Short Communications

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Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Atezolizumab Post Chemo-Radiation

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Abstract

Objective: The use of Durvalumab following chemoradiotherapy in patients with stage III NSCLC, considerably increased PFS (progression free survival) and OS (overall survival). Unfortunately, Durvalumab is currently not reimbursed for this indication in Lebanon so far. We have used Atezolizumab on a series of patients to the similar mechanism of action. We report in this paper the incidence of pneumonitis using this approach. **Methods:** We selected from our lung cancer registry, a group of patients diagnosed with stage III NSCLC, who received Atezolizumab (Tecentriq) as consolidation therapy following concurrent chemoradiation therapy. We specifically look at the incidence and severity of pneumonitis based on Common Toxicity Criteria and Adverse Events (CTCAE). Finally, we analyzed patient and tumor characteristics looking for predictive markers for pneumonitis. **Result:** Of the 14 patients who met our selection criteria, 8 developed pneumonitis and 6 did not. Age, gender and smoking status did not affect the probability of having pneumonitis, with p-values of 0.98,1 and 0.86 respectively. The impact of having PDL-1 status on pneumonitis could not be assessed due to our small sample size. The mean onset of pneumonitis after completion of chemoradiotherapy is 3.62 and after starting Atezolizumab is 2.45 months. **Conclusion:** The administration of Atezolizumab carries a significant risk of developing pneumonitis following chemoradiation therapy for NSCLC. The presence of certain factors and tumor characteristics might affect the chances of having pneumonitis. However due to our small sample size, definitive conclusions could not be drawn.

Keywords: Atezolizumab- non-small cell Lung cancer- durvalumab- pneumonitis

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Introduction

Lung cancer is the second most common cancer and the leading cause of cancer-related death worldwide (Thandra et al., 2021). This is mostly due to its late onset of symptoms and being discovered at advanced stages. Approximately 20 to 30 % of Non-Small Cell Lung Cancer (NSCLC) patients have stage III disease, a large percentage of whom have an unresectable tumor. Concurrent chemotherapy and radiation therapy (Ahn et al., 2015) was the standard of care for patients with unresectable stage III NSCLC for many years. Recently, the PACIFIC trial demonstrated that the addition of Durvalumab significantly extended the progression free survival (PFS) and overall survival of these patients(Faivre-Finn et al., 2021). Durvalumab can cause mild to severe adverse effects such as cough, fatigue, dyspnea, pneumonia, pneumonitis, and others.

Given the unavailability of Durvalumab in Lebanon, we have used Atezolizumab on a series of patients with stage III NSCLC after completion of concurrent chemotherapy and radiation therapy. It was noticed that these patients have a high incidence of pneumonitis. We present in this article the outcome of these patients.

Materials and Methods

Our list of patients was derived from the lung cancer database at the American University of Beirut Medical Center. Eligible patients were 18 years old or older, diagnosed with stage III NSCLC who had concurrent chemotherapy and radiation therapy and were treated with consolidation Atezolizumab since January 2018. No patient contact was done, and all data was collected from the patient's medical records.

The diagnosis of pneumonitis (Zhong et al., 2020) depends on several features, most importantly symptoms (cough, dyspnea, weight loss) and radiological changes such as the development of new areas of consolidation or ground-glass opacities. Pneumonitis was graded according to the Common Toxicity Criteria and Adverse Events (CTCAE) where grade 1 is for asymptomatic pneumonitis, grade 2 is for patients who are minimally symptomatic. More severe symptoms and life-threatening respiratory compromise corresponds to grade 3. Patients with grade

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4 pneumonitis are in acute respiratory distress and they require ventilation. Finally, patients who have grade 5 pneumonitis are deceased.

We determined our p-value using the two-sample t-Test assuming unequal variances. This tool was conducted to compare the means of the patients' characteristics with pneumonitis versus those without pneumonitis. The results are shown in Table 1.

Results

Between January 2018 and January 2022, 14 patients were identified to fit our criteria. The mean age of all the patients was 65.23, with half (n=7) being females and 75% being current/former smokers. 57.1% of the patients had adenocarcinoma, while only 35.7% had squamous cell carcinoma. The status of PDL-1 was reported for 12 patients, with 21.4% having <1% PDL-1, 50% having from 1 to 49% PDL-1 and 14.3% had more than 50%. Out of total patient population, 8 patients were found to have pneumonitis after starting Atezolizumab.

