2019

Are Anti-PD-1/PD-L1 Monoclonal Antibodies Effective in Prolonging Overall Survival in Patients with Advanced Non-small Cell Lung Cancer?

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Are anti-PD-1/PD-L1 monoclonal antibodies effective in prolonging overall survival in patients with advanced non-small cell lung cancer?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018

Abstract

Objective: The objective of this selective EBM review is to determine whether or not anti-PD-1/PD-L1 monoclonal antibodies are effective in prolonging overall survival in patients with advanced non-small cell lung cancer (NSCLC).

Study Design: A systematic review and data analysis of three randomized control trials (RCTs) published after 2010. The studies were located in English written peer reviewed journals.

Data sources: Three RCTs, which evaluated the efficacy of anti-PD-1/PD-L1 monoclonal antibodies, including nivolumab and pembrolizumab, as first and second or consecutive line therapy in patients with advanced NSCLC compared to cytotoxic agents. The studies utilized were found in EBSCO host and PubMed.

Outcomes Measured: The primary endpoint of the studies was overall survival measured by quantifying survival rates at 6, 12, or 18 months.

Results: All three RCTs (Borghaei 2015, Brahmer 2015, and Reck 2016) showed that anti PD-1 monoclonal antibodies are effective in prolonging overall survival in patients with advanced NSCLC whose tumors expressed PD-L1 ($p=.002$, $p<.001$, and $p=.005$ respectively). All three studies proved that immunomodulating agents caused an increase in overall survival rates compared to those treated with chemotherapeutic agents as first and second or consecutive line therapy. Additionally, median overall survival time in months was significantly longer in patients who were treated with immunomodulating agents compared to cytotoxic agents.

Conclusion: Based on the data analyzed from the studies represented throughout this systematic review, anti PD-1 monoclonal antibodies are effective in prolonging overall survival in patients with advanced NSCLC. It is unclear whether or not anti PD-L1 monoclonal antibodies are effective in prolonging overall survival in the same populations of NSCLC patients due to a lack of viable study selection found during the search process. All study conclusions were based on malignancies which expressed PD-L1 in their tumors.

Keywords: NSCLC; PD1/PD-L1 Monoclonal Antibodies; Nivolumab; Pembrolizumab.

Introduction

Lung cancer is a devastating disease that often doesn't present itself until its later stages. Once symptomatic, a patient may present with constitutional manifestations such as fever, night sweats, fatigue, and weight loss. Symptoms related to the local invasion of the cancer include cough, hemoptysis, shortness of breath, back pain, and chest pain. A diagnosis of lung cancer can be made when pathology confirms malignancy of tumors originating in the lung or bronchus. The disease can then be further broken down into non-small cell and small cell, or NSCLC and SCLC respectively. NSCLC is much more common, accounting for approximately 80% of all lung cancer cases and comprises adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other less common malignant subtypes.[1] Of the individuals who are diagnosed with NSCLC, over 50% are diagnosed with advanced disease, which generally includes stage IIIb and IV.[1] This paper evaluates three randomized control trials (RCT's) comparing the effectiveness of anti-PD-1/PD-L1 monoclonal antibodies on prolonging overall survival in patients with advanced non-small cell lung cancer.

As of 2018, lung cancer is the most common cancer diagnosed in males and the third most common cancer diagnosed in females.[2] In addition to its prevalence, lung cancer is the most common cause of cancer related deaths in the United States.[3] For NSCLC, these statistics are due to two very critical diagnostic tools. First, Patients with NSCLC are often asymptomatic until the disease has advanced to terminal stages.[3] Second, there is a lack of standardized screenings for at risk populations.[3] As a result, it is imperative for health care providers to recognize risk factors and educate the patient on the severity of lung cancer to help prevent and detect lung cancer during earlier stages.

