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COPD Exacerbations Affect Clinical Outcome in Advanced Non-Small Cell Lung Cancer: A Retrospective Analysis

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Abstract

Background

Non-small cell lung cancer is the leading cause of cancer death worldwide. COPD represents an independent risk factor for lung cancer.

Objective

The aim of this study was to determine the effects of COPD exacerbations on the outcome of patients treated with cisplatin-pemetrexed in metastatic lung adenocarcinoma.

Methods

120 patients affected by COPD and adenocarcinoma IV stage wild type for EGFR mutation, were elegible for analysis. The initial population was subdivided in two subgroups according to the presence (group 0) or absence of COPD exacerbations (group 1).

Results

The group of patients without COPD exacerbations (group 1) reported a better TTP (log-rank HR of 0.31; p<0.0001) compared with group 0. The TTP median value was longer in group 1 (8.2 vs 6.6 months), and the difference was statistically significant (p<0.0001).

The overall response rate was major in the group 1 compared with the group 0: 45% vs 37% (p<0.001)

Toxicity events were similar in both groups, except for fatigue that was lower group 1 (p<0.0001).

Conclusions

The presence of COPD exacerbations influences the outcome in patients treated for wild type lung adenocarcinoma, both in terms of TTP and in terms of response rate and toxicity.erature.

Keywords: Adenocarcinoma; Molecular Pathogenesis; Chemotherapy; Pletismography

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. Despite the latest advantages in treatment options and the arising awareness about molecular pathogenesis, NSCLC is often diagnosed on an advanced stage and has a poor prognosis. Therefore patients with diagnosis of metastatic NSCLC have indeed a poor prognosis with 5-year survival of about 1% if they have not EGFR, ALK or ROS1 mutation. [2] Chemotherapy agents used in the treatment of advanced non-small cell lung cancer have improved overall survival but they have reached a plateau of effectiveness. First-line therapy with platinum-based combination is always recommended.[3]

The outcome was improved by the use of maintenance therapy patients with tumors non-oncogene addicted. One of the most studied schedule of therapy with this application is pemetrexed combined with cisplatin or carboplatin.[4] Recently, antibodies that target programmed death 1 (PD-1) or its ligand [programmed death ligand 1 (PD-L1)] have become a mainstay of first-line treatment of advanced/metastatic non-small-cell lung cancer (NSCLC) without targetable genetic alterations

COPD is a comorbidity frequently associated with non-small cell lung cancer. It is the fourth cause of death throughout the world, but it's projecting to become the third cause of dead worldwide. [5, 6]

COPD is often associated with exacerbations of symptoms. The exacerbation is defined as an event characterized by increased cough, phlegm and the abnormal production of sputum, with the modification in patient's baseline dyspnea score [7-9].

In the current study we want to highlight the effects of COPD exacerbations on the outcome of patients affected by metastatic wild type non-small cell lung cancer undergoing chemotherapy, focusing on TTP, overall response rate and toxicity.

Patients and Methods

We retrospectively analyzed a sample of 120 patients affected by non-small cell lung cancer and COPD undergoing treatment with cisplatin plus pemetrexed. The inclusion criteria were ECOG PS 0-2, all treated with cisplatin-pemetrexed. Exclusion criteria included severe comorbidities and ECOG PS>2. They were subdivided in two groups according to the presence or absence of COPD exacerbations. The main endpoint was to detect the difference between a group with COPD exacerbations and a group without exacerbations in terms of time to progression (TTP). The secondary endpoint was the difference between them in terms of response rate and toxicity.

Study Design

From September 2016 to December 2017, 120 patients were analyzed being affected by non-small cell lung cancer, stage IV, wild type for EGFR and ALK mutations and with PDL-1<50% treated with cisplatin-pemetrexed schedule, specifically cisplatin 80 mg/mq d 1,21 and pemetrexed 500 mg/mq d 1,21 for 4 cycles followed by maintenance therapy with pemetrexed.

The patients were subdivided in two groups: group 1 did not show COPD exacerbations during the treatment (58 subjects) and group 0, made of patients who reported exacerbations over the period of examination (62 subjects).

The study was carried out at S.Andrea HospiTal- Respiratory Disease Unit and it was approved by S.Andrea-Sapienza Ethic committee.

