Progress of clinical research on targeted therapy combined with thoracic radiotherapy for non-small-cell lung cancer

Hongqing Zhuang^{1,*}

Xianzhi Zhao^{1,*}

Lujun Zhao¹

Joe Y Chang²

Ping Wang¹

¹Department of Radiotherapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin Key Laboratory of Cancer Prevention and Therapy, and Tianjin Lung Cancer Center, Tianjin, People's Republic of China; ²Department of Radiation Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

*These authors contributed equally to this paper

Abstract: The combination of radiotherapy and targeted therapy is an important approach in the application of targeted therapy in clinical practice, and represents an important opportunity for the development of radiotherapy itself. Numerous agents, including epidermal growth factor receptor, monoclonal antibodies, tyrosine kinase inhibitors, and antiangiogenic therapies, have been used for targeted therapy. A number of studies of radiotherapy combined with targeted therapy in non-small-cell lung carcinoma have been completed or are ongoing. This paper briefly summarizes the drugs involved and the important related clinical research, and indicates that considerable progress has been made with the joint efforts of the two disciplines. Many issues, including drug selection, identification of populations most likely to benefit, timing of administration of medication, and side effects of treatment require further investigation. However, further fundamental research and accumulation of clinical data will provide a more comprehensive understanding of these therapies. Targeted therapy in combination with radiotherapy has a bright future.

Keywords: non-small-cell lung carcinoma, radiotherapy, epidermal growth factor receptor, monoclonal antibody, tyrosine kinase inhibitors, antiangiogenic therapies

Introduction

Targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with the specific molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with all rapidly dividing cells. The combination of radiotherapy and targeted therapy is an important approach for application of targeted therapy in clinical practice and represents an opportunity for the further development of radiotherapy itself.

Radiotherapy combined with targeted therapy has considerably furthered the study of non-small-cell lung carcinoma (NSCLC) under the joint efforts of the two disciplines, yielding both exciting results and worrisome reports. However, studies involving targeted therapy have gradually produced cumulative data on the subject. Differences in the experimental results prompted this summary for a more comprehensive and rational understanding of radiotherapy combined with targeted therapy. This retrospective review of the literature indicates that numerous drugs have been used for targeted therapy and that the studies of radiotherapy combined with targeted therapy are diverse and complicated by their variable quality.

Radiotherapy combined with EGFR monoclonal antibodies

Preclinical studies suggested that the epidermal growth factor receptor (EGFR) monoclonal antibody was a radiation-sensitizing agent because it increased the rate

Correspondence: Hongqing Zhuang; Ping Wang
Department of Radiotherapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin, 300060, People's Republic of China
Tel +86 22 2334 1405
Fax +86 22 2334 1405
Email hongqingzhuang@163.com; ping_wang999@163.com

of apoptosis, regulated the cell cycle, reduced radiation resistance, and increased radiation injuries.¹ Early clinical studies of the EGFR monoclonal antibody in combination with radiotherapy primarily included head and neck squamous cell carcinoma, and the study of its combination with radiation therapy for NSCLC was performed relatively late. The EGFR monoclonal antibodies include cetuximab, nimotuzumab, and panitumumab. Clinical research has primarily focused on cetuximab, with fewer studies of the other two drugs. Hughes et al² determined the safety of thoracic radiotherapy combined with cetuximab in the SCRATCH study, and Hallqvist et al³ and Kotsakis et al⁴ conducted two higher quality Phase II clinical studies demonstrating that the toxicity of thoracic radiotherapy combined with cetuximab for NSCLC was similar to that of radiotherapy alone and that cetuximab was slightly more toxic in terms of cutaneous reactions. The remaining studies primarily investigated cetuximab with concurrent chemoradiotherapy;^{5–7} their results indicate that treatment-related toxicity was similar to that occurring with simple concurrent radiotherapy and that the rate of cetuximab-induced grade 3 skin toxicity was approximately 6%–20%. The results of the cetuximab with radiotherapy or chemoradiotherapy studies mentioned above indicate an overall survival rate of approximately 17–25 months in patients with stage III NSCLC, an incidence of grade 3 or higher radiation pneumonitis of approximately 4%–12%, and an incidence of grade 3 or higher esophageal inflammation of approximately 4%–20%. These early studies demonstrated that the toxicity of cetuximab with concurrent radiotherapy or chemoradiotherapy was acceptable but that its impact on the survival of patients with locally advanced NSCLC was minor.