Malignancies originating in the lung and bronchus are the third costliest cancers in the United States.[1] In 2011, the total healthcare costs over one year for lung cancer diagnosis and treatment was estimated to be $125,849 per person.[4] Although necessary, the increased cost of lung cancer is due in part to comprehensive treatment that requires a complete healthcare team to appropriately manage the patient's physical, mental, and emotional health throughout the disease course. Specifically, It is estimated that there will be 2 inpatient hospital admissions, 9 cumulative inpatient care days, and 70 outpatient care visits during a one year period in a patient with NSCLC.[4] Additionally, lung cancer risk increases with an individual's age and older individuals with NSCLC represent a particularly expensive sub group of the overall lung cancer population due to comorbidities, disease burden, and lower overall performance.[5] The cost analyses documented for populations diagnosed with lung cancer demonstrate a significant burden for patients and families.

Preventing lung cancer is the best way to minimize insurance and out-of-pocket costs due to disease treatment. Prevention begins with identifying the most important risk factors and modifying the patient's lifestyle to reduce the likelihood of cancer development. Smoking is the most important known risk factor for lung cancer and accounts for nearly 90% of all diagnoses.[6] Other risk factors for the development of NSCLC include poor diet, genetic susceptibility, and occupational exposures such as asbestos.[6] When risk factors are present, it is uncertain if screening should be implemented. The current screening offered as a USPSTF Grade B is an annual low dose CT scan for adults 55-80 years old who have a 30 year or more pack-year history, but there is controversy surrounding when it should be offered.[7] As an example, it is uncertain if higher risk populations, such as those with chronic bronchitis and emphysema, should be screened earlier or at more frequent intervals.[7]

Individuals who are diagnosed with NSCLC will endure varying degrees of treatment based on the staging and subtype of their cancer. In general, surgical removal of tumor(s) with or without regional lymph node resection is considered first line in patients with stage I-IIIa NSCLC.[8] Cancers with more advanced disease, such as in stage IIIb-IV, indicate chemotherapy as first line therapy. For advanced NSCLC with no known tumor-specific mutations, administration of platinum based chemotherapy "doublets" such as cisplatin and carboplatin is warranted.[8] Conversely, advanced NSCLC patients whose tumors express EGFR mutations are advised to begin treatment with EGFR-TKI's.[9]

Second line treatment for advanced NSCLC is limited and is dependent on the patient's disease progression after first line treatment fails.[10] Docetaxel is the current recommended second line treatment method, but has not been able to prove superiority to other current second line therapies.[10] Programmed death 1/L1 (PD-1/PD-L1) receptors are immunomodulating agents that may offer superiority to the current first and second or third line treatment by prolonging survival in advanced NSCLC patients whose tumors express PD-1/PD-L1. The benefit in these medications is having more personalized treatment for diseases that involve the programmed cell death 1/L1 pathway. The purpose of the medications are to bind PD-1/PD-L1 receptors on B and T cells in the body and form an antibody complex.[11] This prevents any tumor cells that express PD-1/PD-L1 from binding at those same sites on B and T cells. Without tumor cell binding on B and T cells, the immune system will be able to "restore antitumor immunity".[10] PD-1/PD-L1 monoclonal antibodies such as nivolumab and pembrolizumab, may be more effective at prolonging overall survival than the current cytotoxic therapies recommended for first and second or consecutive line treatment.

Objective

The objective of this selective EBM review is to determine whether or not anti PD-1/PD-L1 monoclonal antibodies are effective in prolonging overall survival in patients with advanced non-small cell lung cancer (NSCLC).

Methods

This systematic review evaluates three randomized control trials (RCTs), which were selected after meeting specific criteria. The population of the review included men and women 18 years or older with a confirmed diagnosis of advanced NSCLC and whose tumors expressed PD-1/PD-L1. "Advanced NSCLC" can be defined as stages IIIb or IV. The interventions included treatment with anti PD-1/PD-L1 monoclonal antibodies such as nivolumab and pembrolizumab, in variable doses. There were two comparison groups allowed in the review. The first comparison was to patients who have NOT received any treatment for their metastatic disease and the second comparison was to patients who HAVE received prior treatment that has failed/stopped. The primary outcome measured was overall survival rate over time, which generally occurred at 6, 12, or 18 months.

