

Molecular targeted therapy to improve radiotherapeutic outcomes for non-small cell lung carcinoma

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Abstract: Effective treatments for non-small cell lung carcinoma (NSCLC) remain elusive. The use of concurrent chemotherapy with radiotherapy (RT) has improved outcomes, but a significant proportion of NSCLC patients are too frail to be able to tolerate an intense course of concurrent chemoradiotherapy. The development of targeted therapies ignited new hope in enhancing radiotherapeutic outcomes. The use of targeted therapies against the epidermal growth factor receptor (EGFR) has offered slight but significant benefits in concurrent use with RT for certain patients in certain situations. However, despite theoretical promise, the use of anti-angiogenics, such as bevacizumab and endostatin, has not proven clinically safe or useful in combination with RT. However, many new targeted agents against new targets are being experimented for combined use with RT. It is hoped that these agents may provide a significant breakthrough in the radiotherapeutic management of NSCLC. The current review provides a brief discussion about the targets, the targeted therapies, the rationale for the use of targeted therapies in combination with RT, and a brief review of the existing data on the subject.

Keywords: Targeted therapy; monoclonal antibodies; tyrosine kinase inhibitors; radio-sensitizer; gefitinib with radiotherapy; erlotinib with radiotherapy; cetuximab with radiotherapy

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Introduction

Radiotherapy (RT) plays an important role in the management of lung cancer. RT has an established role not just as an adjuvant therapy to surgery in the curative setting, but also in the definitive setting (as in the use of stereotactic RT for early stage lesions) and in the palliative role (involving treatment of metastatic lesions as well as in facilitating relief from compressive symptomatology) (1,2).

Since the beginning of the era of RT, there has been a quest to enhance outcomes—both by increasing the efficacy of RT, and by reducing radiation associated

toxicities. The earlier years witnessed the use of altered fractionation to improve therapeutic ratio, later there had been experimentation with the use of chemotherapy (both sequential and concurrent) to enhance RT. Concurrent chemoradiotherapy with agents such as carboplatin, cisplatin, paclitaxel, docetaxel are known to enhance response rates, but also while including severe toxicities. The toxicities are sometimes severe to an extent so as to make it unusable in many patients of lung cancer since a large proportion of these patients entail co-morbidities such as diminished respiratory functions, cardiac issues, and age related issues (3).

In the recent years, there has been a significant breakthrough in the radiotherapeutic management of cancer. The use of targeted therapies in concurrent use with RT was seen as an effective approach, while being less toxic than the use of concurrent chemotherapy with RT. The success with the use of cetuximab in concurrent use with RT for head-neck squamous cell carcinoma ultimately led to the experimentation of a similar approach in other malignancies, including non-small cell lung carcinoma (NSCLC) (4). Almost simultaneously, there had been an interest in the use of anti-VEGF targeted therapies in concurrent use with RT (5,6). The discovery of oral tyrosine kinase inhibitors for certain types of NSCLC ushered in unprecedented convenience and efficacy (7,8).

It is hoped that evolution of targeted therapies for lung cancer can open up a new era in the radiotherapeutic management for lung cancer, with multiple experiments evaluating ways of integrating targeted therapy and RT for achieving synergy. While there is no dearth of theoretical targets, the lack of availability of clinically effective agents against these targets has been a source of frustration. This review discusses the current state of research in regards to the use of targeted therapies in concurrent use with RT for NSCLC.

A brief history of targeted therapies for lung cancer

Limitless replicative potential, growth self-sufficiency, anti-apoptotic potential, angiogenesis and the potential for invasion and metastasis are regarded as the 'hallmarks of cancer'. The mentioned abilities are the result of dysregulation of signalling pathways either due to oncogene activation, or via a loss of tumor suppressive gene function. Oncogene activation could imply gene amplification, rearrangements, and point mutations. Loss of tumor suppressor gene function could be due to loss of heterozygosity or by epigenetic transcriptional silencing. Though both 'oncogene activation' and 'loss of tumor suppressor gene function' are known to be involved in the etiopathogenesis of lung cancer, there has been a greater understanding upon the mechanisms of oncogene activation and there exist opportunities at targeting the same (9-12).

