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REVIEW

Targeted therapy combined with thoracic radiotherapy for non-small cell lung cancer

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Abstract

Introduction In recent years, there has been undoubted progress in the evaluation and development of targeted agents for non-small cell lung cancer (NSCLC). At the same time, remarkable progress in radiation therapy (RT) has been developed largely due to our ability to more effectively focus and deliver radiation to the tumor target volume. Both developments brought the idea of combining the radiation with molecularly targeted agents in order to improve outcomes in NSCLC patients who have limited survival times with standard chemoradiotherapy.

Methods We identified patients with gastric cancer treated with post-operative radiation at our institution between 2002 and 2016. Acute and late toxicities were evaluated per RTOG/EORTC Radiation Toxicity Grading Scale. Statistical analysis was performed using Chi-square tests, *t* tests, log-rank, and logistic regression.

Results Cetuximab has no survival benefit, and it seems to be toxic in this patient population. Bevacizumab has severe toxicity including tracheoesophageal fistulae formation in addition to its ineffectiveness. It is difficult to have an opinion about TKIs when combined with RT since most of the studies were conducted on unselected patients. For oligometastatic/oligoprogressive NSCLC patients, it seems to be reasonable to use a combined regimen since combined regimen resulted in superior survival time; however, the patients should be followed up closely with respect to the toxicity. In patients with brain metastases, the use of concomitant RT + TKIs increased survival with acceptable toxicity levels.

Conclusions In this review, we summarize the recent literature about the use of molecularly targeted agents with concurrent RT in NSCLC patients.

Keywords Chemoradiotherapy · EGFR inhibitors · Targeted therapy · Non-small cell lung cancer · Radiotherapy · Targeted therapy

Introduction

Lung cancer is the leading cause of cancer-related deaths in both men and women worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer patients. Radiation therapy (RT) plays a major role in their management resulting up to 70% of patients suitable for treatment for curative intent with inoperable disease [2]. Stage III NSCLC patients represent approximately 30–50% of all NSCLC patients and most of these patients have inoperable T4 and/ or N2/N3 disease and therefore treated with concurrent platinum-based chemotherapy and RT [3]. Even with combined aggressive treatment, the survival of stage III patients are limited and approximately three out of four patients will develop loco-regional and/or distant metastases [2, 4]. A meta-analysis showed that although concomitant chemo-RT is superior to sequential treatment with chemotherapy followed by RT, the concomitant regimen improved loco-regional disease without affecting distant metastases [5].

Stage III NSCLC represents a heterogeneous disease which still has a poor prognosis. The main treatment aims of this patient population are improving local control and eliminate the micro-metastatic disease. The standard treatment of inoperable stage III NSCLC patients is concurrent chemo-RT. However, there is still a need for improving the outcome of this patient population since the loco-regional progression-

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free survival rates are approximately 30% with concurrent chemo-RT. One strategy for improving outcome in stage III NSCLC patients is dose escalation. This strategy was evaluated in Radiation Therapy and Oncology Group (RTOG) 0617 trial [6]. RTOG 0617 was designed to establish whether a 74-Gy dose was better than a 60-Gy dose and whether adding cetuximab to concurrent chemo-RT would confer an overall survival benefit. The result of this study showed that there is no benefit of dose escalation and might be harmful. The commonly accepted radiation therapy dose (60–66 Gy in 1.8- to 2.0-Gy fraction sizes) for patients with stage III NSCLC was established by the Radiation Therapy Oncology Group (RTOG) 7301 trial and has remained unchanged now [6]. From the studies conducted in early-stage NSCLC patients, we learned that the use of biological effective doses (BED) ≥ 100 Gy with stereotactic body radiotherapy (SBRT) techniques resulted in superior outcome in terms of the 5-year overall survival rates [7, 8]. However, when considering the large treatment field of the disease in stage III NSCLC patients, using such high doses may have resulted in severe radiation-related toxicity, and it seems to be impossible using the present technology. On the other hand, traditional cytotoxic chemotherapeutic agents may have reached a therapeutic plateau [2].

In recent years, there has been undoubted progress in the evaluation of targeted agents and immunotherapies in NSCLC patients. Therefore, another strategy for improving outcome in stage III NSCLC patients may be the use of targeted therapies with RT or chemo-RT. The purpose of this review is to summarize the reported and ongoing studies evaluating the use of concomitant RT and targeted therapy in stage III NSCLC patients.

What is the rationale of using concomitant targeted therapy and radiotherapy?

