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Does pembrolizumab have an effect on prolonging overall survival in patients with non-small cell lung cancer expressing programmed death ligand-1 (PD-L1)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not pembrolizumab has an effect on prolonging overall survival in patients with non-small cell lung cancer expressing programmed death ligand-1 (PD-L1).

Study Design: Review of two randomized controlled trials and one cohort study published in English in peer review journals.

Data Sources: Two randomized controlled trials and one cohort study, which evaluated the efficacy of pembrolizumab on non-small cell lung cancer with PD-L1 expression compared to chemotherapy. All studies were found in PubMed database.

Outcomes Measured: Overall survival measured by Kaplan-Meier analysis of overall survival.

Results: Both of the RCT (Reck 2016 and Herbst 2016) showed pembrolizumab to be statistically effective in prolonging overall survival in patients with NSCLC expressing PD-L1 ($p=0.005$ and $p<0.0001$ respectively). Both studies showed a higher increase in overall survival in patients treated with pembrolizumab compared to those treated with traditional chemotherapy. In the cohort study conducted by Goldberg (2016), overall survival was measured to be 7.7 months (95% CI). Pembrolizumab also showed to have a positive effect on brain metastases as well.

Conclusions: All studies included in this systematic review indicate that pembrolizumab is effective in prolonging overall survival in patients with NSCLC expressing PD-L1.

Key Words: Pembrolizumab, NSCLC, chemotherapy, PD-L1

Introduction

Lung cancer is one of the most common cancers in the world. Symptoms typically do not present until the disease has advanced. Lung cancer is characterized by coughing, hemoptysis, dyspnea, chest pain, and weight loss. It is categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 80-85% of all lung cancer. NSCLC includes adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other rare subtypes such as adenosquamous carcinoma and sarcomatoid carcinoma.[1] This paper evaluates two randomized controlled trials (RCT) and one cohort study comparing the efficacy of pembrolizumab in treating NSCLC with the efficacy of the traditional chemotherapy treatments.

In 2017, there have been 222,500 reported new cases of lung cancer and 155,870 deaths from lung cancer.[2] It carries the highest mortality rate compared to other cancers, as it is responsible for 25% of cancer deaths.[2] The largest risk factor is tobacco use. Studies have shown that an average male smoker has a 9 to 10 -fold risk for developing lung cancer. The duration of smoking and the number of cigarettes smoked per day plays a key role in determining the increased risk for lung cancer.[3]

The cost of managing lung cancer is a heavy burden for most patients. The number of healthcare visits increase remarkably with the diagnosis of lung cancer and patients are frequently admitted to a hospital. In a study conducted by Vera-Llonch et al. patients with metastatic lung cancer receiving chemotherapy revealed an average of 1.5 hospital admissions, 8.9 days spent as inpatient, and 69 outpatient visits over the course of 334 days.[4] The same study revealed a total healthcare cost of $125,849 over the course of 334 days. The total cost was broken down to reveal the following: outpatient care was

responsible for 34% of the total cost, inpatient care was responsible for 20%, chemotherapy was responsible for 22%, and other outpatient medications were responsible for 24% of the total costs.

NSCLC is typically treated with surgical resection if indicated and chemotherapy. Chemotherapy is typically combined with an active cytotoxic agent. Common drugs used for treatment include cisplatin, carboplatin, docetaxel, and paclitaxel.[5] These treatments have shown to be effective initial treatments for NSCLC. However, these treatments may not work in certain patients with evolving disease. Recently, research relating to targeting specific receptor pathways has led to the development of immunomodulating drugs. In these trials, the programmed cell death protein 1 (PD-1) pathways have been targeted as the PD-1 receptor has shown to be an immune checkpoint inhibitor.[6] When the PD-1 receptors on B and T cells bind with PD-L1 and PD-L2 ligands on tumor cells, it leads to a suppression of T cells via a negative feedback loop.[6] The tumor cells are then unrecognized in the body's immune response. Pembrolizumab is an IgG4 monoclonal antibody that targets the PD-1 receptor pathway.[6] The antibody binds to the PD-1 receptor on B and T cells and prevent the binding to PD-L1 ligands expressed on tumor cells. An estimated 23-28% of all patients with NSCLC are found to have PD-L1 expression.[7] Pembrolizumab may be more effective than cytotoxic chemotherapy in prolonging overall survival for these patients.

Objective

The objective of this systematic review is to determine whether or not pembrolizumab has an effect on prolonging overall survival in patients with non-small cell lung cancer expressing programmed death ligand-1 (PD-L1).

Methods

This systematic review evaluates two randomized controlled trials and one cohort study. There were specific criteria used for the selection of these studies. The population of the studies targeted men and women over the age of 18 years with NSCLC with PD-L1 expression. The intervention used in the studies was intravenous pembrolizumab of various doses. The comparisons in the studies were various combination chemotherapy treatments including carboplatin, cisplatin, pemetrexed, gemcitabine, paclitaxel, and docetaxel. The primary outcome measured in the studies was overall survival of the patients.

