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LUNG CANCER (H BORGHAEI, SECTION EDITOR)

Role of Anti-EGFR Targeted Therapies in Stage III Locally Advanced Non-small Cell Lung Cancer: Give or Not to Give?

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Abstract

Purpose of Review Identification of targetable mutations such as EGFR has allowed opportunity for Tyrosine Kinase Inhibitor (TKI) therapy for lung cancer treatment. EGFR-TKIs have revolutionized treatment of advanced EGFR mutant Non-Small Cell Lung Cancer (NSCLC), but there is little evidence that EGFR-TKI treatment is effective in stage III NSCLC. Here we discuss recent evidence supporting the use of EGFR-TKI therapy in combination with chemotherapy and radiation in stage III NSCLC.

Recent Findings Recent results of small trials testing EGFR-TKI therapy in combination with chemoradiation showed promising efficacy, improved outcomes, and a tolerable toxicity profile when administered to patients with EGFR mutant stage III NSCLC. However, strong supporting evidence regarding EGFR-TKI therapy in stage III NSCLC is lacking because previous trials involved a small patient population or were terminated due to slow participant accrual.

Summary Despite the lack of large randomized clinical trials, results from early-stage trials highlight promising future directions for investigating the use of EGFR-TKI therapy in stage III NSCLC treatment.

Keywords NSCLC · Stage III · EGFR · Tyrosine kinase inhibitor · Chemoradiation

Introduction

Lung cancer is a condition leading to high morbidity and mortality and it is a leading cause of death in the USA. Non-small cell lung cancer (NSCLC) accounts for 85 to 90% of all the lung cancer cases, most common subtypes being squamous cell carcinomas and adenocarcinomas [1]. For many years, the mainstay of lung cancer treatment has been chemotherapy alone or in combination with radiation and/or surgery, depending on the stage. Identification of targetable mutations in EGFR, ALK, ROS1, BRAF, and c-MET has opened wide opportunities for targeted therapies especially tyrosine kinase inhibitors (TKIs) [2].

TKIs have revolutionized treatment of epidermal growth factor receptor (EGFR) mutation–positive advanced NSCLC. First and second-generation TKIs such as erlotinib, gefitinib, and afatinib have been shown to increase progression-free survival (PFS) as compared with conventional chemotherapy in patients harboring EGFR mutations L858R and exon 19 deletion [3, 4]. The PFS-benefit has been observed in both previously treated and treatment-naïve populations [4, 5]. Osimertinib, a third-generation TKI, irreversibly inhibits the kinase domain of EGFR. It can overcome EGFR T790M, the most common mechanism of resistance to previous generation EGFR-TKIs. It has been shown to improve PFS in treatment naïve as well as previously treated patients with exon 19 deletion, L858R mutation, and/or T790M mutation [6, 7].

Despite their promising effects on stage IV NSCLC, evidence supporting the efficacy of TKIs in stage III NSCLC has been sparse and the mainstay of treatment in stage III NSCLC has been concurrent chemoradiation with/without surgery [8] and immunotherapy [9]. While small prospective clinical trials, retrospective studies, and case series have examined the efficacy of first and second-generation EGFR-TKIs in stage III NSCLC, large comparative studies are lacking. Here, in this systematic review, we examine the efficacy of TKIs as part of definitive treatment with concurrent chemoradiation or as neoadjuvant therapy in stage III NSCLC.

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Methods

Identification and Eligibility of Relevant Studies

A systematic search was performed using the MEDLINE database and from proceedings of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and American Thoracic Society (ATS). Combinations of the following index terms were used: "Non-small Cell lung cancer," "stage III," "Tyrosine Kinase Inhibitors," "gefitinib," "afatinib," and "erlotinib." Studies between 2008 and 2018 were included.

Inclusion and Exclusion Criteria

Inclusion criteria were the following: (1) clinical trial (controlled/uncontrolled) or retrospective studies, (2) stage III non-small-cell lung cancer, and (3) TKI as a part of neoadjuvant or definitive therapy.

Exclusion criteria were the following: (1) studies with stage IV lung cancer or stage IIIB lung cancer treated as stage IV lung cancer (with systemic chemotherapy) and (2) studies using TKI in the adjuvant setting.

