



Chronic obstructive pulmonary disease alters immune cell composition and immune checkpoint inhibitor efficacy in non-small cell lung cancer

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Comment on: Mark NM, Kargl J, Busch SE, *et al.* Chronic Obstructive Pulmonary Disease Alters Immune Cell Composition and Immune Checkpoint Inhibitor Efficacy in Non-Small Cell Lung Cancer. *Am J Respir Crit Care Med* 2018;197:325-36.

Submitted Feb 11, 2019. Accepted for publication Feb 21, 2019.

doi: 10.21037/atm.2019.02.27

View this article at: <http://dx.doi.org/10.21037/atm.2019.02.27>

Chronic obstructive pulmonary disease (COPD) commits more than 5% of the population and it is associated with high mortality with approximately 3.2 million deaths in the world in 2015, a raise of 41.9% compared to 1990 (1).

Its relationship with lung cancer has been studied since 1986 when Skillrud *et al.* (2) correlated decrease in respiratory airflow and chronic inflammation with an increase in lung cancer incidence. Non-small lung cell cancer (NSCLC) is the most common histology with up to 80% of all cases.

COPD is characterized by a reduced airflow capacity due to abnormalities in the ventilation system and alveolar structure. COPD is caused by prolonged exposure to substances (3), specially tobacco (4), causing destruction of the small airways and lung parenchyma through chronic inflammation (5) and other mechanisms like the increased number of goblet cells, hyperplasia of mucoid glands and fibrosis (6).

Patients with a confirmed diagnosis of COPD have a 6 to 13 times fold the risk of developing lung cancer when compared to the normal population (7). Consequently, lung cancer is the first cause of death in patients with CPOD (5), mainly when the emphysematous component is present (8).

The COPD chronic inflammation is characterized by the increased presence in the airway of lymphocytes T CD8+, CD4+, neutrophils, CD68+ monocytes and macrophages (9,10). Even though, it is also observed an increased number

of regulatory T cells (Tregs), PD-L1+ cells and myeloid-derived suppressor cells (MDSCs) (11).

In vitro studies have shown that lymphocytes T CD8+ are related to the origin of CPOD by stimulating the synthesis of IFN- γ (12), showing that the adaptative immune system is activated during a lesion in the lung tissue and helps to perpetuate the cell damage.

Studies conducted by Bhat *et al.* (13) in 2015 showed that blockade of CTLA-4 and PD-1 resulted in increased proliferation of T cells and IFN- γ . Mark *et al.* (14) evaluated an increase in the Th1 subtype of CD4+ T lymphocytes and increased survival when there is PD-1 and PD-L1 blockade in patients with COPD and NSCLC. In the same article, the comparative flow cytometry panel with or without COPD identified similar numbers of CD45+ and myeloid cells, however, patients with COPD had higher levels of CD3+, CD4+ and CD8+.

The data suggest that the chronic inflammatory state, characterized by persistent lung injury, increases the activity of the adaptive system, with a higher recruitment of lymphocytes and the subsequent production of interleukins. However, this increased activity also activates regulatory mechanism that downgrade the immune response, such as Tregs (15) lymphocytes and other immunological checkpoints such as CTLA-4 (16) and PD-L1/PD-1 (17), opening a therapeutic window among patients with COPD who develop NSCLC. Further clinical trials assessing

immune checkpoint inhibitors for patients with COPD who develop advanced lung cancer may confirm this theory, although ongoing clinical trials exclude patients diagnosed with chronic diseases, such as COPD.

The immune system can find and attack tumor cells in a similar way that it is able to destroy pathogenic agents. However, the ability to avoid the immune system is one of the hallmarks of cancer (18). The interaction between the immune system and tumor cells are complex and occurs through several immune checkpoint proteins that inhibits lymphocytes activity. The most studied is the link between the lymphocytic membrane receptor, programmed cell death 1 (PD-1), and its ligands 1 or 2 (PD-L1 or PD-L2), which are often expressed by tumor cells (19).

Immune checkpoints inhibitors can stimulate lymphocytes against tumor cells. Several studies assessed anti-PD-1 or -PD-L1 agents and showed that immune checkpoint inhibitors can improve patients overall survival compared to cytotoxic chemotherapy (20). There is a study that showed enthusiastic 16% 5-year survival rate with nivolumab compared to a reference value of 5% with cytotoxic chemotherapy (21).

On the other hand, immune checkpoint inhibitors can stimulate lymphocytes against healthy lung cancer cells, increasing lung tissue damage and COPD symptoms. Pneumonitis is an immune-related adverse event that occurs in up to 5% of patients taking immunotherapy (22). Although there is a lack of information regarding this, the proportion of patients with immune-related pneumonitis can be higher among patients with COPD.

The main reason for this underrepresentation of COPD patients in clinical trials is the COPD poor prognosis. Immune checkpoint inhibitors can produce durable responses and patients with advanced-stage COPD can live less than it should be enough to have benefit with immunotherapy.

Another concern is the potential interaction between COPD therapy and immunotherapy, especially corticosteroids. In COPD, corticosteroids can reduce the lung tissue inflammation and improve the airflow. Corticosteroids is the treatment during COPD exacerbations and can decrease immune checkpoint inhibitors efficacy. Several studies have shown that corticosteroids for the management of immune-related adverse events in patients receiving immune checkpoint inhibitors did not compromise immunotherapy efficacy (23). Even tough, many clinicians still avoid corticosteroids for patients taking immunotherapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. PN Aguiar Jr reports speaker fees from MERCK CO, outside the submitted work. Prof. De Mello reports consultant/advisory board for Pfizer, Zodiac, MSD; Speaker Honoraria from Astrazenenca, Novartis, Educational Grants: Roche, Merck-Group; Travel Grant: BMS; Expert honoraria from National Science Center, Poland. The other authors have no conflicts of interest to declare.

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Cite this article as: Filho MM, Aguiar PN Jr, de Mello RA. Chronic obstructive pulmonary disease alters immune cell composition and immune checkpoint inhibitor efficacy in non-small cell lung cancer. *Ann Transl Med* 2019;7(Suppl 1):S42. doi: 10.21037/atm.2019.02.27