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Synergistic Potential of EGFR Inhibition and Thoracic Radiation for Locally Advanced Non-Small Cell Lung Cancer with Activating EGFR Mutation

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1. Abstract

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) targeted therapy has made great progress in lung cancer treatment recently, owe to its high response rate and low toxicity, the use of which is recommended as first-line treatment for stage IV non-small cell lung cancer (NSCLC) patients by NCCN guideline. However, approximately one-quarter of patients will develop local progression due to acquired resistance and many ways were tried to overcome it. In recent years, the results of many clinical trials have confirmed that EGFR-TKI has radiotherapy sensitization. The combination of EGFR-TKI and radiotherapy not only can deal with the tumors' radiotherapy resistance and the drug resistance of EGFR-TKI, but also increase the ability to kill tumors. In this review, we discussed the rationality, safety and effectiveness of EGFR-TKI combined with radiotherapy for advanced NSCLC treatment, and confirmed the combination is a promising treatment strategy.

2. Introduction

Lung malignancy constitutes a preeminent contributor to cancer-associated mortality across the globe, with non-small-cell lung cancer (NSCLC) comprising the majority (80%) of all lung cancer incidences [1]. For tumor limited to the lung and with only regional lymph node metastasis, the most effective therapy is surgery. However, 30～60% of early-stage NSCLC patients undergoing radical surgery will experience recurrence within 5 years without adjuvant chemoradiotherapy [2,3]. For locally advanced patients or those with metastatic disease, curative surgical resection is unsuitable for 70% of cases, and conversion therapy plays a specific role in treating patients with local-advanced lung cancers. Platinum-centered chemotherapeutic regimens have long been the mainstay therapeutic approach for managing advanced or recurrent non-small-cell lung cancer (NSCLC) [4]. Nevertheless, such treatments are associated with a mere 8 to 10 month median survival time [5]. Hence, novel and more efficacious interventions are imperative for patients grappling with advanced or recurrent NSCLC.

In the realm of non-small-cell lung cancer (NSCLC) therapeutics, tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) constitute the customary front-line approach for individuals exhibiting tumor-activating EGFR mutations [6]. These genetic anomalies are ascertained in 10-15% of individuals of Caucasian heritage and approximately 30-40% of their Asian counterparts [6]. The most common sensitizing mutations are 19del and L858R, which account for almost 90% of all kinds of activating EGFR mutations [7].

Administration of first-generation and second-generation tyros-

ine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) - such as gefitinib, icotinib, erlotinib, afatinib, and dacomitinib - is associated with a superior response rate and an enhanced progression-free survival (PFS) of 9-14 months for patients with advanced non-small-cell lung cancer (NSCLC) harboring gene mutations [7]. Compared with platinum-based chemotherapy [8-11], most patients will develop progression after 1-2 years of EGFR-TKI treatment, with a median overall survival (OS) estimated at 30 months for these patients[12]. In this study, we investigated the prevalence and clinical implications of the T790M mutation, a known resistance mechanism that reportedly contributes to 50-60% of all cases. Our findings demonstrate that third-generation EGFR-TKIs, specifically those targeting EGFR T790M such as osimertinib, exhibit encouraging clinical benefits. However, despite their initial efficacy, patients eventually develop resistance, as evidenced by previous studies [13-15]. Our results shed light on the challenges and opportunities in treating patients with this mutation and provide insights for future research and clinical practice. Upon acquisition of resistance, local progression manifests in about 25% of patients [16]. In cases of oligo-progressive disease, the combination of EGFR-TKI and local radiotherapy exhibits the potential for enhancing clinical efficacy, providing benefits exceeding 6 months [17]. Therefore, EGFR-TKI combined with radiotherapy has become a promising treatment modality for advanced NSCLC. In this review, we discussed the rationality, safety and effectiveness of EGFR-TKI combined with radiotherapy for advanced NSCLC treatment.

