Review Article

Management of non-small cell lung cancer with *EGFR* mutation: the role of radiotherapy in the era of tyrosine kinase inhibitor therapy—opportunities and challenges

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Contributions: (I) Conception and design: S Ma; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: In recent years, the treatment of advanced non-small cell lung cancer (NSCLC) was greatly promoted by the discovery of oncogenic drivers and the development of targeted therapies specific for these drivers. Somatic mutations in epidermal growth factor receptor (EGFR) are the most common type in patients with NSCLC. Small-molecule tyrosine kinase inhibitor (TKI) targeting EGFR produced relatively high response rate and long duration with acceptable toxicity profile. Also, the life expectancy in patients with active *EGFR* mutation has been significantly prolonged than the past. Additionally, evolution of advanced imaging and radiation techniques has expanded the indications for radiotherapy in complex clinical situation. All of those factors contributed to the widely use of radiotherapy for advanced NSCLC treated with TKI therapy. In this review, we will discuss how to integrate radiotherapy into the comprehensive treatment of patients with TKI therapy in order to maximize the therapeutics effect.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); tyrosine kinase inhibitor (TKI); radiotherapy

Submitted Sep 01, 2017. Accepted for publication Sep 13, 2017.
doi: 10.21037/jtd.2017.09.67
View this article at: http://dx.doi.org/10.21037/jtd.2017.09.67

Background

Lung cancer is the leading cause of cancer-related deaths worldwide that constitute a significant global health burden. In 2017, it is estimated that there will be 222,500 new cases of lung and bronchus cancer and an estimate of 155,870 people will die of this disease in the United States (1). The situation is more serious in China because of the massive population and huge cigarette consumption; according to the cancer statistics released by the national central cancer registry of China in 2016, the estimated new cases and deaths of lung cancer per year were 733,300 and 610,200 in the last decade (2). The overall prognosis of lung cancer is poor due to late-stage detection and ineffective therapies. Approximately 50–60% of the patients are with advanced stages that have no chance of receiving radical surgery or chemoradiotherapy. In addition, cytotoxic chemotherapy agents and combinations yielded low response rates, high toxicity rates, and limited improvements in survival although progress has been made over the past years at a modest pace. In this context, radiotherapy is generally used as a means of palliative care in this setting (3).

Recently, with new advances including the discovery of

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oncogenic drivers and therapies specific for these drivers in non-small cell lung cancer (NSCLC), the application of oral small-molecule tyrosine kinase inhibitor (TKI) targeting these oncogenes was increased in clinic practice, which produced relatively high response rate and long duration with acceptable toxicity profile. Furthermore, the life expectancy in these patients has been significantly prolonged than those in the past with treatment of chemotherapy alone (4,5). In addition, evolution of advanced imaging and radiation techniques has also expanded the indications for radiotherapy in complex clinical situation (6). All of those factors contributed to the widely use of radiotherapy for advanced NSCLC treated with TKI therapy. In this review, we will discuss how to integrate radiotherapy into the comprehensive treatment of patients with TKI therapy in order to maximize the therapeutics effect.

Historical and current perspectives of epidermal growth factor receptor (EGFR) TKI therapy in NSCLC

In the last decade, management of advanced NSCLC has evolved toward stratification of patients based on oncogenic drivers, such as *EGFR* mutation, anaplastic lymphoma kinase (*ALK*), *ROS1* rearrangement etc. (7). Somatic mutations in *EGFR* are the most common type in patients with NSCLC. The overall prevalence for *EGFR* mutations was about 30%, ranging from 38.4% in China to 14.1% in Europe. Besides ethnicity (Western/Asian), other factors, included smoking status (yes/no), sex (male/female) and histology (adenocarcinoma/squamous cell carcinoma), also affected the incidence rates of *EGFR* mutations (8).

The first-generation (gefitinib, erlotinib and icotinib) and second-generation (afatinib) EGFR TKIs are now standard as the first-line treatment for patients with advanced *EGFR*-mutated NSCLC. For patients with active *EGFR* mutations, TKIs produced high response rates up to 75% and improved progression-free survival (PFS) to 9–13 months as compared with chemotherapy in randomized trials (4,9-11). However, majority of the patients developed acquired drug resistance after initial response to TKI, and the median overall survival in those patients was estimated to 30 months. Studies of tumors biopsied at the time of disease progression have elucidated mechanisms of acquired resistance, in which the development of T790M mutation is the most common resistance mechanism (approximately 50–60%) (12,13). That discovery has led to the development of third-generation TKI, osimertinib, which has shown to be superior to standard platinum/pemetrexed chemotherapy in patients whose tumors have developed T790M mutations. Among patients receiving osimertinib, the response rate and median PFS were about 71% and 10.1 months in phase 3 trial (AURA3) (14). Although the overall survival was not available because of immature data, it can be expected that survival will be further extended in this population.