COPD Exacerbation Detection and Measurements

Patients underwent clinical evaluation and functional analysis by spirometry for detection of forced expiratory one second volume (FEV1), and CT staging at the end of three cycles of therapy. The spirometry was performed with body pletismography method (Jaeger system masterscreen, Germany) as follows: briefly, flow sand dynamic volumes were measured with the pneumotacographic method and volumes and resistances with the pletismographic method. Data considered were post-bronchodilator Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1) and FEV1/FVC ratio. The value of FEV1/FVC <70 was considered diagnostic for COPD according to GOLD guidelines.

The response evaluation was established according to RECIST criteria 1.1(7). The response was categorized as below reported:

1. Complete response: disappearance of all tumour lesions
2. Partial response: reduction of> 30% in the total tumour lesions size
3. Stable disease: reduction of <30% of total tumor size
4. Progression disease: occurrence of new lesions or increased of total tumour size>20%.

The CAT questionnaire was administered to each patient and it included 8 items, with a score range from 0 to 40 for detection of clinical symptoms. The cut-off considered indicative for exacerbations was 10.

A blood test was performed for detection of inflammatory markers as procalcitonin (PCT) and reactive C protein (RCP), to confirm the occurrence of exacerbation.

The exacerbation was considered if patient reported increased cough, phlegm and the abnormal production of sputum with colour change, Moreover it was considered in case of change in patient's baseline dyspnea, with antibiotics and/or steroids needed.

Statistical Analysis

Values were all expressed as mean ± standard deviation or median and interquartile range as appropriate. The significance level was set at p value < 0.05. The Fisher's exact test was performed to determine differences between study and control group for categorical variables. The non parametric Mann Whitney test was applied for unpaired data comparing the two groups. The Kaplan-Meier analysis with log rank test were applied for TTP curve comparison. SAS® system version 9.2 (SAS Institute Inc., NC, USA) was used for the analysis.

Results

Patients characteristics are summarized in **Table 1**.

Total patients 120	
Age	69.1 ± 10.2
Males	58%
Bone metastases	28%
respiratory failure	14%
heart diseases	40%
ECOG-PS 1	75%
IV stage	40%
pack-year	33.9 ± 16.7
former smokers	76%

Table 1: Characteristics of all subjects

The average age was 69.1, while males were 58% of all subjects. The ECOG performance status (PS) was 1 for the majority (75%) of subjects, and the mean pack-year was 33.9 with prevalence of former smokers (65%). Respiratory failure was found in 14% of subjects whereas bone metastases were

present in 28% of whole population. The differences between subgroups about continuous and cathegorical variables are displayed. Group 1, without exacerbation, showed a better response rate and a better time to progression than group 0. In particular, the overall response rate was 45% for the group 1compared with 37% for the group 0. The median TTP was 8.2 months for group 1 whilst 6.6 in the group 0 ($p<0.0001$). No significant differences were found about the other parameters considered, such as age, ECOG-PS, FVC% and FEV1% of predicted. Concerning the inflammatory parameters the procalcitonin levels was significantly higher in patients with exacerbations with a median value of 0.15 ($p<0.01$) compared with group 1 in which it was 0.04 ng/ml. RCP level was also higher in group 0 reporting a median value of 7.2 versus 3.5 in the group 1 ($p<0.001$). The CAT questionnaire showed a higher level in patients with exacerbation ($p<0.01$).

A logistic regression analysis showed that the only parameters influencing significantly lung cancer progression are pack-year and exacerbations, $p<0.01$ and $p<0.05$ respectively **[Table 2]**.

Dependent Variable: Time To Progression			
Variable	Odds Ratio	IC	P
COPD	1.03	0.92 to 1.13	NS
Pack-year	1.51	0.21 to 11.52	<0.01
FEV1%	0.83	0.60 to 1.11	NS
ECOG-PS	0.62	0.06 to 5.70	NS
Exacerbations	1.45	1.1-1.71	<0.05

