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Review Article

Attention on Smoking Status to PD-1/PD-L1 Drugs on Non-Small Lung Cancer Patients

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Abstract

Smoking is considered a serious risk factor for developing a large array of cardiopulmonary conditions, in particular, squamous cell carcinoma in non-small cell lung cancer (NSCLC). Smoking cessation has reduced the risk of lung cancers and has benefited cancer patients receiving chemotherapy. While selective chemotherapeutic agents have been developed, analysis of drug efficacy in smoking populations has not been extensively studied. Recently, some clinical trials have shown that smokers with NSCLC have a lower hazard ratio (HR) than that of non-smokers, or heavy smokers have a lower HR than that of light/occasional smokers when receiving chemotherapy. We then looked into these studies, the data in 24 large clinical trials for various chemotherapeutic modalities for NSCLC, including a set of separated data detailing treatment with programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors. These studies included 9,498 ever smokers, 1,811 current smokers, and 4,030 never smokers. Based on the analysis, we found that smokers with NSCLC

had a better treatment response, and this may not be due to isolated incidents or a result of experimental errors, especially in the case of the patient population treated with PD-1 and PD-L1 inhibitors. Interestingly, the HR values of smokers were significantly lower than that of non-smokers with a P-value of 0.0476. Furthermore, a recent study states that smoking status was suggested as the most important, accessible predictor of the efficacy of single drug in the PD-1/PD-L1 inhibitor family in the treatment of NSCLC patients. Although the data in these trials may not represent the entire picture of the effect of PD-1/ PD-L1 inhibitors in smokers with NSCLC, smoking status may be a potential biomarker for predicting the response of these targeted drugs. Future clinical trials should provide further, detailed analysis on the smoking status and related data on the efficacy of chemotherapeutic regimens for NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); PD-/PD-L1 inhibitors; Smoking

Abbreviations: NSCLC: non-small cell lung cancer; HR: hazard ratio; PFS: progression-free survival; OS: overall survival; PD-1: Programmed death-1; PD-L1: Programmed death-ligand-1

1. Introduction

Smoking is considered a serious problem that leads to diseases particularly non-small cell lung cancer (NSCLC). According to the Centers for Disease Control and Prevention (CDC)(https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm) as well as International Agency for Research on Cancer (IARC) (https://www.iarc.fr), smoking is associated with about 80% to 90% of lung cancers. Smokers represent a considerable proportion of populations in developing countries. Smoking cessation is critical for the prevention of lung cancers. While we agree with the fact that smoking increases the risk of lung cancers, there have been no studies on whether smoking negatively impacts chemotherapeutic treatment of lung cancers.

2. Smoking Will Not Be Completely Eliminated For Several Decades

Smoking has a long history. Although considerable effort has been put forth by governments, organizations, and the public, it will not be completely eliminated in the near future. According to the reports from the World Health Organization (WHO) [1], in 2015, over 1.1 billion people smoked tobacco, which represented about one-seventh of the world population. There are currently more than 300 million smokers in China, nearly one-third of the world's total. According to DCD reports [2], an estimated 14.0% of U.S.

citizens were cigarette smokers in 2017, representing a 67% decline since 1965. Despite the improvement in rates, 14% still represented a sizeable proportion as it equates to approximately 34 million people. Such a large number is not likely to decline rapidly because until 2019, “only 37 countries, representing 15% of the world’s population, have completely banned all forms of tobacco advertising, promotion, and sponsorship” [1]. Therefore, smoking behaviors are not expected to completely cease in the near future. Rather, a large population will continue to do so, especially in lung cancer patients in which smokers represent its majority. As such, drug development that targets smokers may be a valuable approach for lung cancer treatment.