In the past, the life expectancy of most patients with metastatic NSCLC is measured in months; radiotherapy is frequently used to palliate symptoms with a low total dose and is often administrated relatively late. With the prolonged survival duration of those patients receiving TKI therapy, the timing and dose of radiotherapy need to be redefined in order to optimize the delivery of radiotherapy.

Palliative radiotherapy in advanced NSCLC treated with EGFR TKI

As for the patients with advanced stage NSCLC, various disease related symptoms often developed at diagnosis due to diverse causes such as superior vena cava obstruction, airway obstruction, bone destruction and brain metastasis. Generally, palliative radiotherapy is administrated immediately in this setting in order to quickly relieve symptoms and improve quality of life (QOL), and symptoms improvement rates of 50–80% were reported in literatures (15,16). Of note, systemic treatment is often delayed until the end of radiotherapy, with the concerns of the increased toxicities of combined modalities. In patients with active *EGFR* mutation, TKI therapy produces a high response rate up to 75%, which is comparable to the efficacy of palliative radiotherapy. In addition, the shorter time of response to TKI therapy may be useful for early symptom improvement for these patients. Imai *et al.* compared the efficacies of radiotherapy and TKI in NSCLC patient harbored sensitive *EGFR* mutation, based on the RECIST criteria (17). In this study, 17 patients were administrated with radiotherapy and 32 patients received TKI therapy. As to their report, the response rates were 64.7% and 81.3% and the time-to-partial response were 40 and 20 days respectively, with evaluation limited to patients with a response. Other studies have also reported that the median time to symptomatic relief was observed within 2–3 weeks for patients treated with EGFR TKIs (18,19). These results suggest that TKI can be considered as the first choice if the primary goal was to achieve prompt symptomatic relief. It is unclear whether

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delivery of concomitant radiotherapy can be resulted in better outcomes, but such an approach of combined treatment deserved additional studies to explore, considered of the favorable toxicity profile when radiotherapy combined with TKI therapy reported in literatures (20,21).

With regard to the radiation prescription, a low dose and shorter overall treatment time are preferred in recent clinical guidelines of American Society for Radiation Oncology (ASTRO) and National Comprehensive Cancer Network (NCCN), due to lower costs and greater convenience in the face of short life expectancy. However, in a recent study based on a national population cohort of metastatic NSCLC administrated with palliative radiotherapy, investigators found that a substantial proportion of patients received a greater number of treatments and higher doses than supported by current evidence (22). This observation reflected that providers may believe that intensive treatment can be delivered with minimal toxicity and will bring additional benefit from even higher doses, although such willingness is not supported by available data. Because of good response to TKI therapy, patients with active *EGFR* mutation can be considered as the candidate to test such tentative idea. In addition, the disease status of some patients became limited after TKI therapy, defined as induced oligo-metastases. Possibly, those patients have the chance to receive curative therapies such as surgery, ablation, or stereotactic body radiation therapy (SBRT). In a recent study aimed to evaluate the pattern of failure in patients receiving TKI therapy, about 20% of the patients were judged feasible for consolidation SBRT (23).

Radiotherapy at the time of disease progression after TKI therapy

In patients received first-line TKI therapy, acquired drug resistance was developed inevitably despite dramatically response initially. In clinical practice, several failure modes were conceived in order to favor strategies for subsequent management. In Yang's study, three modes of dramatic, gradual and local progression were proposed according to specific criteria derived from clinical factors, and continuation of TKI plus local intervention was recommended for the last situation (24). Weickhardt *et al.* investigated the benefits of local ablative therapy to limited systemic disease progression in patients who received TKI therapy and a second PFS of 6 months was observed (25). In another study considering the role of local therapy in patients with acquired resistance, Yu *et al.* reported that the time to progression after local therapy was 10 months and the median time from local therapy until a change in systemic therapy was 22 months (26). Although encouraging results were reported in these studies, it should be noted that the patients enrolled in the studies were strictly selected, and the proportion of such patients was not high accounting for the whole population treated with EGFR TKIs. Also, because of the inherent limitations in retrospective studies, the true benefit of local radiotherapy combined with continuation of TKI therapy argue for additional studies with standardized enrollment and research process in a prospective fragment.

