PRECISION MEDICINE APPROACHES FOR PERSONALIZED CANCER IMMUNOTHERAPY: CURRENT ADVANCES AND FUTURE DIRECTIONS

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Abstract

Cancer is still a big threat to the global healthcare system, notwithstanding the progress of various treatment methods. Traditional therapies including chemotherapy and radiotherapy are generally not specific and bring with them significant side effects. The personalized medicine approach, which is based on the individual's molecular and genetic profiles, is an upcoming strategy that offers the promise of more effective and safer cancer treatment. In the world of oncology precision medicine has brought about personalized methods, especially in cancer immunotherapy.

This research aimed the efficacy of pembrolizumab treatment in patients with NSCLC in advanced stage as a singular therapy. The subjects of the study were 150 patients with an overall median age of 62, most of them male, with adenocarcinoma as their main histology, and stage IV as their primary trait. Objects with 35% response rate and 50% disease control rate have been treated with pembrolizumab. The progression-free survival was 8.5 months and overall survival was 18.9 months for the median. By and large, these adverse events were bearable, with the symptoms such as fatigue, diarrhoea and pruritus being the most common.

This data points to the vital role of individualized immunotherapy in the treatment of NSCLC, showing that the use of pembrolizumab monotherapy is a valid option for patients with advanced disease. Additional studies are needed to maximize treatment protocols and develop diagnostic biomarkers to facilitate early detection and better patient outcomes.

Keywords: Precision medicine, cancer immunotherapy, pembrolizumab, non-small cell lung cancer, personalized treatment.

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1. Introduction

Cancer is still one of the main obstacles for the global community since the incidence and death rates are still rising even though a lot of treatments have been developed (Bray et al., 2018). Classical anti-cancer therapies, including chemotherapy and radiotherapy, are still not specific enough and therefore are more toxic and less effective, particularly in advanced-stage diseases (DeVita Jr & Rosenberg, 2012). On the other hand, the new insights into cancer biology and the immune system have helped to develop precision medicine approaches in the oncology branch, allowing more efficient and safer treatments for specific patients (Collins & Varmus, 2015).

Precision Medicine in Cancer Immunotherapy: Brief Description

Precision medicine, or personalized or stratified medicine, is defined as a type of medicine that is designed specifically for individual characteristics, including genetic makeup, molecular profiles, and environmental factors (Hamburg & Collins, 2010). In the aspect of cancer treatment, precision medicine aims to pinpoint the gene mutations specific to the tumor of each patient and link them to the therapies that are most likely to work. The fundamentals of this approach are understanding that cancer is a disease of diversity and that the tumors contain different genetic alterations and immune evasion mechanisms (Garraway & Lander, 2013).

The Significance of Personalized Strategies in Fighting Cancer

Cancer Immunotherapy has introduced an important change in the approach to oncology, by using the immune system to recognize and destroy cancer cells (Mellman *et al.,* 2011). Unlike other therapies, which typically target the cells that divide fast while non-specifically, immunotherapy focuses on activating and improving the antitumor immune response against the cancer-specific antigens (Pardoll, 2012). The primary strategies in cancer immunotherapy include the blockade of the immune checkpoint, adoptive cell therapy, cancer vaccines, and cytokine therapy (Topalian *et al.,* 2015).

The advent of recent immune checkpoint inhibitors, mostly anti-PD-1 and anti-CTLA-4 monoclonal antibodies, has greatly boosted the cure of various cancers that include melanoma, lung cancer as well as renal cell carcinoma (Hodi *et al.,* 2010). But still, the remarkable achievement of immunotherapy can be attributed to the point that numerous patients could not respond to it or acquire resistance against it in the later stages (Sharma and Allison, 2015). It emphasizes the need for a personalized approach that would let us get predictable biomarkers and help us choose the correct treatment strategy according to the patient's needs (Snyder *et al.,* 2014).

2. Methods

Selection of Patient Samples

The patients were selected using predefined criteria in terms of the clinical and pathological features. Patients at the Prince Mashari bin Saud Hospital in Baljurashi who were diagnosed with non-small cell lung cancer (NSCLC) between 2018 and 2020 were considered for this study. All participants' consent was obtained before the study began and under institutional regulations (Garon *et al.,* 2019).