The studies were obtained via PubMed and they were selected based on relevance to my research topic and the inclusion of patient oriented outcomes. The inclusion criteria used during the selection of the articles were as follows: studies that were published within the past 7 years and the inclusion of patient oriented outcomes – overall survival. The exclusion criteria were patients under the age of 18 years old. All articles were published in English and were published in peer-reviewed journals. Key words used to search for the articles included pembrolizumab and non-small cell lung cancer. The summary of statistics was reported via ARR, NNT, and p-value. The demographics and characteristics of the included studies are outlined in Table 1.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yr)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Herbst[6]	RCT	1034	>18	Pt 18 years and older with NSCLC;Previous tx of 2 or more cycles of platinum-doublet chemotherapy;Tx of tyrosine kinase inhibitor for pt with EGFR-sensitizing	Previous tx with PD-1 checkpoint inhibitors or docetaxel; Pt with active brain metastases or carcinomatous meningitis;	60	Pembrolizumab 10 mg/kg IV over 30 min q 3 wks

				mutation/ALK gene rearrangement; Eastern cooperative Oncology Group (EOCG) performance status of 0 or 1; PD-L1 expression on at least 1% of tumor cells	Pt with autoimmune disease that requires systemic steroids; Pt with interstitial lung disease or hx of pneumonitis that requires systemic steroids		
Reck[7]	RCT	305	>18	Pt 18 years and older w/ stage IV NSCLC w/o sensitizing EGFR mutation or ALK translocation; No previous systemic therapy for metastatic ds; EOCG score of 0 or 1; at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST); Life expectancy of at least 3 months; PD-L1 tumor proportion score of >50%	Pt receiving systemic glucocorticoids or other immunosuppressive tx; Pt w/ untreated brain metastases; Pt received systemic tx for autoimmune disease in the past 2 yrs; Pt with interstitial lung disease; Pt received glucocorticoids for pneumonitis	1	Pembrolizumab 200 mg IV q 35 wks for 35 cycles
Goldberg[8]	Cohort	36	>18	Pt 18 yo and older w/ stage IV melanoma or NSCLC; At least 1 untreated brain metastasis between 5mm and 20 mm; ECOG performance status of 0-1; Life expectancy >3 months; Adequate organ function	Pt w/ neurological sx attributable to brain metastasis; Use of corticosteroids to control neurological sx or perilesional edema; Pt w/ leptomeningeal disease or autoimmune disease; Previous tx of PD-1 or PD-L1 targeting agents	12	Pembrolizumab 10 mg/kg IV q 2 wks

Outcomes

The primary outcome measured in these studies was overall survival of the patients with non-small cell lung cancer treated with pembrolizumab. This was measured and analyzed using the Kaplan-Meier analysis of overall survival.

Results

In a study conducted by Reck et al., 305 patients with untreated advanced NSCLC with PD-L1 expression were randomly assigned with either pembrolizumab or a platinum-based chemotherapy.[7] There were a total of 154 patients in the pembrolizumab group and 151 patients in the chemotherapy group. The most common chemotherapy regimen used was carboplatin plus pemetrexed (67 out of 151 patients). Crossover from the chemotherapy group to the pembrolizumab group was allowed depending on disease progression. At the end of the trial, 66 patients from the chemotherapy group had crossed over to receive pembrolizumab after showing signs of disease progression.

At 6 months, 80.2% (95% CI, 72.9 to 85.7) of patients in the pembrolizumab group were still alive compared to 72.4% (95% CI, 64.5 to 78.9) of overall survival in the chemotherapy group. Patients receiving pembrolizumab had significantly longer overall survival compared to those receiving chemotherapy by the end of the trial. The hazard ratio for death was calculated to be 0.60 with a 95% CI, 0.41 to 0.89; P= 0.005. The NNT calculated was 13 (see Table 2), indicating that 13 people are needed to treat in order for 1 person to have longer overall survival after 6 months of pembrolizumab.

Table 2. Efficacy in pembrolizumab in prolonging overall survival in patients with advanced NSCLC as measured by Reck 2016

Study	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)	P-value	Confidence Interval (CI)
Reck (2016)	0.108	0.078	13	0.005	95% CI, 0.41 – 0.89

In another study conducted by Herbst et al., 689 patients with previously treated NSCLC and PD-L1 expression were randomly assigned to pembrolizumab and docetaxel.[6] There were 346 patients assigned to pembrolizumab and 343 patients assigned to docetaxel. Patients receiving pembrolizumab had longer overall survival than

those receiving docetaxel. The median overall survival was 12.7 months (95% CI, 10.0-17.3) for those receiving pembrolizumab and 8.5 months (95% CI, 7.5-9.8) for those receiving docetaxel. The 1 year overall survival was 52.3% for those receiving pembrolizumab and 34.6% for those receiving docetaxel. The hazard ratio for pembrolizumab 10 mg/kg vs. docetaxel was 0.61 with a 95% CI (0.49-0.75) and $p<0.0001$. The NNT was calculated to be 10 (see Table 3).

