Review Article

Initial Systemic Treatment of Advanced Non-small Cell Lung Cancer

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ABSTRACT

The incidence of lung cancer is rising worldwide and cigarette smoking is recognized major risk factor for lung cancer. Non-small cell lung cancer (NSCLC) constitutes majority of all lung cancer cases. The prognosis for NSCLC remains poor. The five-year survival rate for all NSCLC stages combined is 23% and for stage IV NSCLC alone is 6%. The systemic chemotherapy has proved to prolong survival in some patients with advanced NSCLC. The targeted treatments have recently become available for minority of patients with NSCLC due to identification of sensitizing mutations and improved understanding of downstream molecular pathways. The immune check point inhibitors have redefined treatment for majority of NSCLC patients who lack "sensitizing mutations" for targeted agents. This review discusses current standard treatment for advanced NSCLC in first line setting.

Key Words:Non-small cell lung cancer, Immune check point inhibitors, Immunotherapy, Targeted therapy, Chemotherapy.

Introduction

Almost seventy percent of lung cancer patients present with advanced disease that is not curable. The non-small cell lung cancer (NSCLC) accounts for eighty percent of lung cancers. The systemic chemotherapy has been mainstay of treatment for patients with NSCLC. The systemic chemotherapy has shown to improve survival and quality of life in some patients with advanced stage NSCLC.[1]

The identification of biomarkers in small percentage of advanced NSCLC tumors, most notably *EGFR* (epidermal growth factor receptor) mutations, *ALK* (anaplastic lymphoma kinase) gene rearrangement or *ROS1* gene rearrangement, has redefined treatment options for patients harboring such sensitizing mutations. However, most of NSCLC patients lack these sensitizing mutations and immunotherapy has emerged as an essential part of treatment for such patients.

The intent of treatment for advanced NSCLC patients remains palliative. The goals of treatment include prolonging survival and maintaining quality of life for as long as possible, while keeping the side effects of treatment to minimum.

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The systemic treatment (targeted therapy, chemotherapy and immunotherapy) has demonstrated significant and remarkable improvement in overall survival and quality of life in patients who present with advanced disease upfront or following their initial definitive treatment. The surgical resection or definitive radiation therapy may be appropriate for patients with a solitary metastasis.

The preferred initial therapy for advanced NSCLC is influenced by presence or absence of a sensitizing mutation (EGFR, ALK, ROS1), presence of PD-L1 (programmed death-ligand 1) expression, squamous versus non-squamous histology, extent of disease and any associated symptoms.

NSCLC with sensitizing mutation

The better understanding of molecular biomarkers and downstream pathways that drive malignancy in NSCLC has initiated the formulation of targeted agents. The analysis of tumor for EGFR, ALK, ROS1 and BRAF is strongly recommended for all patients with advanced NSCLC, especially ones with non-squamous histology.

EGFR mutation

The presence of an EGFR mutation is strong predictor of response to EGFR TKIs (tyrosine kinase inhibitors) in advanced NSCLC. In United States, the incidence of EGFR tyrosine kinase mutations in NSCLC of adenocarcinoma histology is around 10-15 percent and is seen more often in nonsmokers. The EGFR mutations can be identified in up to 50 percent of the patients in Asian populations.[2]The EGFR TKIs (geftinib, erlotinib, afatinib and osimertinib) are approved as single agents in first line setting for treatment of patients with sensitizing mutation in EGFR.The EGFR TKIs significantly prolong PFS (progression free survival) as compared to standard platinum-based chemotherapy in this subgroup of patients with sensitizing EGFR mutations.[3-6] The

impact on OS (overall survival) is less evident in the clinical trials since EGFR TKIs were frequently used in second-line setting following progression on chemotherapy. Among the EGFR TKIs, osimertinib (third generation TKI) has demonstrated improved PFS compared to erlotinib and gefitinib (first generation TKIs).[7] Osimertinib has not been compared to afatinib (second generation TKI).

The EGFR TKIs are used only as single agent as no survival advantage has been demonstrated when used combined with chemotherapy. The treatment with an EGFR TKI should be continued until disease worsening or emergence of significant side effects.

