TITLE

EFFECTIVENESS AND SAFETY OF PEMBROLIZUMAB MONOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

ABSTRACT

Introduction: Immunotherapy has become a standard treatment for lung cancer; the objective of this study was to evaluate the effectiveness, safety of pembrolizumab monotherapy in patients with advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) used in real-world clinical practice.

Material and methods: Retrospective observational study of every patients treated with pembrolizumab in our centre from January 2017 to June 2019. Outcomes collected: sex, age, ECOG, PDL-1 levels, previous metastatic line therapies, adverse events (AE) and smoking status.

Results: A total of 62 patients were reviewed. The median age was 62.34±10.62 years, 48 (77.41%) were men and 91.93% of patients had ECOG 0. The median doses administered was 170.5 mg (108-240 mg) and median follow-up was 3 months (range: 1-38). A median of 4 cycles of pembrolizumab (range 1 to 56) were administered as monotherapy. The reason for treatment discontinuation was mainly due to disease progression in 38.70% patients or death in 30.64%. As first-line pembrolizumab monotherapy, median progression free survival was 7.7 months (95% CI: 3.66-11.73) (N=33). With respect to patients who were treated in second-third-line treatment, median PFS was 3.5 months (95%CI: 2.40-4.59) (N=29). As to overall survival, pembrolizumab-treated patients as first-line treatment reached 19 months median OG (95% CI: 13.36-24.63) (N=33) and those treated in second-third-line treatment got 11 months (95% CI: 3.4-18.5). 64.51% of patients presented some AE to pembrolizumab however, only, 9.38% of them were grade 3.

Conclusion: Pembrolizumab represents an effective and feasible alternative in terms of SLP. It is a well-tolerated treatment option.

Key words: Pembrolizumab, Non-small-cell lung cancer, immunotherapy and metastatic.

INTRODUCTION

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide [1].The average age at diagnosis ranges from 55 to 75 years, being more frequent in men than in women [2].

In Spain in 2017, 28.645 cases of lung cancer were diagnosed (23.398 in men and 5.247 in women) [3].

Non-small cell lung cancer (NSCLC) accounts for 80%–90% of all lung cancers, while small cell lung cancer (SCLC) has been decreasing in frequency in many countries over the past two decades [4]. During the last 25 years, the distribution of histological types of NSCLC has changed: in the United States, squamous cell carcinoma (SCC), formerly the predominant histotype, has decreased, while adenocarcinoma has increased in both genders. In Europe, similar trends have occurred in men, while in women, both SCC and adenocarcinoma are still increasing [5]. The World Health Organization (WHO) estimates that lung cancer is the cause of 1.59 million deaths globally per year, with 71% of them caused by smoking. Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades [5].

More than two thirds of patients are diagnosed in an advanced or metastatic stage (stage IIIB and IV) without potentially curative treatment options, therefore their prognostic is very unfavourable, being mean survival about 9-10 months in metastatic disease [6].

Recent advances in the understanding of the pathogenesis of NSCLC has led to the introduction of a wide variety of biological agents into clinical practice. The development of targeted therapy, drugs that inhibit certain receptors, such as mutated EGFR (Epidermal Growth Factor Receptor) or ALK (Anaplastic Lymphoma Kinase), have been shown to be effective in controlling the disease. However, many of these patients develop resistance to these types of drugs or do not have any of these target mutations. Due to this limitation, a new therapeutic strategy has been developed, immunotherapy [7].

Immunotherapy exerts its antitumor action by stimulating the immune response of patients against cancer, unlike classic treatments, which directly attack the tumour. Its main advantage is its ability to control the tumour for very long periods of time in a certain percentage of patients, which varies according to the type of cancer [8].

Immunotherapy called immune checkpoint inhibitors has transformed the treatment of NSCLC. These inhibitors have been shown to improve outcomes, including overall survival (OS), compared to both first-line and second-line chemotherapy when it’s given as monotherapy [9].

Currently, immunotherapy with blocking PD-1 (programmed death receptor 1) receptors antibodies or the action of PD-L1 protein (ligand of programmed death receptor 1) on these receptors has shown efficacy against a large number of tumours, such as melanoma, lung cancer, kidney, bladder, stomach, liver, head and neck, and some gynaecological tumours and

lymphomas. These treatments are usually administered intravenously, and their toxicity is usually lower than conventional treatments, such as chemotherapy [8].

In metastatic NSCLC, three immune checkpoint inhibitors have been approved: nivolumab (anti PD-1), pembrolizumab (anti PD-1) and atezolizumab (anti PD-L1), which can be used as first line of treatment as well as subsequent lines [9].

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment [10].