The interaction of systemic therapy and radiation was described in the 1970s by George Steel [9]. Since in the 1970s, the specificity and diversity of contemporary molecular targeted drugs were not fully imagined, Steel's hypothesis has been proposed for chemotherapeutic agents. Therefore, to describe the exploitable interactions of targeted agents and radiation, a modernization of the Steel hypothesis has been proposed [10, 11]. The interaction of radiation and targeted agents was described by five distinct mechanisms under this revised framework: (1) spatial cooperation, (2) temporal modulation, (3) biologic cooperation, (4) cytotoxic enhancement, and (5) normal tissue protection.

Spatial cooperation refers to combining a drug that is efficacious against systemic disease with radiation that is effective against the loco-regional disease. Radiation therapy targets loco-regional macroscopic and microscopic disease and therefore concurrent or sequential administration with systemic agents may elicit spatial cooperation by separately addressing the distinct risks of loco-regional and distant disease. Likewise, even in diseases where an effective systemic therapy exists, radiation can be used against the bulky disease. Spatial cooperation may also apply to combine radiation with some non-cytotoxic agents that are effective against the minimal disease. There is no need for the radiation to interact with systemic agents at the cellular level; therefore, sequential administration is preferred to reduce toxicity. The use of adjuvant chemotherapy and RT sequentially in breast cancer patients is a good example of spatial cooperation [11, 12].

To limit healthy tissue toxicity, RT is typically applied in a fractionated regimen. Between each fraction of RT, both the tumor cells and healthy cells may undergo DNA damage repair, re-population, re-oxygenation, and cell cycle re-distribution. Various molecular targeted agents may interfere with these processes and alter the relationship of tumor cell killing and dose fractionation, thereby eliciting temporal modulation [12]. According to temporal modulation, RT and targeted therapy should be used concomitantly in order to increase cell killing and consequently increasing the loco-regional control. The use of cetuximab with concomitant RT in locally advanced head and neck cancer patients is a good example of temporal modulation [11].

Biological cooperation refers to strategies that target distinct cell populations or employ different mechanisms for cell killing or delaying tumor regrowth. Tumor tissue is composed of heterogeneous cell populations. It may be composed of well-oxygenated cells, which are radiosensitive, in addition to hypoxic tumor cells, which are known as radioresistant. An example of biologic cooperation could be a drug targeting hypoxic tumor cells thereby complementing the effect of radiation, which is greater in well-oxygenated cells. Another example may be the drugs that target angiogenesis and modulate the hypoxic microenvironment that might otherwise confer relative resistance to radiation. The use of tirapazamine, which is a drug with selective toxicity towards hypoxic mammalian cells, with concomitant RT in locally advanced squamous cell cancer of the head and neck region is a good example of biological cooperation [11, 12].

Cytotoxic enhancement strategy aims to enhance cell killing by modulating the induction or repair of cellular DNA damage. For cytotoxic enhancement, the drug must be present at the time of irradiation, meaning two modalities should be administered concomitantly, as drugs exploiting this mechanism are directly modifying the initial stage of radiation-induced cell killing or repair. The use of concurrent temozolomide with RT in glioblastoma patients is a good example of cytotoxic enhancement.

Several drugs have been proposed to provide cytoprotection of normal cells or to modulate the cytotoxic response of normal tissue. The clinical aim of normal tissue protection is to reduce

the incidence, severity, or duration of early and/or late side effects without compromising tumor control.

The revised Steel hypothesis provides an essential framework for conceptualizing the interaction of radiation and molecularly targeted therapeutics. Importantly, a given molecular targeted agent may simultaneously interact with radiation through more than one of these mechanisms.

Targeted therapy and concomitant radiotherapy in stage III NSCLC patients

The targeted therapies most commonly used in combination with RT for NSCLC patients are (1) epidermal growth factor receptor (EGFR) inhibitors including monoclonal antibody (cetuximab, necitumumab) and tyrosine kinase inhibitors (TKI) (erlotinib, gefitinib, afatinib, osimertinib); (2) anti-angiogenic agents such as bevacizumab, ramucirumab, and nintedanib; (3) anti-anaplastic lymphoma kinase (ALK) treatments such as crizotinib, ceritinib, and alectinib; and (4) anti-ROS treatments such as crizotinib.

EGFR inhibitors and radiotherapy

EGFR is a membrane glycoprotein of the ErbB family of receptor tyrosine kinases. It consists of an extracellular domain, a trans-membrane region, and a cytoplasmic intracellular domain. The overexpression of EGFR plays a key role in cellular proliferation, metastasis, apoptosis inhibition, and chemo-resistance and radio-resistance. EGFR is expressed in approximately 40–80% patients with NSCLC [13]. The scientific rationale to combine RT and EGFR inhibitors is to exploit the mechanism of temporal modulation, which was discussed above, and consequently not restricted to patients with sensitizing mutations in the EGFR gene that are known to confer enhanced sensitivity to EGFR TKI including gefitinib and erlotinib [2]. There is strong evidence to combine EGFR inhibitors and RT, as the EGFR-related pathway is associated with cell proliferation, DNA repair, and survival pathway that are upregulated by radiation itself [2, 14, 15]. Several preclinical studies support the combination of RT with EGFR inhibitors due to their combined action on cell proliferation and DNA repair pathways [14–17]. Therefore, the use of either EGFR monoclonal antibody or EGFR-TKI is associated with radiosensitivity. Due to the beneficial effects of this combined approach, this treatment is combined.