Early intervention of radiotherapy in TKI therapy

Accumulating data revealed how tumors become resistant to EGFR TKI. The most common known mechanism is the acquisition of T790M that renders the kinase resistant to the first-line TKI (27,28). Studies showed that T790M existed at a low frequency within the tumor cells pretreatment and became the dominant clone after selection pressure of EGFR-TKI therapy (29). In addition, preclinical studies also demonstrated that a second mutation of T790M could be successfully induced in PC-9 lung cancer cells after about 120 days culture with TKI (30). These results indicated that both mechanisms of *de novo* and induced T790M could be present in the course of TKI treatment. In fact, cancer cells harbored T790M exhibited enhanced sensitivity to radiation (31), suggesting the potential role of radiotherapy in the management of EGFR-TKI related resistance. If intervention of radiation was administrated at the time of best response of TKI therapy, instead of disease progression, it may benefit patients by reducing the chance or delay the time of T790M-mediated EGFR TKI resistance. Meanwhile, radiotherapy provides opportunities of reducing systemic reseeding from the growth of resistant clones harbored T790M in the original sites. Actually, there were several clinical reports that supported such deduction. In a study of 25 patients with IIIb/IV NSCLC who responded to upfront TKI treatment, concomitant radiotherapy of 40–50 Gy in 16–20 fractions were delivered with tomotherapy for individual metastatic lesions (32). The overall response rate was 84.0% and the median PFS was 16 months. The 3-year overall survival rate was 62.5% and toxicities were generally tolerated. These encouraging results indicated that radiotherapy might aid

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expansion the effectiveness of TKI therapy in those patients who are responding to TKI treatment. In another two studies using TKI combined with radiotherapy in stage III/IV NSCLC, although enrolled patients was not selected based on the *EGFR* mutation status, the median PFS of 10–14 months and survival time of 20–22 months were observed with acceptable toxicities, indicated the feasibility of targeted therapy combined with advanced radiotherapy in clinical practice (33,34). Recently, we launched a phase II trial of hypofractionated radiotherapy for limited metastatic NSCLC harboring sensitizing *EGFR* mutations, the inclusion patients are required to be oligometastatic disease (≤5 discrete lesions of disease, exclusive of the brain metastases) after 3 months of TKI therapy, evaluated by PET/CT scan. The scheduled time of radiotherapy is 3 months after TKI therapy in patients responded to TKI, and the primary objective is to extent PFS to 16 months.

Now, for patients with active *EGFR* mutations who progress during or after first-line targeted therapy, subsequent therapy depends on the specific genetic alteration, the histologic subtype, and whether the patients have symptoms. Osimertinib is recommended for patients with T790M positive. Of interest, we recently revealed the correlations of the disease failure sites with the frequency and abundance of T790M mutations in 314 patients who progressed during TKI treatment. In these patients, plasma T790M mutations were detected in 46.8% of the populations by droplet digital PCR, and T790M mutation was associated with extensive progression of the tumor, suggesting that NSCLC tumor cells with acquired T790M mutation may indicate distinct natural history and are with capability of cancer cell invasion and migration. Other studies reported that plasma T790M mutation could be detected approximately at 2.2 months prior to clinical progression, indicating that the spread of tumor cell with T790M mutation in circulation might be an early event in the course of disease metastasis (35,36). Upon the sustaining TKI exposure, T790M mutation is more likely to develop and gain the upper hand in the original disease sites, and then the growth of resistant T790M cancer cell clones can systemically reseed and finally lead to distant failures in new sites of disease. Therefore, early intervention to eradicate residual disease after TKI therapy, which may contain low abundance of *de novo* or acquired T790M mutation, can provide an opportunity to reduce the risk of subsequent extensive progression. Taking together, the value of early intervention in patients treated with TKI therapy is worth to be further investigated.

Management of brain metastasis in patients with EGFR mutation

Brain metastasis and EGFR mutation

Many patients with NSCLC have brain metastases (30–50%), which is one of the most devastating complications threatening to life (37,38). Of note, the risk of brain metastases is relatively high in patients with *EGFR* mutation at the time of diagnosis, as well as during the course of follow up in those who administrated with surgery. Shin *et al.* reported a dramatic correlation of *EGFR* mutation status and brain metastasis (adjusted odds ratio =3.83, P=0.001) in 314 patients with testing of *EGFR* mutation and brain magnetic resonance imaging at diagnosis (39). In this study, they also found that, in a subgroup analysis of 133 patients treated with surgical resection, *EGFR* mutation status was a poor prognostic factor for the risk of brain metastasis [hazard ratio (HR) =4.49, P=0.026] after adjustment for pathologic N stage. In addition, during the course of TKI therapy in advanced NSCLC, about 30% of the treatment failure was the present with new lesions or progression of original sites intracranial, which may be related to the low drug concentration of first-line TKIs in the cerebrospinal fluid and the prolonged survival in those patients. Because of the high percentage and the devastating outcomes of brain metastases, how to optimize the management of brain metastasis has become a clinical challenge of the comprehensive treatment for patients with *EGFR* mutation.

Whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS)

For patients with brain metastases, both WBRT and SRS can be considered, mainly depend on the number/volume of brain metastases and the performance status of the patient. Generally, WBRT is recommended for multiple metastases (e.g., >3) and SRS is preferred for limited brain metastases. Accumulating evidences have indicated that TKI is also efficient for brain metastases in patients with *EGFR* mutation. Chinese Thoracic Oncology Group (CTONG) 0803 showed that single-agent erlotinib was active and well tolerated in patients with asymptomatic brain metastases, the median PFS and overall survival were 15.2 and 18.9 months for patients with activating *EGFR* mutation (40). Encouraged by these findings, and the concern of the potential neurocognitive function in the use of WBRT, CTONG 1201 was initiated to compare the efficacy of TKI

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(icotinib) versus WBRT with or without chemotherapy in NSCLC patients with *EGFR* mutation, who were naive to treatment with EGFR-TKIs or radiotherapy, and had at least three metastatic brain lesions. In this phase III prospective study, 176 patients were recruited and 158 cases were used for the final analysis. The results showed intracranial disease control rates of 85% and 67%, and median intracranial PFS of 10.0 and 4·8 months in the icotinib and WBRT groups, respectively. In addition, the evaluation of cognitive ability was available in 59 patients based on mini-mental state examination (MMSE) questionnaires, and no difference was found in these two groups. Also, there were no significant differences between groups for overall survival or time to increased brain metastases symptoms (41). Although the primary endpoint, intracranial PFS, was met in this study, there were some deficiencies in the design of the trial, for example, a combination therapy group was lacking.

It is well known that symptom control and QOL are the primary goal in the management of advanced NSCLC. Therefore, the phase III trial only provided evidences that first-line TKI might be considered as a therapeutic option in the treatment of EGFR-mutant NSCLC with brain metastases, and WBRT is still the standard of care in this setting. Actually, EGFR TKI and WBRT should be complementary rather than competitive, how to combination of both to make the patient live better is the most of important. Very recently, Magnuson *et al.* reported a multi-institutional retrospective analysis aiming to determine the optimal management of patients with EGFR-mutant NSCLC who develop brain metastases, and three modes of combination of TKI and radiotherapy was investigated (42). Their results showed that the median overall survival in patients received SRS followed by TKI, WBRT followed by TKI, and TKI followed by SRS/WBRT were 46, 30, and 25 months, respectively, indicating that the use of upfront EGFR-TKI and deferral of radiotherapy were associated with inferior survival in this setting. Besides the longest overall survival, SRS followed by TKI provided the opportunity for patients to avoid the potential neurocognitive sequelae of WBRT. Concomitant use of TKI may have the advantage of a synergistic effect on the brain metastases, but at the price of possibly increased risk of neurotoxicity. Such attempt had been reported in a lot of retrospective and prospective studies, but often with small sample size (20). Primary outcomes in these studies varied and the data were measured and reported in a non-uniform way. So, it is still difficult to draw any conclusion about the efficacy and safety based on current data, although some reports showed that WBRT concurrent with TKI does not seem to increase neurotoxicity. Taking together, appropriate timing of radiotherapy is critical in the management of EGFR mutant NSCLC, investigation of the use of TKI in combination with radiotherapy (WBRT/SRS) and optimal sequences between TKI and radiotherapy are warranted in future studies.

Prophylactic cranial irradiation (PCI)

PCI has been successfully used in patients with small-cell lung cancer in limited and extensive stage, which significantly reduced intracranial progression and prolonged over survival (43). However, the value of PCI in NSCLC remains controversial (44). No survival benefit and only decrease and/or delay of brain metastases were observed in many phase-III trials. The lack of survival benefit may be partially attributed to unintentionally selected patients with a high risk of brain metastasis. In addition, decline in tested and self-reported cognitive functioning after PCI in lung cancer were reported in a pooled secondary analysis of Radiation Therapy Oncology Group (RTOG) randomized trials 0212 and 0214 (45). To prevent these adverse early cognitive effects of cranial radiation, modern radiotherapy techniques [intensity-modulated radiation therapy (IMRT)] have been used for avoiding the hippocampal neural stem-cell niche during WBRT. RTOG 0933 was a single-arm phase II study of radiotherapy for brain metastasis, and the results from this study showed that hippocampal-avoidance WBRT was associated with preservation of memory and QOL as compared with historical series (46). Notable, patient with *EGFR* mutation has the relatively high risk of developing brain metastases, and the reported intracranial progression during the course of TKI therapy is approximately 30% (39). Therefore, it is interesting to explore the role of PCI in the patients treated with TKIs, provided that preservation of memory and QOL can be ensured with modern radiotherapy techniques.

