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EDITORIAL

Antibiotics and proton pump inhibitors suppress the efficacy of immunotherapy against non-small cell lung cancer

Lung cancer remains a major public health problem in the world, despite the fact that its death rate is declining in most Western countries.[1] Compared with Western countries, the incidence of lung cancer in China is still rising. Additionally, lung cancer is still the leading cause of cancer-related deaths in China.[2] The most common type of lung cancer is non-small cell lung cancer (NSCLC), which accounts for ~85% to 90% of all lung cancer cases.[3] Unfortunately, the majority of NSCLC patients have already developed metastasis at the time of diagnosis and ultimately succumb to their disease. Palliative chemotherapy is the standard treatment for advanced NSCLC. However, the clinical efficacy of conventional chemotherapy regimens has not been satisfactory.

In recent years, immunotherapies have proven to be effective in extending the life span of cancer patients.[4] The most studied immunotherapeutic drugs in the treatment of NSCLC are immune checkpoint inhibitors (ICIs), such as anti-programmed cell death protein-1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) antibodies.[5] Some important clinical trials have indicated that the use of ICIs has significant clinical benefits in the treatment of NSCLC. For example, the phase II POPLAR trial (NCT01903993)[6] demonstrated a median overall survival of 12.6 months in the atezolizumab arm versus 9.7 months in the docetaxel arm (hazard ratio [HR], 0.73; 95% confidence interval [CI]: 0.53–0.99; $P = 0.04$). Similarly, the phase III OAK trial (NCT02008227)[7] also reported a significant improvement in median overall survival for atezolizumab versus docetaxel (13.8 months vs. 9.6 months; HR, 0.73; 95% CI: 0.62–0.87, $P = 0.0003$). Although the use of ICIs has achieved clinical success, only a minority of NSCLC patients exhibit durable responses.[8, 9] Variable response rates can result because of several factors, including low tumor mutational burden,[10] lack of tumor-infiltrating lymphocytes (TILs),[11] functional exhaustion of TILs,[12] and more.

Increasing evidence suggests that the gut microbiota can modulate the host antitumor immune responses and the response to ICIs.[13] However, the mechanisms behind this and the influencing factors that can modulate the gut microbiome to enhance/suppress immunotherapy responses in cancer treatment remain to be fully explored. Some comedications, such as proton pump inhibitors (PPIs) and antibiotics (ATBs), have been shown to play a critical role in regulating the immune response in cancer treatment via modulating the viability and composition of intestinal microbiota. For example, Imhann *et al.*[14] reported that bacterial richness was decreased and T cell tolerance was enhanced in cancer patients who received PPIs. Moreover, Consonni *et al.*[15] in their retrospective analysis of patients with NSCLC found that ATBs could reduce the clinical benefit of ICIs. All these previous studies were limited as they were single-arm, single-center, retrospective studies. Therefore, the results of these studies may have been biased to a certain extent, and may have not accurately assessed the loopholes of prescribing comedications with immunotherapies. In a study recently published in the *Annals of Oncology*, "Efficacy of chemotherapy and atezolizumab in patients with NSCLC receiving antibiotics and proton pump inhibitors: pooled post hoc analyses of the OAK and POPLAR trials", Chalabi *et al.*[16] performed an unplanned study using pooled data from the OAK and POPLAR trials to assess the impact of PPI and ATB use on the survival of NSCLC patients who received ICI treatment.

In the study, a total of 1512 NSCLC patients were investigated (1225 and 287 from the OAK trial and POPLAR trial, respectively). Among them, 234 (30.9%) patients in the atezolizumab group and 260 (34.4%) in the docetaxel group received PPI treatment, while 169 (22.3%) and 202 (26.8%) received ATB, respectively. Multivariate analyses indicated that both PPI (HR, 1.26; 95% CI: 1.10–1.44) and ATB (HR, 1.20; 95% CI: 1.04–1.39) use were associated with shorter overall survival. However, PPI and ATB use did not affect the survival of NSCLC patients in the docetaxel group. In contrast, within the atezolizumab group, both overall survival (9.6 vs. 14.5 months; HR, 1.45; 95% CI: 1.20–1.75; $P = 0.0001$) and progression-free survival (1.9 vs. 2.8 months; HR, 1.30; 95% CI: 1.10–1.53; $P = 0.001$) were significantly shorter in patients who received PPI treatment. In the same patient group, ATB use was associated with shorter overall survival (8.5 vs. 14.1 months; HR, 1.32; 95% CI: 1.06–1.63; $P = 0.01$). As far as we know, this study is the first to analyze the data from multicenter, randomized, controlled clinical trials, and included more than 1500 NSCLC patients. It is also the first to report that PPI and/or ATB use in patients with advanced NSCLC may affect the efficacy of ICIs and is associated with poor outcomes.

Of note, this study was subjected to certain limitations. First, it was a retrospective study in which all data were from the study subgroups without prespecification. Thus, these data may be insufficient to support the authors' conclusions.

Moreover, actual results may differ from those described in this study as some differences in the baseline clinical characteristics of NSCLC patients were observed. Last but not least, since this was a retrospective study, the authors were unable to collect biological parameters about the inhibitory efficacy of PD-L1 and to analyze the effects of ATB and PPI on these parameters.

Given that prospective studies exploring the effects of PPIs and ATBs on ICI treatment are not currently feasible, we should continue to monitor similar investigations from forthcoming randomized controlled clinical trials. Although this study cannot prove that PPIs and ATBs affect the survival of NSCLC patients by suppressing the treatment effect of ICIs, it still advises clinicians that they should carefully evaluate the need for PPIs and ATBs in their patients who are undergoing ICI treatment.

Disclosure

The author declares no competing interests.

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