EFFICACY AND SAFETY OF PEMBROLIZUMAB MONOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS TREATED AT HANOI MEDICAL UNIVERSITY HOSPITAL

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This study evaluated the efficacy of pembrolizumab monotherapy response rate and progression-free survival and its tolerabilty in advanced non-small cell lung cancer patients. Thirty patients with lung cancer in metastatic or recurrent settings were treated with pembrolizumab monotherapy at Hanoi Medical University Hospital from October 2017 to October 2021. The mean age was 65.37 ± 5.46 (40-81). Most patients were male (86.7%). Most had non-squamous cell carcinoma (70%) and a Tumor Proportion Score (TPS) ≥ 50% (63.3%). The complete response rate was 3.3%, the partial response rate was 36.7%, and the stable disease rate was 43.3%. The overall control rate was 83.3%. Patients with TPS ≥ 50% had significantly higher response rate (47.4% vs 27.3%, p > 0.05). Median PFS was 9.6 ± 0.84 months; the figure for patients with TPS ≥ 50% was higher than for patients with TPS 1-49% (10.9 months vs. 7.2 months), p < 0.05. Only 6.2% had hyperthyroidism, and 3.1% had hypothyroidism, all in grade I. Therefore, pembrolizumab treatment in advanced non-small cell lung cancer is effective with a high disease control rate and is well-tolerated.

Keywords: Pembrolizumab, non-small cell lung cancer.

I. INTRODUCTION

According to GLOBOCAN 2020, lung cancer is currently the most common cancer and the leading cause of cancer-related death globally. In Vietnam, lung cancer also ranks first in both incidence and mortality rate in men.[1] Although many advances in diagnosis have been made in lung cancer; many patients are still presented to the hospital in the metastatic stage when the disease has already spread to other organs.[2]

In the past, systemic chemotherapy was the mainstay of treatment in advanced NSCLC (recurrence or metastatic stage). However, the overall survival was just approximately 12 months or shorter.[3] Targeted therapy emerged and was highly effective in patients with sensitizing mutations and mainly in the adenocarcinoma group. However, patients with no sensitizing mutations still gain little benefit with chemotherapy alone.

Immunotherapy has revolutionized cancer treatment in many solid tumors, especially lung cancer, using checkpoint inhibitor drugs. In the tumor microenvironment, some tumor cells can evade the immune attack by overexpressing PD-L1, which combines with PD-1 receptors on the surface of lymphocytes. This interaction inhibits the activation of T-cells, thus suppressing T-cell attack and inducing tumor immune escape. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptors (programmed cell death-1) on the surface of lymphocytes. It blocks its interaction with the PD-L1 receptors on the surface of tumor cells.[4] Many randomized trials worldwide have shown that pembrolizumab

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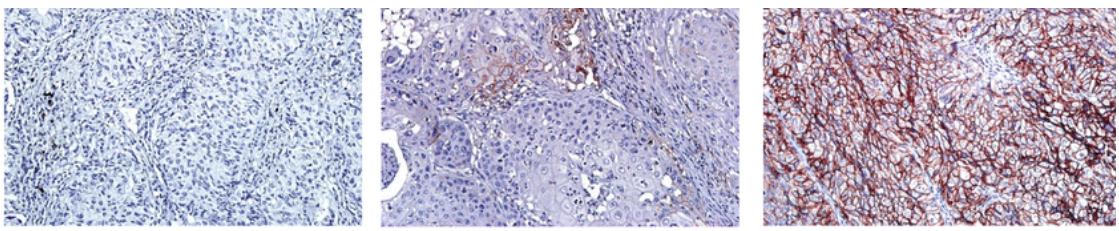
improved progression-free and overall survival compared with chemotherapy in lung cancer patients with good tolerability.[5,6]

In Vietnam, pembrolizumab treatment in the advanced stage NSCLC has been approved by the Ministry of Health since October 2017. However, up to now, studies reporting treatment results as well as toxicities of this drug in Vietnam are limited. Therefore, we conducted this study to evaluate the treatment results of pembrolizumab in advanced non-small cell lung cancer at Hanoi Medical University Hospital, focusing on the clinical benefits including the response rate and progression-free survival, and the safety profile.