Table 3. Efficacy of pembrolizumab 10 mg/kg in prolonging overall survival in patients with advanced NSCLC as measured by Herbst 2016

Study	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
Herbst 2016	0.249	0.109	10

Goldberg et al. conducted a cohort study in which they followed 18 patients with NSCLC that were positive for PD-L1 expression and had untreated brain metastases.[8] They were treated with 10 mg/kg of pembrolizumab every 2 weeks and data were collected at 12 months. They measured brain metastases response to pembrolizumab as well as overall survival. At 12 months, 6 out of 18 enrolled patients showed brain metastasis response (33%; 95% CI, 14-59). Median overall survival was calculated to be 7.7 months with a 95% CI (3.5 – not reached). By the 12 month follow up, 8 patients have died from disease progression and 1 patient died from unknown reasons. Adverse reactions to treatments included grade II acute kidney injury via interstitial nephritis, grade III pneumonitis, grade III colitis, and grade IV hyperkalemia. The patient with grade III colitis discontinued treatment of pembrolizumab. There were no treatment related deaths reported. The study is still on going and they plan on publishing more reports as the data matures.

Discussion

A diagnosis of lung cancer carries heavy weight considering it has the highest mortality rate compared to other types of cancers. Although surgical resection and combination chemotherapy treatments are effective in treatment of most lung cancers, there still remains a population of patients with advanced disease that do not benefit from traditional therapy. As medical research advances and alternative treatment options such as pembrolizumab arise, patients are given the opportunity to remain hopeful and prolong overall survival. This systematic review encompasses studies that display the therapeutic benefits of using PD-L1 as a biomarker for therapy. These studies are also among the first to use PD-L1 as a biomarker. The patient populations that experience therapeutic benefits from pembrolizumab are those with advanced NSCLC who express PD-L1.

It is important to note the adverse effects related to pembrolizumab in comparison to those related to traditional chemotherapy. In the study conducted by Reck et al., adverse effects related to pembrolizumab occurred in 73.4% of the patients while 90% of those receiving chemotherapy experienced treatment related adverse effects.[7] The most common adverse effects from pembrolizumab were reported to be diarrhea, fatigue, and pyrexia. The most common adverse effects from chemotherapy were anemia, nausea, and fatigue. In the study conducted by Herbst et al., adverse effects related to pembrolizumab occurred in 66% of patients receiving 10 mg/kg compared to 81% of patients receiving docetaxel.[6] In both studies, immune related adverse effects occurred more in those receiving pembrolizumab. The most common immune related adverse effects were hypothyroidism, pneumonitis, and hyperthyroidism. Hypothyroidism affected 8% of those receiving pembrolizumab compared to <1% of those receiving docetaxel.

Pneumonitis affected 4-5% of those receiving pembrolizumab compared to 2% of those receiving docetaxel. Hyperthyroidism affected 4-6% of those receiving pembrolizumab compared to 1% of those receiving docetaxel[6].

Brain metastases occur in 10% of patients with NSCLC. [9] There is a poor outcome for patients diagnosed with brain metastases from NSCLC. A median overall survival length of 4 months has been shown in patients treated with whole brain radiation therapy (WBRT). [9] The study conducted by Goldberg et al., demonstrated a positive response of brain metastases from NSCLC from pembrolizumab with a median overall survival of 7.7 months. [8] As this is a cohort study, it does not allow for the comparison of the overall survival value. Another limitation is the low enrolled patient numbers in the study. As this study is ongoing, comparison of overall survival in those being treated with pembrolizumab and those treated with WBRT should be completed.

Conclusion

Pembrolizumab shows to be effective in prolonging overall survival compared to traditional chemotherapy in these studies. For patients who express PD-L1 with advanced NSCLC, this could be indicated as first-line therapy. Pembrolizumab can also be used in those who failed combination chemotherapy treatments as well. Further evaluations on pembrolizumab's adverse effects could be studied in the future. The studies chosen in this systemic review indicate fewer adverse effects associated with pembrolizumab compared to traditional chemotherapy treatments. The quality of life in those extra months of survival is of great importance. As pembrolizumab becomes indicated as first-line therapy for these patients, adverse effects should continue to be monitored and studied. For patients who express PD-L1 with advanced NSCLC with brain metastases, the

ongoing data collection should compare median survival in patients with brain metastases being treated by various methods such as WBRT. Further research with larger population sizes and randomized controlled trials are needed to compare overall survival in patients with brain metastases.

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