The articles selected for this systematic review were obtained through EBSCO host and PubMed. They are English written, peer reviewed articles and were chosen based on their relevance to the research topic and whether or not the outcome was patient oriented. Additional inclusion criteria for the selection of the studies were: studies published after 2010, tumors expressing programmed death ligand, and primary outcomes measured by overall survival rate. Patients under the age of 18 and patients diagnosed with SCLC were among exclusion criteria. Keywords used during the search of the articles included NSCLC, PD1/PD-L1 monoclonal antibodies, nivolumab and pembrolizumab. A statistical summary of data was reported as p-value, RBI, ABI, and NNT. Confidence intervals were also included to demonstrate the

accuracy of the results. Demographics and characteristics of individuals included in the study are reported below (see table 1).

Table 1 - Demographics & Characteristics of Included Studies

Study	Type	# of Pts	Avg. Age in yrs	Inclusion Criteria	Exclusion Criteria	W /D	Intervention
Borghaei (2015)	RCT	582	62	Patients with: stage IIIb, IV or recurrent Non-Squamous NSCLC who received a previous dose of platinum-based doublet chemotherapy and either radiation or surgical tumor resection. Patients had to be over 18 years old, have an ECOG score of 0 or 1, and have adequate organ function.	Patients with: autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior treatment with immune-stimulatory antitumor agents, and prior use of docetaxel.	22	Use of Nivolumab at a dose of 3 mg/kg every 2 weeks
Brahmer (2015)	RCT	272	63	Patients with: stage IIIb, IV or recurrent Squamous NSCLC who received a previous dose of platinum-based doublet chemotherapy and either radiation or surgical tumor resection. Patients had to be over 18 years old, and have an ECOG score of 0 or 1.	Patients with: autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior treatment with immune-stimulatory antitumor agents, and prior use of docetaxel.	12	Use of Nivolumab at a dose of 3 mg/kg every 2 weeks
Reck (2016)	RCT	355	65	Patients with stage IV NSCLC who were at least 18 years old, had no known ALK or EGFR mutations, and had an ECOG score of 0 or 1. Patients must not have received any prior systemic therapy for metastatic disease.	Patients receiving immunosuppressive treatment such as glucocorticoids, with untreated brain metastatic lesions, active autoimmune disease, or history of interstitial lung disease.	1	Use of Pembrolizu-mab given via IV at a dose of 200 mg every 3 weeks for 35 cycles

Outcomes

In the studies selected for this systematic review, the primary outcome was overall survival of advanced NSCLC patients treated with PD-1/PD-L1 monoclonal antibodies as a first and second or consecutive line therapy. Borghaei et al. and Brahmer et al. measured outcomes by

assessing median overall survival time in months, 1 year overall survival rate, 18 month overall survival rate, and death hazard ratio[10,12] Reck et al. measured outcomes by assessing median overall survival time in months, overall survival rate at 6 months, and hazard death rate.[13] Overall survival was estimated via the Kaplan-Meier method. Response rate and progression free survival were measured as secondary endpoints, but are not being evaluated as they are outside of the scope of this systematic review. Symptomatic scales such as the Lung Cancer Symptom Scale and the European Quality of Life-5 Dimension Questionnaire were evaluated as part of progression free survival and will not be included in this review.

Results

In a study conducted by Borghaei et al., 582 patients with advanced non-squamous NSCLC who were previously treated with a platinum-based doublet chemotherapy regimen were randomized to receive nivolumab or docetaxel.[10] 292 of the 582 patients received nivolumab while 290 of the 582 patients received docetaxel. No crossover was indicated for patients to switch from docetaxel to nivolumab or vice versa.

The median overall survival in patients who received nivolumab as a second line therapy was 12.2 months (95% confidence interval (CI), 9.7 to 15.0), and the median overall survival in patients who received docetaxel as a second line therapy was 9.4 months (95% CI, 8.1 to 10.7).[10] The 1 year overall survival rate was 51% (95% CI, 45 to 56) for individuals who received nivolumab and 39% (95% CI, 33 to 45) for individuals who received docetaxel.[10] An additional follow-up conducted at 18 months showed that overall survival rates declined to 39% (95% CI, 34 to 45) in the nivolumab group versus 23% (95% CI, 19 to 28) in the docetaxel group.[10] The hazard ratio for death was calculated to be .73 (96% CI, 0.59 to 0.89, p=.002).[10] Utilizing data from the 1 year survival rate, the numbers needed to treat (NNT) was 9 (see Table 2). This

indicates that for every 9 people treated with nivolumab, 1 person will live longer than if they had taken docetaxel. Overall, patients with advanced non-squamous NSCLC who received nivolumab as a second or consecutive line therapy lived significantly longer compared to those treated with docetaxel.