In our selected patients, age, gender, and smoking status distribution were similar between the group of patients who developed pneumonitis and the group who did not (p values of 0.98, 1 and 0.86 respectively). In both groups, 50% of the patients had PDL-1 positivity between 1 and 49% of cells. 12.5% of patients with pneumonitis had PD-L1 negative tumors versus 33.3% in those without pneumonitis. However, two of the patients with pneumonitis have unknown PDL-1 status therefore a conclusion cannot be drawn regarding the PDL-1 status.

The only variable that seemed to affect the odds of developing pneumonitis is histology. In patients diagnosed with squamous cell carcinoma, all of them developed pneumonitis (35.7%). Patients who developed pneumonitis, 62.5% were known to have squamous cell carcinoma. These findings do raise the question regarding the effect of histology on the development of pneumonitis. Although, the p-value of 0.078 does not support this observation, we cannot draw a conclusion given the small pool of patients.

Three of our patients developed grade 1 pneumonitis more than 4 months after completion of their chemoradiotherapy regimen and 3.62 months after starting Atezolizumab. However, patients with grade 2 pneumonitis were diagnosed earlier, 2.89 months after finishing chemoradiotherapy and less than 2 months after starting Atezolizumab. Evidently, the more severe and rapid onset grade 3 pneumonitis appeared 3.22 months after the completion of chemoradiotherapy and around

Table 1. Patients' Characteristics and Their Percentages in Each Category

Characteristics	All Patients n=14	Patients with Pneumonitis n=8	Patients without Pneumonitis n=6	p-value
Mean Age (Years)	64.72	64.7	64.67	0.98
Sex				
Female, n (%)	7 (50%)	4 (50%)	3 (50%)	1
Male, n (%)	7 (50%)	4 (50%)	3 (50%)	
Smoking Status				0.86
Current Smokers, n (%)	7 (50%)	4 (50%)	3 (50%)	
Ex-Smokers, n (%)	4 (28.6%)	2 (25%)	2 (33%)	
Non-Smokers, n (%)	3 (21.4%)	2 (25%)	1 (16.7%)	
Histology				
Adenocarcinoma	8 (57.1%)	3 (37.5%)	5 (83.3%)	0.078
Squamous Cell Carcinoma	5 (35.7%)	5 (62.5%)	0 (0%)	
Unknown	1 (7.2%)	0 (0%)	1 (16.6%)	
PDL-1 Status				0.19
<1%	3 (21.4%)	1 (12.5%)	2 (33.3%)	
1-49%	7 (50%)	4 (50%)	3 (50%)	
>50%	2 (14.3%)	1 (12.5%)	1 (16.7%)	
Unknown	2 (14.3%)	2 (50%)	0 (0%)	

† Kruskal-Wallis ANOVA, two sided P.value<0.0

Table 2. The Onset of Pneumonitis after Starting Chemoradiotherapy or Atezolizumab

Grade	Mean Onset of pneumonitis after completion of Chemoradiotherapy in months	Mean onset of pneumonitis after starting Atezolizumab in months
1	4.76	3.62
2	2.89	1.76
3	3.22	1.96
Average	3.62	2.45

2 months after receiving the first dose of Atezolizumab.

On average, the odds of developing pneumonitis are 3.62 months after chemoradiotherapy completion and 2.45 months after the start of Atezolizumab. The findings are shown in Table 2.

Discussion

The standard of care for patients with unresectable stage III NSCLC has been established as concurrent chemotherapy and radiation for many years. A meta-analysis of 14 randomized controlled trials established the advantage of concurrent chemoradiotherapy in comparison to sequential chemoradiotherapy. It was found that the use of concurrent chemoradiotherapy improved the survival rates at 2, 3, 4 and 5 years (Xiao and Hong, 2021). The American Society of Clinical Oncology recommended at least 2 to 4 cycles of platinum-based chemotherapy along with thoracic radiotherapy (Xiao and Hong, 2021).

In the phase III Pacific trial, the addition of one year of durvalumab after concurrent chemo/radiation therapy in patients with unresectable stage III NSCLC yielded significant improvement in median progression-free survival and overall survival (Antonia et al., 2017). This lead to its approval in this indication in multiple countries.

