

Chronic Pulmonary Obstructive Disease (COPD) Implications in Lung Cancer Systemic Therapy

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Abstract

This short review discuss the importance of COPD like the most frequent comorbidity of patients with lung cancer. This comorbidity is important for surgeons end radiotherapists too, but we will discuss especially about the influence of COPD on the antitumor systemic treatment represented by chemotherapy, targeted therapy and immunotherapy. Despite the fact that some aspects are not fully clarified, it seems that COPD does not have a major influence on the choice of systemic therapy for lung cancer.

Keywords: Chronic Pulmonary Obstructive Disease (COPD); Lung Cancer; Chronic Obstructive Bronchitis; Emphysema

Introduction

Lung cancer represents a significant public health problem worldwide for medical systems. Unfortunately, more than half of the patients with lung cancer are diagnosed at an advanced stage. Another difficulty in the management of these patients is that they have more comorbidity and diagnosis procedures and the treatment itself can be complicated. COPD, according to current data, is the most frequent associated disease found in lung cancer patients. MDS manual defined: "Chronic obstructive pulmonary disease (COPD) is airflow limitation caused by an inflammatory response to inhaled toxins, often cigarette smoke. COPD comprises Chronic obstructive bronchitis (clinically defined) and Emphysema (pathologically or radiological defined)" [1].

For oncologist and pneumologist is important to know that COPD has been identified as a risk factor for lung cancer. This chronic disease has symptoms that are similar to lung cancer: cough, dyspnea, cyanosis, etc. The association of COPD with lung cancer involves discussing several issues:

- COPD and lung cancer pathogenesis.
- COPD like independent risk factor for lung cancer for a nonsmoker.
- What is the impact of COPD for the survival of lung cancer patients?
- Treatment for lung cancer associated whit COPD patients.

COPD and lung cancer common pathways for pathogenesis, COPD independent risk factor for lung cancer for a nonsmoker

COPD and lung cancer are the most important diseases that cause mortality in lung diseases worldwide. The mutual etiology underlying the two diseases is, for the most part, (90%) exposure to tobacco.

In the pathogenesis of COPD there is more evidence supporting the role of immune dysfunction, was found also that lung microbiome is affected. An underlying genetic susceptibility in developing COPD and lung cancer was also described in specific medical literature. In the mechanism of pathogenesis of the two disease epigenetic factors involving DNA methylation and microRNA expression are presumed to be involved and to the same extent chronic inflammation. To clarify the pathogenesis of lung cancer and COPD are necessary more studies. [2].

A study revealed that every smoker who does not have COPD had a lower risk of developed cancer than the group of nonsmokers who have COPD (more than double the risk of developing lung cancer). Another finding of this study was that the highest risk of developed cancer was for patients with COPD and who had smoked. The authors of the study concluded that despite the gravity of these two diseases' association, a good treatment plan could determine that a person lives for more years with a good quality of life [3].

Which is the impact of COPD in survival of patients with lung cancer

The researchers studied the Impact of COPD in survival of patients with lung cancer a retrospective study of Wang W and collab. Found that the association between COPD and lung cancer, end more frequent association with emphysema predominant phenotype, represented an independent prognostic and risk factor for only squamous carcinoma of the lung [4].

Treatment of lung cancer patients with concomitant COPD

For specialists in medical oncology, the impact of COPD on the tolerability of systemic antitumor treatment is significant. In this short review, we do not discuss COPD's impact on surgical therapeutic decisions or radiotherapy indications. Still, of course, these therapeutic decisions are also influenced by COPD's presence and severity and should be discussed in the tumor board.

In stage I non-small cell lung cancer (NSCLC) surgery is the standard of care. Still, stereotactic ablative radiotherapy (SABR) is increasingly used to treat patients at high-risk for surgical complications.

A study suggests that more efforts are needed to develop a standard of care unanimously accepted. And also to incorporate patient preferences when making treatment decisions for stage I NSCLC [5].