Cetuximab and radiotherapy

Cetuximab is a recombinant human/mouse chimeric EGFR monoclonal antibody. The mechanism of action for cetuximab in tumor cells is thought to involve the binding of cetuximab to the EGFR, preventing normal ligand binding and subsequent activation of the receptor's tyrosine kinase activity. The outcome of this blockade is reflected in the disruption of any number of processes regulated by EGFR pathways in a given tumor cell. Several mechanisms have been identified in preclinical models whereby cetuximab inhibits the growth and survival of EGFR-positive tumors. These include the (1) inhibition of cell cycle progression; (2) inhibition of survival pathways; (3) inhibition of tumor cell motility and invasion; (4) inhibition of angiogenesis; and (5) interruption of EGFR-activated survival and proliferation signaling by cytotoxic drugs or radiation [18]. There are many preclinical studies showing that cetuximab can enhance the cytotoxic effect of chemotherapeutic drugs or ionizing radiation [19, 20].

There are many phase I and II clinical trials investigating the role of concomitant cetuximab with thoracic RT in NSCLC patients [6, 21–28] (Table 1). Cancer and Leukemia Group B group (CALEB) conducted a randomized phase II trial to investigate two novel chemotherapy regimens in combination with concurrent thoracic RT [21]. Radiation Therapy Oncology Group (RTOG) 0324 study was a phase II trial investigating the cetuximab combined with radiochemotherapy in stage III A/B unresectable lung cancer [6]. Both studies had encouraging results.

The result of the RTOG 0617 phase III study clarified the role of concomitant cetuximab with thoracic RT in NSCLC patients and therefore merits special mention [7]. RTOG 0617 is a 2 × 2 factorial designed study evaluating both the role of high dose versus standard dose RT (74 Gy vs. 60 Gy) and benefit of concurrent and consolidation chemotherapy consisted of carboplatin and paclitaxel with or without cetuximab. After a median of 18.4 months of follow-up, the best results with respect to OS and loco-regional control were obtained in the lower RT dose group. The use of cetuximab treatment did not increase median OS; however, the toxicity was significantly increased in the cetuximab arms (general toxicity 70 vs. 86%; non-hematological toxicity 50 vs. 70%). The long-term results of RTOG 0617 also confirmed these results [22].

As a conclusion, the use of concomitant cetuximab with RT is not recommended in stage III NSCLC patients since this treatment is toxic and has no benefit.

EGFR TKI and radiotherapy

The first available targeted therapies for advanced NSCLC were gefitinib and erlotinib, both of which are small-molecule TKIs against EGFR, also known as HER1 or ErbB-1. The dimerization of EGFR activates its tyrosine kinase, which in turn activates intracellular signal transduction pathways involved in many cellular processes. Early work on EGFR in lung cancer has shown that EGFR overexpression is commonly seen in NSCLC, motivating the development of EGFR TKIs [29].

Table 1 Studies investigating the use of concomitant cetuximab with thoracic radiotherapy in non-small cell lung cancer patients

Study	Phase, clinical setting	*N*	Induction tx	Concomitant tx	Maintenance tx	RT dose (Gy)	Median OS (month)	Lung toxicity (%)
CALEB 30407 [21]	II	A: 48 B: 53	– –	Carboplatin + pemetrexed Carboplatin + pemetrexed + cetux	Pemetrexed Pemetrexed	70 70	21.2 25.2	12 2 patients pulmonary toxicity & ex 11 3 patients pulmonary toxicity & ex
	II	75	Cisplatin/docetaxel	Cetuximab	–	68	17	4.2
Kotsakis [23]	II	38	–	Cetuximab	Carboplatin + paclitaxel + cetux	73.5	17.1	11 PTE patients pulmonary toxicity & ex
RTOG0324 [6]	II	87	–	Carboplatin + paclitaxel + cetux	Cetux ➔cetux + carboplatin + paclitaxel	63	22.7	7 5 patients treatment-related toxicity & ex
NEAR [24]	II	30	–	Cetuximab	Cetuximab	66	19.5	23.3
N0422 [25]	II	57	–	Cetuximab	–	60	15.1	–
SWOG 0429 [26]	I	24	–	Cetuximab	Cetuximab	64.5	14	1 patient PTE
SCRATCH [27]	I	12	Platin	Cetuximab	–	64	N/A	8 1 patient ex
Dingemans [28]	I	24	Gemcitabine + carboplatin	Cisplatin + vinorelbine + paclitaxel + cetuximab	–	69	N/A	6 PTE 1 patient fatal hemorrhage & ex
RTOG 0617 [22]	III	544	–	Carboplatin/paclitaxel Carboplatin/paclitaxel/ cetuximab	Carboplatin/paclitaxel Carboplatin/paclitaxel/ cetuximab	60/74 60/74	28.7/20.3 25/24	Cetuximab induced toxicity & ex↑