The study of the phenomenon of oncogene activation led to the discovery of 'oncogene addiction' wherein a 'driver oncogene' is crucial for the tumor cells' survival and proliferation. The commonly activated driver oncogenes in lung cancer include *EGFR*, *KRAS*, *HER2*, *MYC*, *MET*,

EML4-ALK and *BCL2*. Since the targeting of a 'driver oncogene' would lead to specific killing of the 'oncogene addicted' tumor cells, these 'driver oncogenes' can in a way be regarded as the 'Achilles heel' of the tumor (13,14).

Clinically, *EGFR* mutations are the most common in lung cancer, and are of special interest due to the availability of multiple drugs to target *EGFR*. *EGFR* is a member of a family of transmembrane receptor kinases which also includes *HER2*, *HER3* and *HER4*. *EGFR* and its associated receptor family are necessary for survival and are involved in maintenance of tissues including skin, heart, lungs and the central nervous system. Thus, it is not surprising that mutations of *EGFR* are oncogenic. The prevalence of *EGFR* mutations in lung cancer are difficult to estimate as it varies with ethnicity, sex and smoking status. Overall, *EGFR* mutations are expected in about 20–40% of Asian NSCLC patients. Mutations involving the kinase domain region (located from exon 18–21) of *EGFR* gene are 'activating mutations' since these mutations result in constitutive kinase activity of the receptor kinase, conferring ability of auto-activation (15,16).

Initial studies (such as BR.21 & INTEREST) evaluated *EGFR* tyrosine kinase inhibitors in NSCLC patients who had received prior treatment with chemotherapy, and without regards to either the patient's histopathology or the *EGFR* mutation status. Despite this, there was an evidence of benefit with the use of gefitinib/erlotinib in comparison to placebo/chemotherapy (17,18).

The phase-III OPTIMAL trial was conducted to evaluate the PFS benefit with the use of erlotinib versus chemotherapy with gemcitabine-carboplatin. When used as first-line treatment in Chinese patients with *EGFR* mutated NSCLC. The median progression free survival (PFS) was better with erlotinib in comparison to chemotherapy (13.1 vs. 4.6 months; $P < 0.0001$). These results were confirmed in the EURTAC study involving European patients (19,20).

While gefitinib and erlotinib represent oral TKIs which are effective against mutated *EGFR*, there exists an older class of targeted therapy agents, namely 'monoclonal antibodies'. Monoclonal antibodies act on the extracellular aspect of the receptor, unlike the tyrosine kinase inhibitors which act on the intracellular domain. The anti-*EGFR* monoclonal antibody has already proven efficacy in patients of head-neck squamous cell cancers and colorectal adenocarcinomas (21-23). Their use in lung cancer has rather been an extrapolation based upon results in other sites. While cetuximab has been the most commonly used anti-*EGFR* monoclonal antibody in use, newer

agents include panitumumab and nimotuzumab which are expected to provide similar efficacy at lesser toxicity as they have a diminished murine component in comparison to cetuximab (24-26).

Next to *EGFR*, the second mutation of particular importance happens to be the translocation mutation *EML4-ALK*, which is a lot less common in comparison to *EGFR*. Despite constituting just 3–6% of lung adenocarcinoma, it is of special interest because of the availability of an effective agent, namely crizotinib to target *EML4-ALK* mutation (27,28).

The VEGF pathway can be blocked by using monoclonal antibodies targeting VEGF, the use of VEGF receptor inhibitors (aflibercept), and by the use of small molecule tyrosine kinase inhibitors such as sunitinib and sorafenib to target the tyrosine kinase domain of VEGF receptor. The ECOG 4599 and the European AVAIL were two large phase III trials which helped gain approval for bevacizumab use in lung cancer, but strictly to be avoided in squamous cell carcinoma histology. Toxicities such as hemorrhage, esophageal toxicity could be severe. The results with aflibercept for platinum and erlotinib resistant lung cancer have been far from satisfactory in phase II trials. Small molecule tyrosine kinase inhibitors pazopanib, sunitinib, sorafenib and mosatenib are yet to be proven for safety and efficacy in phase III trials (29-32).