The preliminary results of a recent prospective randomized Phase III clinical study (RTOG-0617)⁸ provided updated evidence of the impact of cetuximab with concurrent chemoradiotherapy on survival in patients with stage III NSCLC. This study investigated 465 patients receiving cetuximab over a median follow-up period of 18.7 months. Cetuximab was given on a base of carboplatin and docetaxel chemotherapy with concurrent radiotherapy. The median overall survival in patients receiving chemoradiotherapy with cetuximab and chemoradiotherapy alone was 23.1 months and 23.5 months, respectively; overall survival at 18 months was 60.8% and 60.2% (hazard ratio 0.99; $P=0.484$) and median progression-free survival was 10.4 months and 10.7 months. The overall incidence of combined adverse events for patients receiving chemoradiotherapy with cetuximab and chemoradiotherapy alone was 85.2% and 69.5%, respectively ($P<0.0001$), and

the overall incidence of nonhematologic adverse events was 70.5% and 50.7% ($P<0.0001$). These findings indicate that addition of cetuximab to a base of chemoradiotherapy did not benefit patients with unresectable stage III NSCLC. However, more side effects occurred. Subgroup analysis showed that patients with high EGFR expression had better responses to cetuximab, but the impact of this drug on survival requires further investigation.

Nimotuzumab showed benefits when combined with concurrent chemotherapy in the treatment of head and neck cancers. Nimotuzumab with chemoradiotherapy for NSCLC is currently being investigated. Zhou et al⁹ have reported their preliminary results for nimotuzumab with radical radiotherapy for stage III squamous cell lung carcinoma and found no side effects, including rashes and allergies, attributable to nimotuzumab (Table 1). However, to acquire more detailed results and determine the impact on survival, further investigation is required. Research on panitumumab with concurrent chemoradiotherapy in stage III NSCLC is also under way (ClinicalTrials.gov identifier NCT00979212), but no results have been published as yet.

TKIs and radiotherapy

The tyrosine kinase inhibitors (TKIs) primarily include gefitinib and erlotinib. Fundamental research shows that the radiosensitivity mechanism of TKIs is similar to that of EGFR monoclonal antibodies, but the results of clinical trials have not been identical. In an early Phase II study (CALGB 30106) of gefitinib with thoracic chemoradiotherapy for stage III NSCLC,¹⁰ concurrent or subsequent thoracic chemoradiotherapy was designed for gefitinib followed by gefitinib for maintenance. However, this study was closed prematurely because of the results of the S0023 study¹¹ in which gefitinib showed no benefit in maintenance therapy compared with placebo. The survival rate for the 63 patients in this study was not improved significantly when compared with standard concurrent chemoradiotherapy. Overall survival was 13 months in the high-risk group (95% confidence interval [CI] 8.5–17.2) and 19 months in the low-risk group (95% CI 9.9–28.4). Rothschild et al¹² and Ball et al¹³ reported two Phase I clinical studies of gefitinib with concurrent thoracic radiotherapy or thoracic chemoradiotherapy, in which clinical toxicity could be tolerated but survival was not significantly improved. Center et al¹⁴ and Stinchcombe et al¹⁵ increased the dose of thoracic radiotherapy to 70 Gy, but their survival results were also disappointing.

Gefitinib with thoracic radiotherapy provides small benefits in Asian populations. Ohe et al¹⁶ administered

Table 1 Published trials of key agents in combination with radiotherapy

Therapy	Reference	Phase clinical setting	Patients (n)	Induction	Concurrent	Consolidation/maintenance	Radiotherapy	Median OS (months)	Toxicity
Cetuximab	Hughes et al ²	I	12	Platinum-based chemotherapy	Cetuximab	–	64 Gy/32 fractions	N/A	Grade 3 fatigue (8%) and pneumonia (8%); grade 5 bronchopneumonia (one patient)
	Hallqvist et al ³	II	75	Cisplatin/docetaxel	Cetuximab	–	68 Gy/34 fractions	17	Grade 3 esophagitis (1.4%); skin reactions (1.3%); grade ≥ 3 pneumonia (4.2%)
	Kotsakis et al ⁴	II	38	–	Cetuximab	Carboplatin + paclitaxel + cetuximab	73.5 Gy/35 fractions	17.1	Grade 3 fatigue (5%); grade 5 pneumonia (one patient); no patient with grade ≥ 3 esophagitis
	RTOG-0617 Masters et al ⁶	III	465	–	Carboplatin + paclitaxel + cetuximab	–	60 Gy/30 fractions	23.1	Grade ≥ 3 nonhematologic toxicity 70.5%; grade 4/5 nonhematologic toxicity 35.8%
Nimotuzumab	Zhou et al ⁹	II	11	–	Carboplatin + docetaxel + nimotuzumab	Carboplatin + docetaxel	50–66 Gy/25–30 fractions	Not reached	Grade 3 pneumonia (18.2%); esophagitis (18.2%); thrombocytopenia (18.2%); grade 4 neutropenia (36.4%)
Gefitinib	CALEB 30106 Ready et al ¹⁰	II	Poor risk status 1: 21 Good risk status 2: 29	Carboplatin/paclitaxel	Gefitinib	Gefitinib	66 Gy/33 fractions	Status 1: 19 Status 2: 13	Status 1: grade ≥ 3 pneumonia (15%); esophagitis (19%); fatigue (24%); electrolyte disturbances (10%); diarrhea (10%) Status 2: grade ≥ 3 pneumonia (16%); esophagitis (31%); fatigue (33%); electrolyte disturbances (16%); diarrhea (18%)
	Rothschild et al ¹²	I	Step 1: 5 Step 2: 9	–	Step 1: Gefitinib Step 2: Gefitinib + cisplatin	Both steps: Gefitinib	45 Gy/25 fractions and then 18 Gy/9 fractions boost primary and involved nodes	382 days combined	Step 2: One patient with grade 3 pneumonia and one patient with grade 2 hepatic enzyme increase
	Ball et al ¹³	I	28	–	Carboplatin + gefitinib $\pm$ paclitaxel	$\pm$ Surgery	60 Gy/30 fractions	N/A	No DLTs observed
	Center et al ¹⁴	I	16	–	Docetaxel + gefitinib	Docetaxel	70 Gy/35 fractions	21	Grade 3/4: hematologic (27%); esophagitis (27%) Grade 3/5: lung toxicity (20%), two patients with grade 5 lung toxicity
	Stinchcombe et al ¹⁵	I	23	Carboplatin/paclitaxel/irinotecan + pegfilgrastim	Carboplatin + paclitaxel + gefitinib	–	74 Gy/37 fractions	16	Grade 3: esophagitis (19.5%); one patient with late spinal cord syndrome