OS, overall survival; *PTE*, pulmonary thromboembolism; *RT*, radiotherapy; *RTOG*, Radiation Therapy Oncology Group; *SWOG*: Southwest Oncology Group

Table 2 Studies investigating the use of concomitant gefitinib with thoracic radiotherapy in non-small cell lung cancer patients

Study	Phase, clinical setting	*N*	Induction tx	Concomitant tx	Maintenance tx	RT dose (Gy)	Median OS (month)	Lung toxicity (%)
CALEB 30106 [30]	II	60	Carboplatin/taxan	Gefitinib carboplatin/taxol + gefitinib	Gefitinib	66 Gy	19 ay (PR) 13 ay (GR)	15 + 16:31
JCOG 0402 [31]	II	38	Cisplatin + vinorelbine	Gefitinib	Gefitinib	60 Gy	28.1 ay	5
Stinchcombe et al. [32]	Tolerability	23	Carboplatin/irinotecan/ paclitaxel + pegfilgrastim	Carboplatin + paclitaxel + gefitinib	–	74 Gy	16 ay	–
Center et al. [33]	I	16	–	Docetaxel + gefitinib	Docetaxel	70 Gy	21 ay	20
Rothschild et al. [34]	I	14	–	Gefitinib ± cisplatin	Gefitinib	63 Gy	12.5 ay	21
Okamoto et al. [35]	Feasibility/ tolerability	9	Gefitinib	Gefitinib	Gefitinib	60 Gy	11.5 ay	26
Levy et al. [36]	II	50	–	Gefitinib	Cisplatin + vinorelbine	66 Gy	11 ay	12.5
SWOG 0023 [37]	III	243	–	Cisplatin + etoposide ➔docetaxel	Gefitinib placebo	61 Gy	23 ay 35 ay	3 2 ex due to treatment-related toxicity

CALEB, Cancer and Leukemia Group B; *JCOG*, Japan Clinical Oncology Group; *OS*, overall survival; *RT*, radiotherapy; *SWOG*, Southwest Oncology Group

Several phase II and III studies have been conducted in an attempt to evaluate the efficacy of TKIs combined with thoracic RT (Tables 2 and 3). The results were conflicting and the risk of severe pneumonia seems to be high.

Gefitinib Cancer and Leukemia Group B (CALEB) 30106 is an important phase II study evaluating the use of gefitinib after sequential/concomitant chemo-RT in unresectable NSCLC patients [30]. In CALEB 30106 study, 63 patients were entered before the study closing early due to the inferior results of Southwest Oncology Group (SWOG) study, which showed that maintenance gefitinib treatment resulted in a worse outcome than with placebo [30]. In CALEB 30106 study, the patients were stratified as poor-risk stratum (≥ 5% weight loss

Table 3 Studies investigating the use of concomitant erlotinib with thoracic radiotherapy in non-small cell lung cancer patients

Study	Phase, clinical setting	*N*	Induction tx	Concomitant tx	Maintenance tx	RT dose (Gy)	Median OS (month)	Lung toxicity (%)
Komaki et al. [38]	II	48	–	Carboplatin/taxan + erlotinib (except for chemotherapy days)	Paclitaxel	63 Gy	25.8 ay	6
MARTE [39]	II	60	–	Pemetrexed + erlotinib Gemcitabine+ erlotinib	–	50.4–59.4 Gy	14.4 ay	5
Martinez et al. [40]	II	23	–	-/Erlotinib	-/Erlotinib	66 Gy	N/A	4
Choong et al. [41]	I	17 17	Carboplatin/ paclitaxel	Cisplatin + etoposide + erlotinib Carboplatin + paclitaxel + erlotinib	-Docetaxel	66 Gy	10.2 ay 13.7 ay	3
Wan et al. [42]	I/II	8	Erlotinib	Erlotinib	Erlotinib	45 Gy 60 Gy	N/A	40
CALGB 30605 (Alliance)/RTOG 0972 (NRG) [43]	II	75	Carboplatin + nab-paclitaxel	Erlotinib	–	66 Gy	17 ay	1