More targets such as *KRAS*, *BRAF*, *MET*, *ILGF-1* and others are foci of on-going research, with no major data available for drawing impressions at this time (33-38).

Rationale for combining targeted therapies & RT

The combination of EGFR inhibitors with RT for NSCLC has strong theoretical rationale, as well as the backing of a body of evidence that can be interpolated from other sites such as head-neck & colorectal (39,40). RT induced tissue damage leads to increased EGFR expression which may be contributory to the dreaded phenomenon of accelerated tumor cell repopulation. Anti-EGFR monoclonal antibodies are especially effective in situations involving EGFR over-expression, thus rationalizing their use in concurrent use with RT. The use of anti-EGFR oral tyrosine kinase inhibitors is known to inhibit radioresistance by various mechanisms involving the cell growth pathways. It has been experimentally observed that anti-EGFR tyrosine kinase inhibitors are known to inhibit radioresistance by various mechanisms involving the cell growth pathways. It has also been observed that anti-EGFR tyrosine kinase inhibitors

is known to inhibit radioresistance by various mechanisms involving the cell growth pathways including the reduction of percentage of tumor cells in the radioresistant ‘S-phase’ of the cell cycle, affect Rad51 expression, and reduce the radiation induced EGFR autophosphorylation (41). Also, the use of EGFR tyrosine kinase inhibitors in patients with *EGFR* activating mutations may lead to a rapid regression, hence reducing hypoxia and enhancing radiosensitivity (42-44).

The tumor vasculature is markedly disorganized in comparison to normal vasculature. The altered tumor vascular endothelium may lead to hypoxia, which not only causes increased radioresistance, but also promotes distant metastases. Also, RT is known to induce an increase in VEGF. Thus the use of anti-angiogenic therapy in concurrent use is rational, at least from a theoretical standpoint (45-47).

Existing experience on targeted therapies in use with RT

RT with anti-EGFR monoclonal antibodies

The first anti-EGFR monoclonal antibody to be used with RT is cetuximab. Cetuximab is a chimeric monoclonal antibody (partly murine, partly human), thus holding an occasional risk of allergic reaction. Newer agents include nimotuzumab and panitumumab. Nimotuzumab being a ‘humanized’ monoclonal antibody has modified protein sequences to increase similarity to human antibodies. Panitumumab is a fully human monoclonal antibody. While all of three agents act on the same target (the EGF receptor), the difference lies in the extent of expected toxicities. Further, cetuximab being an IgG1 may have the ability to activate complement pathway and cause antibody dependent cellular cytotoxicity, a feature which may theoretically be lacking in the IgG2 antibodies such as panitumumab. It is unknown at this time as to whether newer molecules (nimotuzumab & panitumumab) are equally effective as cetuximab, though newer molecules are likely to be less toxic (48-50).

The use of anti-EGFR monoclonal antibodies in concurrent use with RT has been summarized in *Table 1*. Though a pooled interpretation is difficult due to the varying complexity of study designs, the following inferences can be drawn at this time—that the use of anti-EGFR monoclonal antibodies in unresectable NSCLC is a good alternative to concurrent chemotherapy in patients unlikely to tolerate concurrent chemotherapy during RT;