3. Examination of Current Clinical Trials

While smoking is recognized to be harmful for human health as well as for lung cancer treatment, a few clinical trials demonstrated that smokers with NSCLC responded better than non-smokers to treatment. The first volume of Lancet Oncology in 2018 included two publications on clinical trials for multiple drug treatments on patients in clinical trials on NSCLC. One such trial by Zhong et al. [3] included

data on smoking status (Table 1). Their data indicated that the HR value of smokers was slightly less than the value in non-smokers, with a P-value of 0.896. This work was not the first trial showing that smokers had a lower HR. As early as 2014, Butts et al. stated that smokers had a much lower HR than that of non-smokers in their two sets of data, with HR of overall survival (OS) 0.75 and 1.07 in two sets of subjects who had ever smoked a cigarette (ever smokers) and 1.51 and 4.90 in two sets of subjects who had never smoked (never smokers) [4] (Table 1). Furthermore, Govindan et al. [5] recently reported that heavy smokers had a lower HR (0.88) than light or non-smokers (1.19) (Table 1). Although there were no P-values provided to show the statistical significance in these cases, the data indicated that smoking had no negative impact on the patients' response to drug treatment. (Table 1).

4. Definitive Conclusions Cannot Be Drawn From Most Large-Scale Clinical Trials

The relationship between smoking status and treatment response in NSCLC patients resulted in a mixed picture. In the beginning, we started performing a PubMed search on May 10, 2018 by using the keywords "non-small-cell-lung-cancer trial III" with the restriction that the studies must be clinical trials performed in humans in the last 10 years. A total of 868 publications were identified. We examined these publications and collected the data from a total of 31 large clinical trials, each of which has at least 100 patients. Among them, 24 studies, with a total of over 14 thousand patients, compared the HR values of never smokers with ever smokers (Table 1). These were all randomized Phase 3 clinical trials. Data from 8 out of these studies included the HR values of current smokers. The results in the 24 large clinical trials are listed in Table 1. These data did not show a statistically significant difference between non-smokers and smokers. First, P-values between non-smokers and smokers were calculated from all the studies. These calculations, however, resulted in a nonsignificant P-value, 0.922. Next, P-values were calculated from data in studies where current smokers were differentiated from former smokers. Our analysis resulted in a P-value of 0.670 between never smokers and current smokers, seemingly suggesting that smoking cessation did not improve the efficacy of chemotherapy in treating NSCLC. However, there is not enough data differentiating lung cancers by sub-type (e.g., adenocarcinoma, squamous, etc.) nor to perform a sub-group patient analysis (sex, age, ethnicity, etc). Drawing a definitive conclusion from various clinical trials is difficult due to the existence of many confounding factors and issues in study design. Differentiating heavy from light smokers, those who had quit smoking for a longer than those who had recently quit, and between genders in the smoking population would help eliminate confounding factors and improve the study design to further investigate this clinical question.

5. Analysis of Treatment Efficacy Should be Based on Individual Drugs

One question that we explored was whether the effect of chemotherapy on smokers was dependent on the specific modality. Considering the complexities in cancer treatment, analyses of individual efficacies in chemotherapeutic treatments for smokers with NSCLC is essential. Perhaps there might be some treatments better suited for patients with a more extensive smoking history. We found in recent reports that the response to treatment by PD-1 and PD-L1 inhibitors were positive in smokers. The last four entries listed in Table 1 summarized the results from four clinical trials in which patients were treated with PD-1 and PD-L1 inhibitors. The first study by Reck et al. investigated treating NSCLC patients with Pembrolizumab, a PD-1 inhibitor.[6] (Table 1), in which the data showed that both current and former smokers had lower HR values than non-smokers. In the second study by Borghaei et al. NSCLC patients were treated with Nivolumab, a different PD-1 inhibitor [7]. Although the authors did not differentiate between current and former smokers, they found that smokers had a lower

HR value than non-smokers. The next two reports by Socinski et al. and Barlesi and colleagues analyzed NSCLC treatment with Atezolizumab and Avelumab, respectively [8-9] (Table 1). These two drugs belong to the PD-L1 class. In both trials, the current and former smokers responded to treatment better than non-smokers. It is intriguing that four clinical trials studying chemotherapy efficacy in NSCLC patients based on the same drug class all resulted in lower HR values in smokers. Furthermore, all of these clinical trials tested the efficacy of a single drug and resulted in a statistically significant P-value of 0.048 when comparing smokers to nonsmokers. Thus, there were no confounding factors that would need to be considered such as those in a multi-regimen based chemotherapy.