(Continued)

Table 1 (Continued)

Therapy	Reference	Phase clinical setting	Patients (n)	Induction	Concurrent	Consolidation/maintenance	Radiotherapy	Median OS (months)	Toxicity
	Ohe et al ¹⁶	II	38	Vinorelbine + cisplatin	Gefitinib	Gefitinib	60 Gy/30 fractions	28.1	Grade ≥ 2 : pneumonia (5%); grade 3/4 transaminase elevation (37%)
Gefitinib/erlotinib	Wang et al ¹⁷	II	Gefitinib: 19 Erlotinib: 7	–	Gefitinib/erlotinib	Gefitinib/Erlofinib	Median: 70 Gy/30 fractions; individualized SBRT	21.8	Grade 3: esophagitis (4%); fatigue (4%); pneumonia (4%)
Erlotinib	Komaki et al ¹⁸	II	48	–	Carboplatin + paclitaxel + erlotinib	Paclitaxel	63 Gy/35 fractions	25.8	Grade 3: acne (two patients); esophagitis (one patient); pneumonia (two patients)
	Ramella et al ¹⁹	II	60	–	Pemetrexed + erlotinib or gemcitabine + erlotinib	–	50.4–59.4 Gy/individualized fractions	14.4 (non-squamous carcinoma); 4.9 (squamous carcinoma)	Grade 3: rash (7%) Grade ≥ 3 : esophagitis (2%); pneumonia (5%); hepatic enzyme increase (16.6%)
	Wan et al ²⁰	I/II	8	Erlotinib	Erlotinib 100 mg or 150 mg daily	Erlotinib	45 Gy/15 fractions or 60 Gy/30 fractions	N/A	In 60 Gy/30 fractions and 150 mg/day erlotinib arm, one patient with grade 5 pneumonia and one patient with grade 3 pneumonia
Bevacizumab	Lind et al ²⁴	I	6	Cisplatin-based	7.5 mg/kg or 15 mg/kg	–	66 Gy/33 fractions	N/A	Two patients with grade 3 pneumonia
	Socinski et al ²⁷	II	45	Bevacizumab + paclitaxel + carboplatin	Bevacizumab + paclitaxel + carboplatin $\pm$ erlotinib	Erlotinib + bevacizumab	74 Gy/37 fractions	18.4	pneumonia: two patients with grade 2 pneumonia Grade ≥ 2 : esophagitis (53.8%); Grade 3/4: esophagitis (29%); one patient with grade 3 tracheoesophageal fistula
	Spigel et al ²⁵	II	29	Irinotecan + carboplatin	Irinotecan + carboplatin + bevacizumab	Bevacizumab	61.2 Gy	N/A	Grade 3/4 toxicity included: diarrhea (21%), esophagitis (14%), fatigue (17%), pain (14%), neutropenia (18%), leukopenia (10%), and thrombocytopenia (28%). Two patients with tracheoesophageal fistula (one resulting in death); one patient died from an aerodigestive hemorrhage
Endostatin	Zhou et al ³¹	I/II	47	–	Docetaxel + cisplatin + endostatin	–	60–66 Gy/30–33 fractions		Grade 3/4: esophagitis (8.5%); pneumonia (11%); one patient with grade 5 pneumonia

Abbreviations: OS, overall survival; DLT, dose-limiting toxicity; SBRT, stereotactic body radiotherapy; N/A, not available.

gefitinib with thoracic radiotherapy in Japanese patients with unresectable NSCLC who had undergone induction chemotherapy, and the results of the Phase II clinical study showed an encouraging median survival time of 28 months. However, only about 61% of patients completed the treatment, and the remaining patients discontinued treatment because of grade 2 or higher radiation pneumonitis. Wang et al¹⁷ investigated EGFR TKI therapy with thoracic radiotherapy for NSCLC and reported that the occurrence of radiation pneumonitis was not severe. Therefore, the toxicity of gefitinib with thoracic radiotherapy and survival requires further study. More stringent control of the lung dose and selection of populations likely to benefit from such treatment should direct future research.