Table 1 Anti-EGFR monoclonal antibodies for use with radiotherapy

Study	Type	Subjects	Design	Inference
N0422 (51)	Phase II	n=57; poor performance status; median age 77	Cetuximab + RT (60 Gy/30#); evaluated percent of patients alive at 11 m	70% patients alive at 11 m (expected was 50%); median survival 15.1 m; no treatment related deaths; but >50% patients had grade3 adverse effects (rash, dysphagia etc.)
NEAR (52)	Phase II	n=30; patients unfit for chemoradiotherapy; median age 71	IMRT + cetuximab (concurrent & maintenance)	Response rate 63%; median OS 19.5 m; 1 yr survival 66.7%; well tolerated; use of IMRT and non-use of chemotherapy may have enhanced tolerability
RTOG 0324 (53)	Phase II	n=93; unresectable stage III NSCLC	RT (63 Gy/35#) with concurrent chemotherapy + cetuximab	Response rate 62%; median survival 22.7 m; 2 yr OS 49.3%; 20% grade 4 toxicity; 5 grade 5 events (deaths)
RTOG 0617 (54)	Phase III	n=166; unresectable stage III NSCLC	Concurrent chemotherapy with paclitaxel-carboplatin to all; RT either low dose (60 Gy) or high dose (74 Gy); with or without cetuximab; 2x2 factorial design; randomized 1:1:1:1	Higher dose RT potentially harmful; addition of cetuximab added no OS benefit when patients were already on concurrent chemotherapy
RTOG 0839 (55)	Phase II	On-going; potentially operable locally advanced NSCLC	Pre-operative chemoradiotherapy with or without panitumumab	To assess pathological complete response rates with panitumumab and to assess OS & toxicity rates in comparison with RTOG 0324 which had utilized cetuximab
SATELLITE (56)	Phase II	n=75; stage III NSCLC	After 2 cycles of induction chemotherapy, 3DCRT to 68 Gy/34# with cetuximab	1-year OS 66%; 3-year OS 29%; feasible and tolerable; may be a valid alternative to concurrent chemotherapy
SWOG S0429 (57)	Phase II	n=24; stage III NSCLC unable to receive chemo due to co-morbidities	RT 64.8 Gy/36#; concurrent and maintenance cetuximab	Median survival 14 m; PFS 8 m; response rate 47%; well tolerated regimen even when concurrent chemotherapy not tolerable
Choi et al. (58)	Phase I	n=15; stage IIB-IV NSCLC unsuitable for radical therapy	Palliative RT 30-36 Gy in 10-12#; with weekly nimotuzumab (varying doses)	Well tolerated & feasible; response rate 46.7%; no skin rash or allergy
Bebb et al. (59)	Phase I	n=18; stage IIB-IV NSCLC unsuitable for radical therapy	Palliative RT 30-36 Gy in 10-12#; with weekly nimotuzumab (varying doses)	Attractive for patients with poor performance status or co-morbidities; absence of rash; 66% response rate

EGFR, epidermal growth factor receptor; RT, radiotherapy; NSCLC, non-small cell lung carcinoma; Gy, Gray; #, Fraction; IMRT, intensity modulated RT; OS, overall survival; PFS, progression free survival; m, months; yr, years.

that the addition of anti-EGFR monoclonal antibodies when concurrent chemotherapy is already being used may not lead to additional benefit (as also observed in the scenario with head & neck squamous carcinoma); that radiation dose escalation may not translate to any benefit; and that anti-EGFR monoclonal antibodies may be effective as radiosensitizers in all NSCLC histologies, even if mutational status is not specifically known (51-59).

RT with EGFR tyrosine kinase inhibitors

While anti-EGFR monoclonal antibodies seem to be active in proportion to the level of EGFR expression, the activity of EGFR tyrosine-kinase inhibitors depend upon the presence of specific activating mutation of the *EGFR*. Gefitinib and erlotinib are the approved EGFR tyrosine kinase inhibitors in use. These orally administered