Table 1: HR values and smoking status of patients with non-small-cell lung cancer in large clinical trials.

First author/publication information	**HR* type**	**#Total patients**	**(HR) Ever smoker**	**# Ever smoker**	**(HR) Never smoker**	**# Never smoker**	**(HR) Current smoker**	**# Current smoker**
Miller/Lancet Oncol. 2012 May;13(5):528-38	PFS	585	2.19	27	1.2	245	0.81	118
Miller	OS	585	0.3	27	0.36	245	0.46	118
Wu/Lancet Oncol. 2013 Jul;14(8):777-86	PFS	451	0.87	101	0.4	219	0.77	131
Wu/Lancet Oncol. 2014 Feb;15(2):213-22	PFS	364	0.39	12	0.24	280	0.81	72
Rosell/Lancet Oncol. 2012 Mar;13(3):239-46	PFS	173	1.05	34	0.24	120	0.56	19
Ciuleanu/Lancet Oncol. 2012 Mar;13(3):300-8.	OS	424	1.1	123	0.86	74	0.9	227
Johnson/J Clin Oncol. 2013 Nov 1;31(31):3926-34.	PFS	743	0.79	178	0.34	66	0.74	129
Peters/N Engl J Med. 2017 Aug 31;377(9):829-838	PFS	303	0.42	96	0.44	190	1.16	17
Cappuzzo/Lancet Oncol. 2010 Jun;11(6):521-9	PFS	989	0·66	242	0·56	152	0·80	490
Cappuzzo/	OS	989	0·75	242	0·69	152	0·88	490
Zhong/Lancet Oncol. 2018 Jan;19(1):139-148	OS	414	0.56	52	0.61	167	-	-
Govindan/ J Clin Oncol. 2017 Oct 20;35(30):3449-3457	OS	1302	0.88 (Heavy smoke)	1147	1.19	141 (all others)	-	-
Antonia/N Engl J Med. 2017 Nov 16;377(20):1919-1929	PFS	713	0.59	649	0.29	64	-	-
Shaw/Lancet Oncol. 2017 Jul;18(7):874-886	PFS	231	0.68	95	0.41	132	-	-

Soria/N Engl J Med. 2018 Jan 11;378(2):113-125.	PFS	556	0.48	199	0.45	357	-	-
Butts/Lancet Oncol. 2014 Jan;15(1):59-68	OS	806	0.75	762	1.51	44	-	-
Butts	OS	433	1.07	402	4.9	31	-	-
Pirker/Lancet Oncol. 2012 Jan;13(1):33-42	OS	776	1.02	609	0.94	165	-	-
Pirker	OS		0.74		0.62		-	-
Pirker/Lancet. 2009 May 2;373(9674):1525-31	OS	1125	0.89	879	0.79	244	-	-
Zhou/Lancet Oncol. 2011 Aug;12(8):735-42	PFS	154	0.21	45	0.14	109	-	-
Zhang/Lancet Oncol. 2012 May;13(5):466-75	PFS	375	0.52	136	0.86	160	-	-
Mitsudomi/Lancet Oncol. 2010 Feb;11(2):121-8	PFS	172	0.575	54	0.466	118	-	-
Paz-Ares/Lancet Oncol. 2012 Mar;13(3):247-55	PFS	539	0.7	419	0.41	116	-	-
Herbst/Lancet. 2011 May 28;377(9780):1846-54	OS	636	1.06	569	0.44	67	-	-
Patel/J Clin Oncol. 2013 Dec 1;31(34):4349-5	OS	1529	1.02	1339	0.72	182	-	-
Herbst/Lancet Oncol. 2010 Jul;11(7):619-26	PFS	1391	0.84	1060	0.62	331	-	-
	OS		0.95		0.77		-	-
Reck/N Engl J Med. 2016 Nov 10;375(19):1823-1833	PFS	305	0.47	216	0.9	24	0.68	65
Borghaei/N Engl J Med. 2015 Oct 22;373(17):1627-39.	PFS	582	0.7	458	1.02	181	*0.7***	*458*
Socinski/N Engl J Med. 2018 Jun 14;378(24):2288-2301.	PFS	800	0.58	585	0.8	108	*0.58*	*585*
Barlesi/Lancet Oncol. 2018 Nov;19(11):1468-1479	OS	1321	0.83	444	1.69	84	*0.83*	*444*
Sum∑			23.225	9498	20.216	4030	6.21	1811
P value never smoker vs ever smoker			0.9228					
P value never smoker vs current smoker			0.670					
P value ever smoker vs ever smoker from data of four publications (PD-1 inhibitors)			0.0476					