Erlotinib with thoracic radiotherapy has achieved relatively good results. Komaki et al¹⁸ investigated erlotinib with thoracic chemoradiotherapy for unresectable stage III NSCLC. A clinical program of erlotinib 150 mg/day with concurrent thoracic radiotherapy (63 Gy/35 fractions) and a chemotherapy program of paclitaxel and carboplatin followed by two cycles of paclitaxel and carboplatin chemotherapy in sufficient doses were designed. Grade 3 esophagitis occurred in only one of the 48 enrolled patients, and radiation pneumonitis occurred in three cases. No grade 4–5 treatment-related side effects were observed. Median progression-free survival and overall survival were 13.6 months and 25.8 months, respectively. Only 12% of the enrolled patients showed the EGFR-related site-sensitive mutation.

Ramella et al¹⁹ reported another Phase II clinical study of erlotinib with gemcitabine or pemetrexed and concurrent thoracic radiotherapy (50.4–59.4 Gy) for patients with recurrence of disease after chemotherapy and showed better efficacy and acceptable toxicity. Subgroup analysis showed that overall survival (14.4 months versus 4.9 months, $P=0.01$) and progression-free survival (7.5 months versus 4.6 months, $P=0.06$) of patients with non-squamous cell carcinoma (40 cases) were better than in patients with squamous cell carcinoma (20 cases).

However, in another study, Wan et al²⁰ investigated erlotinib with thoracic radiotherapy for stage III NSCLC in patients with poor general performance status (ie, 2). Fatal grade 5 radiation pneumonitis occurred in one of the five patients receiving erlotinib 150 mg/day, and grade 3 radiation pneumonitis occurred in one case. These side effects prompted premature closure of this study. A retrospective study by Chang et al²¹ documented radiation pneumonitis in 21 of 25 enrolled patients treated with erlotinib or gefitinib

and thoracic radiotherapy, and two of these cases were grade 5 (Table 1).

Some clinical trials of TKI with thoracic radiotherapy or thoracic chemoradiotherapy are currently in progress (NCT00620269, NCT00553462, NCT01091376 for erlotinib; NCT01391260 for gefitinib). These studies have greater depth and focus more on populations with EGFR mutations or those in poor general condition. More studies of TKIs with thoracic radiotherapy or thoracic chemoradiotherapy have been performed, with some suggesting that TKIs enhance the efficacy of radiotherapy; however, randomized controlled large-scale studies are lacking. The issue of radiation pneumonitis and esophageal toxicity when TKIs are combined with thoracic radiotherapy requires further investigation.

Radiotherapy with antiangiogenic therapies

The antiangiogenesis drugs currently available are bevacizumab and endostatin. Few studies have been reported on vascular blockers, antiangiogenesis drugs, drugs inhibiting degradation of the basement membrane, and agents inhibiting cell integrin, and are not described in this report. The antiangiogenic sites for bevacizumab and endostatin are different, but their radiosensitivity mechanisms are similar. Numerous preclinical studies have shown that these agents exert their radiation-sensitizing properties via the promotion of oxygenation by rationalizing the blood vessels of the tumor, inhibiting the radiation-induced increase in vascular endothelial growth factor expression, and reducing their resistance to complement each other, leading to enhancement of the antitumor effects.^{22,23}

Clinical research is somewhat lacking in comparison with fundamental research. Several early Phase I–II studies of bevacizumab with thoracic radiotherapy were closed prematurely because of side effects, such as radiation esophagitis, esophageal fistula, and radiation pneumonitis, and clinical data regarding patient survival have not been reported.^{24–26} Socinski et al²⁷ reported a clinical study of thoracic radiotherapy with bevacizumab and erlotinib for stage III NSCLC. Patients underwent induction chemotherapy of paclitaxel and carboplatin with bevacizumab, and then received concurrent chemoradiotherapy and bevacizumab. The radiation dose was 74 Gy, the concurrent paclitaxel dose was 45 mg/m², carboplatin was given weekly in accordance with an area under the curve of 2, and bevacizumab 10 mg/kg was administered twice weekly. Erlotinib was either not administered during radiotherapy,

or administered at doses of 100 mg/day, or 150 mg/day. Maintenance therapy with erlotinib and bevacizumab was continued after chemoradiotherapy. The objective response rate was 60% (95% CI 44–75) in the 45 enrolled patients, median progression-free survival was 10.2 months (95% CI 8.4–18.3), and median overall survival was 18.4 months (95% CI 13.4–31.7). Concurrent chemoradiotherapy did not improve the outcome when compared with standard treatment for localized advanced NSCLC. The incidence of grade 3 esophagitis was 19.2% in this study and the incidence of grade 2 esophagitis was 53.8%.

