occur more frequently in younger patients, women and non-smokers [3]. A variety of environmental factors have been linked to the etiology of BAC [4].

The majority of BACs are incidentally detected as a solitary nodule present on chest X-rays image. Solitary peripheral BAC grows slowly for several years without dissemination [5]. The treatment of choice for such localized, nodular lesions remains lobectomy or pneumonectomy [6]. In other cases, BAC may display a more aggressive pattern of growth, turning into widespread bilateral disease with progressive respiratory failure [7].

Unresectable BAC is relatively refractory to radiotherapy and chemotherapy, and the main goal of the treatment is palliation. As cases of BAC are usually included in the adenocarcinoma NSCLC histotype, results investigating activity of single agents or combination chemotherapy in BAC are rarely reported in clinical trials of advanced NSCLC.

The present phase II study in patients with stages IIIB, IV or recurrent bronchioloalveolar carcinoma was initiated by the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Group to investigate the activity of single agent paclitaxel 200mg/m² over 3 h infusion 3-weekly.

2. PATIENTS AND METHODS

2.1. Eligibility

Eligible patients were required to have histologically proven bronchioloalveolar carcinoma. The accepted diagnostic criteria based on gross examination and light microscopy were: absence of a primary adenocarcinoma in other locations, absence of a demonstrable central bronchogenic origin, a peripheral location in the lung parenchyma, intact interstitial framework of the lung, a histological appearance setting it apart from other lung tumors, with a characteristic pattern of growth: cuboidal or cylindrical cells lining up the alveolar septa with preservation of basic pulmonary architecture. Other inclusion criteria were the presence of at least one target bidimensionally measurable lesion, not previously irradiated in unresectable stages IIIB or IV (according to the International Staging System for Lung Cancer [8]) or recurrent disease; BAC with diffuse multinodular lesions involving the lungs bilaterally or unilaterally (in the latter the lesions must involve more than one lobe) with at least one target bidimensionally measurable lesion, not previously irradiated; ECOG performance status 0-2; life expectancy greater than 3 months; age range between 18 and 75; adequate bone marrow reserve with Absolute Neutrophils Count (ANC) $\geq 1.5 \times 10^9 \text{L}^{-1}$; serum creatinine $< 1.5 \times$ upper limit of normal range; liver function tests (alkaline phosphatase, SGOT, SGPT) and bilirubin $< 2 \times$ upper limit of normal range. Patients previously treated with radiotherapy had at least one bi-dimensionally measurable lesion outside the irradiated fields. Radiotherapy should have been completed 4 weeks before the patient enrollment in the study.

Exclusion criteria included previous chemotherapy; known CNS disease; pregnancy or lactation; history of ischemic or congestive heart disease, arrhythmia requiring chronic medications; history of clinically or electrographically documented myocardial infarction; active or prior primary cancer (except basal cell carcinoma of the skin or carcinoma in situ of the cervix); clinical evidence of uncontrolled infection; any pre-existing motor or other serious sensory neurotoxicity \geq grade 2 according to NCIC CTC criteria; any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. Written informed consent to participate in the study was obtained from all the patients. The protocol was approved by local Ethical Review Boards of all the participating institutions and the Protocol Review Committee of the EORTC.

Patients were registered at the EORTC Data Center prior to the start of treatment, and after verification of the eligibility criteria and selection of the target lesions.

2.2. Treatment plan

Paclitaxel was administered at a dose of 200 mg/m² i.v. as a 3 h infusion on day 1. Treatment cycles were repeated every 21 days. Patients were treated for a minimum of two cycles unless serious toxicity or complications occurred. Otherwise, treatment was continued until progression or up to a maximum of six cycles.

Because of potential allergic reactions to paclitaxel, patients received a premedication, according to the following scheme: dexamethasone 20 mg i.v. (or equivalent) 12 and 6 h prior to paclitaxel, diphenhydramine (or equivalent) 50 mg i.v. 30 min prior to paclitaxel, cimetidine or ranitidine 300 mg i.v. 30 min prior to paclitaxel.

Dose of paclitaxel was modified according to hematological toxicity. Dose levels of 200, 175, 150, 135mg had been fixed with a decrease by one dose level in case of: ANC $<0.5 \times 10^9 \text{ L}^{-1}$ lasting for ≥ 7 days, any episode for febrile neutropenia ($T \geq 38.5^\circ$ and ANC $<1 \times 10^9 \text{ L}^{-1}$), grade 4 anemia ($<6.5\text{g}/100\text{mL}$), grade 4 thrombocytopenia ($<25 \times 10^9 \text{ L}^{-1}$).