*PFS= progression-free survival, OS= overall survival; ** These HR data include all smokers, therefore are listed in both columns of ever smoker and current smoker.

6. Identifying Specific Drugs for Smokers with NSCLC Is Essential For Providing Better Patient Outcomes

While we do not argue the high risk of developing lung cancer with smoking, we believe that smokers may respond better to the treatment with certain chemotherapeutic agents than non-smokers. Certainly, our analysis can be interpreted in many ways. Idiosyncratic characteristics in a small number of patients in both smoker and non-smoker groups could have affected the HR values. More data will increase the statistical power in future studies. Another explanation is that genotypes or individualized environmental factors may have influenced the HR of patients in certain subgroups. Nevertheless, we believe that studying the differences in treatment responses between smokers and non-smokers is essential in improving outcomes in patients with NSCLC. If certain agents are indeed more effective in smokers than non-smoker or vice-versa, treatment plans with PD-1 and PD-L1 inhibitors should be individualized.

In a recent report from a multicenter, retrospective study, Ng et al. reported that "smoking status potentially was the most important, easily available predictor of single PD-1/PD-L1 inhibitors (PDi) efficacy" [10]. We noticed that the HR values of never, former, and current smokers in this study were 1, 0.488, and 0.116 respectively. This observation was especially interesting because an earlier study reported that smoking could induce the expression of PD-L1 and KRAS-mutant cells in NSCLC heterogeneously expressed PD-1/PD-L1/PD-L2 [11]. Therefore, we strongly believe that more attention should be devoted to investigating the differences in chemotherapy efficacy in smokers versus nonsmokers with NSCLC. Perhaps PD inhibitors work better in smokers because of smoking-induced cellular expression of PD-1/PD-L1. An alternative explanation that might be worthwhile to be considered is that smoking causes an idiosyncratic synergy with PD inhibitor agents, due to increased sensitivity to chemotherapy in those who smoke. Certain dosages of tobacco under certain durations and individualized conditions may be the factor in contributing to this "sensitivity". As of now, it is certainly difficult to atrribute a single explanation for chemotherapeutic sensitivity in NSCLC. Food-induced or oral tolerance has been well recognized as well as respiratory immune tolerance in asthma [12], but pulmonary immunological tolerance in NSCLC is an area that requires further research.

If there is a chance that smoking induces immune sensitivity to chemotherapy in NSCLC or other pulmonary neoplasms, this knowledge would greatly benefit the human population in developing countries, not only for smokers but also for those developing cancer from second-hand smoke. First, the smoking population is perhaps the largest disease-prone population in the world. To explore the possibility of smoking-induced chemotherapy sensitivity or other related possibilities, clinical studies to follow should perform a detailed analysis based on smoking status. They should include patient factors such as but not limited to previous smokers, current smokers, light and heavy smokers, male and female smokers, ethnicity, and age. In addition, analyses should be conducted to investigate whether any other parameters influence the response to treatment. Factors such as starting age of smoking, duration of a smoking period, types of smoking apparatus, and number of packs a day should also be considered.

Smoking is a major risk factor in developing lung cancer. However, its potential for inducing chemotherapy sensitivity has not been adequately studied. Other harmful materials or behaviors have been extensively studied and have been implemented in improving health in patients (Table II). For example, the use of opioids in reducing pain balanced by its respiratory risks [13]. With alcohol, positive cardiovascular effects in moderation balanced by negative neurological consequences in excess [14] have been widely

recognized and investigated. In addition, arsenic trioxide's cytotoxic effects were discovered to be useful in cancer treatment[15]. Harmful behaviors have both a relatively positive as well as a well-recognized negative result. Early in this decade, melamine finds its way in adulterated milk [16]. Also, vitamin D is important for bone growth but results in harmful hypercalcemia when in excess [17]. Even running marathons, a nationally recognized sport, has pros and cons [18]. While smoking cessation can improve pulmonary function, perhaps tailoring the use of PD-1 and PD-L1 agents to smokers can result in even better patient outcomes.