3. The rationale and timing of combination of EGFR TKI and radiotherapy

3.1. Mechanisms and management of EGFR TKIs acquired resistance

In recent years, the normative first-line treatment for patients with advanced stage NSCLC bearing an EGFR 19del or L858R mutation has been first- or second-generation TKIs. Unfortunately, in spite of the initial efficacy, patients with EGFR mutations inevitably encounter resistance, leading to disease progression. A study demonstrate that resistance mechanism in EGFR classical mutation (EGFRcm) include three types: the modification of target gene, the activation of alternative or bypass pathway and the occurrence of histological or phenotypic transformation. The acquisition of resistance to gefitinib or erlotinib through T790M mutations and exon 20 insertion (20-ins) mutation represents the most prevalent mechanism observed in clinical settings. Notably, T790M mutations is responsible for approximately 50% to 60% of cases of acquired resistance[18,19]. MET amplification represents the predominant alternate bypass pathway, contributing to roughly 5-10% of cases of acquired resistance [20,21]. Other alternative pathways such as PIK3CA mutation, HER2 amplification and BRAF mutation et al have also been reported. [22,23]. However, after EGFR TKIs develop acquired resistance, about 5% patients can experience transformation from adenocarcinoma to small-cell lung cancer (SCLC) [23].

In the setting of acquired resistance, roughly one-fourth of patients will encounter local progression [16]. For patients with oligo-progressive disease, EGFR-TKIs such osimertinib targeting EGFR T790M is found to have clear clinical benefits, but these patients will also develop resistance [13-15]. Several studies have demonstrated that the combination of EGFR-TKI and radiotherapy as a locally effective therapy for NSCLC with EGFR mutations and metastatic sites [24,25].

3.2. The rationale and preclinical research behind combining EGFR-TKI with radiotherapy

Radiation therapy combined with EGFR-TKI for develop resistance NSCLC patients seems to be a reasonable and promising treatment option. The present study elucidates the putative mechanism of radiation-induced tumor reaggregation by in vitro experiment demonstrating the effect of radiation on the autophosphorylation of epidermal growth factor receptor (EGFR) and subsequent cell proliferation in diverse cell lines. [26,27] Our results demonstrate a marked radiation-induced increase in EGFR autophosphorylation, suggesting a crucial role for EGFR in the promotion of radiation-triggered tumor reaggregation via enhanced cellular proliferation. Second, EGFR inhibitors can enhance the effects of radiation by targeting tumor cells while protecting healthy cells from the side effects of radiation [28]. Third, EGFR-TKIs have a radiotherapy sensitization effect, and this mechanism of sensitization is the result of multiple roles. Upon stimulation, the intrinsic apoptotic pathway is activated, leading to cell cycle arrest at G0/G1 and subsequent reduction of S phase cell population. The observed decrease in S phase cell count is particularly noteworthy as these cells exhibit a higher degree of resistance to the effects of ionizing radiation.

A basic research demonstrated that gefitinib can cause redistribution of the cell cycle, resulting in the transfer of 10% to 15% of cells from the radio-resistant S phase to the G0/G1 phase, thereby increasing the radiosensitivity of the entire cell population[24]. Additionally, gefitinib has been found to effective in promoting tumor cell apoptosis and reduce radiation resistance. Phase I pharmacodynamic testing revealed that gefitinib can up-regulate the expression of p27, inhibiting Cyclin D1 and increasing the apoptosis index [25]. Various preclinical studies have confirmed that the promotion of apoptosis is also an important mechanism underlying the radiosensitivity of EGFR-TKIs. Furthermore, EGFR-TKI can inhibit radiation-induced EGFR autophosphorylation, block EGFR downstream signaling pathways, and reduce radiation resistance. Finally, EGFR-TKIs can inhibit the repair of radiation damage, primarily the repair of DNA double-strand breaks (DSBs) [29]. Finally, by inhibiting the repair of radiation damage, especially the damage repair of DNA double-strand breaks (DSBs), EGFR-TKIs plays its specific suppressive roles against tumor growth [29].

Combining gefitinib with single or fractional radiotherapy has been shown to significantly inhibit tumor growth (P≤0.001) and is equivalent to increasing the radiation dose by 60% [30]. In the NSCLC allogeneic tumor transplantation model, erlotinib (0.8 mg/d) combined with radiotherapy (12 Gy/2 Gy/21 d, 2 f/w) can inhibit tumor growth for up to 55 days [31]. Therefore, EGFR-TKIs can inhibit the accelerated proliferation of cells induced by radiation. Chinnaiyan et al. [31] have suggested that erlotinib may affect the host microenvironment by inhibiting tumor angiogenesis, improving hypoxia, and further enhancing internal radiosensitivity. Preclinical studies conducted in vivo and in vitro have shown that gefitinib can inhibit angiogenesis, reduce the expression of vascular-derived growth factors (such as VEGF and TGF-β), and decrease the number of blood vessels in tumor xenografts [32,33].