CALEB, Cancer and Leukemia Group B; *JCOG*, Japan Clinical Oncology Group; *OS*, overall survival; *RT*, radiotherapy; *SWOG*, Southwest Oncology Group

and/or performance status 2) and good-risk stratum (performance status 0–1 weight loss and < 5%). Results of CALEB 30106 study was disappointing, with median overall survival rates of poor-risk and good-risk patients were 13 months and 19 months respectively, meaning that the poor-risk patients had worse OS than good-risk patients. Acute high-grade infield toxicities were not clearly increased compared with historical chemo-RT data. Thirteen out of 45 tumors analyzed had activating EGFR mutations and 2 out of 13 also had T790M mutations. Seven tumors out of 45 had KRAS mutations. There was no apparent survival difference with EGFR-activating mutations versus wild type or KRAS mutation versus wild type.

In phase SWOG 0023 study, stage III A/B NSCLC patients received cisplatin 50 mg/m^2 on days 1 and 8 plus etoposide 50 mg/m^2 on days 1 to 5, every 28 days for 2 cycles with concurrent thoracic radiation (1.8- to 2-Gy fractions per day; total dose 61 Gy) followed by 3 cycles of docetaxel 75 mg/m^2 [37]. Patients whose disease did not progress were randomly assigned to gefitinib 250 mg/day or placebo until disease progression, intolerable toxicity, or the end of 5 years. The study's main objective was the OS. The study was closed early due to the inferior outcome and preliminary results were reported. Results were discouraging, with a higher OS in the placebo arm (35 months (m) vs. 23 m in the treatment arm, $p = 0.013$, HR 0.633), increased PFS (11 vs. 8.3 m), and more toxicity-related deaths in the gefitinib arm (2 vs. 0%).

In a Japanese study, the safety and toxicity profile of daily gefitinib (250 mg) administration with concurrent definitive thoracic RT (60 Gy) in patients with unresectable stage III NSCLC was examined [35]. This trial was closed early according to the protocol definition, because of higher levels of pulmonary toxicity and progressive disease than expected; therefore, it did not support the further trials of gefitinib and RT for unselected NSCLC patients. The authors recommended the use of gefitinib and RT for locally advanced NSCLC in patients with sensitizing EGFR mutations.

Table 2 shows the important studies evaluating the use of gefitinib and RT in unresectable stage III NSCLC patients. The results were conflicting; however, most of the studies were conducted on unselected patients [30–37]. It seems that further studies with patients with EGFR mutations were needed before understanding the role of gefitinib and RT in this patient population.

Erlotinib CALEB 30605 (Alliance)/RTOG 0972 (NRG) is a phase II study that was designed to evaluate 2 cycles of induction chemotherapy with carboplatin and paclitaxel followed by RT and concomitant erlotinib in patients with unresectable stage III A/B lung cancer and poor prognostic factors [43]. The authors evaluated the tumor samples (available in 42% of cases) to check for the presence of the EGFR mutation. Maintenance erlotinib was not permitted due to the inferior results reported with maintenance gefitinib in SWOG 0023 [37]. The overall response rate was 67% and the disease control rate was 93%. The median PFS and OS were 11 and 17 months, respectively. The overall 12-month OS was 57%, which narrowly missed the pre-specified target for significance, and the authors concluded that the 12-month OS was not sufficiently high to warrant further studies.

M.D. Anderson Center designed a single-arm prospective phase II trial study to explore if adding erlotinib would increase the effectiveness of chemo-RT without increasing toxicity [38]. The results were promising with respect to OS (82.6, 67.4, and 35.9% at 1, 2, and 5 years, respectively) and toxicity (grade 3 in 11 patients, grade 4 in one patient, and no cases of grade 5 toxicity). Median time to progression was 14.0 months and did not differ by EGFR status. Therefore, the study did not the study did not meet its primary endpoint, which was time to progression. Additionally, EGFR status did not affect the outcome. In addition, a substantial proportion of the patients developed distant progression (27 cases, 11 of which were brain metastases), leading the authors to conclude that more effective chemotherapy schemes are needed.

Martinez et al. investigated the feasibility, tolerability, and efficacy of the concurrent addition of erlotinib to the standard three-dimensional conformal thoracic RT in patients with unresectable or locally advanced NSCLC who are not candidates for receiving standard CT in a phase II trial [40]. In this study, the use of erlotinib with RT showed an extended cancer-specific survival (CSS) and a higher rate of complete responses compared with RT alone. There was no difference with respect to OS. The use of erlotinib and RT concomitantly increased toxicity including cutaneous toxicity, dyspnea, fatigue, hyperemia, diarrhea, and infection. Erlotinib did not increase the toxicity produced by RT. This finding did not support the use of combined therapy in molecularly unselected lung cancer patients.