Another study revealed that about one-third of patients with comorbid COPD might be ineligible for lung cancer surgery that would otherwise be technically operable due to poor physical condition [6].

Non-surgical treatment

Unfortunately, data on the effectiveness of chemotherapy in COPD-associated lung cancer remain limited; one of the accentuated side effects determined by COPD, which has been reported, is the increase in the risk of chemotherapy-induced febrile neutropenia [7]. The database showed that pulmonologists' involvement in the team of treatment of patients with early-stage NSCLC and COPD led to an improvement in the operability rate and reduce mortality risk [8]. Multidisciplinary treatment (MDT) should be incorporated into treating lung cancer concomitant with COPD because it can improve adherence to evidence-based guidelines and timeliness of care for patients with lung cancer [9]. If we discuss chemotherapy, the benefits may outweigh the risks in NSCLC patients with severe to very severe COPD, found a study of Dong W and collab [10]. For patients with Small Cell Lung Cancer (SCLC), a study demonstrated that despite that over half of the SCLC patients receiving chemotherapy had COPD, this comorbidity had no impact on these patients' survival [11]. The treatment with TKI was investigated in the study of Chia-Che Wu et collab. Patients receiving EGFR-TKI in this study where two groups of patients

with lung cancer one with COPD and another without COPD. Was also made an analysis by subgroups by: age, sex, comorbidities, specific treatment for cancer. From a total number of 21.026 patients with NSCLC who were enrolled in the study 47.6% had COPD. The median overall survival (OS) was 2.04 vs. 2.28 years, $p < 0.001$ in favor of those without COPD and progression free survival (PFS) was 0.62 vs. 0.69 years, $p < 0.001$, also in favor of those without COPD. Conclusion was that patients with lung cancer treated with EGFR-TKI had a worse survival outcome if they had pre-existing COPD [12].

In another study, patients were randomly treated with platinum-based chemotherapy or TKIs. The Kaplan–Meier curve survival curves didn't signal significant differences in overall survival between two groups of patients with and without COPD: log-rank $P = 0.65$. Performance status influenced the results respect the adjusted hazard ratio (HRadj) which was statistically significant (HRadj = 1.33, 95% confidence interval [CI]: 1.11 - 1.59; $P = 0.002$). Clinical stage was also influenced: (HRadj = 0.67 (95% CI: 0.50 - 0.89; $P = 0.006$). COPD status was not influenced: HRadj = 1.20, (95% CI: 0.83 - 1.50; $P = 0.46$). The conclusion of this study was that advanced lung cancer treated with standard care (stages IIIB and IV), COPD does not have a negative impact on overall survival [13].

Combination of chemotherapy with Bevacizumab was also studied. Also in was compared association of Bevacizumab plus carboplatin end paclitaxel. The founding was that patients with COPD had a decrease of neutrophil count, higher lymphocyte cell count and also was a lower neutrophil/lymphocyte ratio, but surprising a high progression free survival then was described to the patients with COPD and lung cancer [14].

The impact of treatment with checkpoint inhibitors was also studied. The results from this study indicate that patients with COPD associated with lung cancer are highly susceptible to PD-1 checkpoint inhibitors and have longer PFS and OS. The investigators of that study concluded that larger population models would be needed to verify these results and determine if COPD severity impacts anti-PD-1 efficacy [15].

Conclusion

COPD is frequent in Lung cancer patients. A multidisciplinary team is needed for the decision of therapy of these patients. Regarding systemic therapy, it is known that most cytostatics used in lung cancer do not have significant lung toxicity. The evolution of patients with NSCLC and COPD in treatment with TKIs is controversial because, in some studies, these patients' evolution was unfavorable. In other studies, patients behaved like patients who did not have COPD. Also, the influence of COPD on treatment with PD1 and PDL1 inhibitors is still unclear.

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