Treatment with pembrolizumab for patients with NSCLC includes from the previously treated population, as the first line; according to Summery Product of Characteristic (SmPC). Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations [10]. Also it is indicated for the treatment of locally advanced or metastatic NSCL in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA [10].

The KEYNOTE-010 study confirmed the benefit of treatment with pembrolizumab in NSCLC patients previously treated with 1% PDL1 expression and involved approval of this drug in patients with advanced NSCLC in progression to a doublet of chemotherapy based on platinum [11].

This was a phase II/III study in a population with NSCLC previously treated with PD-L1 expression on at least 1% of tumour cells. A total of 1,304 patients were randomized to receive pembrolizumab 2 mg / kg or 10 mg / kg every 3 weeks, or docetaxel 75 mg / m2 every 3 weeks. The primary endpoints were overall survival and progression-free survival both in the total population and in patients with PD-L1 expression on at least 50% of tumour cells. In the total population, median overall survival was 10·4 months with pembrolizumab 2 mg/kg, 12·7 months with pembrolizumab 10 mg/kg, and 8·5 months with docetaxel. Median progression-free survival was 3·9 months with pembrolizumab 2 mg/kg, 4·0 months with pembrolizumab 10 mg/kg, and 4·0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel or for pembrolizumab 10 mg/kg versus docetaxel. Among patients with at least 50% of tumour cells expressing PD-L1, overall survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14·9 months *vs* 8·2 months; and with pembrolizumab 10 mg/kg than with docetaxel (17·3 months *vs* 8·2 months). Likewise, for this patient population, progression free survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel

(median 5·0 months *vs* 4·1 months) and with pembrolizumab 10 mg/kg than with docetaxel (5·2 months *vs* 4·1 months) [11].

The KEYNOTE 024 study involved a paradigm shift in the treatment of advanced, previously untreated NSCLC, with the introduction of PD-L1 expression as a biomarker for the indication of treatment with pembrolizumab as first-line monotherapy.

The KEYNOTE 024 study is a phase III study conducted in 305 patients with advanced NSCLC, not previously treated, in any histological subtype, with 50% PDL1 expression and without the presence of epidermal growth factor (EGFR) mutations and / or translocations of the anaplastic lymphoma kinase (ALK) gene, in which patients were randomized to receive pembrolizumab at a dose of 200 mg every 3 weeks or a doublet of platinum-based chemotherapy selected by the researcher. The study was positive on its primary goal, PFS, which reached 10.3 months for the group of patients receiving pembrolizumab versus 6.0 months for patients treated with chemotherapy. The OS was 30 months versus 14.2 months (HR 0.63; p = 0.002) also in favour of the group of patients treated with pembrolizumab. It is important to note that this survival benefit was observed despite the high cross-linking of the study: 82 out of a total of 151 patients treated with chemotherapy received pembrolizumab progression. In terms of toxicity, the incidence of serious adverse effects was significantly lower in the group of patients treated with immunotherapy (26.6% vs. 53.3%) [12].

The main objective of this study is to analyze the effectiveness and safety of patients with non-small cell lung cancer, treated with pembrolizumab as monotherapy in routine clinical practice, to generate additional knowledge that can be useful in decision-making in a real-world setting.

Material and Methods

Retrospective, observational study carried out from January 2017 to June 2019, in a tertiary hospital. Pembrolizumab-treated patients with locally advanced or metastatic non-small cell lung carcinoma IV were eligible for participating in the study and were 18 years or older. Exclusion criteria: patients from whom adequate clinical and/or analytical information was not available for further analysis, also if they had sensitizing EGFR mutations, ALK translocations, or active autoimmune disease requiring systemic therapy or were receiving systemic glucocorticoids or other immunosuppressive therapy.

Outcomes collected:

1. Demographic variables: age and sex.
2. Clinical variables: PD-L1 level expression at the beginning of the treatment, number of metastases, previous chemotherapy treatments and performance-status score according to Eastern Cooperative Oncology Group (ECOG) (on a scale from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates no symptoms, and 1 mild

symptoms). Also variables that we collected were smoking status (current, former or never), comorbidities, histology and stage.

3. Effectiveness variables: OS as a primary endpoint and PFS as a secondary endpoint, assessed with the use of the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in cancer immunotherapy trials (iRECIST) [13]. The OS was calculated from the 1st day of pembrolizumab administration until death. The PFS was calculated from the 1st day of the administration of pembrolizumab until any progression based on imaging available (local or distant).
4. Safety of treatment was graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Select adverse events (those with potential immunologic causes) were grouped according to prespecified categories.