For advanced NSCLC patients receiving first-line treatment, disease progression events commonly occur in the original disease site rather than the distal region. Based on this finding, local consolidation therapy may lead to better survival rates than maintenance therapy alone. The results of all the studies mentioned above show that the PFS of the experimental group (local consolidative therapy) is three times higher than that of the control group (maintenance treatment group). The local consolidative therapy group exhibited a median PFS of 11.9 months (90% CI 5•7–20.9), while the maintenance treatment group had a median PFS of 3.9 months (90% CI 2.3–6.6), with a hazard ratio of 0.35 and a log-rank p-value of 0.0054 [34,35]. Recently, a study has shown that the OS of the local consolidation treatment (LCT) group was significantly improved compared to the maintenance treatment group, with a median OS of 41.2 vs. 17.0 months (P=0.017). Combining local consolidation therapy with systemic therapy is an effective and feasible strategy for treating metastatic lung cancer [36].

3.3. Timing in combination with radiotherapy in NSCLC treated with EGFR-TKI

Tang et al. reported [37] that more than 40% of NSCLC patients occur progression at original site after using EGFR-TKI, which indicated that this part of patients may benefit from radiotherapy. This study also analyzed the response time of NSCLC patients with EGFR-TKI treatment or the best time for tumor shrinkage, the tumor shrinks significantly in the first 2 months. The time point indicating low tumor burden can serve as a useful reference for determining the optimal timing of local treatment. According to a recent investigation, commencing localized intervention concurrently or in proximity to TKI induction, instead of delaying until the maximum tumor response or disease advancement, could potentially curtail the initial accrual of malignant clones and lower the possibility of subsequent metastatic events. Moreover, reducing tumor volume can minimize normal tissue damage and allow patients to receive stereotactic ablative body radiotherapy (SABR) or stereotactic radiosurgery (SRS). Therefore, introducing local therapy near the initiation of TKI treatment appears to be a reasonable approach. Additionally, reducing tumor volume may mitigate harm to healthy tissues and enable the administration of stereotactic ablative body radiotherapy (SABR) or stereotactic radiosurgery (SRS) to patients. Consequently, incorporating local therapy early in the course of TKI treatment seems to be a plausible strategy.

M. Nishino et al. conducted a retrospective analysis, which showed that 8 weeks after the initial TKI treatment is a crucial time point for evaluating survival rate basing on tumor response [38]. Wu's study revealed that 64% of patients who eventually achieved complete response (CR) or partial response (PR) achieved it at 8 weeks, with a median time to response of 7.4 weeks [39]. Yi et al. also found that the first 2 months of TKI therapy led to significant tumor shrinkage in NSCLC patients [37]. Wu et al. reported a median response time of 6 weeks in the EGFR mutation-positive subgroup [40]. These findings suggest that a plateau is reached with relatively low tumor burden after the first 6-8 weeks of TKI therapy, which can be considered as a reference time for local radiotherapy intervention. These data absolutely provide valuable insights for selecting the optimal timing of local therapy.

4. Methods

The review data were identified by searching the PubMed database using the search terms 'EGFR-TKI', 'EGFR mutation', 'tyrosine kinase inhibitor', 'thoracic radiotherapy', 'non-small-cell lung cancer', 'gefitinib', 'erlotinib', 'Osimertinib', 'almonertinib', 'T790M', and 'clinical trial'. Approximately 10 years' worth of articles were enrolled (Figure 1).

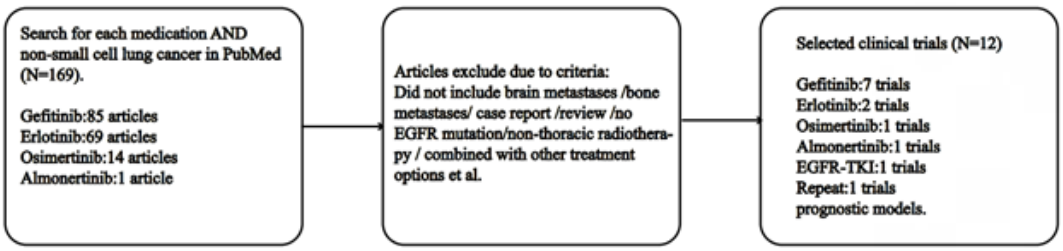

Figure 1: Workflow of the study. Selection process for trials included in systematic review. This figure outlines the process in which articles were searched and selected in our review.