A Phase I clinical study (NCT00531076)²⁴ of bevacizumab with radiotherapy in patients with unresectable locally advanced NSCLC was closed prematurely because of a high incidence of radiation pneumonitis. A total of six patients were enrolled in this study; two developed grade 2 radiation pneumonitis and two developed grade 3 radiation pneumonitis. A Phase II clinical study of bevacizumab with concurrent chemoradiotherapy in small cell lung cancer²⁵ reported severe tracheal esophageal fistula in two of 29 enrolled patients, and another three patients died of massive hemorrhage of unknown cause (suspected tracheo-esophageal fistula). Grade 3 esophagitis occurred in all patients receiving maintenance therapy with bevacizumab after concurrent chemoradiotherapy. Other studies have reported similar results.^{28,29}

Several studies have reported that bevacizumab with thoracic chemoradiotherapy does not improve treatment efficacy but increases the risk of side effects. Ma et al³⁰ investigated concurrent administration of thoracic radiotherapy and endostatin for unresectable stage III NSCLC. However, this study was closed prematurely because grade 3 or higher radiation pneumonitis occurred in four of the 12 enrolled patients. The Cancer Hospital of Sun Yat-sen University has reported the results of a multicenter Phase I–II clinical trial of endostatin with concurrent chemoradiotherapy for unresectable stage III NSCLC.³¹ A total of 47 patients were enrolled in the study from 2009 to 2011. Patients received three-dimensional conformal radiotherapy of 60–66 Gy for 6–7 weeks concurrent with two cycles of chemotherapy comprising docetaxel 65 mg/m² and cisplatin 65 mg/m². Daily intravenous endostatin 7.5 mg/m² was administered one week before radiotherapy and in weeks 2, 4, and 6. Forty-four patients completed the efficacy and safety assessments, and 42 completed the assessment of short-term efficacy; there were five cases of complete remission, 29 cases of partial remission, three cases of stable disease, and five cases of progression, giving an efficacy rate of 77%. One-year survival and progression-free survival was

81% and 51%, respectively. Of the 12 deaths, eight were from cancer, two were of unknown cause, one was the result of infection, and one because of radiation pneumonitis. Grade 3 acute radiation esophagitis and pneumonitis occurred in four patients, and grade 5 radiation pneumonitis occurred in one case. In summary, no large-scale clinical studies of radiotherapy with antiangiogenic drugs for NSCLC have been reported (Table 1). More evidence is required from clinical trials to determine the efficacy and safety of antiangiogenic drugs with thoracic radiotherapy for NSCLC.

Current problems with concurrent radiotherapy and targeted therapy

Selection of advantageous drugs for targeted therapy with radiotherapy

Few comparative studies are available on the efficacy of targeted drugs in combination with radiotherapy. Therefore, drug selection presently lacks supportive clinical evidence. The results for simultaneous combinations of drugs with different mechanisms of action and radiotherapy to maximize the enhancing effect of radiotherapy are not conclusive.³² However, numerous factors drive angiogenesis and degradation and occlusion of blood vessels. Therefore, a single antiangiogenic drug, even drugs with the same mechanism such as antiangiogenic therapies, cannot completely solve the vascular problems. Whether combinations of different antivascular agents would improve tumor suppression is not known.³³ For example, bevacizumab with endostatin inhibits vascular endothelial growth factor and exerts an antitumor effect via changes in proliferation of vascular endothelial cells. Furthermore, radiation itself is an important antiangiogenic therapy, and combination of different antiangiogenic therapies improves the therapeutic effect. However, two problems have arisen. First, the effect of activation of additional factors using combinations of several treatment modalities on the organization and control of tumor angiogenesis is not known. Second, the adverse consequences of a combination of several treatment modalities require further investigation. EGFR monoclonal antibodies and TKIs inhibit EGFR but have yielded different results in clinical trials; the reasons underlying this differential effect are not known. These inconsistent results challenge drug selection for radiotherapy in combination with targeted therapy.

Selection of populations likely to benefit from targeted therapy with radiotherapy

The selection of populations likely to benefit from targeted therapy with radiotherapy is problematic. EGFR mutations

at related sites are an important indicator of therapeutic sensitivity for some targeted therapies, such as TKIs. However, the relevance of EGFR mutation to efficacy in radiotherapy with a TKI is not known. This problem has arisen for several reasons. First, few studies are available on the issue of efficacy. Experimental studies *in vitro* showed that tumor cells with mutations are more sensitive to radiation,^{34,35} but this comparison was between different cell lines. The EGFR mutations were different, but the effects of other genes present in the cells being compared could not be excluded. The relationship between radiation and mutations is not known. This study could not establish efficacy in tumor cell samples derived from the same cell lines with only different EGFR site mutations. Second, whether there is a significant increase in the tumoricidal activity of a TKI when it was combined with radiotherapy is not known because either treatment alone kills tumor cells. The determining role of the EGFR mutation may be weakened under the dual functions of radiotherapy and TKI. Third, tumor heterogeneity and limitations in the detection of EGFR mutation itself complicate the analysis. The uncertainty of the EGFR mutation itself, the lack of dynamic monitoring, and the lack of a unified detection platform may also contribute to the uncertainty of EGFR mutation detection.³⁶ Therefore, many factors affect the relationship of the efficacy and predictors of radiotherapy with targeted therapy. A large-scale, randomized controlled study is a better way of answering these questions.

