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Mini Review

EGFR Mutant Non-Small Cell Lung Cancer: Current Status and Future Perspective

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Abstract

Epidermal growth factor receptor (EGFR) mutant Non-small cell lung cancer (NSCLC) carries better prognosis compared to other varieties of NSCLC even when treated by chemotherapy. The usage of EGFR inhibitors (EGFRI) is associated with better response rate (up to 87.8%) and improved Progression free survival (PFS) compared to chemotherapy. The outcome of therapy depends on type of EGFR mutant present as well as the prescribed EGFRI. In general improvement in Overall survival (OS) is not seen with use of EGFRI. Commonly expressed EGFR mutants include del790 and L858. They are sensitive to reversible EGFRI gefitinib and erlotinib. Progression of disease on EGFRI is associated with several factors. De-novo presence of mutant T790M is seen in 50% of tumors at progression. Osimertinib is a third generation irreversible EGFRI which acts on commonly expressed EGFR mutant as well as T790M. It provides better outcome as a second line therapy. Recently, it is found to be better than reversible EGFRI in first line therapy also. There are also some efforts to improve outcome by focusing on better EGFRI and/or combining EGFRI with other therapies like chemotherapy, vascular endothelial growth factor (VEGF) inhibitors and immunotherapy. This mini review provides overview of current status and potential future therapies.

Keywords: EGFR Mutant NSCLC; EGFR Inhibitors; Immunotherapy

Introduction

EGFR mutant NSCLC ranges from 7% to 64 % of NSCLC in various parts of the world with the highest (64%) in Vietnam and lowest (7%) in Austria [1]. It is most common amongst Mongols and least amongst Caucasians. Development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has been challenging. Its success shifted focus from histological subtypes to molecular subtypes in prognostication as well as management and paved way for development of non-cytotoxic small molecules targeting molecular subtypes in NSCLC which are more effective and less toxic.

Gefitinib was the first tyrosine kinase inhibitor (TKI) in the category. It was originally evaluated for non-selected population of NSCLC. This was followed by erlotinib. Evaluation of results of large scale clinical evaluation revealed responders as women, never smokers, and those of Asian ethnicity with adenocarcinoma histology and hardly any effect in squamous NSCLC. Further research revealed presence of EGFR-activating gene mutation to be the most reliable predictors of identifying a subset with improved efficacy [2] as revealed by tumor response up to 80%; progression free survival compared to cytotoxic chemotherapy with reduced toxicity [3,4]. Gefitinib and erlotinib are reversible TKI and are also known as first generation EGFR inhibitors (EGFRI). They are followed by reversible EGFRI, afatinib. This is followed by approval of third generation EGFRI, osimertinib which is also active against T790M, the major mutation seen at time of progression following response with first and second generation EGFRI.

EGFR mutations in NSCLC

EGFR mutations are mainly seen in adenocarcinoma subtype of NSCLC and occasionally in squamous NSCLC. EGFRI worked best in adenocarcinoma subtype compared to squamous NSCLC prior to identification of EGFR mutation as a biomarkers for efficacy of EGFRI. EGFR mutations seen in NSCLC are mainly of three types: (1) in-frame deletions in exon 19; (2) missense mutations in exons 21, 18 and 20; (3) in-frame duplications/insertions in exon 20. Exon 19 deletion 729 and exon 21 point mutations L858R, are two most common mutations and account for approximately 80–90% of the EGFR mutations detected in NSCLC. Both are associated with response to first generation EGFRI- gefitinib and erlotinib. Resistance to erlotinib and gefitinib include exon 19 deletion D761Y, exon 20 mutation D770, T790M, V769L and N771T. Of these, T790M is seen in approximately 1% of newly diagnosed NSCLC with EGFR mutations but in 50%-60% of those who progress on erlotinib and gefitinib following initial response [2].