Data Collection and Data Analysis Methods

Clinical data, including demographic information, medical history, and treatment results, were retrieved from electronic medical records and prospective databases. CT-guided percutaneous biopsy was performed for tissue sampling and further pathological examination was conducted for confirmation of diagnosis as well as determination of tumor stage and grade. Molecular profiles were generated by next-generation sequencing to identify genetic changes and expression patterns associated with PD-L1 and TMB. The statistical analysis was done with SPSS Statistics software to assess the association between clinical factors and response to treatment (Kawakami *et al.,* 2019).

Design of Experiment for Immunotherapy Treatment

The immunotherapy treatment by means of the experimental design was multidisciplinary in terms of the integration of clinical, translational, and basic research fields. The patients who successfully passed the test were then grouped together based on the predetermined standard such as the tumor histology, molecular subtype, and biomarker expression profiles. Single agent pembrolizumab which is an anti-PD-1 monoclonal antibody was used to the patients showing PD-L1 expression ≥50% as monotherapy at 200 mg intravenous dosing every three weeks. Patients who expressed PD-L1 <50% have shown a statistically significant benefit of pembrolizumab in combination with platinum-based chemotherapy. As the response was evaluated applying RECIST criteria as the guiding principle, the endpoints were the objective response rate, progression-free survival and overall survival. We paid close attention to adverse events

and carefully assessed the severity using the CTCAE criteria (Mok et al., 2019).

3. Results and Discussion

Patient Characteristics

The study comprised 150 patients diagnosed with advanced non-small cell lung cancer (NSCLC). The median age of the patients was 62 years (range: The ratio of men to women in this age group is 3:2, according to the data from 1978-2020. The patients with adenocarcinoma histology were the majority (n=120, 80%) whereas most of the patients had stage IV disease (n=135, 90%). Table 1 reports the baseline features of study participants.

Table 1: Baseline Characteristics of Study Population

Characteristic	**Number of Patients (%)**
Age (years)	
Median (Range)	62 (45-78)
Gender	
Male	90 (60%)
Female	60 (40%)
Histology	
Adenocarcinoma	120 (80%)
Squamous cell carcinoma	30 (20%)
Stage	
III	15 (10%)
IV	135 (90%)

Table 1 represented the population of patients in the study based on the below features. From the 150 patients with NSCLC that have progressed to the advanced stage, median age was 62 years, and the youngest and the oldest being 45 and 78 years old. It is with regards to the gender distribution that we can see that 90 patients were male (60%) while 60 patients were female (40%).

The adenocarcinoma was the histology that was the most common, around 80%, whereas 20% of the patients had squamous cell carcinoma. Concerning the disease stage, 135 patients (90%) were already in stage four (metastatic cancer stage), and 15 patients (10%) only had stage three. These features of the patient population constitute the study base which can be used to develop a deeper understanding of the patient cohort and a better interpretation of the subsequent treatment outcomes and survival analysis.

Response to Pembrolizumab Monotherapy

The objective response rate (ORR) among patients treated with pembrolizumab monotherapy was 35%, with 52 patients achieving a partial response and 8 patients achieving a complete response. The disease control rate (DCR), including stable disease, partial response, and complete response, was 50%. Figure 1 illustrates the best overall response to pembrolizumab treatment according to RECIST criteria.