Dose modifications for non-hematological toxicity were as follows: a decrease by one dose level in case of grade 2 peripheral neuropathy or grades 3 and 4 mucositis. Patients went off protocol in case of symptomatic arrhythmia or AV block, in case of any grades 3 and 4 toxicity or when no resolution occurred after two dose reductions.

When a dose reduction was required no dose re-escalation was allowed subsequently.

The disease was assessed every 6 weeks until documented progression, and treatment side effects were assessed separately for each cycle of therapy. Baseline characteristics and safety analyses are presented based on all registered patients who started protocol treatment while the objective response rate is reported based on all eligible patients who started protocol treatment.

Treatment was given until progression of the disease, unacceptable toxicity or patient refusal. Central review of the radiological images was planned in order to confirm responses.

2.3. Statistical methods

This was an open non-randomised multicenter phase II trial. The primary objective of the trial was to assess the objective response rate of paclitaxel in patients with BAC, according to the "WHO criteria" [9]. Secondary endpoint was the evaluation of toxicity. Acute side effects were graded according to the Common Toxicity Criteria defined by the National Cancer Institute (NCI) of the US and as extended by the NCI of Canada (NCIC) [10]. A two-step Simon design was applied: 16 or 25 eligible patients were planned to be enrolled, according to the number of responses observed in the first 16 eligible patients. With a response rate of 30% in the studied population, paclitaxel should be further investigated in BAC; with a response rate less than 10%, the drug should be rejected from further testing. Types I and II errors were both set up to 10%.

Although not originally foreseen as endpoints, Kaplan-Meier curves were computed on all patients to describe overall survival and progression free survival. Overall survival is defined as time from registration up to death from any cause while progression free survival is defined as time from registration up to progression of disease or death due to any cause. Considering the low number of patients on which these curves are based, these results should be interpreted with care and the wide confidence intervals accompanying these estimates should be taken into consideration when interpreting the results.

The protocol originally included assessment of biological parameters. However, as it was practically possible to collect pathology slides only for two patients, attempts to complete such an analysis were dropped.

3. RESULTS

Between January 1997 and October 2000, a total of 20 patients were registered in this phase II study by seven different institutions. One patient was judged ineligible at the final analysis due to previous malignancy. At the time of the analysis all registered patients had terminated protocol treatment. Characteristics of patients who started protocol treatment (N=19) are described in Table 1. The majority of patients presented type II BAC (63.2%) and the remaining ones type I BAC (36.8%). Most patients presented performance status (PS) 1. All registered patients started protocol treatment except one, who died of trauma-related causes before starting chemotherapy. Considering all patients who started treatment (N=19), the median number of cycles of treatment was 3 (range 0-6) and only 35% of patients received the planned six cycles of chemotherapy. Five patients got at least one dose reduction or delay. Overall, dose was reduced in 10% of cycles, while 10% of cycles were delayed. The median relative dose intensity for paclitaxel among patients who started protocol treatment was of 99.6% (range: 84.6-119.4%).

Hematological toxicity was generally mild: only one patient experienced grade 4 anemia, one patient presented leucopenia of grade 3, while four patients had grades 3 and 4 neutropenia. No grades 3 and 4 thrombocytopenia was reported (Table 2).

None of the patients experienced hypersensitivity reactions. Incidence of grades 3 and 4 toxicity was very limited. Grades 3 and 4 lethargy (fatigue, malaise) in three patients, grade 3 infection in one patient, grade 3 headache in one patient, grade 3 peripheral neuropathy in two patients, grades 3 and 4 dyspnea in three patients, grade 3 alopecia in seven patients and grade 3 other pulmonary toxicity (pleural effusion) in one patient were reported. No patient stopped treatment due to toxicity. No toxic death was reported in this study (Table 2).

Considering the 18 eligible patients who started protocol treatment, only one partial response (PR) was observed corresponding to a response rate of 5.6% (95% CI: 0.1-27.3%). However, after an independent review, two PR were confirmed, thus bringing the response rate up to 11.1% (95% CI: 1.4-34.7%). Nine patients had stable disease (50%), three patients had progressive disease (16.7%) and the status for four remaining patients was qualified as not assessable for response (22.2%).

Based on these results, it was decided to definitely close this study after this first stage.

At the time of the analysis all patients who started protocol treatment except one had progressive disease, and 12 of them received further chemotherapy at relapse. All patients who started protocol treatment have died, mainly due to the disease progression (90%).

Overall median survival was 8.6 months (95% CI: 5.8-14.5) and a 1-year survival rate 35.0% (95% CI: 14.1-55.8). Median progression free survival for all patients was 2.2 months (95% CI: 1.5-6.0).