EGFR mutations and prognosis

EGFR mutant positive tumors generally carry better prognosis compared to wild type tumors even when treated with chemotherapy. Of common mutants Leu858 mutant has better prognosis with chemotherapy in compared to del19 mutant (26.9 months vs 20.7 months). T790 positive tumors has better prognosis compared to T790 negative tumors (ORR 57% vs 29% and PFS 11 months vs. 7 months). EGFR inhibitors provides better outcome in Exon 19 mutations (highest response rate 70%) followed by

exons 21, 18, and 20 [5]. De l19 mutants have significantly longer median survival times (up to 38 months) than those with Leu858R mutation (up to 17 months) [6-8]. Patients with EGFR compound mutants (exon 19 deletions or L858R plus T790M) reached the maximum benefit (PFS and overall survival) from erlotinib treatment compared to those with exon 19 deletions or L858R alone [9].

EGFR inhibitors

Currently there are four EGFR inhibitors (EGFRI) approved world-wide for treatment of NSCLC and include gefitinib, erlotinib, afatinib and osimertinib. Objective responses generated by EGFRI are partial in nature and hardly associated with a complete response [10]. Progression free survival and overall survival following EGFRI is proportional to the amount of tumor shrinkage [11].

First generation or reversible EGFRI provide better response rate and PFS compared to chemotherapy in patients harboring commonly expressed EGFR mutants (del19 and L858R) without improvement in OS . This may be due to crossover after the progression in both arm.

Second generation or irreversible EGFR inhibitor Afatinib is more effective against del19 and not so much against L858R. It improved survival [Hazard Ratio (HR) 0.59; 95% Confidence Interval (CI) 0.45 - 0.77] in del19-positive tumors compared to Leu858Arg-positive and chemotherapy [12]. It is inferior to chemotherapy (HR 1.25; 95%CI 0.92 - 1.71) in to leu858Arg-positive tumors [13]. It is also effective against exon 18 mutants and other exon 19 mutants. It is not effective against T790 mutant responsible for resistance to reversible EGFR.

Osimertinib is a third generation EGFRI active against commonly expressed EGFR mutant (del19 and L958R) as well as T790M which is major cause of acquired resistance following response to other EGFRI [14]. Osimertinib is approved for use in patients who progress on first line TKI. It is most active against T790M positive tumors compared to T790 negative tumors (response rate 61% vs 21%; Median PFS 9.3 months vs 2.8 months) [15]. It is also superior over standard platinum–pemetrexed chemotherapy with respect to response rate (71% vs. 31%), progression-free survival (PFS) (10.1 months vs. 4.4 months) and quality of life [16].

As a first line therapy, in EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC, it significantly improved the median progression-free survival (18.9 months vs. 10.2 months; hazard ratio for disease progression or death (HR 0.46; 95% CI 0.37 - 0.57; $p < 0.001$) compared to standard EGFR-TKIs. The median duration of response was 17.2 months (95% CI 13.8 - 22.0) with osimertinib versus 8.5 months (95% CI 7.3 - 9.8) with standard EGFR-TKIs. Efficacy was superior in both those with CNS disease at enrollment and those without brain metastases. Adverse events of grade 3 or higher were less frequent (34% vs. 45%) with osimertinib than with standard EGFR-TKIs [17].

EGFR mutation and Immune Checkpoint proteins

EGFR mutant NSCLC is associated with increased Programmed death ligand 1 (PD-L1) expression by tumor tissue [18-20] which is seen in more than 50% of the cases Programmed cell death-protein 1 (PD-1 and Fox-P3 expressing lymphocytes are seen in tissue of EGFR mutant NSCLC [22] of around 1/3 of tumors [21].

EGFR inhibitors and immune checkpoint proteins:

Subgroup analysis of the previously reported trails showed that EGFRI treatment of EGFR mutant NSCLC is associated with better outcome- PFS (16.5 months vs 8.6 months; $p = 0.001$) and OS (35.3 months vs 9.8 months; $p = 0.04$) in PD-L1 expressing tumors compared to those not expressing PD-L1 [6,21]. Outcome is also proportional to level of PD-L1 expression [7]. However, no relationship was found between PD-1 expression and response to EGFR inhibitors [21].