Optimization of targeted therapy with radiotherapy

This is a relatively complex issue, with numerous aspects, such as timing, duration, and administration dose, needing to be taken into account. Different administration timing for antiangiogenic therapies is based on different theories. Induction therapy primarily normalizes the blood vessels. Concurrent administration primarily inhibits the radiation-induced increase in vascular endothelial growth factor expression and consolidates that administration, which may relate cell death in the proliferative phase. Specific timing of administration may play a more important role, but the relevant research is lacking. Administration prior to radiotherapy based on the vascular normalization theory is currently accepted but problematic. The time window of vascular normalization is approximately 6 days,^{37,38} and radiotherapy is hyperfractionated for administration 5 times per week. Radiotherapy also plays an important part in the occlusion of local vessels. Optimization of antiangiogenic therapy concurrent with radiotherapy and its mechanisms requires

fundamental research to provide experimental evidence for clinical practice. The timing of administration of TKI with radiotherapy includes initiation and cessation times.^{39,40} Oral administration of TKI may be initiated before radiotherapy or concomitantly. Administration before radiotherapy considers synchronization of the cell cycle and the steady-state plasma TKI concentration. Concomitant administration with radiotherapy is primarily based on clinical convenience. Initiation of radiotherapy after the drug reaches steady-state plasma concentrations might worsen the clinical condition of a critically ill patient. The duration of oral TKI therapy is also an issue. Some clinical studies have reported that oral TKI therapy was not discontinued after the end of radiotherapy regardless of EGFR mutation status as long as the patient was tolerant until systemic progression was observed, which is worthy of further discussion. For example, the benefits and risks of continuation of oral TKI therapy until systemic progression in patients with wild-type EGFR who have lesions in complete remission after radiation are not known. Administration of an oral TKI concurrent with radiotherapy for one month after radiotherapy is important if radiation sensitization and death in the proliferation phase are considered. The treatment strategy should be individualized one month after the end of radiotherapy in accordance with the patient's clinical situation.⁴¹ The current results of the Phase I clinical dose from the climbing trial are primarily applied to determine the target dose when combined with radiotherapy. However, we need to consider the patient's ability to tolerate the dose and whether the targeted therapy in combination with radiotherapy requires the same concentration as targeted therapy alone. In summary, optimization of targeted therapy with radiotherapy requires further study.

Side effects of molecular targeted therapy with radiation

Most people thought it had better effect and fewer side effects when combining molecular targeted therapy with radiotherapy. However, with increased clinical use of molecular targeted therapy with radiation, people understand the treatment more comprehensively. We also found that it had some side effects which cannot be ignored. For example, when antiangiogenesis drugs are combined with thoracic radiation therapy, serious tracheoesophageal fistula, radiation esophagitis, and radiation pneumonitis may appear.^{24,25} Some studies showed that when integration of TKI with molecular targeted therapy applied to clinical, there was a high probability of radioactive pneumonia.^{16,21} Did these side effects happen due to the problem of experimental design or targeted

therapy combined with thoracic radiotherapy did increase treatment toxicity? Why did different studies show different types of toxicity? Further exploration are needed which need to cause our attention.

Future prospects

Targeted therapy represents the most important progress made in medical oncology in the 21st century,^{42–44} which has also been the fastest-growing period for radiation therapy. The integrated development of radiotherapy and targeted therapy conforms to the general trends in disciplinary development. Considerable progress has been made with the joint efforts of the two disciplines. Many problems require further investigation, including drug selection, identification of patients likely to derive benefit, timing of drug administration, and the side effects of treatment. However, further fundamental research, accumulation of clinical data, and summaries of the clinical evidence for targeted therapy in combination with radiotherapy will provide a more comprehensive, accurate, and deeper understanding of these therapies. Targeted therapy in combination with radiotherapy has a bright future with broader and more targeted clinical applications.

Acknowledgment

This research was supported by the National Natural Science Foundation of China (81301925).

Disclosure

The authors report no conflicts of interest in this work.