Table 2: Logistic regression analysis

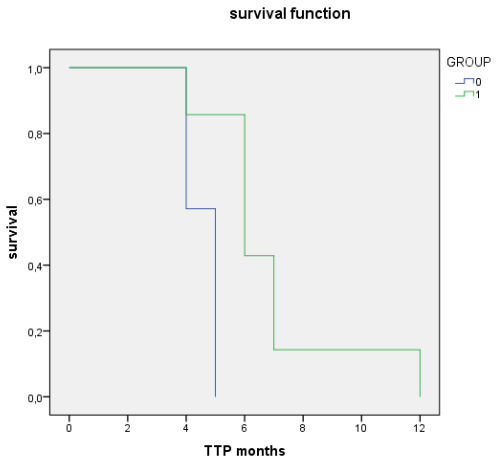

Figure 1 shows the Kaplan-Meier curve for TTP comparing the groups reporting a HR of 0.35 between group 1 and control group, $p<0.0001$.

Discussion

Lung cancer and COPD represent leading causes of morbidity and mortality worldwide. They share a common environmental risk factor which is cigarette smoke exposure.

The primary goal of the current study was to quantify the impact COPD exacerbation on clinical outcomes in non-small cell lung cancer patients undergoing chemotherapy.

The current study confirms the benefits and the efficacy of treatment with cisplatin combined with pemetrexed, pointing out the negative impact in this population of COPD with exacerbations.

The response rate and time to progression were indeed better in patients without COPD exacerbations. Furthermore, the toxicity regarding the parameter fatigue was lower in group 1 than in group 0.

The coexistence of the two diseases weakens the action of chemotherapy. Both diseases recognize in smoking habit the main risk factor and we found that this factor affects by itself the response to the treatment.

The effectiveness of pemetrexed combined with cisplatin that were used in this setting of patients has been extensively demonstrated. Currently, chemotherapy with these agents, combined with immunotherapy represents the first-line standard treatment in patients with adenocarcinoma harbouring no driver mutation. [10] The improving of progression-free survival and overall survival were achieved in clinical studies, such as the so-called Paramount trial that reported longer survival in patients treated with maintenance following four cycles of treatment with doublet, with HR of PFS of 0.60. [11]

Consistently with literature, we demonstrate in the current study that COPD is a comorbidity that frequently occurs associated with lung cancer. [12]

The above mentioned disease is characterized by a potential functional worsening, due to the occurrence of exacerbations caused by viral or bacterial agents. Chronic obstructive pulmonary disease (COPD) is characterized by the decline of lung function due to the combination of airway obstruction and inflammation.

Currently, three factors appear to be important in the pathogenesis of COPD: cigarette smoking, infections, and inhalation of dust. Exacerbations are the most common observable cause of death in COPD in which bacteria play the main role. [13]

Exacerbations are defined as an increase or a new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid. [14]

The main functional parameter, post-bronchodilator FEV1 is inversely associated with the frequency of exacerbations. [15]

Hospitalization for acute exacerbation usually occurs in the latest stages of chronic obstructive pulmonary disease (COPD) and represents more than 70% of all COPD related medical care cost. [16]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines highlights the prevention and treatment of exacerbations as primary objectives for COPD management. For

patients with a history of COPD exacerbations, treatment with inhaled corticosteroid/long-acting ß2-adrenergic agonist (LABA) combination therapies is the recommended option. [17]

The clinical symptoms worsening is associated with the alterations of some inflammatory markers such as procalcitonin whose detection plays an important role in identifying the presence of local infection or systemic infection. [18]

As we can see in the present study, patients with exacerbations had an increased level of both procalcitonin and CRP suggesting the presence of inflammation that in turn could influence the therapy response. The CAT questionnaire is a clinical test currently used to identify patients with exacerbation.

These results raise the possibility that these variables may be used as identifier of patients at higher risk of disease progression.

As a consequence of the above description clinicians should highlight the importance of smoking cessation not only to prevent COPD and lung cancer but also to promote the effectiveness of lung cancer treatment.[19-22]

Conclusions

This retrospective study demonstrates that COPD exacerbations could influence the outcome of patients affected by advanced lung cancer. In particular, patients with NSCLC without exacerbations report greater benefits from chemotherapy treatment both in terms of time to progression and toxicity. This evidence suggests that management of COPD, including prevention of exacerbations and smoking cessation could improve the efficacy of lung cancer treatment.

Conflict of Interest

There are no conflicts of interest to declare with regard to this paper.

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