Treatment with EGFR inhibitors convert PD-L1 positive tumors to PD-L1 negative tumors. On discontinuing EGFR inhibitors, tumor again becomes PD-L1 positive [23]. This is reverse of T790 mutation behavior i.e. Tumor becomes T790 positive while receiving EGFR inhibitor and negative once EGFR inhibitor is discontinued. Interestingly, PD-L1 expression goes down with development of resistance [24].

Rash following EGFR inhibitors

Skin rashes are common side effect of EGFR inhibitors and are associated with improved outcome [25]. Skin rash is independent prognostic parameter for better PFS (HR 0.34; 95% CI 0.18 - 0.63; $p = 0.001$) and OS (HR 0.30; 95% CI 0.20 - 0.48; $p = 0.004$) [26]. Skin rash comprise of Lymphocytic infiltration which has abundance of T cells (predominantly CD4-positive T cells) and CD1a-positive Langerhans cells throughout the dermis and epidermis. Mononuclear myeloid cells like macrophages and activated dendritic cells dominate in dermis. This is accompanied by increased expression of CCL-2, and CXCL-10 in lesional epidermis and may explain immune infiltration [27]. Rashes are effectively treated with minocycline which is known to induce cell mediated immune suppression Th2 type of response [28].

Improving the outcome of EGFR mutant harboring NSCLC

Current EGFRI provide highest response rate amongst all approved therapy in management of NSCLC. However objective responses generated by EGFRI are partial in nature [10] hardly any complete response and the improvement in PFS is modest. The progression (acquired resistance) is associated with

1. Finding of other mutations (T790M in 50%, D761Y, L747S, T845A)
2. Tumor induced angiogenesis
3. Alternate tyrosine kinase activation
4. Loss of target
5. Activation of downstream intracellular target [29]

Effort to improve outcome are directed to improve response rate, extent of response and duration of response leading to improved OS. Based on success of second and third generation EGFRI efforts are made to have better EGFRI which will have a possible better activity against commonly expressed mutant. Efforts are also made to combine various agents to improve outcome.

Better EGFR inhibitors

Multiple irreversible EGFRI are evaluated in preclinical settings. They do not seem to provide advantage over osimertinib and so further development of the majority was discontinued. There are attempts to have therapies targeting Mesenchymal-epithelial transition factor (MET) which is another major mechanism of resistance [30].

Combination therapy

To improve outcome EGFRI are combined with chemotherapy, VEGF inhibitors and immunotherapy.

Chemotherapy

As a first line

Synchronous Combination of Chemotherapy and EGFR TKIs

The synchronous combination of chemotherapy and TKIs is not superior to chemotherapy or EGFR TKIs alone for the first-line treatment of NSCLC [29,31,32]. Combination of gefitinib with carboplatin+ pemetrexed seems promising with significant increase in mPFS (18.3 vs 15.3 mos), mOS (41.9 vs 30.7), and reversible hematological grade 3 or higher AEs [33].

Intercalated therapy

Compared to EGFR TKIs monotherapy, the intercalated combination of chemotherapy and EGFR TKIs seemed superior to EGFR TKIs alone in terms of PFS, objective response rate (ORR) and disease control rate (DCR) (PFS: HR 0.75; 95% CI 0.62-0.91, P = 0.004; ORR: RR 1.49, 95% CI 1.12-2.00, P = 0.007 and DCR: RR 1.33, 95%CI 1.15 - 1.54 , P < 0.001) in advanced NSCLC therapy [34,35].

Addition of chemotherapy following progression on TKI

Addition of chemotherapy to reversible EGFRI [36] following progression does not provide any benefit for ORR (RR 0.95, 95%CI 0.68 - 1.33; p = 0.75) and PFS (HR 0.89; 95% CI 0.69 - 1.15; p = 0.38). OS was even shorter (HR 1.52; 95% CI 1.05 - 2.21, p = 0.03).