References

- Zhuang HQ, Yuan ZY. Process in the mechanisms of EGFR inhibitor combined with radiotherapy. *Chin Clin Oncol*. 2009;14:560–563.
- Hughes S, Liong J, Miah A, et al. A brief report on the safety study of induction chemotherapy followed by synchronous radiotherapy and cetuximab in stage III non-small cell lung cancer (NSCLC): SCRATCH study. *J Thorac Oncol*. 2008;3:648–651.
- Hallqvist A, Wagenius G, Rylander H, et al. Concurrent cetuximab and radiotherapy after docetaxel-cisplatin induction chemotherapy in stage III NSCLC: SATELLITE – a phase II study from the Swedish Lung Cancer Study Group. *Lung Cancer*. 2010;71:166–172.
- Kotsakis AR, Ramalingam SS, Tardini AA, Heron DE, Smith R, Friedland D. Multicenter phase II study of cetuximab (C) with concomitant radiotherapy (RT) followed by consolidation chemotherapy (CT) in locally advanced non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2011;29 Suppl:Abstr 7019.
- Blumenschein GR Jr, Paulus R, Curran WJ, et al. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. *J Clin Oncol*. 2011;29:2312–2318.
- Dingemans A-MB, van Baardwijk G, Reymen A, et al. Determination of standard dose cetuximab together with concurrent individualised, isotoxic accelerated radiotherapy and cisplatin-vinorelbine for patients with stage III non-small cell lung cancer (NSCLC): a phase I study (NCT00522886). *J Thorac Oncol*. 2011;6:Abstr MO02.02.
- Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol*. 2011;29:3120–3125.
- Masters G. Cetuximab no benefit with chemoradiation in lung cancer. Abstract PL03 presented at the 15th World Conference on Lung Cancer, International Association for the Study of Lung Cancer, October 27–30, 2013, Sydney, Australia.
- Zhou LL, Liu J, Gong R-M, et al. A Phase II trial of nimotuzumab in combination with chemoradiotherapy in locally advanced lung squamous cell carcinoma. *J Thorac Oncol*. 2011;6:Abstr P4.280.
- Ready N, Janne PA, Bogart J, et al. Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. *J Thorac Oncol*. 2010;5:1382–1390.
- Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol*. 2008;26:2450–2456.
- Rothschild S, Bucher SE, Bernier J, et al. Gefitinib in combination with irradiation with or without cisplatin in patients with inoperable stage III non-small cell lung cancer: a phase I trial. *Int J Radiat Oncol Biol Phys*. 2011;80:126–132.
- Ball D, Burmeister B, Mitchell P, et al. Phase I trial of gefitinib in combination with concurrent carboplatin, paclitaxel and radiation therapy in patients with stage III non small cell lung cancer (“CRITICAL”). *J Thorac Oncol*. 2007;2:S633–S634.
- Center B, Petty WJ, Ayala D, et al. A phase I study of gefitinib with concurrent dose-escalated weekly docetaxel and conformal three-dimensional thoracic radiation followed by consolidative docetaxel and maintenance gefitinib for patients with stage III non-small cell lung cancer. *J Thorac Oncol*. 2010;5:69–74.
- Stinchcombe TE, Morris DE, Lee CB, et al. Induction chemotherapy with carboplatin, irinotecan, and paclitaxel followed by high dose three-dimension conformal thoracic radiotherapy (74 Gy) with concurrent carboplatin, paclitaxel, and gefitinib in unresectable stage IIIA and stage IIIB non-small cell lung cancer. *J Thorac Oncol*. 2008;3:250–257.
- Ohe Y, Nishiwaki Y, Yokoyama A, et al. Safety and efficacy trial of cisplatin (P) with vinorelbine (V) followed by gefitinib (G) and concurrent thoracic radiotherapy (TRT) for unresectable locally advanced non-small cell lung cancer (LA-NSCLC): Japan Clinical Oncology Group (JCOG) 0402. *J Clin Oncol*. 2010;28 Suppl 15: Abstr 7084.
- Wang J, Xia TY, Wang YJ, et al. Prospective study of epidermal growth factor receptor tyrosine kinase inhibitors concurrent with individualized radiotherapy for patients with locally advanced or metastatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:e59–e65.
- Komaki R, Blumenschein G, Wistuba I, et al. Phase II trial of erlotinib and radiotherapy following chemoradiotherapy for patients with stage III non-small cell lung cancer. *J Clin Oncol*. 2011;29 Suppl: Abstr 7020.
- Ramella S, Trodella L, Alberti A, et al. Multimodal treatment with Radiochemotherapy and Erlotinib in advanced NSCLC (MARTE trial). *J Thorac Oncol*. 2011;6:Abstr MO02.04.
- Wan J, Cohen V, Agulnik J, et al. Unexpected high lung toxicity from radiation pneumonitis in a phase I/II trial of concurrent erlotinib with limited field radiation for intermediate prognosis patients with stage III or inoperable stage IIB non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys*. 2009;75 Suppl 1:S110.
- Chang CC, Chi KH, Kao SJ, et al. Upfront gefitinib/erlotinib treatment followed by concomitant radiotherapy for advanced lung cancer: a mono-institutional experience. *Lung Cancer*. 2011;73:189–194.
- Zhuang HQ, Yuan ZY, Wang P. Research progress on the mechanisms of combined bevacizumab and radiotherapy. *Recent Pat Anticancer Drug Discov*. 2014;9:129–134.