Table 1: Demographics (patients Who started protocol treatment, N=19)

	No. of patients (N=19)	Percent
Type I BAC	7	36.8
Type II BAC	12	63.2
WHOPS		
0	5	26.3
1	9	47.4
2	5	26.3
Median age (years) (range)		64 (42-73)
Male/female	10/9	52.6/47.4
Prior surgery	7	36.8
Total no. of cycles (N=71)		
1	2	10.5
2	4	21.1
3	5	26.3
4	1	5.2
6	7	36.8
Dose reductions	7 cycles	9.9 ^a
YES		

^a Percentage over total number of cycles (N=71).

Table 2: Hematological and non-hematological toxicity (patients who started protocol treatment, N=19)

	No. of patients with grade 2	No. of patients with grade 3	No. of patients with grade 4	Percent of patients with grades 3 and 4
Anemia	1	0	1	5.3
Leucopenia	4	1	0	5.3
Neutropenia	6	2	2	21.1
Thrombocytopenia	0	0	0	0
Lethargy	3	2	1	15.8
Infection	1	1	0	5.3
Headache	1	1	0	5.3
Mialgia/arthritis	4	0	0	0
Nausea/vomiting	3	0	0	0
Alopecia	7	7	0	36.8
Pulmonary	4	3	1	21.1
Peripheral neuropathy	2	2	0	10.5

4. Discussion

Patients with BAC have often been excluded from clinical trials due to technical difficulties in measuring pulmonary lesions. Even the recently adopted RECIST criteria are not suitable for measuring diffuse, interstitial disease.

The histological appearance of BAC is characterized by the growth of malignant cells along alveolar walls [11]. Distinction of BAC from other histological subtypes of adenocarcinoma of the lung is usually difficult. The diagnostic concordance in subtyping and grading of adenocarcinomas of the lung is low among pathologists [12]. A minor component of the BAC pattern is common in many lung adenocarcinomas and the criteria for designating an adenocarcinoma as BAC are not well defined. A proposed classification considered tumors as BAC if more than 75% of the tumor had a BAC growth pattern, as mixed tumors with 50-75% BAC pattern and as invasive adenocarcinomas when less than 50% of BAC pattern is found: in these series 5-year survival rates of patients with BAC or mixed tumors (63 and 60%, respectively) were reported to be significantly better than in patients with other adenocarcinomas [13]. Recently, a prognosis similar to the one observed in pure BAC was confirmed for adenocarcinomas with foci of BAC (adenocarcinoma with BAC features) and BAC with areas of invasive adenocarcinoma (BAC with invasion) [14]. BAC may thus be further classified into three subtypes showing different biologic features: mucinous, non-mucinous and a mixed variant, with focal areas of adenocarcinoma and a variable predominance of pure BAC.

In the study reported by Ranson et al. [15] paclitaxel as single agent proved to be more effective than supportive care in advanced NSCLC, with a response rate of only 16% but with a significant increase in median survival of over 2 months. The correlation of response rate with survival is not always maintained in advanced NSCLC; survival is considered to be a more reliable parameter of efficacy.

In 2001, SWOG reported the results of the largest trial performed in BAC [16]. Paclitaxel was administered by 96 h infusion (140 mg/m²) in 53 patients and this regimen yielded a 12% response rate, with a median survival of 10 months and a 1-year survival of 45%. These data are quite similar to those obtained in the present study with paclitaxel administered as 3 h infusion. However, in the 96 h continuous infusion trial, six treatment-related deaths were reported, due to neutropenic and non-neutropenic infections. In our study, neutropenia was self-limited and manageable and no toxic deaths occurred. Three-hour infusion is notably easier to administer on an outpatient basis and it has proved to be more secure in terms of hematological toxicity.

Recently, targeted therapies have shown an interesting activity profile in BAC. EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib have been recently tested. A multivariate analysis performed on results from a study with gefitinib in advanced NSCLC revealed that BAC feature represented an independent factor associated with response to gefitinib therapy [17].

In a phase II trial from SWOG, gefitinib was shown to be active in both untreated and previously treated patients with advanced BAC [18]. In 101 chemotherapy-naïve patients (out of a total 129 in the study) a 19% response

rate was achieved with a median survival of 15 months. In the responding population, two positive predictive factors were isolated: female gender and the presence of rash.

Erlotinib has yielded a 26% response rate in 50 patients with BAC in a preliminary report [19]. Over two thirds of cases were chemotherapy-naïve and positive predictive factors were a never-smoking status and once again female gender. Rash was not predictive for response in that trial.

The EGFR tyrosine kinase inhibitors are also quite appealing in NSCLC due to their favorable toxicity profile. The recent discovery that EGFR mutations might be of crucial importance to the activity of gefitinib in NSCLC [20,21], and that several responders presented BAC, makes the process of patient selection for these novel therapies even more motivating.