Table 3 shows the important studies evaluating the use of erlotinib and RT in unresectable stage III NSCLC patients [38–43]. From the relevant literature, it can be concluded that the efficacy of the combined regimen is still unknown. Moreover, we should be aware of the unexpected toxicity of combined regimen particularly for lung toxicity, which was reported up to 40%. Likewise, in the case of gefitinib, most of the studies were conducted on the unselected patient population. Therefore, the use of biomarkers for the identification of patients that are most likely to benefit from this treatment is an essential next step in the research of this condition.

Combining an anti-EGFR agent with RT or chemo-RT has been shown to be feasible in several studies is used in patients with and without EGFR mutations [33–35, 41, 42]. According to the studies investigating the use of a combined approach, the addition of chemotherapy to the anti-EGFR agent and RT may possibly increase the risk of fatal pneumonitis and hematologic toxicities [33, 34]. Furthermore, the use of concurrent chemotherapy, radiotherapy, and EGFR TKI may not be better

than combined TKI and radiotherapy [30]. This implies the potential risk of increased toxicity when combining chemotherapy, EGFR, TKI, and RT and also the importance of drug treatment sequencing for chemotherapy and TKI.

Anti-angiogenic agents and radiotherapy

Molecular oxygen (O_2) is a potent chemical radio-sensitizer. Oxygen deprivation (hypoxia) is a feature of solid tumors that promotes genomic instability, enhanced aggressiveness, and metastases and is an important factor in treatment resistance and poor survival. Cells that are anoxic during irradiation are about three times more resistant to radiation than cells that are well oxygenated at the time of irradiation. Hypoxia is an attractive therapeutic target that is yet to be successfully exploited in most cancers, including NSCLC. Hypoxia-targeted therapies are associated with a favorable therapeutic ratio because hypoxia is nearly exclusively restricted to cancer cells. However, NSCLC hypoxia-targeted therapy trials have not yet translated into patient benefit [44, 45].

The concept of targeting angiogenesis for therapeutic effect in cancer was initially conceived as a means of depriving tumors of oxygen and nutrients. However, subsequent preclinical studies demonstrated that inhibition of angiogenesis may result in normalization of tumor vasculature and enhanced perfusion in certain contexts. The potential role of antiangiogenic agents in enhancing tumor oxygenation makes them attractive candidates for combination with radiotherapy [11, 46]. As discussed above, using antiangiogenic drugs with RT is an example of a "biological cooperation" strategy according to Steel hypothesis.

The majority of agents available for clinical testing of this strategy target the vascular endothelial growth factor (VEGF) receptor-signaling pathway. The mostly studied drug is "bevacizumab" which is a humanized anti-VEGF monoclonal IgG_1 antibody. Spigel et al. conducted two independent phase II clinical trials in small-cell lung cancer (SCLC) and NSCLC using bevacizumab in combination with chemotherapy and RT [47]. In both trials, the authors observed unexpected tracheoesophageal fistulae development, prompting early trial closures. There were two patients who developed tracheoesophageal fistulae (one resulting in death). A third patient died from an aerodigestive hemorrhage. All three patients had grade 3 esophagitis during chemo-RT and bevacizumab induction therapy. Therefore, these two trials suggested that bevacizumab and chemo-RT were associated with a relatively high incidence of tracheoesophageal fistulae formation.

In SWOG S0533study, patients unresectable stage IIIA (N2) or stage IIIB NSCLC were classified as low-risk and high-risk patients [48]. Low-risk patients were defined as (1) non-squamous histology or mixed histology with < 50% squamous cell carcinoma; (2) a primary tumor with no cavitation and not within 1 cm of a major blood vessel; and (3) no history of hemoptysis (bright red blood of half a teaspoon or more) within 28 days before registration. The patients were allocated into 3 cohorts as the first patient cohort would receive bevacizumab 15 mg/kg only during consolidation docetaxel after completion of concurrent CRT. If safe, based on predefined protocol-specific criteria, the second cohort would receive bevacizumab starting on day 15 of induction CRT. The last cohort of patients would start bevacizumab on day 1 of CRT. The primary objective of this study was to assess toxicities, especially the risk of hemorrhage, associated with the combination of bevacizumab with combined modality therapy. After the completion of cohort 1 with 29 patients, the study was early closed because of higher rates of pulmonary toxicity. There were 2 episodes of grade 5 pulmonary hemorrhage both of which were in the high-risk group. Median overall survival was 46 months for low-risk and 17 months for high-risk strata. This study demonstrated that bevacizumab was not safely integrated into CRT for stage III NSCLC in patients considered at high risk for hemoptysis.

As a conclusion, the use of concomitant bevacizumab and RT is not recommended in stage III NSCLC patients due to severe side effects, including tracheoesophageal fistulae formation and pulmonary hemorrhage.