Data Extraction

Two independent reviewers conducted review of all the studies identified by using a standardized data extraction form. Any discrepancies were resolved by consensus. After secondary exclusion, the final chosen studies were carefully re-examined. Data extraction from eligible articles was in compliance with Preferred Reporting Items for Systematic Review. All variables of interest were organized into formalized tables.

From each article, study name, type, number of patients, type and dose of TKI, type of chemotherapy used, radiation dose, mean age, performance status, gender and ethnic distribution, EGFR status, and smoking status were extracted when available.

Outcomes

Overall survival (OS) has been chosen as the primary end point. Other outcomes recorded were PFS, response rate, complete response and partial response, and time to disease progression (TTP), which was accepted as surrogate of PFS [10]. Median follow-up was recorded, when available.

Results

Study Selection

Our initial literature search yielded 344 studies. Three hundred twenty-seven studies were excluded after initial review of the title and abstract. A total of 18 studies were included for full manuscript review. After reviewing full manuscripts, 8 studies were included for analysis [11••, 12•, 13–18]. Four trials were single-arm phase 2 trials and 3 trials were randomized phase 3 trials. One was a case series report. Seven studies examined EGFR-TKI concurrent with chemoradiation as definitive therapy and 1 case series report looked at neoadjuvant TKI followed by chemoradiation.

Patient Characteristics

Study characteristics are given in Table 1. Patient characteristics are summarized in Table 2. The total number of patients among 8 studies was 461. Median age of patients ranged from 60 to 65. Most of the patients had stage III lung cancer; Ramella et al. included stage IV patients that comprised 35% of the study population. EGFR status was either negative or unknown in most of the patients. Lee et al., Xing et al., and Levy et al. included EGFR mutant patients (total 56 patients). Predominant race, predominant gender, and smoking status were available in some studies and were variable among studies. Predominant histology was adenocarcinoma. Two studies used gefitinib, the rest used erlotinib. Xing et al. used TKI concurrent with radiation in their experimental/TKI arm. All other studies used TKI in combination with chemoradiation, either concurrent or sequential. Treatment details are presented in Table 1.

Efficacy Outcomes

Median PFS ranged from 4.7 to 14 months. Median OS ranged from 23 to 39.3 months. Overall response rates to TKI plus concurrent chemoradiation varied widely among the studies from as low as 19% to as high as 85%. Available outcomes with confidence intervals are given in Table 3.

Xing et al. performed a randomized trial in EGFR mutant metastatic NSCLC and found statistically significant improvement in PFS with erlotinib plus chemoradiation compared with chemoradiation alone (HR 0.53, 95% CI: 0.006–0.463, $p < .001$). This finding is echoed in a randomized controlled trial in patients with EGFR mutant NSCLC by Lee et al. with higher median OS and PFS in the erlotinib arm, but it did not reach statistical significance. On the other hand, Kelly et al. reported worse PFS when adding gefitinib therapy to chemoradiation in patients not selected by EGFR mutation status. Heterogeneity of the studies did not allow any pooled analysis or meta-analysis.

Toxicity

From our review of included studies, it does not appear that TKI lead to any increased toxicity. Indeed, Xing et al. reported similar incidence (86.7%) of adverse events in TKI arm and

Table 1 Studies characteristics

Author	Type of trial	No. patients	Line of Rx	Neoadjuvant/ definitive	Control arm	Type of chemo	RT dose	TKI arm	Medication and dose	Comparison	Mutations included
Ramella et al. [14]	Observational study	60 (39 stage III)	Second-line	Definitive	None	Not given	59.4	Erlotinib + CCRT	Erlotinib 150 mg PO daily	Single arm	EGFR wild type
Komaki et al. [15]	Phase 2	48	First-line	Definitive	None	Paclitaxel/carboplatin	63 Gy	Erlotinib + CCRT	Erlotinib 150 mg PO daily	Single arm	EGFR wild type
Griesinger et al. [18]	Case series	5	First-line	Neoadjuvant	None	Taxane/Platinum	None	TKI interclated with chemotherapy + adjuvant RT	Erlotinib 150 mg PO daily/Gefitinib 250 mg daily	None	Exon 19 and 21 mutation
Kelly et al. [13]	Randomized phase III	243	First-line	Definitive	CCRT	Cisplatin/Etoposide f/b docetaxel	61 Gy	CCRT f/b Gefitinib	Gefitinib 250 mg/d	Randomized	None checked
Lee et al. [12•]	Phase II randomized	12	First-line	Definitive	CCRT	Irinotecan Cisplatin	60Gy	Erlotinib + CCRT	Erlotinib150 mg daily	Randomized	Exon 19 20 21
Xing et al. [11••]	Phase II	40	First-line	Definitive	CCRT	Etoposide/Cisplatin	200 cGy	Erlotinib + RT	Erlotinib150 mg daily	Randomized	Exon 19.21
Levy et al. [17]	Phase II	16	First-line	Definitive	None	cisplatin/vinorelbine	66 Gy	Gefitinib + RT f/b chemotherapy	Gefitinib 250 mg/d	Single arm	EGFR (4), ALK ROS
Casal et al. [16]	Phase II	37	First-line	Definitive	None	Cisplatin/Doce/RT		CCRT f/b Erlotinib	Erlotinib 150 mg/day	Singe arm	Not defined

