RESEARCH ARTICLE

Clinical Characteristics of Patients with Bronchioloalveolar Carcinoma: A Retrospective Study of 44 Cases

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Abstract

Background: Bronchioloalveolar carcinoma (BAC) is considered a subtype of adenocarcinoma of the lung. Recently BAC has been variously termed adenocarcinoma *in situ*, minimally invasive adenocarcinoma, lepidic predominant invasive adenocarcinoma, and invasive mucinous adenocarcinoma. The aim of the study was to analyze and detect prognostic factors of patients with BAC over a 7-year period. Materials and Methods: This retrospective single-center study included 44 patients with BAC. The impact on survival of fifteen variables (gender, age, smoking status, cough, dyspnea, hemoptysis, fever, chest pain, sputum, metastasis number, Karnofsky performance status, pT, pN, TNM stage, cytotoxic chemoterapy) were assessed. Results: Median age was 55 years (38-83). Most patients were male (63.6%) and stage IV (59.1%). Twenty-one patients (47.7%) received cytotoxic chemotherapy (platinum-based regimens) for metastatic disease. Objective response rate was 33.3% (4 partial, 3 complete responses). Stable disease was observed in nine in patients (42.8%). Disease progression was noted in 5 (23.8%). The median OS for all patients was 12 months (95%CI, 2.08-22.9 months). Independent predictors for overall survival were: Karnofsky performance status (HR:3.30, p 0.009), pN (HR:3.81, p 0.018), TNM stage (HR:6.49, p 0.012) and hemoptysis (HR:2.31, p 0.046). Conclusions: Karnofsky performance status, pN, TNM stage and hemoptysis appear to have significant impact on predicting patient survival in cases of BAC.

Keywords: Bronchioloalveolar carcinoma - treatment - survival - prognostic factors

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Introduction

Lung cancer is the most common cancer worldwide (Jemal et al., 2011). Bronchioloalveolar carcinoma (BAC) accounts for approximately 3-4% of all lung cancers (Read et al., 2004). In past years, BAC rose from less than 5-24.0%. A greater proportion of women and nonsmokers present with BAC than with other types of NSCLC (Barsky et al., 1994). Recently BAC recalled as adenocarcinoma *in situ*, minimally invasive adenocarcinoma, lepidic predominant invazive adenocarcinoma, invasive mucinous adenocarcinoma (Travis et al., 2011).

Prognosis for patients with BAC better than invasive adenocarcinoma. For BAC that outcomes in localize disease are exceptional following surgical resection (Rusch et al., 2006). Although advanced stage is most common.The treatment for patients with advanced BAC are limited (Kris et al., 2006). Responsiveness to standard cytotoxic chemotherapy has been worse (Miller et al., 2005). Prospective studies of paclitaxel as therapy for advanced BAC documented modest survival (Scagliotti et al., 2005; West et al., 2005). In addition to targeted therapy have a role in treating patients with advanced disease. In patients with advanced BAC not selected on the basis of EGFR mutation was no statistically significant difference between erlotinib and chemotherapy (carboplatin plus paclitaxel) treatment for overall survival (Cadranel et al., 2011). However in presence of a somatic mutation in the epidermal growth factor receptor (EGFR) is highly associated with sensitivity to EGFR tyrosine kinase inhibitors, and for the ALK fusion oncogene, which is highly associated with sensitivity to crizotinib (Zhou et al., 2011; Rosell et al., 2012; Shaw et al., 2012).

We retrospectively evaluated the clinical features of 44 patients with BAC in the 7-year period.

Materials and Methods

This retrospective study was performed using data base including 2499 patients diagnosed as primary lung cancer. Total 44 patients with BAC were determined in the 7-year period. Patient demographics, cancer history, smoking history, other clinical features and underwent treatment were documented. Staging was performed using American Joint Committee on Cancer staging criteria (AJCC, 2010). Tumors were evaluated by an experienced pathologist, according to the 2004 World Health Organization (WHO) classification for NSCLC (Schiller et al., 2002). All specimens were formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin. The clinic parameters

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of those patients with BAC are shown in Table 1.

Statistical analysis

All statistical analyses were performed using SPPS version 15.0 for Windows (Statistical Package for Social Sciences, Chicago, IL). The p values <0.05 were considered statistically significant. Statistical differences between the means were analyzed by the independent-samples t-test. Survival probability was calculated using the product limit method of Kaplan and Meier, in consideration of overall deaths rate. Differences in survival between groups were determined using the log-rank test. The effect of each significant predictor identified via univariate analysis was assessed via multivariate analysis using Cox's proportional hazards model.

Results

A total of 44 patients with BAC. Median age was 55 years (38-83). Most patients were male (63.6%) and stage IV (59.1%). In all, 21 tumors (47.7%) were located in right lung and 15 tumors (34%) were located in bilateral lung. Two patients (18.2%) underwent bilobectomy, 7 patients (63.6%) underwent lobectomy and 2 patients (18.2) underwent segmentectomy. Neoadjuvant therapy was received in 1 patients (0.2%); adjuvant chemotherapy and/or radiation therapy was administered in 8 patients (18.1%). Two patients (0.04%) underwent only surgery treatment.