The information was obtained from the electronic clinical/medical records and the prescription and validate oncology treatments program (ONCOWIN®).

PD-L1 Biomarker Analysis

PD-L1 protein expression was evaluated by the use of a validated automated immunohistochemical assay (Dako North America) that used a rabbit monoclonal antihuman PD-L1 antibody (clone 28– 8, Epitomics). Samples were categorized as positive when staining of the tumour-cell membrane (at any intensity) was observed at prespecified expression levels of 1%, 5%, or 10% of cells in a section that included at least 100 tumour cells that could be evaluated.

Statistical analysis.

A descriptive analysis was performed for qualitative variables, using frequency tables. Quantitative variables were summarized using standard centralization and dispersion measures. The Kaplan-Meier method was used to calculate overall survival and progression-free survival. We compared the SG and SLP curves to conclude if there was statistically significant differences between patients with squamous and non-squamous NSCLC using the Mantel and Haenszel test. All analyses were performed by using SPSS v.17.

The study was approved by the Centre's Clinical Research Ethics Committee.

Results

1. Baseline characteristics of patients

A total of 62 patients diagnosed from stage IV NSCLC were included in this study. The median age of patients was 62.34±10.62 years, being most of them men (n=48, 77.41%). Referring to patient's initial performance status, 57 (91.93%) had an ECOG performance-status score of 0.

Thirty-three (53.22%) patients received pembrolizumab as first-line treatment whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS),except two patients, twenty-six (41.93%) as second-line and three (4.83%) as third-line treatment. The median doses administered was 170.5 mg (108-240 mg) and median follow-up was 3 months (range: 1-38). A median of 4 cycles of pembrolizumab (range 1 to 56) were administered as monotherapy. The reason for treatment discontinuation was mainly due to disease progression in 38.70% patients or death in 30.64%. Although seven of them (11.29%) go on receiving treatment. Baseline characteristics of patients are shown in table 1.

2. Effectiveness

As first-line pembrolizumab monotherapy, median progression free survival was 7.7 months (95% CI: 3.66-11.73) (N=33). With respect to patients who were treated in second-third-line treatment, median PFS was 3.5 months (95%CI: 2.40-4.59) (N=29). Global PFS was 5.6 months (95%CI: 3.69-7.50) (N=62). As to overall survival, pembrolizumab-treated patients as first-line treatment reached 19 months median OG (95% CI: 13.36-24.63) (N=33) and those treated in second-third-line treatment got 11 months (95% CI: 3.4-18.5). Median global OG was 16 months (95% CI: 6.93-25.06) (N=62).

3. Safety

Adverse events were as expected for pembrolizumab. Any grade adverse events (AEs) have been described in 40 patients (64.51%) during study period. The most common AEs were asthenia (occurring in 45.16% of patients, n=28), arthralgia in 12.90% (8), after hypothyroidism in 9.67% (6) and diarrhoea (8.06%, n=5). Also, patients suffered from nausea, hyporexia, and pruritus (6.45%, n=4). The rest of AEs happened with a frequency less than 5% (Table 2). According to the severity of the AEs, 90.63% (87) of them were grade (G) 1-2, and only 9.38% (9) of the AEs were G3 (Table 3). No grade 4 adverse reaction were reported.

No AE associated with the infusion was recorded. Regarding immune-related AEs, six cases of hypothyroidism occurred, all of them controlled with hormone replacement therapy, three cases of pneumonitis. Three cases of colitis and two cases of nephritis. Regarding treatment suspension, 6.45% (4) required temporary treatment suspension, three cases due to colitis and one owing to pneumonitis; and 3.22% patients (2) had permanently discontinued due to G3 nephritis. I was not observed any association between line of treatment and the appearance of AE nor with their severity.

Discussion

This real-world retrospective observational study evaluated pembrolizumab either as first-line treatment for advanced NSCLC patients with a TPS ≥50% or second-line for patients with a TPS<50%>1%. The primary and secondary endpoint in our study were to assess OS and PFS, respectively, in both groups of patients.

The median overall survival seen in the pembrolizumab group in our PD-L1 TPS 50% or greater population was 19 months (95% CI: 13.36-24.63), which matches with the results reported in the study, KEYNOTE-042 [14] (20·0 months, 95% CI 15·4–24·9) and the study HOPE-001 [15], 17.8 months (95% CI: 17.8-NA) months. However, it is numerically lower than that reported in KEYNOTE-024 (12) although the 95% CIs overlap (19 months, 95% CI: 13.36-24.63 in our study *vs* 30·0 months, 18·3 to not reached in KEYNOTE-024(12)) and conversely it is higher than the obtained in the PEMBREIZH study (16), 15.2 months (95% CI, 13.9 to not reached), although the 95% CIs overlap, again.