CCRT concurrent chemoradiation, *f/b* followed by, *EGFR* epidermal growth factor receptor

chemotherapy arm. Rash and skin toxicity are common side effects of TKI therapy which were consistently observed in all the studies. Depending on the nature of accompanying therapies (chemotherapy or radiotherapy), the incidence of rash varied from 7 to 20% (Table 4). The incidence of grade 3 toxicity and incidence of rash and pulmonary toxicity, when available, is listed in Table 4. Toxicity profiles largely depended on whether chemotherapy was included in treatment regimen and the type of chemotherapy used. Lee et al. reported similar incidences of radiation pneumonitis in TKI arm versus chemotherapy arm (0 vs 6.5%). The most common toxicity seen with EGFR-TKI therapy was rash. The most common toxicity in chemoradiation arm was hematological toxicity. Rash, nausea, vomiting, diarrhea, pneumonitis, and hepatotoxicity were major side effects seen when TKI was given in combination to Chemoradiation (Lee et al., Levy et al., Ramella et al., and Komaki et al.). However, the incidence of serious adverse events, as delineated in Table 4, is largely dependent on the type of chemotherapy used and not higher than toxicity observed with concurrent or sequential chemoradiation [8]. The incidence of adverse events with gefitinib, given sequential to chemoradiation, has been noted to be 7% in a study done by Kelly et al., toxicity death rates of 2%.

Discussion

This systematic review is one of the first to examine the efficacy of EGFR-TKIs in stage III NSCLC.

The randomized phase II trial of erlotinib in combination with radiation versus chemoradiation alone by Xing et al. provides strong evidence of efficacy of TKI in EGFR mutant population [11••]. They included patients with both EGFR exon 19 del and exon 21 L858R. Because the efficacy of TKI is demonstrated principally in EGFR mutant advanced NSCLC, these findings are not entirely surprising [19, 20], and suggest benefit of TKI in localized NSCLC. Lee et al. [12•], in their small randomized study of EGFR mutant population, compared erlotinib plus radiation versus erlotinib plus chemoradiation. They observed longer OS and PFS with erlotinib plus RT, but these results are not statistically significant. Failure to reach statistical significance might be due to the small sample size (7 in TKI arm and 5 in chemotherapy arm). Although not statistically significant, these results—in combination with the results of phase II trial done by Xing et al.—suggest efficacy of TKI in EGFR mutant population. It can be postulated that TKI—when combined with radiation—may be efficacious in stage III lung cancer and obviate the need for chemotherapy in EGFR mutant population.

On the other hand, gefitinib, when used sequential to chemoradiation in a large randomized trial SWOG S0023 in unselected patients by Kelly et al. [13], failed to show any