23. Zhuang HQ, Yuan ZY. Process in the mechanisms of endostatin combined with radiotherapy. *Cancer Lett.* 2009;282:9–13.
24. Lind JS, Senan S, Smit EF. Pulmonary toxicity after bevacizumab and concurrent thoracic radiotherapy observed in a phase I study for inoperable stage III non-small-cell lung cancer. *J Clin Oncol.* 2012;30:e104–e108.
25. Spigel DR, Hainsworth JD, Yardley DA, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. *J Clin Oncol.* 2010;28:43–48.
26. Mangoni M, Vozenin MC, Biti G, et al. Normal tissues toxicities triggered by combined anti-angiogenic and radiation therapies: hurdles might be ahead. *Br J Cancer.* 2012;107:308–314.
27. Socinski MA, Stinchcombe TE, Moore DT, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. *J Clin Oncol.* 2012;30:3953–3959.
28. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006;355:2542–2550.
29. Stinchcombe T, Socinski M, Moore D, et al. Phase I/II trial of bevacizumab (B) and erlotinib (E) with induction (IND) and concurrent (CON) carboplatin (Cb)/paclitaxel (P) and 74 Gy of thoracic conformal radiotherapy (TCRT) in stage III non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2011;29 Suppl:Abstr 7016.
30. Ma S, Xu Y, Sun X, et al. Endostar in combination with radiotherapy and paclitaxel/carboplatin in patients with unresectable non-small cell lung cancer of stage III: preliminary results of a phase II study. *J Clin Oncol.* 2011;29 Suppl:Abstr 7043.
31. Zhou QC, Bao Y, Yu ZH, et al. A prospective phase I/II study of recombinant endostatin (Endostar) combined with concurrent radio-chemotherapy in patients with unresectable stage III non-small cell lung cancer. *Chin J Radiat Oncol.* 2012;21:500–504.
32. Bagri A, Kouros-Mehr H, Leong KG, Plowman GD. Use of antiVEGF adjuvant therapy in cancer: challenges and rationale. *Trends Mol Med.* 2010;16:122–132.
33. Wachsberger P, Burd R, Dicker AP. Tumor response to ionizing radiation combined with antiangiogenesis or vascular targeting agents: exploring mechanisms of interaction. *Clin Cancer Res.* 2003;9:1957–1971.
34. Sos ML, Rode HB, Heynck S, et al. Chemogenomic profiling provides insights into the limited activity of irreversible EGFR inhibitors in tumor cells expressing the T790M EGFR resistance mutation. *Cancer Res.* 2010;70:868–874.
35. Das AK, Sato M, Story MD, et al. Non-small-cell lung cancers with kinase domain mutations in the epidermal growth factor receptor are sensitive to ionizing radiation. *Cancer Res.* 2006;66:9601–9608.
36. Taniguchi K, Okami J, Kodama K, et al. Intratumor heterogeneity of epidermal growth factor receptor mutations in lung cancer and its correlation to the response to gefitinib. *Cancer Sci.* 2008;99:929–935.
37. Winkler F, Kozin SV, Tong RT, et al. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. *Cancer Cell.* 2004;6:553–563.
38. Tong RT, Boucher Y, Kozin SV, Winkler F, Hicklin DJ, Jain RK. Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors. *Cancer Res.* 2004;64:3731–3736.
39. Yi HG, Kim HJ, Kim YJ, et al. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective for leptomeningeal metastasis from non-small cell lung cancer patients with sensitive EGFR mutation or other predictive factors of good response for EGFR TKI. *Lung Cancer.* 2009;65:80–84.
40. Koh PK, Faivre-Finn C, Blackhall FH, et al. Target agents in non-small cell lung cancer (NSCLC): clinical developments and rationale for the combination with thoracic radiotherapy. *Cancer Treat Rev.* 2012;38:626–640.
41. Zhuang HQ, Yuan ZY, Wang J, et al. Research progress on criteria for discontinuation of EGFR inhibitor therapy. *Onco Targets Ther.* 2012;5:263–270.
42. Guo S, Zou J, Wang G. Advances in the proteomic discovery of novel therapeutic targets in cancer. *Drug Des Devel Ther.* 2013;7:1259–1271.
43. Sakhrani NM, Padh H. Organelle targeting: third level of drug targeting. *Drug Des Devel Ther.* 2013;7:585–599.
44. Zhuang H, Yuan Z, Wang J, Zhao L, Pang Q, Wang P. Phase II study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma. *Drug Des Devel Ther.* 2013;7:1179–1186.

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which

Submit your manuscript here: <http://www.dovepress.com/drug-design-development-and-therapy-journal>

Dovepress

has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.