Our PFS findings are consistent with those of pembrolizumab in the phase 3 KEYNOTE-042 trial. The median PFS in our study of 7.7 months was similar to that in KEYNOTE-042 (7.1 months) and HOPE-001 study (8.3 months). Although, there are differences as to PFS obtained in KEYNOTE 024 (12) trial and PEMBREIZH study (16), 10.3 and 10.1 months, respectively.

These differences between studies could be explained by different factors. The differences between KEYNOTE-024 and KEYNOTE-042 were attributed to heterogeneity of KEYNOTE-042 population (14), KEYNOTE-024 was done mainly in North America and western Europe, with only 13% of patients enrolled in east Asia,10 whereas KEYNOTE-042 was done mainly in Asia-Pacific, eastern Europe, and South America, and enrolled 29% of patients in east Asia (12). However,

our cohort is homogenous, but the sample size is much smaller compared to the previous studies, we have 4.83% ECOG≥2 patients and brain-metastases patients (33.33%) which could be important factors that influenced on PFS and OS. Even differences in histological tumour features could have an effect on PFS, since squamous cell carcinoma seems to be associated with longer PFS on immunotherapy (11, 17-18).

Patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells received pembrolizumab as second-third-line treatment, reaching a median PFS of 3.5 months (95%CI: 2.40-4.59). This result is in the line with that achieved in the Keynote-10 study in which median PFS was 3.9 months (95%CI: 3.1-4.1) (11) and in the Keynote-001 study, median PFS: 3.0 (95%CI: 2.2-4.0) (19). As to OS, the result obtained [11 months (95% CI: 3.4-18.5)], is also consistent with that previously reported in the Keynote-10 study, 10.4 months (95% CI 9.4–11.9) and in the Keynote-001 study, median OS was 9.3 (8.4-12.4). It is remarkable in our cohort the huge confidence interval obtained, OS: 11 months (95% CI: 3.4-18.5), which could be related to sample size and also that there are seven patients who remain alive after 20 months of starting the pembrolizumab treatment however, 10 patients passed down before 6 months. This heterogeneity as to response to the treatment shows a clear relationship with the matastases that patients present before starting treatment, that is to say, patients who have bone, liver and central nervous system have reached less OS.

This study provides information about efficacy and safety of pembrolizumab in real world setting, and includes patients that would not have been eligible for clinical trials. Our study also assesses two different profiles of patients: those who were previously treated for NSCL and received pembrolizumab after failure of other therapeutic approaches and those treated as first line treatment. Our study has several limitations: small sample size and it is a retrospective study and some information could not be found in clinical records, which makes safety analysis difficult.

As to treatment-related side effects, 64.51% of patients suffered from some adverse event what matches the results achieved in the KEYNOTE-010 study and in the KEYNOTE-042 clinical trial (patients treated with pembrolizumab 2 mg/kg), where 63% patients got some side effects (11, 14). Also, it is remarkable that 14.51% of patients suffered from grade 3-5 side effects which coincides with what is described in KEYNOTE-10 and KEYNOTE-042 study population and (14.51% vs 13%-18%). Although more grade 3 colitis were picked up in our study (4.2% vs 1%).

Immune-mediated adverse event were observed in our cohort as well, which were responsible for some disruptions and discontinuations of the treatment such as it is explained in Summery Product Characteristics. The most important were hypothyroidism (9.67%), colitis (4.83%), pneumonitis (4.83%), this is consistent with previous studies (11, 14), where hypothyroidism and pneumonitis were highlighted.

It is important to add that it was not observed any relationship between level of PD-L1 expression on tumour cells and the incidence of side effects which was higher in patients older than 65 and ECOG-PS ≥1.

Conclusion

Although our sample size was small, our data supports the use of pembrolizumab as a treatment option for advanced or metastatic NSCLC patients. This data is relevant from a clinical point of view in real life since it is a heterogeneous, prevalent population with a poor prognosis that requires active treatments. In general, pembrolizumab is a well-tolerated treatment option without serious immune-related adverse effects.

Immunotherapy has chronicized the disease in some patients, although the vast majority of patients still cannot benefit from this aspect. This is in patients with rapid disease progression since immunotherapy as a treatment option that takes longer to take an effect than chemotherapy, limiting its use in these patients. Different response mechanisms from those known so far, such as pseudoprogression or hyper-progressive disease, will determine the most appropriate treatment decisions in the future.

In a real-world setting, this study demonstrated the efficacy and safety of pembrolizumab monotherapy with an overall response and PFS consistent with that of previous key clinical trials.

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