ALK gene rearrangement

ALK gene rearrangement is detected in 4-5 percent of NSCLC of adenocarcinoma histology in United States, mostly in nonsmokers and younger patients. The advanced NSCLC with positive *ALK* gene rearrangement should be treated with ALK TKIs (tyrosine kinase inhibitors). Alectinib is preferred first-line therapy in this subgroup of patients. Alectinib has better systemic and intracranial efficacy than crizotinib and has more favorable side effect profile.[8,9] Ceritinib is second generation ALK inhibitor and is approved as first line drug for *ALK* gene rearrangement positive advanced NSCLC.[10-13] Brigatinib, another next-generation ALK inhibitor, has been approved for administration in patients with *ALK*-positive advanced NSCLC, who have either worsened or are intolerant to crizotinib.[14] Brigatinib may offer better systemic and intracranial disease control with less toxicity than ceritinib but has not been yet approved in first line setting. The treatment with ALK TKI is generally continued until there is disease progression or development of significant toxicities.

ROS1 gene rearrangement

The *ROS1* tyrosine kinase gene rearrangement is observed in 1-2 percent of NSCLC, mostly in younger patients, nonsmokers and adenocarcinoma histology.[15]

Crizotinib has shown marked effectiveness in advanced NSCLC with *ROS1* gene rearrangement in first and subsequent lines of treatment.

In an international study crizotinib usage in patients with *ROS1*-rearranged NSCLC led to objective response rate (ORR) of 72 percent, median duration of response of 17.6 months and median PFS of 19.2 months.[16] More than 80 percent of patients in this study had received at least one prior chemotherapy regimen.

In another phase II trial of crizotinib in East Asian patients with *ROS1*-rearranged NSCLC, the median PFS was 15.9 months.[17]

Ceritinib (second generation TKI) has demonstrated activity in *ROS1*-rearranged NSCLC. In a phase II trial involving patients with advanced *ROS1*-rearranged NSCLC, the ORR with crizotinib was 62 percent, duration of response was 21 months, median PFS was 9.3 months and median overall survival was 24 months. Moreover, the PFS was 19.3 months for patients who had not received crizotinib previously. Sixty percent of patients with brain metastases achieved some degree of disease control.[18] Certinib has not been compared to crizotinib in *ROS1*-rearranged patients.

Other mutations

The less common sensitizing mutations including *BRAF*, *RET*, *TRK*, *MET*, and *KRAS* have been identified and specific inhibitors are available. Such patients should be included in clinical trials, whenever possible. The *BRAF* mutations have been identified in 1-3 percent of patients with NSCLC (mostly smokers). The dabrafenib and trametinib combination has been approved for patients with *BRAF* V600E mutant advanced NSCLC, who have progressed on chemotherapy.[19]

NSCLC without sensitizing mutation

Immune check point inhibitors

In patients without sensitizing *EGFR* or *ALK* mutations, the use of pembrolizumab (immune check point inhibitor) has emerged as the first-line drug for advanced NSCLC irrespective of histologic subtype or intensity of PD-L1 expression on tumor cells. In patients with PD-L1 negative NSCLC, pembrolizumab and doublet chemotherapy combination is superior to chemotherapy alone. In patients with PD-L1 positive NSCLC (especially with PD-L1 expression more than 50 percent), better efficacy of pembrolizumab and chemotherapy combination over pembrolizumab alone remains undetermined [figure 1].

KEYNOTE-024 randomized trial demonstrated that anti-PD1 therapy (pembrolizumab) was superior to platinum-based combination chemotherapy in first-line setting for advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and without sensitizing *EGFR* mutations or *ALK* rearrangements (The 50% cutoff for PD-L1 expression was used based on data from the KEYNOTE-001 trial that had shown higher objective response rate in this subgroup of patients). Pembrolizumab arm had significantly better progression-free and overall survival as compared to standard chemotherapy arm, which involved pemetrexed maintenance therapy for non-squamous NSCLC patients. Pembrolizumab group had higher response rate, longer duration of response, and less treatment-related side effects than chemotherapy group.[20,21]

KEYNOTE-189 phase III trial demonstrated better overall survival and progression free survival with pembrolizumab, cisplatin/carboplatin and pemetrexed combination versus placebo, cisplatin/carboplatin and pemetrexed in patients with non-squamous NSCLC. Median progression free survival was 8.8 months in the pembrolizumab-chemotherapy arm and 4.9 months in the placebo-chemotherapy arm. The estimated overall survival at 12 months was 69 percent in the pembrolizumab-chemotherapy arm as compared to 49 percent in the placebo-chemotherapy arm. Although the survival benefit associated with addition of pembrolizumab was seen in all subgroups of PD-L1 tumor proportion scores but the greater benefit was observed in the subgroup with a PD-L1 tumor expression of 50% or more.[22]