BAC represents a peculiar tumor subtype worthy of separate clinical trials. An improved knowledge of molecular features of BAC is essential for the development of strategies based on molecular targeted therapies.

Acknowledgements

The authors would like to acknowledge the EORTC Data Center and in particular Dr. Channa Debruyne and Dr. Alexandre Passioukov for their medical expertise as well as Dr. Stefan Schoenberg for his participation in the response review organised for this study. The authors would also like to thank Bristol-Myers Squibb for providing paclitaxel as an investigational agent free of charge.

References

- [1] Ginsberg RJ, KrisMK, Armstrong JG. Cancer of the lung. In: DeVita Jr VT, Hellman S, Rosenberg SA, editors. Cancer. Principle and practice of oncology. 4th ed. Philadelphia: J.B. Lippincott Company; 1993. p. 673-723.
- [2] Barkley JE, Green MR. Bronchioloalveolar carcinoma. J Clin Oncol 1996;14:2377-86.
- [3] Morabia A, Wynder EL. Relation of bronchioloalveolar carcinoma to tobacco. BMJ 1992;304:541-3.
- [4] Read WL, Page NC, Tierney RM, Piccirillo JF, Govindan R. The epidemiology of bronchioloalveolar carcinoma. Proc Am Soc Clin Oncol 2002;21:317a. Abstract 1267.
- [5] Daly RC, Trastek VF, Pairolero PC, Murtaugh PA, Huang MS, Allen MS, et al. Bronchoalveolar carcinoma: factors affecting survival. Ann Thorac Surg 1991;51:368-77.
- [6] Okubo K, Mark EJ, Flieder D, Wain JC, Wright CD, Moncure AC, et al. Bronchoalveolar carcinoma: clinical, radiologic and pathologic factors and survival. J Thorac Cardiovasc Surg 1999;118:702-9.
- [7] Barsky SH, Cameron R, Osann KE, Tomita D, Holmes EC Rising incidence of bronchioloalveolar lung carcinoma and its clinicopathological features. Cancer 1994;73:1163-70.
- [8] Mountain CF. Revision in the international system for staging lung cancer. Chest 1997;111:1710-7.
- [9] World Health Organization. Handbook for reporting results of cancer treatment. Publication 48. Geneva (Switzerland): WHO; 1979.
- [10] <http://ctep.info.nih.gov/reporting/ctc.html>.
- [11] Clayton G. Bronchioloalveolar carcinomas cells type, patterns of growth, and prognostic correlates. Cancer 1986;57:1555-64.
- [12] Sørensen JB, Hirsch FR, Gazdar A, Olsen JE. Interobserver variability in histopathologic subtyping and grading of pulmonary adenocarcinoma. Cancer 1993;71:2971-6.

- [13] Castro CY, Coffey DM, Medeiros U, Cagle PT. Prognostic significance of percentage of bronchioloalveolar pattern in adenocarcinomas of the lung. *Ann Diagn Pathol* 2001;5(5):274-84.
- [14] Ebright M, Zakowski M, Martin J, Venkatraman ES, Miller VA, Bains MS, et al. Clinical pattern and pathological stage but not histological features predict outcomes for bronchioloalveolar carcinoma (BAC). *Ann Thorac Surg* 2002;74:1640-6.
- [15] Ranson M, Davidson N, Nicholson M, Falk S, Carmichael J, Lopez P, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small cell lung cancer. *J Natl Cancer Inst* 2000;92:1074-80.
- [16] Vance PB, Crowley JC, Livingston RB, Gandara DR. A phase II Southwest Oncology Group trial (S9714) utilizing paclitaxel by 96-h infusion in stage IIIb and IV bronchioloalveolar carcinoma of the lung (BAC). *Proc Am Soc Clin Oncol* 2001;20:336. Abstract 1340.
- [17] Miller VA, Kris MG, Shah N, Patel J, Azzoli C, Gomez J, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small cell lung cancer. *J Clin Oncol* 2004;22:1103-9.
- [18] West HL, Franklin WA, Gumerlock P, Vance RB, Lau DHM, Chansky K, et al. ZD1839 (Iressa) in advanced bronchioloalveolar carcinoma (BAC): a preliminary report of SWOG S0126. *Lung Cancer* 2003;41 (Suppl. 2):S56. Abstract 0-187.
- [19] Patel JD, Miller VA, Kris MG, Shah N, Pizzo B, Tyson L, et al. Encouraging activity and durable responses demonstrated by the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (OSI-774) shows in patients with advanced bronchioloalveolar cell carcinoma (BAC). *Lung Cancer* 2003;41(Suppl. 2):S56. Abstract 0-188.
- [20] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129-39.
- [21] Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497-500.