Table 2 Patient characteristics

Study	Mean age (year)	Male (%)	Female (%)	Predominant ethnicity (%)	Disease stage	Predominant tumor histology (%)	Performance status	Proportion of smokers (%)	EGFR status (wild/unknown)
Komaki et al. [15]	63	60	40	White (86)	III	Adenocarcinoma (50%)	> 80	86%	Predominantly wild type
Levy et al. [17]	NA	75	25	NA	III	Adenocarcinoma (50%)	NA	NA	Predominantly wild type
Lee et al. [12•]	61	33	66	NA	III	Adenocarcinoma (90%)	0–1	33%	Mutated
Ramella et al. [14]	65	67	33	NA	65% stage III	Adenocarcinoma (65%)	0–1	NA	Unselected
Xing et al. [11••]	NA	NA	NA	NA	III	NA	0–1	NA	Mutant
Kelly et al. [13]	62	79	39	Caucasian (90)	III	Adenocarcinoma and SCC (30%, 30%)	0–1	NA	Unselected
Casal et al. [16]	62	94.6	5.4	Caucasian (97.3)	III	SCC: 75.7%	0–1	97.3%	Unselected
Griensinger et al. [18]	62	40	60	NA	III	Non-squamous NSCLC	NA	40%	EGFR mutated

NA not available, *EGFR* epidermal growth factor receptor, *SCC* squamous cell carcinoma, *NSCLC* non-small cell lung cancer

Table 3 Treatment outcomes of studies using TKI in locally advanced stage III cancer

Author.	Response rate (%) TKI/ Chemo	CR (%) TKI/ Chemo	PR (%) TKI/ Chemo	Median follow-up months	Median survival (OS-95% CI) months TKI/Chemo	HR/CI for OS TKI/Chemo	Median survival (PFS-95%CI) months TKI/Chemo	HR/CI for PFS TKI/Chemo	*p* value
Ramella et al. [14]	53.30	13.30	40.00	33.7	23	NA	4.7	NA	–
Komaki et al. [15]	85	26	59	37	36.5 (CI 25.5–47.5)	NA	14 (9.0–18.6)	NA	
Griesinger et al. [18]	60	60	0	46	Not given	NA	Not given	NA	–
Kelly et al. [13]	NA	NA	NA	27	23/35	HR: 0.6333 (0.44–.91)	8.3/11.7	0.80 (0.58–1.10)	$p > .05$
Lee et al. [12•]	71.4/80	0/0	71.4/80	23.6	39.3 (0.7–83.3)/31.2 (0.1–90.2)	NA	11.6 (0.1–23.2)/8.1 (2.7 to 13.6)	NA	$p > .05$
Xing et al. [11••]	60/38	NA	NA	NA	NA	NA	27.86/6.41	0.053, (0.006–0.463)	$p < .001$
Levy et al. [17]	19	0%	19%	Not given	11	NA	5.0	NA	–
Casal et al. [16]	35	22.2	12.8	Not given	18.7 (11.8–NA)	NA	7.3 (5.8–16.9)	NA	–

CR complete response, *PR* partial response, *HR* hazard ratio, *CI* confidence interval, *NA* not available, *TKI* tyrosine kinase inhibitor, *Chemo* chemotherapy

survival benefit. Historically, TKIs have been unable to improve outcomes in EFGR unmutated or unselected populations [21]. A phase III trial of gefitinib in EGFR unselected population resulted in modest response rates and no survival benefit [22]. The results from S0023 may underscore inefficiency of tyrosine kinase inhibitors in EGFR unmutated/unselected populations. Another observation is that adenocarcinoma comprised only 30% of study histology. The frequency of EGFR mutations in squamous cell carcinoma is low and thus EGFR-TKI therapy is not associated with high response efficacy in this histology [23].

Studies show that median overall survival in stage III NSCLC treated with chemoradiation is 9.7 months with 1-, 2-, and 5-year overall survival rates being 55%, 26%, and 23%, respectively [24, 25]. Median overall survival shown in single-arm studies presented above is much higher [14–17]. This may suggest potential survival benefit of TKIs, although EGFR status is either not known or wild type in all studies. Variation in median overall survival in single-arm trials presented above is probably the result of study heterogeneity. Lower median overall survival noted in the study by Ramella et al. [14] is probably reflecting suboptimal outcomes in pretreated patients as patients in this study received erlotinib plus chemoradiation in the second-line setting. Preclinical studies suggest that erlotinib enhances cytotoxic effects of radiation [26]. This could possibly explain higher PFS and response rates in studies using TKI concurrently with chemoradiation [15] as compared with studies using TKI as maintenance therapy [16]. Significantly lower response rates seen in a small single-arm trial conducted by Levy et al. [17] are before administration of chemotherapy and therefore, do not reflect response rates to the entire regimen. Small case series reported by Griesinger et al. [18] show promising response to TKI, but survival data is not available.