II. PATIENTS AND METHODS

1. Patients

Patients were diagnosed with recurrent or metastatic non-small cell lung cancer, according to AJCC TNM 2017, at Hanoi Medical University Hospital from October 2017 to October 2021. They must have tumors express high PD-L1 level (TPS ≥ 50%) (detected by Immunohistochemistry staining for PD-L1 with 22C3 PharmDx), or TPS from 1 - 49% but refused to take concurrent chemotherapy or have a contraindication for chemotherapy. Eligible patients had to receive at least three cycles of pembrolizumab and had good performance status (ECOG 0,1). Only patients with measurable target lesions to evaluate using RECIST 1.1 were eligible. Patients could receive pembrolizumab as first-line treatment or second-line treatment, after progressing on first-line chemotherapy alone. Patients had one of the following characteristics were excluded: EGFR or ALK sensitizing-mutations, a synchronous second cancer, history of being treated with previous immunotherapy, autoimmune diseases, organ transplants or taking anti-rejection drugs received treatment of systemic corticosteroids for > 3 days or required daily systemic corticosteroid therapy (treatment is allowed when corticosteroids are discontinued at least seven days before pembrolizumab infusion), or history of HIV infection or active hepatitis B and C.



PD-L1 TPS < 1% PD-L1 TPS 1 to 49% PD-L1 TPS ≥ 50%

Figure 1. Examples of PD-L1 expressions

III. METHODS

In this descriptive, retrospective study, data were collected from 30 eligible patients for analysis by using convenience sampling. Study endpoints include pretreatment clinicopathological characteristics, treatment response, the relationship between response rate and PD-L1 expression level, progression-free survival, hematologic toxicities, and non-hematologic toxicity. Pembrolizumab was administered intravenously with the recommended dose of 200 mg every three weeks. No prophylactic drug was used before

pembrolizumab infusion as the guidance of the manufacturer. Patients was evaluated for toxicities and tolerability before starting the next cycles. Patients with clinical symptoms of hyperthyroidism or hypothyrodism would be confirmed by blood test. Patients with symptoms of intersitial lung disease would undergo CT-scan of the chest to exclude other causes. Other toxicities were evaluated according to CTCAE 5.0 classification. Statistical analysis was performed with the use of SPSS 20.0. This study was approved by the Director Board of Hanoi Medical Univerisity Hospital. All information was only used for scientific purposes.

III. RESULTS

1. Clinicopathological characteristics

Table 1. Clinicopathological characteristics

		n	Rate (%)
Mean age		65.37 ± 5.46 (40 - 81)	
Sex	Male	26	86.7
	Female	4	13.3
PS	ECOG 0	19	63.3
	ECOG 1	11	36.7
Histopathology	Squamous cell carcinoma	09	30.0
	Non-squamous cell carcinoma	21	70.0
PD-L1 expression level	TPS ≥ 50%	19	63.3
	TPS 1 - 49%	11	33.7

The majority of patients were male (86.7%). Most patients had non-squamous carcinoma (70%). TPS ≥ 50% accounted for nearly two-thirds of all patients (63.3%).

Table 2. Treatment results

		n	Rate (%)
Line of pembrolizumab treatment	First line	13	43.3
	Second line	17	56.7
Number of cycles	≤ 6	17	56.7
	> 6	13	43.3
Outcome	Complete response	1	3.3
	Partial response	11	36.7
	Stable disease	13	43.3
	Progressive disease	5	16.7

One patient achieved a complete response (3.3%). Partial response accounted for 36.7%, Stable disease accounted for 43.3%. The disease control rate was 83.3%.

Table 3. Relationship between PD-L1 expression level and response rate

	PD-L1 ≥ 50%		PD-L1 1 - 49%		Total	p
	n	%	n	%		
Response	9	47.4	3	27.3	12	0.279
Non-response	10	52.6	8	72.7	18	
Total	19	100	11	100	30	

The response rate in the high PD-L1 expression group (PD-L1 ≥ 50%) was higher than the lower expression PD-L1 group (1 - 49%) (47.4% vs. 27.3%). The difference in response rate between the two groups was not statistically significant, $p > 0.05$.

Median progression-free survival was 9.6 ± 0.84 months. The high PD-L1 expression group (PD-L1 ≥ 50%) had a longer median PFS than that of the lower PD-L1 expression group (PD-L1 1-49%) (10,9 ± 1,05 months vs. 7.2 ± 0.83 months). The difference between the two groups was statistically significant, $p < 0.05$.

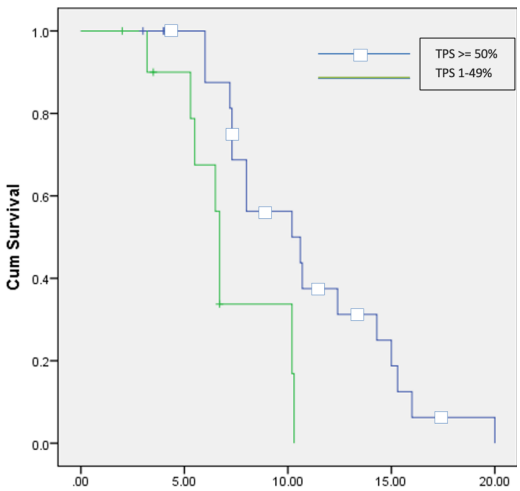


Figure 2. Progression-free survival (months)

Table 4. Immune-related toxicities

Toxicities	Grade 1		Grade 2		Grade 3,4	
	n	%	n	%	n	%
Hypothyroidism	1	3,3	0	0	0	0
Hyperthyroidism	2	6,7	0	0	0	0
Enteritis	0	0	0	0	0	0
Intertesital lung disease	0	0	0	0	0	0
Cutaneous reaction	0	0	0	0	0	0
Infusion reaction	0	0	0	0	0	0

Only two patients had hyperthyroidism (6.7%). One patient had hypothyroidism (3.3%). All were in grade 1.