Table 2 – Efficacy of nivolumab as a second line therapy in prolonging overall survival in patients with advanced NSCLC, measured by Borghaei 2015

Study	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Numbers Needed to Treat (NNT)	Death Hazard Ratio P-Value	Death Hazard Ratio Confidence Interval (CI)
Borghaei (2015)	.307	.120	9	.002	96% CI, .59-.89

In a similar study conducted by Brahmer et al., 272 patients with advanced squamous non-small cell lung cancer who were previously treated with a regimen containing platinum-based chemotherapy were randomized to receive nivolumab or docetaxel.[12] 137 of the 272 patients received nivolumab while 137 of the 272 patients received docetaxel. No crossover was indicated during the study.

The median overall survival in patients who received nivolumab as a second line therapy was 9.2 months (95% CI, 7.3 to13.3), and the median overall survival in patients who received docetaxel as a second line therapy was 6.0 months (95% CI, 5.1 to 7.3).[12] The 1 year overall survival rate was 42% (95% CI, 34 to 50) for individuals who received nivolumab and 24% ((95% CI, 17 to 31) for individuals who received docetaxel.[12] The hazard ratio for death was calculated to be .59 (95% CI, 0.44 to 0.79, P<0.001).[12] Utilizing data from the 1 year survival rate, the numbers needed to treat (NNT) was 6 (see Table 3). This indicates that for every 6 people treated with nivolumab, 1 person will live longer than if they had taken docetaxel.

Therefore, patients with advanced squamous NSCLC who received nivolumab lived significantly longer compared to those treated with docetaxel.

Table 3 – Efficacy of nivolumab as a second line therapy in prolonging overall survival in patients with advanced NSCLC, measured by Brahmer 2015

Study	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Numbers Needed to Treat (NNT)	Death Hazard Ratio P-Value	Death Hazard Ratio Confidence Interval (CI)
Brahmer (2015)	.750	.180	6	<.001	95% CI, .44-.79

Lastly, a study by Reck et al. was conducted to test the efficacy of pembrolizumab against advanced NSCLC. The study included 305 patients who had not been previously treated with any form of chemotherapy or radiation. 154 patients were treated with pembrolizumab and 151 patient were treated with chemotherapy.[13] The most common chemotherapeutic combination was carboplatin and pemetrexed, which was given to 67 out of the 151 patients. Crossover was allowed during this study if disease had progressed beyond an acceptable margin.[13] In total, 66 people in the chemotherapy group crossed over to the pembrolizumab group.

The 6 month overall survival rate in patients who received pembrolizumab as a first line therapy was 80.2% (95% CI, 72.9 to 85.7) and the 6 month overall survival rate in patients who received chemotherapy as a first line therapy was 72.4% (95% CI, 64.5 to 78.9).[13] The hazard ratio for death was calculated to be .60 (95% CI, 0.41 to 0.89; P= 0.005).[13] Utilizing data from the 1 year survival rate, the numbers needed to treat (NNT) was 13 (see Table 4). This indicates that for every 13 people treated with pembrolizumab, 1 person will live longer than if they had taken chemotherapy. Therefore, patients with advanced NSCLC who received pembrolizumab as first line therapy lived significantly longer compared to those treated with chemotherapy alone.

Table 4 – Efficacy of pembrolizumab as first line therapy in prolonging overall survival in patients with advanced NSCLC, measured by Reck 2016

Study	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Numbers Needed to Treat (NNT)	Death Hazard Ratio P-Value	Death Hazard Ratio Confidence Interval (CI)
Reck (2016)	.108	.078	13	.005	95% CI, .41-.89

Discussion

Advanced non-small cell lung cancer is a terminal illness that typically weighs heavily on a patient in all aspects of their lives. Treatment options often exclude surgical tumor resection and focus solely on systemic cytotoxic agents that have limited efficacy. With advances in funding and research, metastatic lung neoplasia may be treated by modifying the immune response to the disease. The goal of this systematic review was to assess the efficacy of anti PD-1/PD-L1 monoclonal antibodies in multiple stages of a patient's treatment regimen, including as first and second line therapies. While the data collected points towards immunomodulators being effective in prolonging overall survival, several limitations and safety concerns have been identified relating to the context of this paper.