Anti-ALK/ROS agents and radiotherapy

NSCLC patients with ALK-positive tumors are sensitive to the oral small molecule tyrosine kinase inhibitor crizotinib. Crizotinib has recently demonstrated superior efficacy as compared to standard chemotherapy and has become the new standard in second-line management of ALK + metastatic NSCLC [49]. Whether crizotinib has the potential to replace chemotherapy in combination with RT in multimodal management of locally advanced NSCLC patients is not clear. However, there is some preclinical evidence showing the radiosensitivity property of crizotinib in ALK + cell culture [50]. A randomized phase II trial (RTOG 1306) is currently underway to assess erlotinib and crizotinib as induction therapy followed by radiochemotherapy in patients with confirmed EGFR mutation or with ALK-rearrangement positive NSCLC [51].

Targeted therapy and concomitant radiotherapy in stage IV-oligoprogressive/oligometastatic NSCLC patients

Systemic therapy in metastatic NSCLC has undergone a major theory shift in the past decade, from the primary use of cytotoxic chemotherapy to the discovery of driver mutations and the subsequent discovery and use of genotype-directed targeted therapies. Although cytotoxic drugs still form the backbone of systemic treatment in most patients with advanced disease, genetic alterations can be identified in about 50–60% of lung

adenocarcinoma. About 10–15% of lung adenocarcinomas have an activating EGFR mutation, 25% a KRAS mutation, 5–10% an ALK rearrangement [52]. In metastatic NSCLC patients with EGFR-mutated or ALK-rearranged tumor, the recommended first-line treatments are anti-EGFR TKIs (gefitinib, erlotinib, afatinib) and anti-ALK (crizotinib, ceritinib) respectively [53, 54]. Despite the impressive increase in tumor response observed with these drugs, the median disease-free survival is only 8–13 months for stage IV patients. Most of the patients develop multiple metastases during progressive disease; however, there is a subgroup of patients presenting with oligoprogressive disease under TKIs. In this latter patient subgroup, most of the disease is controlled by the targeted therapy, except for a small, limited number of drug-resistant tumor clones (usually from 3 to 5 metastases are accepted), which lead to oligoprogression. Although standard treatment in progressive disease is to switch another TKI or chemotherapy, a subset of patients develops oligoprogressive disease, suggesting that most of their disease burden depends on driver mutation signaling. Development of resistant clones leads to sites of disease progression; these oligoprogressive sites offer the opportunity to develop treatment strategies that enable the continuation of targeted therapy while local treatment methods, such as stereotactic ablative body RT (SABR), are used. This strategy can delay the initiation of an alternate systemic therapy such as chemotherapy, which can minimize toxicity from treatment [52, 54].

Table 4 shows the studies investigating the use of RT + TKIs in advanced stage NSCLC patients with oligoprogression. From the relevant literature data, it can be concluded that the use of local therapies including SRS, SBRT, or other ablative therapies with TKI in oligoprogressive disease seems to be reasonable since this strategy increases the survival [55–58]. This treatment strategy was also approved at a recent consensus conference of the European Society for Medical Oncology (ESMO) [59].

Targeted therapy and concomitant radiotherapy in NSCLC patients with brain metastasis

Approximately 20–40% of NSCLCs, particularly those with adenocarcinoma histology will eventually develop brain metastasis with the poor OS of and severe neurological symptoms [60]. For this patient population, current treatment options include surgical resection, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) alone, or combined strategies. RT remains the standard therapy for brain metastases from NSCLC; however, long-term results remain disappointing with median survival time in the range of 2.4–4.8 months due to the limitations of RT [61, 62]. There are many studies in the literature investigating the use of concomitant RT with conventional chemotherapeutics agents, such as platinum, nitrosourea, paclitaxel, and temozolomide, suggest no significant improvement in OS compared with RT alone owing to their low capacity of penetrating the brain-blood barrier (BBB) [60].

The use of EGFR TKIs in NSCLC patients with brain metastases remains challenging. However, since TKIs are molecules with a low molecular weight and a non-polar nature, TKIs are able to cross the BBB, although only to a limited extent, which is why their inoperative exposure within the central nervous system (CNS) plays an important role in the refractory condition of brain metastases to TKIs, even when extracranial disease in EGFR-mutant NSCLC is controlled [64]. Additionally, brain metastases may disrupt the integrity of BBB, so the penetration ability of TKIs to CNS with metastases could be improved [23]. Interestingly, the impenetrability of BBB also plays a positive role in brain metastases. Since the inadequate drug penetration into the cerebrospinal fluid (CSF) across a relatively intact BBB, the CNS metastases might be still without secondary resistance mutations, despite the concurrent acquisition of resistance mutations outside the CNS. Therefore, if the intracranial concentration levels of the TKIs are sufficient, then the intracranial metastases may remain sensitive to TKI [61].