IV. DISCUSSION

In our study, the overall response rate was 40%, of which there was one patient with complete response, accounting for 3.3%, and partial response accounting for 36.7%. Our results are similar to the results of the Keynote 024 study, of which the response rate is 44.8%.[5] The objective response rate in the group of patients with PD-L1 expression levels from 1 to 49% in our study was 27.3%, while this rate in the PD-L1 ≥ 50% group was 47.4%, which is similar to Keynote 042 study results (27% and 46.9%, respectively).[7] The role of PD-L1 expression in immunotherapy response has been discussed in many previous studies. The higher the level of PD-L1 expression, the higher the response rate.[8] This hypothesis was supported by the results of the Keynote 001 study, the first in a series of Keynote studies involving pembrolizumab. Specifically, the group with PD-L1 above 50% achieved an overall response rate of 39.1%, while this rate in the PD-L1 group from 1 - 49% was only 13.7%.[9] The results of the subgroup analysis in Keynote 024, Keynote 042, and Keynote 010 studies also showed similar results. In our study, the overall response rate between the PD-L1 ≥ 50% group was higher than the PD-L1 1 - 49% group, but the difference was not statistically significant ($p > 0.05$). This may be partly due to the limited sample size, and some patients received pembrolizumab as a second-line treatment in our study.

The response rate in our study is lower than the results of many trials evaluating the combination of pembrolizumab and chemotherapy. Specifically, the response rate in the Keynote 189 study in patients with non-squamous cell carcinoma who received a combination regimen of pembrolizumab and dual platinum-based chemotherapy was 47.6%. For patients with squamous cell carcinoma, this response rate in the Keynote 407 study was 57.9%. This difference is thought to be due to chemotherapy's role, which could increase the immunotherapy response. Specifically, several hypotheses have been studied that chemotherapy reduces the number of immunosuppressive cells and directly increases the activity of T lymphocy and natural killer cells (NK cells) through antigen expression. This mechanism enhances the efficacy of pembrolizumab in the treatment of lung cancer.[10,11]

In our study, the median progression-free survival (PFS) was 9.6 ± 0.84 months, ranging from 2.5 months to 20.75 months. In which the high PD-L1 expression group (PD-L1 ≥ 50%) had a longer median PFS than that of the lower PD-L1 expression group (PD-L1 1-49%) (10,9 ± 1,05 months vs. 7.2 ± 0.83 months). The difference between the two groups was statistically significant, $p < 0.05$. This result is similar to the results of the Keynote 024 trial when evaluating the effectiveness of pembrolizumab in the group of PD-L1 ≥ 50% with a median progression-free survival of 10.3 months.[5] The Keynote 042 trial of Pembrolizumab treatment on patients with PD-L1 expression levels above1% also had similar survival results to our study, in which PFS in the PD-L1 group ≥ 20% and PD-L1 from 1-19% was 6.2 months and 5.4 months, respectively.[7] Thus, patients with higher PD-L1 expression levels may benefit when treated with pembrolizumab.

The rate of immune-related toxicities in our study was 10%, lower than the results of the Keynote 024 study (29.2%), in which the incidence of high-grade toxicity severe (grade 3 or higher according to CTCAE 5.0) was also lower (0% vs. 9.7%). Specifically, the

results of our study showed that only 3.3% and 6.7% of all patients had hypothyroidism and hyperthyroidism, respectively; both were at grade 1. This result is similar to the study results of RoyS Herbst et al., with 8% of patients with hypothyroidism and 4% of patients with hyperthyroidism. None of the patients had enteritis, interstitial lung disease, and cutaneous or infusion reactions. Other researchs also reported a very low rate of these toxicities, accounting for less than 1%.[5,7,13] However, more studies in the Vietnamese population with larger sample sizes are still needed to have a more accurate evaluation of the immune-related adverse events associated with pembrolizumab.

CONCLUSION

Treatment with the immune checkpoint inhibitor Pembrolizumab in advanced non-small cell lung cancer in Vietnam brought about positive clinical benefits, with the disease control rate up to 83.3% and median progression-free survival up to 9.6 months. Pembrolizumab is also safe and well-tolerated with only 10% of patients suffering from immune-related toxicities, all of which were just in grade 1.

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