5. Clinical trials of combination of EGFR TKI and radiotherapy

5.1. Combination of TKI (gefitinib and erlotinib) and TRT

To evaluate the efficacy of EGFR-TKI combined with thoracic radiotherapy (TRT), we investigated several clinical trials of combined EGFR-TKI and TRT (Table 1). In this Phase II investigation published in the Journal of Nature, the safety and toxicity profiles of daily administration of gefitinib (250mg) or erlotinib (150mg) in conjunction with concurrent TRT were evaluated in patients with unresectable stage III NSCLC [41]. Ten eligible patients (five males and five females) enrolled in this study, four exhibited a mutation in L858R, while six individuals displayed a 19del. One patient accepted gefitinib (250mg /day), the others accepted erlotinib (150mg /day). All patients accepted TRT (54-60 Gy/ 27-30 F/5.5-6W) within 2 weeks of initiation of EGFR-TKI treatment until disease progression or appear severely adverse events (AEs). In this study, the primary toxicities associated with the combination therapy of TKI and TRT were observed to be grade≥3 radiation pneumonia (20%) and rash (10%). Besides, radiation pneumonia averagely occurred 40 days following radiation therapy. Despite one patient succumbing to pneumonitis due to refusal of treatment, the remaining patients demonstrated remarkable improvement upon receiving complete treatment with glucocorticoid, leading to a satisfactory control and prevention of pneumonia recurrence. The acceptable risk of adverse events was demonstrated, with a median follow-up time of 19.8 months (5.8-34.0 months) among all patients and five patients remained alive at the last follow-up. The objective response rate (ORR) and disease control rate (DCR) of TKI combined with TRT were 50% and 100% respectively and 1-year PFS rate was 57.1%. At ENSURE study, TKI therapy alone ORR was 62.7% and DCR was 89.1%, respectively and 1-year PFS rate was 43%. This investigation scrutinized the combination of TKI and TRT with respect to its toxicity and tolerability. The research findings evince that the combined therapeutic approach engendered a level of toxicity and tolerability that is deemed acceptable. Furthermore, the survival outcomes were deemed satisfactory. Akamatsu's prospective study will assess safety and feasibility of daily gefitinib concurrent with TRT with unresectable NSCLC patients of stage III [42]. A total of twenty-seven eligible patients of harboring L858R and 19del mutation were enrolled in this trial. Twenty-seven patients will accepted TRT to a dose of 64Gy concurrently with oral gefitinib (250 mg/d). To assessed TRT quality, the author collected the pretreatment diagnostic chest radiographs; chest CT is required every 2 months (at the first 6 months) and every 6 months after half a year. The author previously reported that the 2-year PFS rate of LA-NSCLC patients may be an alternative indicator of 5-year survival [43] and they assumed a 2-year PFS rate maybe improved from 20% to 40%. The results of this prospective study will be influential on the future therapy strategy toward harboring EGFR mutation population. In another prospective II study [44], advanced NSCLC patients experience a good OS were treated with gefitinib 250mg daily over 8 weeks, followed by concurrent chemotherapy (cisplatin and docetaxel 40mg/m2 days 1,8,29, and36) and three-dimensional conformal radiotherapy to 60Gy. EGFR mutations (19del and L858R) were detected in 21 patients. According to the previous data, which cisplatin chemotherapy with concurrent TRT, 2-year survival rate is 60.3% [45]. In the context of metastatic disease, pre-clinical implementation of EGFR-TKI treatment did not confer a statistically significant advantage in patient prognosis for those harboring EGFR mutations, as compared to the wider patient cohort (median survival time of 13.6 versus 10.4 months, respectively; P=.034) [46]. However, a subsequent phase III investigation of chemoradiotherapy exhibited a marked increase in therapeutic efficacy, with an approximate 15% rise in survival benefit observed [45]. A randomized phase II study demonstrated gefitinib plus platinum therapy reached a survival rate at 24 months >80% for NSCLC patients with sensitive EGFR mutations [47]. Based on a previous study, the author indicated that a survival rate at 24 months >85%. A feasibility study assessed the effect of gefitinib (250mg) with concurrent TRT for stage III unresectable NSCLC patients [48], 9 eligible patients included in this study accepted induction gefitinib alone. During the initial 2-week period of the clinical trial, two patients were excluded from further treatment due to the progression of a chronic ailment. Of the remaining seven patients, three underwent combined treatment with gefitinib and concurrent TRT, but were unable to complete the planned therapy due to either pulmonary toxicity or progressive disease. Notably, two of these patients were found to carry EGFR mutations (19del) and showed a PR, achieving an impressive OS exceeding five years. These findings hold promise for the potential application of EGFR-targeted therapy in certain cancer patients. Two patients harboring EGFR mutations OS were 73.6+ months and 63.7+ months, respectively. In summary, the results of this study suggest that the proposed therapeutic approach shows great potential in the treatment of LA-NSCLC patients possessing sensitizing EGFR mutations. These findings offer a valuable contribution to the field of cancer research, and may pave the way for further investigations into the efficacy of EGFR-targeted therapy for this patient population. Akamatsu's II study assessed safety and feasibility of daily gefitinib concurrent with TRT with unresectable LA-NSCLC with EGFR mutation patients [49]. In this study, 27 patients with the L858R and 19del mutations were enrolled and received gefitinib (200mg/d) along with concurrent TRT. This study investigated the tolerability and potential efficacy of gefitinib in combination with concurrent TRT for patients with EGFR mutations and locally advanced non-small cell lung cancer (LA-NSCLC). Grade 3 fatigue, nausea, vomiting and skin reaction appetite loss were the primary toxicities observed in 3.7% of patients receiving concurrent TRT. At the two-year mark, patients with unresectable stage III non-small cell lung cancer (NSCLC) who received gefitinib in