As the two medications studied for effectiveness, nivolumab and pembrolizumab were relatively safe medications offered compared to the current chemotherapeutic treatment options available for advanced NSCLC. Borghaei et al. and Brahmer et al. both identified that there were fewer adverse reactions with nivolumab compared to the chemotherapeutic agent, docetaxel.[10,12] Both studies evaluating nivolumab also reported similar adverse effects. Borghaei et al. documented that 16% of patients reported fatigue, 12% reported nausea, 10% reported decreased appetite, and 10% reported asthenia with nivolumab.[10] Less common adverse events included rash, pruritis, erythema, diarrhea, hypothyroidism, increased liver function tests, and

pneumonitis.[10] Brahmer et al. identified similar frequent side effects of nivolumab, including 16% of patients reported fatigue, 11% reported decreased appetite, and 10% reported asthenia.[12] The safety profile of pembrolizumab was comparative to nivolumab, and showed that the most frequent adverse effects were immune-mediated responses to the medication.[13]

One important aspect relating to the use of monoclonal antibodies in treatment for advanced NSCLC is at what point the medications should be started. Through topic research, it was very clear that anti PD-1/PD-L1 monoclonal antibodies were studied as consecutive-line therapy in greater lengths. While Reck et al. focused on pembrolizumab as a first line agent for lung metastasis, both of the nivolumab studies conducted by Borghaei et al. and Brahmer et al. focused on therapy following a platinum-based doublet chemotherapy regimen.[10,12,13] Efficacy was proven in all studies, but more research should be conducted to evaluate patient survival at several intervals following diagnosis, with and without prior and/or concurrent therapy.

A major limitation identified in the research of this evidence based medicine topic was the lack of available studies showing the efficacy specifically for PD-L1 monoclonal antibodies. Nivolumab and pembrolizumab are specifically known as PD-1 monoclonal antibodies, and these two medications were the only immunomodulators evaluated in this paper. Three PD-L1 monoclonal antibodies that have been approved as immunomodulating agents, including atezolizumab, avelumab, and durvalumab. These medications have not been evaluated in this paper due to the lack of articles found during the selective search process. Nivolumab and pembrolizumab have been FDA approved since 2014, allowing more time for research to be conducted on their efficacy.[10,12] Atezolizumab, avelumab, and durvalumab were approved in 2016, 2017, and 2017 respectively and thus have less research available on their efficacy. Additionally, avelumab has not been approved yet for the treatment of advanced NSCLC.[14] With

more funding and time, a greater number of RCT's, cohort studies, and other analyses will be conducted across the entire PD-1/PD-L1 spectrum. With more studies available, a more comprehensive answer to the EBM question can be established.

Conclusion

Anti PD-1 monoclonal antibodies are effective in prolonging overall survival in patients with advanced NSCLC. Unfortunately, it is unclear whether or not anti PD-L1 monoclonal antibodies have similar efficacy because there was very limited research evaluating medications that fall within its class. Nivolumab and pembrolizumab, which are anti PD-1 monoclonal antibodies, can be implemented in patients whose tumors express PD-L1 as first or consecutive line therapy as they are generally considered safer and more effective to the current recommended therapy. Atezolizumab, avelumab, and durvalumab should be evaluated under similar parameters to the studies discussed in this paper to understand their efficacy in prolonging overall survival in patients with NSCLC.

When the primary outcome of a study is prolonging or increasing overall survival, any increase from the current therapy available should be evaluated further and offered to patients with diseases who may benefit. In the upcoming years, it is expected that immunomodulating agents will make a greater impact in treating lung metastasis due to the promising results already seen. In a future study design, it would be adventitious to include all medications under the programmed death pathway and compare efficacy as first and second or consecutive line therapy. Additionally, inclusion of more study types, such as a cohort or prospective/retrospective analyses should be included. This information could determine which medication out of the drug class may offer the highest superiority in treating patients with advanced NSCLC whose tumors express PD-L1

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