KEYNOTE-407 phase III trial demonstrated that pembrolizumab in combination with standard chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel) is superior to chemotherapy alone in first line setting in patients with metastatic squamous NSCLC. The median overall survival increased by 4.6 months (15.9 months vs. 11.3 months) and median progression free survival by 1.6 months (6.4 months vs. 4.8 months). Pembrolizumab combination arm demonstrated superior response rate and duration of response. There was no difference in outcomes regardless of whether the patients received paclitaxel or nab-paclitaxel. The survival benefit in pembrolizumab combination group was independent of intensity of PD-L1 tumor expression.[23]

Pembrolizumab is the only PD-1 inhibitor, which has shown superior survival over chemotherapy both as single agent and in combination with chemotherapy for first line treatment of advanced NSCLC, regardless of histology.

The data from phase III IMpower131 trial showed that PD-L1 inhibitor atezolizumab in combination with carboplatin and nab-paclitaxel decreases the risk of disease progression or death compared to carboplatin and nab-paclitaxel alone by 29% in first line treatment of patients with metastatic squamous NSCLC. There has been no improvement in overall survival thus far.[24]

Single agent pembrolizumab can be used in upfront treatment of patients with advanced NSCLC with PD-L1 expression score of more than 50% due to correlation between higher PD-L1 expression in tumors and greater benefit with pembrolizumab. The usefulness of PD-L1 expression is limited and unclear in patients receiving combination of pembrolizumab and chemotherapy, given that the chemo-immunotherapy is superior to chemotherapy alone across all categories of PD-L1

Tumor mutational burden has emerged as another biomarker for immune checkpoint inhibition, which appears to be non-overlapping with PD-L1 expression. In the phase III CheckMate 227 trial, the use of nivolumab (immune check point inhibitor) and ipilimumab (Cytotoxic T-lymphocyte antigen 4 inhibitor) as first line treatment decreased the risk of disease progression or death by 42% as compared to chemotherapy among patients with all subtypes of NSCLC with a high tumor mutational burden.[25] The contraindications for immune check point inhibitor include connective tissue disease, interstitial lung disease and rheumatologic disease.

Chemotherapy

Patients with advanced NSCLC and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or better have shown improved survival and quality of life with use of platinum doublet chemotherapy regimen. No platinum-based doublet is superior to another for unselected patients. Pemetrexed has been approved for first-line, second-line, and maintenance treatment of nonsquamous NSCLC. A phase III trial has shown that use of pemetrexed/cisplatin as first line therapy for patients with nonsquamous NSCLC has improved overall survival as compared to gemcitabine/cisplatin group.[26] The maintenance pemetrexed has shown to have superior OS as compared to placebo following initial chemotherapy with pemetrexed or taxane-based regimens.[27,28] In the United States, carboplatin doublets are preferred over cisplatin doublets due to less toxicities with former.

Antiangiogenesis

The addition of the antivascular endothelial growth factor antibody bevacizumab to a platinum-based doublet results in improved response rate and PFS, and higher OS compared with chemotherapy alone. However, this combination has not been directly compared with the addition of pembrolizumab to platinum-based chemotherapy regimen. The cross-trial comparisons suggest improved outcomes with pembrolizumab over bevacizumab when used in combination with platinum-based regimens.

The triple-drug regimen of carboplatin, paclitaxel and bevacizumab (followed by bevacizumab maintenance) has been approved for non-squamous NSCLC based on ECOG 4599 study. The median overall survival (OS) was 12.3 months in the bevacizumab and chemotherapy combination group and 10.3 months in the chemotherapy-only group. The median progression free survival (PFS) in the two groups was 6.2 and 4.5 months, respectively. The clinically significant bleeding and treatment-related deaths were higher in the bevacizumab

and chemotherapy combination arm.[29]

In a meta-analysis of four trials (2194 patients) bevacizumab addition to platinum-based doublets significantly increased both OS and PFS compared with chemotherapy alone. The effect on OS was significantly greater among patients with adenocarcinoma compared with other histology. The addition of bevacizumab did increase the risk of grade 3 or higher toxicities.[30]

PRONOUNCE trial compared pemetrexed and carboplatin induction followed by pemetrexed maintenance versus paclitaxel, carboplatin and bevacizumab induction followed by bevacizumab maintenance in patients with advanced non-squamous NSCLC. There was no significant difference in terms of overall survival or PFS between both arms. Different toxicities were noted in both arms.[31]