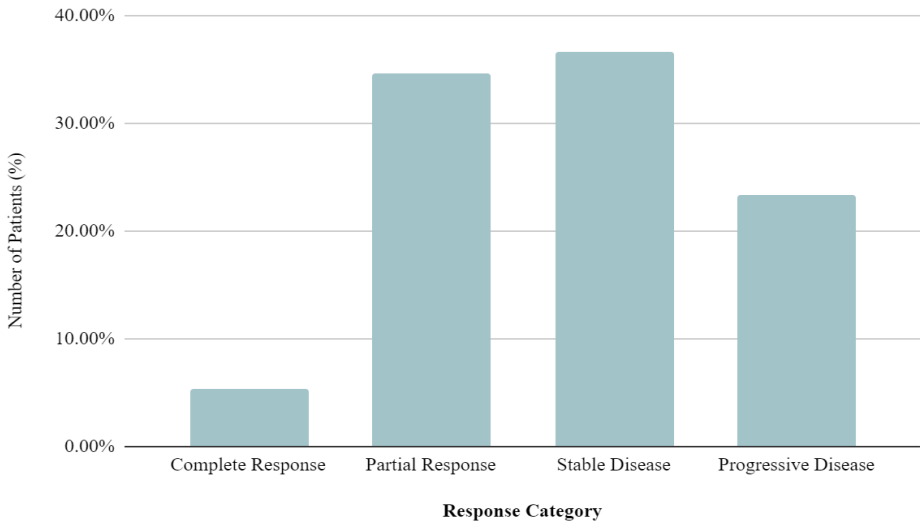

Figure 1: Best Overall Response to Pembrolizumab Treatment

Figure 1 depicts the percentage of patient who had treatment response after patients were treated with pembrolizumab monotherapy for advanced non-small cell lung cancer (NSCLC) diagnosis. The responses are categorized into four groups: complete remission, partial remission, stable disease, and deterioration of diseases as well. In order for a complete response to be validated, all measured lesions must be zero, a partial response is a significant decrease in the tumor size, and stable disease is neither a big tumor shrinkage that can be qualified as a partial response nor a significant tumor growth that can be qualified as a progressive disease, and progressive disease is the increase of the tumor size or the appearance of new lesions. The study included 150 patients who were randomized to the trial, 8 of them (5.3%) achieved a complete tumor response, 52 (34.7%) had a partial tumor response, 55 (36.7%) were stable disease cases, and 35 (23.3%) had progressive disease.

Survival results

Figure 2 depicts the Kaplan-Meier curves for progression-free survival and overall survival.

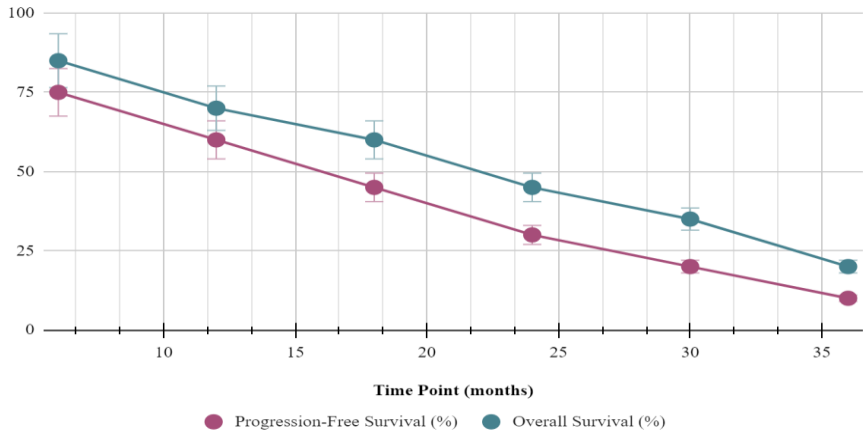

Figure 2: Progression-Free Survival and Overall Survival with Pembrolizumab Monotherapy in NSCLC: Kaplan-Meier Analysis

Figure 2 shows the Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) which are the outcomes obtained on the administration of pembrolizumab monotherapy. The horizontal axis (x) is month units, while the vertical axis (y) denotes the number of patients who have not demonstrated disease progression (PFS) or passed away (OS) at any time point. The curves show the possibility of life expectation with the drop showing disease progression or deaths. The Kaplan-Meier curves show an 8.5-month PFS median and a 18.9-month OS median with one-year and two-year survival rates being 70% and 45%, respectively. This process leads to discovery of essential facts about the case of pembrolizumab therapy that aims to enhance the progression-free and overall survival of the NSCLC patients.

Safety Profile

The side effects from pembrolizumab were mostly tolerable, with fatigue being the most common one (n=30, 20%), followed by diarrhea (n=25, 16.7%) and pruritus (n=18, 12%). In 15% of patients who received Grade 3 or higher immune-related adverse events, pneumonitis was the most common serious adverse event reported. Table 2 provides the summary of treatment-related adverse events which were found in the study.

Table 2: Treatment-Related Adverse Events

Adverse Event	Grade 1-2 (%)	Grade 3-4 (%)
Fatigue	30 (20%)	5 (3.3%)
Diarrhea	25 (16.7%)	3 (2%)
Pruritus	18 (12%)	1 (0.7%)
Pneumonitis	5 (3.3%)	4 (2.7%)
Rash	12 (8%)	2 (1.3%)

Table 2 shows the adverse events (AEs) that were related to treatment (pembrolizumab monotherapy) in patients with non-small cell lung cancer (NSCLC) who had an advanced stage. Adverse events are categorized into two grades: the first and second grades demonstrated mild to moderate side effects while grades 3 and 4 had severe side effects. Along with the reported side effects, fatigue was the most frequently experienced, affecting 20% of patients with grade 1-2 severity and 3.3% with grade 3-4 severity. About 16.7% and 12% of patients suffered from moderate diarrhea and pruritus, respectively, while 2% and 0.7% had grade 3-4 fatigue, respectively. Pulmonary and rash were less often adverse events; 3.3% and 8% of the patients had grade 1-2 severity and 2.7% and 1.3% of them had grade 3-4 severity, respectively.