Responses and survival

Twenty-one patients (47.7%) received cytotoxic chemoterapy (platinum-based regimens) for metastatic disease. Tumor response was classified according to registered criteria. Objective response rate was 33.3% (4 partial response, 3 complete response). Stable disease was observed in nine in patients (42.8%). Disease progression was noted in 5 patients (23.8%). In all, 36 patients (81.8%) died during the study follow-up. For all the patients who were enrolled to the study, median OS was 12 months (95%CI, 2.08-22.9 months) (Figure 1). Clinicopathological prognostic factors were evaluated by univariate analysis. According to this analyses; higher stage (p 0.001), higher pathological T (pT) (p 0.001), higher pathological N (pN) (<0.001), dyspnea (p 0.020), hemoptysis (p 0.039) and Karnofsky performance status (0.001) were all associated with worse overall survival (Table 2). All significant clinicalpathological prognostic

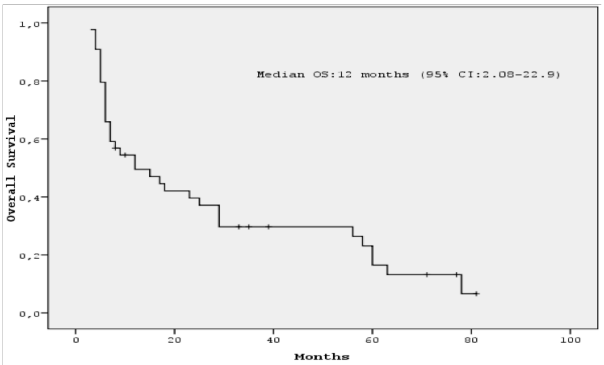

Figure 1. Overall Survival in all Patients

Table 1. Patient Characteristics

Characteristics		Percent (n)
Sex	Male	63.6 (28)
	Female	36.4 (16)
Median Age		55
Smoking status	Ever smokers	34.1 (15)
	Current smokers	43.2 (19)
	Former smokers	22.7 (10)
Cumulative smoking	1-19 pack years	24.3 (7)
	20-39 pack years	20.6 (6)
	40+ pack years	55.1 (16)
Diagnosis Stage	Stage I	11.4 (5)
	Stage II	9 (4)
	Stage III	20.5 (9)
	Stage IV	59.1 (26)
Pathological T factor	T1	4.5 (2)
	T2	27.3 (12)
	T3	4.5 (2)
	T4	54.5 (24)
	TX	6.8 (3)
Symptoms	Cough	43.2 (19)
	Dispne	40.9 (18)
	Hemoptysis	15.9 (7)
	Fever	6.8 (3)
	Chest Pain	22.7 (10)
	Sputum	9.1 (4)
	Weakness	52.3 (23)
Karnofsky score	0-70	22.7 (10)
	80	29.5 (13)
	90	22.7 (10)
	100	25.0 (11)
Metastases Site	Liver	4.5 (2)
	Adrenal gland	2.3 (1)
	Bone	11.4 (5)
	Brain	9.1 (4)
	Lung	45.5 (20)
Resection	Complet resection	76.9 (10)
	Partial recection	23.1 (3)
Operation type	Lobectomy	63.6 (7)
	Bilobectomy	18.2 (2)
	Segmentectomy	18.2 (2)
Adjuvant Radiotherapy or chemoradiohterapy		18.1 (8)
Chemoterapy (for metastases)		45.4 (20)
Neoadjuvant treatment		0.2 (1)

Table 2. Univariate Survival Analysis for Overall Survival

Factor	HR (95%CI)	p value
Gender (male versus female)	1.82 (0.90-3.67)	0.092
Age (≥65 vs <65)	1.27 (0.63-2.55)	0.493
Smoking status (yes vs no)	1.21 (0.57-2.57)	0.616
Cumulative smoking* (<20 vs ≥20)	0.16 (0.12-2.42)	0.163
Cough (yes vs no)	0.74 (0.38-1.43)	0.370
Dyspnea (yes vs no)	0.45 (0.23-0.88)	**0.020**
Hemoptysis (yes vs no)	0.40 (0.17-0.93)	**0.039**
Fever (yes vs no)	0.39 (0.11-1.36)	0.143
Chest Pain (yes vs no)	0.77 (0.36-1.65)	0.517
Sputum (yes vs no)	0.43 (0.14-1.25)	0.124
Metastases number (<2 vs ≥2)	0.87 (0.31-2.37)	0.786
KPS± (<80 vs ≥80)	2.20 (1.05-4.60)	**0.036**
pT (pT1,2 vs pT3,4)	3.10 (1.93-13.4)	**0.001**
pN (pN0,1 vs pN3,4)	4.81 (2.60-15.8)	**<0.001**
Stage I,II vs Stage III,IV	6.87 (2.31-20.3)	**0.001**
Cytotoxic chemoterapy (yes vs no)	1.77 (0.90-3.47)	1.770