Addition of chemotherapy to irreversible EGFRI [8]

Addition of paclitaxel to afatinib in those who progressed on afatinib as a second line following clinical benefit resulted in improved PFS (median 5.6 versus 2.8 months; HR 0.60; p = 0.003) and ORR (32.1% versus 13.2%, p = 0.005) compared to single agent chemotherapy. There was no difference in OS.

VEGF Inhibitors

Erlotinib + Bevacizumab: In a phase II trial, addition of Bevacizumab to erlotinib improved median progression-free survival in EGFR mutant NSCLC i.e. 16.0 months (95% CI 13.9 - 18.1) vs 9.7 months (95% CI 5.7 - 11.1); (HR 0.54; 95% CI 0.36 - 0.79; log-rank test p = 0.0015) without significant additional toxicity [37]. It seems better results are seen in T790M-positive group [38].

Immunotherapy

Response to immunotherapy (ORR and duration of PFS) is associated with increase in intratumoral CD8+T cells [39] and increase in ratio of CD8+T cells (at peak) to tumor burden [40]. Objective responses generated by EGFR inhibitors though large in number are partial in nature [24] hardly any complete response and not durable as seen with checkpoint inhibitors [41] though EGFRI are associated with immune activation [42]. Anti-PD1/PD-L1 therapy is associated with poor response in EGFR mutant tumors compared to EGFR wild type NSCLC [43]. It is hypothesized that effective combination of EGFR inhibitors with immunotherapy will be synergistic [44] and result in durable response in larger number of patients with EGFR mutant NSCLC.

Checkpoint inhibitors

In effort to improve outcome, EGFRI and checkpoint inhibitors have been evaluated and are being evaluated as a combination therapy PD-L1 inhibitor, durvalumab with osimertinib [45]/ gefitinib [46] was unable to provide any significant benefit. However, a significant increase in AEs was seen, 55% grade 3/4 AEs. Durvalumab combination with osimertinib has found to increase incidence of interstitial lung disease [45]. Nivolumab/Atezolizumab + erlotinib and Trametinib + gefitinib has been administered with acceptable toxicity in small patient population [47]. However, based on available information it is expected that non-specific immune stimulation in form of checkpoint inhibitor may not be the answer at least for del19, L858R and T790M positive tumors.

Active immunotherapy

Active immunotherapy can activate innate (non-specific) and/ or adaptive (specific) cell mediated immune response. For killing of tumor cell, ratio of immune cells and tumor cells is important. With innate immune response this ratio is difficult to achieve in patients with large tumor burden. The ratio can be achieved by directing immune cells to tumor cells. This is possible with adaptive immune response, provided immune response is generated against tumor associated antigen. Desmocollin-3(DSC3) is one such antigen which is absent in adenocarcinoma of lung including EGFR mutant NSCLC [48], but is expressed in tumor cells following exposure to effective chemotherapy as well as EGFR inhibitors [49,50]. Induction of DSC3 happen at sub-therapeutic dose also.

CADI-05 is an active immunotherapy which when administered, induces cell mediated immune response targeting DSC3 expressing tumors [51]. CADI-05 induced DSC-3 targeting immune response is associated with infiltration of the tumor with activated CD8, CD4, NK, NKT cells and macrophages [52], decreased tumor infiltrating immune suppressive cells [52]. This results in improved response rate, PFS and OS [51] in NSCLC. Improved outcomes with CADI-05 are best seen in squamous NSCLC which generally expresses DSC3 [51]. This is achieved without additional systemic side effects [51]. Unlike chemotherapy, EGFR inhibitors are given daily, combining them with CADI-05 is expected to improve outcome significantly as EGFRI administration will result in expression of DSC3 on tumor cells which will be killed by DSC3 targeting immune response generated following administration of CADI-05. Since, CADI-05 directs activated immune cells to the tumor, there is a potential to observe a decrease in incidence of rashes (common side effect) seen with EGFRI.

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