Management of local advanced NSCLC with TKI and radiotherapy

The combination of chemotherapy and radiotherapy is the standard of care in the management of locally advanced NSCLC. Concurrent chemoradiotherapy is the preferred approach for patients with good performance status; but

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the improved therapeutic effect may be at the cost with increased toxicities. Currently, the clinical outcomes are still unsatisfactory, and the 5-year survival rate of is approximately 20%. In recent published studies, attempts to improvement of the radiation dose (RTOG 0617) and use of a new generation of chemotherapy regimen (PROCLAIM) failed to demonstrate survival benefits compared with concurrent platinum-based doublet chemoradiotherapy conventionally used in clinical practice (47,48). Uncertainties resulted from high treatment-related toxicities and poor completion rates of chemoradiotherapy in these trials should be rethink profoundly in future studies, and further improvement in locally advanced NSCLC will require the development of more effective combined modality therapies with low toxicities.

The rational for integration of EGFR TKI in the comprehensive treatment of locally advanced NSCLC includes high expression of EGFR in 40–80% NSCLC and autophosphorylation of the EGFR induced by irradiation (49). Preclinical studies showed that EGFR TKI, such as gefitinib and erlotinib, have radiosensitizing effects at multiple levels including cell cycle arrest, apoptosis, accelerated repopulation and DNA damage repair (50). However, in previous clinical studies, incorporation of TKI in the combined chemoradiotherapy for locally advanced NSCLC was not associated with improved treatment outcomes (51); possible explanations include the cell cycle specific antagonism when combined with concurrent chemotherapy and the unselected patients in these trials. Recently, RECEL trial reported the preliminary results in 2017 American Society of Clinical Oncology (ASCO) annual meeting. This was a multicenter, randomized, open-label, phase II trial of erlotinib versus etoposide plus cisplatin with concurrent radiotherapy in unresectable stage III NSCLC with *EGFR* activating mutation. The median PFS in this trial was significantly improved in the erlotinib group (n=20) compared with the control group (n=21) (27.9 *vs.* 6.4 months, HR 0.053, P<0.001). Both arms had same incidence of adverse effects (CTCAE grade >1), and most common sAE (grade >3) was rash (20%, 3/15) and hematological toxicity (26.7%, 4/15), respectively. Given the excellent outcomes in advanced NSCLC treated with EGFR TKIs, it is not surprising to have obtained such results in this trial. The questions need to be answered in future studies include the best duration of TKI therapy, the optimal combination algorithms of radiotherapy and TKI, and the potential beneficial population based on molecular characterization.

Conclusions

In NSCLC, patients with active *EGFR* mutation belong to a special group who has particular biological behavior and clinical management algorithms. Although wonderful outcomes of immediate responded to targeted therapies, and new generations of targeted drugs continued to be developed, all of these drugs are inevitably faced with the problem of resistance because of the tumor heterogeneity and evolutionary characteristics, and the inherent limitations of targeted treatment strategy. Advances in functional imaging and cutting-edge radiation techniques greatly expand the application field of radiotherapy in advanced NSCLC. Increasing evidences have been showed that integration of modern radiotherapy in the management of patients treated with EGFR TKI will be contributed to the improvement of treatment outcomes, early intervention of radiotherapy for limited disease, optimization the sequence of TKI and cranial radiotherapy, PCI and combination of TKI and thoracic radiotherapy in locally advanced NSCLC deserve further research in future studies.

Acknowledgements

Funding: This paper was supported by grants from the National Nature Science Foundation of China (grant no. 81301927), Zhejiang Provincial Nature Science Foundation (grant no. LY13H160023) and Hangzhou Medical Major Disease Project (grant no. 20130733Q03).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Xia B, Zhang S, Ma S. Management of non-small cell lung cancer with *EGFR* mutation: the role of radiotherapy in the era of tyrosine kinase inhibitor therapy—opportunities and challenges. J Thorac Dis 2017;9(9):3385-3393. doi: 10.21037/jtd.2017.09.67

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