These studies provide evidence of safety of TKI concurrent or sequential to chemoradiation and suggest potential efficacy of TKI in stage III NSCLC. As study population and design are heterogenous and results are variable, no definite treatment recommendations may be made. Definitely, randomized controlled trials examining efficacy of TKI in stage III NSCLC are needed to answer this question and provide insight into the role of TKI in stage III NSCLC. Recently, a randomized controlled trial from China studied efficacy of neoadjuvant erlotinib for stage III-N2 NSCLC. Neoadjuvant erlotinib led to higher PFS and major pathological response rates when compared with neoadjuvant gemcitabine plus cisplatin. This study provides proof of efficacy of erlotinib in stage III NSCLC [27••].

The role of EGFR-TKIs as adjuvant therapy is being actively evaluated in early-stage NSCLC. A recently conducted meta-analysis of 7 randomized controlled trials suggests that adjuvant TKIs lead to improvement in disease-free survival in stage II–IIIA non-small cell lung cancer [28]. Our review suggests potential benefit of EGFR-TKIs in EGFR mutant stage III non-small cell lung cancer. While large randomized trial is needed to test this hypothesis, it has been initiated but terminated in the past due to slow accrual.

As new advances in treatment of stage III NSCLC emerge, more questions arise about place of TKI in the treatment of EGFR mutant stage III lung cancer. Recently published PACIFIC trial has proved benefit of maintenance durvalumab in stage III NSCLC [9]. A subgroup analysis assessing the association between EGFR status and efficacy of durvalumab did not reveal reduced activity in patients with EGFR mutations but the number of patients with EGFR mutations was small in this study (6%); therefore, this finding requires validation in subsequent studies. Moreover, studies have suggested modest efficacy of immunotherapy in EGFR mutant advanced NSCLC [29]. Therefore, it is questionable if durvalumab maintenance therapy provides any significant benefit in EGFR mutant stage III NSCLC but considering remarkable beneficial effect of maintenance therapy in stage III NSCLC, it will be interesting to explore efficacy of TKI in maintenance setting in EGFR mutant stage III NSCLC patients in comparison with durvalumab.

Table 4 Summary of toxicity

Study	≥ Grade 3 toxicity	Incidence (%) of rash/skin toxicity (grade 3 unless indicated otherwise)	Incidence (%) of pulmonary toxicity (grade 3 unless indicated otherwise)	Other toxicities observed
Lee et al. [12•]	60	20	0	Fatigue, Anorexia, Esophagitis
Xing et al. [11••]	47	20	Not reported	Hematological toxicity
Komaki et al. [15]	25	15	4.50	Esophagitis
Ramella et al. [14]	81	7	8	Transaminitis, cytopenias
Levy et al. [17]	47	81 (grade ≥ 1)	50 (grade ≥ 1)	Gastrointestinal toxicity
Kelly et al. [13]	20 (during Gefitinib therapy)	7	3	Diarrhea/vomiting
Griesinger et al. [18]	Not reported	Not reported	Not reported	Not reported
Casal et al. [16]	Not reported	30.6	Not reported	Diarrhea

Limitations

Our systemic review is not without limitations. Heterogeneity of the studies limits any meaningful pooled analysis or meta-analysis. Most of the studies are non-randomized trials with small sample size. Most of the studies do not provide information on methods of sample selection, randomization, and blinding. This limits appropriate evaluation for risk of bias.

Conclusion

EGFR-TKI therapy in combination with chemoradiation showed early promising efficacy in molecularly defined EGFR mutant stage III non-small cell lung cancer and can potentially lead to improved outcomes in this patient population. While this finding needs to be tested in large multi-institutional randomized clinical trials, previous attempts have been terminated due to slow accrual and low number of patients.

Compliance with Ethical Standards

Conflict of Interest Sanjal Desai declares that she has no conflict of interest. Chul Kim received one-time travel support from Caris Life Sciences to an advisory board meeting in 2017; is the site PI for the CANOPY-1 trial (NCT03631199), funded by Novartis; and has received research support from AstraZeneca for an investigator-initiated trial of durvalumab in patients with viral infection and NSCLC. Irina Veytsman declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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