combination with sequential or concurrent chemoradiotherapy demonstrated promising outcomes. The objective response rate (ORR) was 81.5% (95% CI: 63.3-91.3%), and the progression-free survival (PFS) rate was 29.6%. Median PFS and overall survival (OS) were 18.6 months (95% CI: 12.0-24.5 months) and 61.1 months (95% CI: 38.1 months to not reached), respectively. Furthermore, a phase II study evaluated the addition of gefitinib to chemoradiotherapy in patients with unresectable stage III NSCLC. Patients at high risk (≥5% weight loss) received radiotherapy and gefitinib, while those at low risk (<5% weight loss) received additional weekly paclitaxel and carboplatin. The median PFS for low-risk and high-risk patients was 13.4 months (95% CI: 6.4-25.2 months) and 9.2 months (95% CI: 6.7-12.2), respectively, while the median OS for low-risk and high-risk patients was 19 months (95% CI: 9.9-28.4 months) and 13 months (95% CI: 8.5-17.2), respectively. These findings suggest that gefitinib may offer a promising approach for the treatment of patients with unresectable stage III NSCLC.Among all patients, 13 had activated EGFR mutations, two of whom had T790M mutations. In this study, the author found no significant improvement in survival between patients with wild-type EGFR or EGFR mutations. The results showed promising survival outcomes for low-risk patients with wild-type EGFR or EGFR mutations who received sequential chemoradiotherapy and gefitinib. However, disappointing results were observed for low-risk patients with activating EGFR mutations who received concurrent chemoradiotherapy and gefitinib. The CALGB 30605 trial is a phase II study that investigated the combination of gefitinib and radiation for stage III NSCLC. The study showed that for high-risk patients receiving a combination of EGFR with radiation alone had better outcomes. This was a prospective, single-arm, phase 2 trial conducted by Komaki to investigate whether the combination of the erlotinib and concurrent chemoradiotherapy may experience a improved survival and disease control without increasing toxicity in previously untreated LA-NSCLC [51]. 48 patients were enrolled in the study and received intensity modulated radiation therapy(IMRT, 63Gy/35 fractions) 5 times a week, along with chemotherapy and EGFR-TKI for 7 weeks. The most common chemotherapy treatment is paclitaxel at a dose of 45 mg/m2 plus carboplatin (area under the curve [AUC]=2) and erlotinib is added at a dose of 150mg/d, followed by consolidation paclitaxel-carboplatin. No patients experienced grade 5 toxicity. The primary toxicities were ≥3 grade Esophagitis (2.2%); pneumonitis (6.5%); skin toxicity (13%) and acneiform rash (4.3%), which was acceptable. In this study, a total of 41 individuals were assessed for EGFR mutations, revealing 27 with wild-type and 4 with mutated EGFR (all adenocarcinoma). The median PFS and OS were found to be 14.0 and 36.5 months, respectively. The 1, 2, and 5 year OS rate were 82.6%, 67.4%, and 35.9%, respectively, and did not differ significantly based on EGFR status. The addition of erlotinib to chemoradiation for previously untreated stage III NSCLC was found to produce excellent OS and low toxicity, although PFS did not meet expectations. In a separate phase II study, Fu assessed the safety and toxicity for the combination of radiotherapy and gefitinib (250mg/d) for LA-NSCLC patients who were unsuitable for surgery and concurrent chemoradiotherapy. In this study, 28 patients were enrolled, with 13 participants providing molecular data and six patients exhibiting EGFR-mutation. 21 (75.0%) of them had a PR, while 5 (17.9%) experienced a stable disease (SD), resulting in an ORR of 75.0% and a DCR of 92.9%. The median OS and PFS were 26 and 11 months, respectively, while the survival rates and PFS rates at 3-, 4-, and 5-year were 39.0%, 30.1%, 30.1% and 14.3%, 9.5%, and 9.5%, respectively. Primary toxicities observed with the use of IMRT combined with gefitinib included grade 3 diarrhea (3.6%), esophagitis (3.6%), and hypohepatia (3.6%), with no cases of grade 3 acute irradiation pneumonitis. Based on these findings, the author concluded that thoracic IMRT combined with gefitinib is well-tolerated and can improve ORR (Table 2). In this study, patients with EGFR-activating mutations (n=6) demonstrated a significantly improved median OS (39 months) compared to those with EGFR wild-type or non-adenocarcinoma (n=20; 20 months). Group 1 patients won't reject EGFR-TKI treatment alone until tumor progression, while group 2 patients who accepted EGFR TKI treatment received TRT subsequently. The author concluded that TRT may be associated with improved OS for patients with unresectable EGFR-mutant lung adenocarcinoma and are responded to EGFR-TKI treatment. Currently, large-scale, prospective, randomized studies examining the efficacy of TRT combined with EGFR-TKI treatment for patients with unresectable EGFR-mutant NSCLC still lacks.