There are certainly enormous hurdles in studying smoking-induced pulmonary immunological sensitivity to chemotherapeutic agents. While conclusive results cannot be reached because of the dearth of data on smoking status, current studies seemingly suggest that there is a possibility for smoking-induced immunity and better efficacy with PD-1 and PD-L1 agents in selected patients. Considering the large population of smokers and its negative systemic impacts, this clinical question should be further explored through more comprehensive studies in the future.

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Competing Interests

The authors declare no conflicts of interest.

Authors' Contributions

SG, SW JL MR, LW, WG conceived and designed the experiments; JL, LW performed data searching and collection; JL, LW, TZ analyzed the data; JL, LW SG, SW JL, LW, WC, WG interpreted the results; JL, LW, TZ, WC drafted the manuscript; TZ, SW, MR, WC, SG, WG edited the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Patient Consent for Publication

Not applicable.

References

1. Global Health Observatory (GHO) data. World health organization.
2. Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults—United States, 2017. Morbidity and Mortality Weekly Report 67 (2018): 1225-1232.
3. Wen-Zhao Zhong, Qun Wang, Wei-Min Mao, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 19 (2018): 139-148.
4. Butts C, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lungcancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 15 (2014): 59-68.
5. Govindan R, Szczesna A, Ahn MJ, et al. Phase III Trial of Ipilimumab Combined with Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer. J Clin Oncol 35 (2017): 3449-3457.
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al. KEYNOTE-024 Investigators. Pembrolizumab versus

Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 375 (2016): 1823-1833.

7. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 373 (2015): 1627-1639.
8. Socinski MA, Jotte RM, Cappuzzo F, et al. IMpower150 Study Group. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 378 (2018): 2288-2301.
9. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol 19 (2018): 1468-1479.
10. Ng TL, Liu Y, Dimou A, et al. Predictive value of oncogenic driver subtype, programmed death-1 ligand (PD-L1) score, and smoking status on the efficacy of PD-1/PD-L1 inhibitors in patients with oncogene-driven non-small cell lung cancer. Cancer 125 (2019): 1038-1049.
11. Calles A, Liao X, Sholl LM, et al. Expression of PD-1 and Its Ligands, PD-L1 and PD-L2, in Smokers and Never Smokers with KRAS-Mutant Lung Cancer. J Thorac Oncol 10 (2015): 1726-1735.
12. Sekerel BE, Sahiner UM, Can M, et al. The effects of inhaled formoterol on the autonomic nervous system in adolescents with asthma. Ann Allergy Asthma Immunol 107 (2011): 266-272.
13. Becker WC, Fiellin DA. Abuse-Deterrent Opioid Formulations - Putting the Potential Benefits into Perspective. N Engl J Med 376 (2017): 2103-2105.
14. Baumann S, Gaertner B, Haberecht K, et al. Who benefits from computer-based brief alcohol intervention? Day-to-day drinking patterns as a moderator of intervention efficacy. Drug Alcohol Depend 175 (2017): 119-126.
15. Ghavamzadeh A, Jalili M, Rostami S, et al. Comparison of induction therapy in non-high risk acute promyelocytic leukemia with arsenic trioxide or in combination with ATRA. Leuk Res 66 (2018): 85-88.
16. Gabriels G, Lambert M, Smith P, et al. Melamine contamination in nutritional supplements--Is it an alarm bell for the general consumer, athletes, and 'Weekend Warriors'? Nutr J 14 (2015): 69.
17. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. N Engl J Med 345 (2001): 66-67.
18. Žákovská A, Knechtle B, Chlíbková D, et al. The Effect of a 100-km Ultra-Marathon under Freezing Conditions on Selected Immunological and Hematological Parameters. Front Physiol 8 (2017): 638.