Table 5 shows the literature data regarding use of TKIs and concomitant RT in NSCLC patients with brain metastases. The results of the studies are conflicting [61]. However, there are two recent meta-analyses demonstrating the survival benefit of combined approach [58, 61]. The first one evaluated 8 trials comparing TKI plus RT to a non-TKI group (RT alone or chemo-RT), concluding that TKI plus RT provided a significant increase in response rates, time to progression, PFS, and OS. With respect to the toxicity, only skin rash was also significantly greater in the TKI group [60]. The other meta-analyses have the same results as it showed that RT plus

Table 4 Studies investigating the use of concomitant TKI and RT in patients with NSCLC in oligoprogression after initial systemic treatment

Author	N/EGFR (+)	Oligoprogression criteria	*N* = TKI + RT	Survival (month)
Lyengar	24/13 (−)/11 unknown	≤6 extracranial	16/erlotinib	DFS: 14.7
Gan	38/all ALK (+)	≤4 extracranial	14/crizotinib	DFS 28 vs. 10.1
Yu	184/all EGRF (+)	≤5 extracranial	18/erlotinib, crizotinib	DFS: 10
Weickhardt	65/27EGRF (+)/38 ALK (+)	≤4 brain + extracranial	18/erlotinib, crizotinib	DFS: 6.2

DFS, disease-free survival; *RT*, radiotherapy

Table 5 Studies investigating the use of concomitant TKI and RT in NSCLC patients with brain metastases

Study	Phase, clinical setting	*N*	TKI + RT	RT	OS (month)
Lee	Phase II	40/40	Erlotinib + WBI (20 Gy/5 fx)	Placebo + WBI (20 Gy/5 fx)	3.4 vs. 2.9
Zhuang	Phase II	23/31	Erlotinib + WBI (30 Gy/10 fx)	WBI 30 Gy/10 fx	10.7 vs. 8.9*
Sperduto (RTOG 0320)	Phase III	41/44	Erlotinib + WBI/SRS	WBI/SRS	6.1 vs. 13.4
Pesce	Phase II	16/43	Gefitinib + WBI (30 Gy/10 fx)	Temozolomide + WBI	6.3 vs. 4.9*
Wang	Prospective	37/36	Gefitinib + 3DCRT (50 Gy/25 fx)	VMP + 3DCRT(50 Gy/25 fx)	13.3 vs. 12.7*
Cai	Retrospective	104/178	TKI + WBI/SRS/SURG	WBI/SRS/SURG	31.9 vs. 17*
Fan	Retrospective	75/111	TKI + WBI/SRS/SURG	CT + WBI/SRS/SURG	12 vs. 9*

*$p < 0.05$

**Toxicity: only in RTOG 0320 study grade 3–5 toxicity is higher in combined arm (11% vs. 49%)

CT, chemotherapy; *OS*, overall survival; *RT*, radiotherapy; *RTOG*, Radiation Therapy Oncology Group; *SRS*, stereotactic radiosurgery; *WBI*: whole brain irradiation; *3DCRT*, three-dimensional conformal radiotherapy

EGFR TKIs produced superior response rate and disease control rate (DCR) and markedly prolonged time to central nervous system progression (CNS-TTP) and OS of NSCLC patients with brain metastases. However, combined groups had a higher rate of incidence of overall adverse effects, especially rash and dry skin [58].

It is very difficult to have an exact conclusion from the currently available data; however, it seems to be reasonable to use combined treatment with close follow-up in suitable patients.

Conclusion

To date, there is no targeted therapy that has demonstrated a survival benefit when combined with RT in stage III NSCLC patients. Cetuximab has no survival benefit, and it seems to be toxic in this patient population. Bevacizumab has severe toxicity including pulmonary hemorrhage and tracheoesophageal fistulae formation in addition to its ineffectiveness. It is difficult to have an opinion about TKIs when combined with RT since most of the studies were conducted on unselected patients. There is a need for new studies about the use of TKIs and concomitant RT in patients with specific mutations. The results of ongoing RTOG 1306 study will clarify most of the questions.

For oligometastatic/oligoprogressive NSCLC patients, it seems to be reasonable to use combined regimen since combined regimen resulted in superior survival time; however, the patients should be followed up closely with respect to the toxicity. In patients with brain metastases, the use of concomitant RT + TKIs increased survival with acceptable toxicity levels. This strategy also seems to be reasonable in selected patients. Again, the patients should be followed by closely particularly for skin toxicities.

The use of targeted therapies combined with RT is an exciting and promising approach to NSCLC. However, there are many questions that should be resolved including optimal patient selection and the timing, duration, and fractionation schedule for RT. Well-designed prospective randomized studies are needed to clarify these issue.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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