Point Break trial compared carboplatin, pemetrexed and bevacizumab induction followed by pemetrexed and bevacizumab maintenance versus carboplatin, paclitaxel and bevacizumab induction followed by bevacizumab maintenance in patients with advanced non-squamous NSCLC. The overall survival did not improve with the carboplatin, pemetrexed and bevacizumab regimen compared with the carboplatin, paclitaxel and bevacizumab regimen, although progression free survival was significantly better with carboplatin, pemetrexed and bevacizumab. The both regimens were well tolerated but had different toxicity profiles.[32]

Antiangiogenesis and immunotherapy

The addition of the checkpoint inhibitor atezolizumab to chemotherapy and bevacizumab has shown improved efficacy over chemotherapy and bevacizumab in non-squamous NSCLC, irrespective of PD-L1 expression. In IMpower-150 study among the patients without sensitizing EGFR and ALK mutations, the median progression free survival was significantly longer in the ABCP (atezolizumab, bevacizumab, carboplatin, paclitaxel) group than in the BCP (bevacizumab, carboplatin, paclitaxel). Similarly, median overall survival among the patients without sensitizing EGFR and ALK mutations was longer in the ABCP arm than in the BCP arm (19.2 months vs. 14.7 months; P=0.02).[33] In this trial ABCP (atezolizumab, bevacizumab, carboplatin, paclitaxel) group was not compared to ACP (atezolizumab, carboplatin, paclitaxel) group so it is unclear whether adding bevacizumab to chemo-immunotherapy improves outcome.

Maintenance

The maintenance therapy is offered if there is no evidence of disease progression following 4-6 cycles of induction treatment. Majority of patients will have received pembrolizumab, bevacizumab, or pemetrexed as part of their first line treatment. These agents may be continued, depending upon tolerance, as maintenance. Pembrolizumab may continue as single agent or can be combined with pemetrexed. Similarly, bevacizumab may continue with or without pemetrexed.

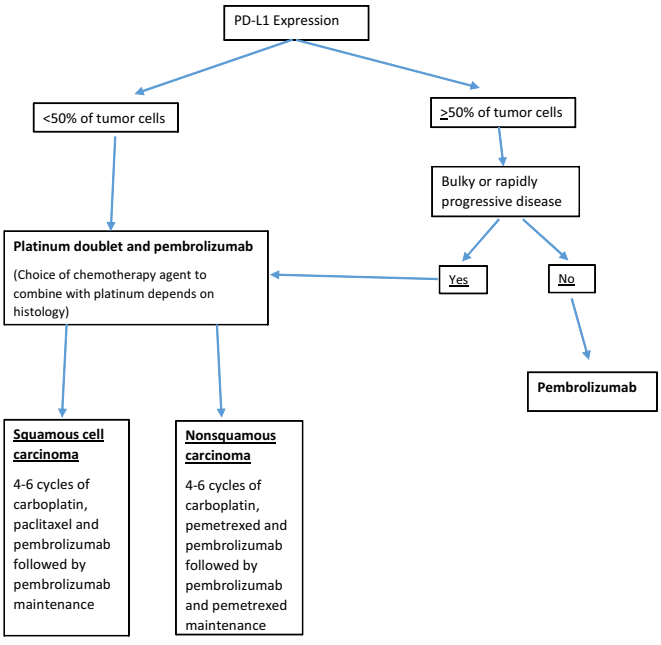
Conclusion

In conclusion, for advanced NSCLC patients (regardless of histology) without a sensitizing mutation and with PD-L1 expression of at least 50 percent, single agent pembrolizumab is judicious choice. However, for patients with high tumor burden or rapidly progressive disease the combination of pembrolizumab with chemotherapy may also be offered.

For patients with advanced non-squamous NSCLC without a sensitizing mutation and with PD-L1 expression less than 50 percent, carboplatin and pemetrexed combined with pembrolizumab for four to six cycles followed by pemetrexed and pembrolizumab maintenance is considered a standard therapy.

For patients with advanced squamous NSCLC, without a sensitizing mutation and with PD-L1 expression less than 50 percent, carboplatin, and either paclitaxel or nabpaclitaxel combined with pembrolizumab for four to six cycles followed by pembrolizumab maintenance is now a standard treatment.

Figure 1. Initial management of advanced NSCLC without a sensitizing mutation



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Dr. Muhammad Kamran Siddique: Concept of review, Literature review, writing the initial draft of the manuscript and approving final version.

Dr. Ehsan-ur-Rahman: Literature review, writing review, editing and approve final version.

Dr. Muhammad Saqib Khan: concept of manuscript, literature review, manuscript writing and approve final version.