Table 1: Tyrosine kinase inhibitors against EGFR and TRT in clinical trials

Year, name	Phase	group	TKI	RT	chemotherapy	≥3adverse events	Efficacy	
							RR/ORR/DCR	Survival
Zheng et al 2019[41]	II	10	Gefitinib/ Erlotinib	54-60 Gy	None	radiation pneumonia 20% rash 10%	TKI+TRT: ORR:50% DCR:100%	TKI+TRT: mPFS:13months
								The 1-year PFS rate:57.1%
							TKI: ORR:62.7%	TKI: mPFS:11months
							DCR:89.1%	The 1-year FFS rate:43%

Akamatsu et al 2019 [42]	A prospective II study	27	Gefitinib	64 Gy	None	NR	Secondary end points: ORR; PFS, OS, and safety. primary end point: the PFS rate at 2 years	
							assumed improved PFS rate at 2 years from 20% to 40%	
Hotta et al 2016 [44]	A prospective II study	21	Gefitinib	60 Gy	concurrent chemotherapy: cisplatin/docetaxel	NR	primary end point OS at 24 months	
							Secondary end points: OS toxicity; RR	
Okamoto et al 2011 [48]	A feasibility study	7	Gefitinib	60 Gy	None	Elevated ALT 33% elevated AST 33%; pneumonitis 11%	RR:57%	MOS 11.5 months
Akamatsu et al 2021[49]	II	27	Gefitinib	64Gy	None	fatigue, skin reaction and appetite loss (3.7% each).	ORR:81%	PFS rate at 2 years:29.6%; mPFS 18.6 months; mOS 61.1months
Ready et al 2010 [50]	II	21	Gefitinib	66 Gy	Induction chemotherapy: carboplatin/paclitaxel	Acute high-grade infield toxicities were not clearly increased compared with historical CRT data	RR:53%	MOS 19 months
		39						
Komaki et al 2015 [51]	A prospective II study	46	Erlotinib	63Gy	Induction and concurrent chemotherapy: carboplatin/ paclitaxel	Esophagitis 2.2%; pneumonitis 6.5%; skin toxicity 13%; acneiform rash 4.3%	The primary endpoint: PFS; secondary endpoints OS; toxicity; response; dis-ease control and whether any endpoint differed by EGFR mutation status	
Fu et al 2020 [52]	II	28	Gefitinib	60-66Gy	None	Diarrhea 3.6%; Esophagitis 3.6%; Hypohepatia 3.6%	ORR 75%; DCR 92.9%	mPFS 11months MOS 26months; The3-,4-,5-yearsurvivalrateswere39.0,30.1and30.1%, respectively. The3-,4-,5-yearPFSrateswere14.3,9.5and9.5%.
Yen et al 2018 [53]	A prospective randomized study	TKI 295	EGFR-TKI	45-74Gy	None	NR	OS	

Abbreviations: TKI= Tyrosine kinase inhibitors; RT=response rate; RR=response rate; ORR=objective response rate; DCR=disease control rate; MPFS=median progression-free survival; MOS=median overall survival; NR=not report.