In the Pacific trial, 96.8% of the patients who received Durvalumab were recorded to have adverse effects versus 94.9% in the placebo group (Antonia et al., 2017). The most common side effects were cough, fatigue, and pneumonitis. Pneumonitis was the leading cause to the discontinuation of Durvalumab. It occurred in 33.9% of the patients versus 24.8% in the placebo arm. However, they were mostly low grade, and the prevalence of grade 3-4 pneumonitis was similar in both groups (3.4% in Durvalumab arm versus 2.6% in the placebo arm).

Atezolizumab's adverse effect can range from mild to severe, it rarely causes life-threatening conditions (Xu et al., 2018). In fact, a systemic review compared the safety of different immune checkpoint inhibitors, and Azetolizumab was found to have the highest safety level among them.

In this article, we report the total of 14 patients who received Atezolizumab post chemoradiotherapy, and we report a high rate of pneumonitis in these patients.

The odds of developing pneumonitis, was irrespective of gender, age and smoking status, as described in the result section. The findings of PDL-1 were inconclusive, since 14.3% of the patients had unknown status and the pool of subjects is relatively small. Histology might play a role in determining the odds of developing pneumonitis, however, as we stress again, having a small pool of patients, results in ambiguous conclusions. An article (Suresh et al., 2018) discussing the emergence of pneumonitis in patients receiving immune checkpoint immunotherapy found the squamous subtype to be associated with a significantly higher rate of pneumonitis.

Pneumonitis can occur during the phase of chemoradiotherapy or after. In all patients, pneumonitis started 3 months after the end of chemoradiotherapy on average. It is important to note that the patients who received Paclitaxel and Carboplatin chemotherapy regimen are at a higher risk to develop pneumonitis compared to the general population regardless of immunotherapy intake. A randomized phase III trial compared the overall survival between patients diagnosed with stage III NSCLC, who received Etoposide and Cisplatin versus those who received Paclitaxel and Carboplatin. In the second group (Wa et al., 2010), the incidence of grade 2 and more radiation pneumonitis, is notably higher than that in the first group (33.3% vs 18.9%). A phase II trial (Lin et al., 2020) combining atezolizumab with chemoradiation in patients with unresectable NSCLCs argued that pneumonitis in these patients is mainly attributable to radiotherapy and questioned the contribution of immunotherapy.

It has been stipulated that the rate of pneumonitis with anti-PD 1 agents is mildly higher than that with PDL-1 inhibitors (Lin et al., 2020). Although the notion is still theoretical and unproven till now, it is being further explored in ongoing trials.

In our series, grade 1 pneumonitis patients were diagnosed incidentally on chest CT, which is performed routinely for treatment monitoring. They were able to finish their course of Atezolizumab and the use of steroids was not necessary. On average, the detection of grade 1 pneumonitis, was 4.76 months after the end of chemoradiotherapy versus 3.62 months after the start of Atezolizumab. For grades 2 and 3, the development of pneumonitis was faster. For grade 2 pneumonitis, it was detected 2.89 months and 1.76 months after the end of chemoradiotherapy and the start of Atezolizumab respectively. And for grade 3, it was 3.62 and 2.45 months respectively. Patients with grade 2 pneumonitis were complaining of mild symptoms such as cough and dyspnea and accordingly chest CT were performed, that confirmed their diagnosis.

All of our patients diagnosed with grade 3 received corticosteroid therapy and Atezolizumab was discontinued.

One major limitation of our report is the small sample size, which limited our ability to do meaningful statistical assessment trying to discern which patient and tumor characteristics put them at higher risk of developing pneumonitis. The data about histology showing that patients with squamous cell cancer are at higher risk seems strong, even-though it did not reach statistical significance. This is in accordance with other reported studies.

Larger studies looking at the incidence of pneumonitis in this setting are definitely needed. Our report is meant to raise a concern that needs to be confirmed or refuted in a larger prospective study

Author Contribution Statement

Dr. Arafat Tfayli and Dr. Lili Jose Saade wrote the main manuscript text, in addition both authors reviewed the manuscript.

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Approval

The study was approved by the Institutional Review

Board at the American University of Beirut.

Ethical Declaration

Our data was extracted from the lung cancer registry of the American University of Beirut.

Data Availability

Our data is enclosed within this manuscript.

Conflict of Interest

No conflicts of interest to disclose.

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