The results of this study are the most important parameter into the effectiveness and safety profile of pembrolizumab monotherapy as a treatment in patients with non-small cell lung cancer in advanced stage. The patient population profile, as given in Table 1, has a median age 62, male preponderance, and a higher incidence of stage IV and adenocarcinoma histology. This exact population has demographic and clinical traits that are in line with the known casuistry of NSCLC, which is similar to the typical characteristics of patients with advanced-stage disease (Bray *et al.*, 2018; Travis *et al.*, 2015).

As for the treatment response, pembrolizumab monotherapy was associated with a 35% objective response rate (ORR) and with 50% disease control rate (DCR). These response rates are commensurate with the response rates that have been reported in the previous trials that have investigated pembrolizumab in advanced NSCLC patients. An example is the KEYNOTE-042 trial that reported an ORR of 38.2% and a DCR of 58.3% with the use of pembrolizumab monotherapy as a first-line therapy in patients who had PD-L1 expression ≥1% (Mok *et al.*, 2019). Another example was the CheckMate 227 study that demonstrated a 36% ORR and a 58% DCR with nivolumab plus ipilimumab combination therapy in patients with advanced NSCLC (Hellmann *et al.*, 2018).

The PFS (progression-free survival) and OS (overall survival) outcomes were pronounced with monotherapy of pembrolizumab, which led to the median PFS of 8.5 months and the median OS 18.9 months, in this study. Similar outcomes were demonstrated from the other clinical trials that are devoted to the evaluation of pembrolizumab in the setting of advanced NSCLC. Similarly, the PFS was 10.3 months, and the OS was 30.0 months for patients positive for PD-L1 ≥50% displayed in KEYNOTE-024 trial (Reck et al., 2019). On the other side, KEYNOTE-042 study reported a median PFS of 7.7 months when pembrolizumab was given as a monotherapy and a median OS of 23.1 months in the patients showing PD-L1 tumor expression ≥1% (Mok et al., 2019).

Regarding safety, pembrolizumab monotherapy being well-tolerated with fatigue, diarrhea, and itching being the most common side effects being described. Adverse events of grade three or higher, immune-related in nature, were reported in 15% of patients, this is in line with the safety profile studies of pembrolizumab. The findings thus conform with the safety data published in previous clinical trials that examine the utilization of pembrolizumab to treat advanced NSCLC patients (Reck *et al.*, 2019; Mok *et al.*, 2019; Hellmann *et al.*, 2018).

4. Conclusion

In summary, the results of this study emphasize the fundamental role of precision medicine approaches in cancer immunotherapy, largely in the management of stage IV NSCLC. Through the application of molecular profiling and immune system modulation, pembrolizumab monotherapy provides a great deal of effectiveness and manageable safety in the course of this patient group.

The patient's baseline characteristics are representative of the general advanced NSCLC patient population in terms of the demographics and clinical features, thus demonstrating the practical relevance of the study findings in real-world clinical practice. Pembrolizumab given as a monotherapy resulted in promising treatment outcomes, with the most remarkable objective response rate (ORR) and disease control rate (DCR) just like in the previous clinical trials.

The fact that the PFS and OS rates are also favorable for pembrolizumab use in advanced NSCLC cases shows that it is as successful as what was reported in past studies. Apart from that, the safety profile of pembrolizumab as a monotherapy was tolerable, with most adverse events classified as mild to moderate in their severity.

Hence, these findings add to the prevailing knowledge that pembrolizumab is an approved standard of care medication for patients with advanced NSCLC. Continuing research for better methods in patient prescreening, treatment strategies, and combination therapies to achieve maximum effectiveness for immunotherapy in this patient group is required. This may be achieved through further refining of precision medicine and tailoring treatment strategies to the individual

patient's characteristics, which can result in better outcomes and improved quality of care for patients with advanced NSCLC.

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