Table 2: Tyrosine kinase inhibitors against EGFR and TRT in clinical trials

Year, name	Phase	group	TKI	RT	chemotherapy	≥3adverse events	Clinical outcome
Zhu et al. 2021 [57]	A prospective II study	43	almonertinib	60Gy	None	radiation pneumonitis	Primary endpoint: the incidence of grade ≥3 radiation pneumonitis; secondary endpoints are local control rate; PFS; OS
Jia et al. 2020 [58]	II	11	Osimertinib	30Gy-64Gy	None	radiation pneumonitis 54.5%	high rate of grade 2 or worse radiation pneumonitis in patients treated with TRT and simultaneous osimertinib

Abbreviations: TKI= Tyrosine kinase inhibitors; RT=response rate; TRT=thoracic radiation therapy; PFS=median progression-free survival; MOS=-median overall survival.

5.2. Combination of third-generation TKI (Osimertinib and almonertinib) and TRT

Third-generation EGFR-TKIs have already shown its potential in increasing radiosensitivity in NSCLC patients with EGFR-mutant. Yu et al. demonstrated that third-generation EGFR-TKIs could reduce the count of cell in G2/M-phase and block radiation-induced DNA DSB repair, thereby increasing radiosensitivity. Ma et al. demonstrated that third-generation EGFR-TKIs could delay post-irradiation damaged DNA repair and induce apoptosis through the EGFR signaling pathway. Additionally, Wang et al. found that first-generation EGFR-TKIs inhibited not only EGFR-mutant, but wild-type EGFR tumors. The low selectivity of the third-generation EGFR TKIs, exemplified by Osimertinib for EGFR wild-type may account for the low occurrence rate of severe interstitial pneumonia. Almonertinib, an exemplified third-generation EGFR-TKI, was evaluated for safety and efficacy in a prospective phase II study by Zhu et al for patients with unresectable stage III NSCLC receiving TKis combined with TRT. Induction and concurrent groups were enrolled based on lung V20 levels, and the primary endpoint was the occurrence of severe (grade ≥3) radiation pneumonitis. Secondary endpoints included local control rate, PFS, and OS. In another study by Jia et al., the incidence of radiation pneumonia was evaluated in T790M or EGFR mutant NSCLC patients treated with osimertinib and TRT. The occurrence rate of grade ≥3 radiation pneumonitis was 63.6% (7/11) compared to erlotinib and TRT, and the rate of grade 3 or worse was significantly higher at 54.5% (6/11). However, the small sample size and potential bias in Jia's retrospective study may affect the results. Although several studies have shown the potential value of EGFR-TKI concurrent TRT, the increased incidence of radiation pneumonitis limits its clinical application. Therefore, more knowledge is needed to evaluate the safety of third-generation EGFR-TKI combined with TRT for LA-NSCLC patients, and prospective studies are warranted.

6. Conclusion

In this study, the authors explored the efficacy and safety of combining EGFR-TKI with radiotherapy in patients with advanced NSCLC harboring EGFR mutation. Phase II data showed promising results in terms of survival and tolerability, supporting the use of this combination therapy. What's more, immunotherapy has provided even greater opportunities for the integration of radiotherapy, thereby presenting numerous possibilities and more studies are needed to determine optimal radiation timing and dose. Regarding the combination of osimertinib with TRT, a phase II study showed a higher incidence rate of grade ≥3 radiation pneumonitis compared to first-generation TKI combined with TRT. However, the small sample size and potential for bias warrant further investigation. Currently, there are limited clinical trials assessing the safety of this combination therapy. Therefore, additional prospective studies are needed to determine its safety for locally advanced NSCLC patients. Overall, the integration of radiotherapy in the management of EGFR-mutant NSCLC has shown potential for improved outcomes, and future research should continue to investigate the optimal approach.

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