*pack years, ±Karnofsky performance status (KPS)

Table 3. Multivariate Survival Analysis for Overall Survival

Factor	HR (95%CI)	p value
Dyspnea (yes vs no)	0.96 (0.41-2.24)	0.92o
Hemoptysis (yes vs no)	2.31 (0.94-5.7)	**0.046**
KPS± (<80 vs ≥80)*	3.30 (1.34-8.11)	**0.009**
pT (pT1,2 vs pT3,4)	1.46 (0.52-4.05)	0.463
pN (pN0,1 vs pN3,4)	3.81 (2.01-14.22)	**0.018**
Stage I,II vs Stage III,IV	6.49 (1.49-28.17)	**0.012**

*Karnofsky performance status (KPS)

factors tested via univariate analysis were evaluated using Cox's proportional hazards model (Table 3). Independent predictors for overall survival were: KPS (HR:3.30, p 0.009), pN (HR:3.81, p 0.018), TNM stage (HR:6.49, p 0.012) and hemoptysis (HR:2.31, p 0.046).

Discussion

In this study we have retrospectively reviewed the clinical characteristics of the patients diagnosed with BAC according to the 2004 WHO classification. Despite the advantageous prognosis for patients with BAC according to other adenocarcinoma subtypes, responsiveness to standard cytotoxic chemotherapy has been worse. The Eastern Cooperative Oncology Group (ECOG) trial (E1594), median survival time of 12 months was longer than that of 8 months for the overall patients (Schiller et al., 2002). Whereas on the other retrospective analysis it was determined that median survival rate was 15 months in the advanced-stage BAC patients, median survival rate was determined as 10 months in advanced-stage NSCLC patients. Median survival rate was determined as 12 months in a prospective study made with phase II patients with infusional paclitaxel (24 h continously infused) (West et al., 2005). In the same study, the objective response rate was found as 14%, whereas 40% had stable disease. In our study, the overall response rate was 76.1%. This result is better than the aforementioned study. But in our study the median survival rate was slightly lower than the literature rates in reverse to the cytotoxic chemotherapy (median survival, 12 months).

EGFR mutations in NSCLC, KRAS mutation and ALK translocation detection is important in terms of targeted therapies. In case of detection of EGFR mutation, the use of EGFR tyrosine kinase inhibitors (erlotinib) provides a more advantageous outcome. In patients with mutant KRAS wild type dependent erlotinib treatment response is worse and survival is shorter (Brugger et al., 2011; Johnson et al., 2013). Used in the presence of ALK translocations, ALK tyrosine kinase inhibitors (crizotinib) significantly prolongs survival rate (Shaw et al., 2012).

TNM staging in the NSCLC is the most influential factor on prognosis. According to the Surveillance, Epidemiology and End Results (SEER) database the median survival time of 60 months was reported for clinical stage I patients, and the median survival time was reported to be 6 months for the clinical stage IV patients (Groome et al., 2007). According to our data median overall survival rate of all patients was 12 months. Also according to the TNM stage in pN was found to be an independent risk factor (HR: 3.81, p=0.018). Similiar to our study, previously conducted similar studies also showed the number of positive lymph nodes (Fukui et al., 2006; Lee et al., 2008; Bria et al., 2009) as strong independent prognostic factor in NSCLC patients.

Poor performance status (PS) is defined by one of the other poor prognostic risk factors. Lower performance statuswas defined as one of the worst 6 risk factors for NSCLC (ECOG 1 or 2; HR, 1.46) (Hoang et al., 2005). In another study, a statistically significant difference was found in NSCLC patients with WHO PS=0 and PS=1 in the median survival rate (51.5 months versus 15.4 months, respectively, p<0.0001) (Kawaguchi et al., 2010). Our results also showed a significant correlation between poor performance status and prognosis (KPS <80 vs KPS ≥80, HR 3.30, p=0.009). The effect of Hemoptysis on the prognosis of lung cancer could not have been clearly identified. In one study, lung cancer was found to have a particularly strong relationship with hospital mortality (Lee et al., 2012). In our study, the risk of death was higher in patients with hemoptysis (HR: 2.31, p=0.046). No statistically significant relationship was found between the other symptoms, smoking status and the number of metastases and the prognosis.

In conclusion, the most important factors limiting this study are the retrospective, single-center experience and the small number of patients. According to the results of this study cytotoxic chemotherapy does not seem very efficient in BAC. According to the results of our study and previous studies, targeted therapies individualized according to the molecular specificationsshould be kept at the forefront before the cytotoxic chemotherapy. Also in our study, TNM stage, positive lymph nodes, poor performance status, and hemoptisis were found to be independent prognostic risk factors.

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