Table 2 EGFR targeting tyrosine kinase inhibitors for use with radiotherapy

Study	Type	Subjects	Design	Inference
CALEB CALGB 30106 (60)	Phase II	n=63; unresectable stage III NSCLC	Patients divided as per risk; poor risk received RT with gefitinib; good risk received RT with gefitinib & paclitaxel-carboplatin	Benefit noted both for mutated and wild type EGFR when gefitinib added to RT; no additional benefit of adding gefitinib to chemoradiotherapy
Choong <i>et al.</i> (61)	Phase I	n=17; unresectable stage III NSCLC	Complex study design involving RT, chemotherapy & erlotinib	No survival advantage; but only 21% of patients were of adenocarcinoma histology
JCOG 0402 (62)	Phase II	n=38; unresectable adenocarcinoma	Induction chemotherapy followed by RT 60 Gy/30# plus gefitinib	Response rate 73%; median survival 28.5 m; 2-year survival 65.4%
Okamoto <i>et al.</i> (63)	Phase I	n=9; unresectable stage III NSCLC	14-day induction gefitinib followed by RT 60 Gy/30# plus gefitinib	Only 2 of 9 patients confirmed to harbor EGFR mutations, and these two had OS >5 years
Center <i>et al.</i> (64)	Phase I	n=16; inoperable stage III NSCLC	RT (70 Gy/35#) plus oral gefitinib and weekly docetaxel	Feasible with moderate toxicity; overall response rate 46%; median survival 21 m
Rothschild <i>et al.</i> (65)	Phase I	n=14; unresectable NSCLC	Gefitinib plus cisplatin chemoradiotherapy	Feasible; toxicities caused by cisplatin and not gefitinib; EGFR mutation status not given impetus
Stinchcombe <i>et al.</i> (66)	Phase II	n=23; unresectable NSCLC stage III	Induction chemotherapy (carboplatin-irinotecan-paclitaxel) followed by RT (74 Gy) with carboplatin-paclitaxel and gefitinib	Partial response rate of 24%; disappointing results in spite of extremely intense regimen
SWOG S0023 (67)	Phase III	n=243; stage III NSCLC	Concurrent chemoradiotherapy followed by docetaxel; maintenance gefitinib	Selection of patients not done with regards to either histology or EGFR mutation status; gefitinib not used concurrently
Wang <i>et al.</i> (68)	Phase II	n=26; stage III-IV NSCLC	Individualized RT based on tumor size and volume constraints; given either gefitinib or erlotinib; median RT dose 70 Gy	1 year OS 53%; 3-year OS 30%; 96% local tumor control rate; favorable toxicity, reasonable outcome; no chemotherapy used

EGFR, epidermal growth factor receptor; RT, radiotherapy; NSCLC, non-small cell lung carcinoma; Gy, Gray; #, Fraction; OS, overall survival; PFS, progression free survival; m, months.

drugs offer the advantage of convenience, too. The experience with the use of oral EGFR inhibitors with RT is summarized in *Table 2*. It can be remarked at this time that unlike anti-EGFR monoclonal antibodies which can be used in all of NSCLC regardless of the *EGFR* mutation status, the use of EGFR tyrosine kinase inhibitors must be restricted to adenocarcinoma histology harboring *EGFR* activating mutations. Also, while addition of gefitinib/erlotinib to RT may be helpful, there seems to be no benefit with the addition of gefitinib/erlotinib when concurrent chemotherapy is already being utilized. Currently, lack of large volume of data is a serious issue which hinders the drawing of conclusions. Also, many of the existing data

is from trials which did not provide impetus to patient selection based on histology and mutational status (60-68).

RT with anti-angiogenic agents

About a decade ago, the approval of bevacizumab as an anti-VEGF monoclonal antibody had led to the emergence of high hopes (69,70). However, it was soon realized that the use of bevacizumab had to be strictly avoided in patients with squamous cell carcinoma histology and in those with central thoracic lesions due to serious toxicity risks. Even when used for patients with adenocarcinoma histology, the use with concurrent chemotherapy and RT has led to

Table 3 Promising newer targeted therapies for concurrent use with RT

Class	Drug
Anti-HER2	Trastuzumab
Proteasome inhibitor	Bortezomib
MAPK inhibitor	Selumetinib
EML4-ALK inhibitor	Crizotinib
PARP inhibitor	Olaparib
Anti-mTOR	Sirolimus
HSP90 inhibitor	Celastrol
HDAC inhibitor	Vorinostat

RT, radiotherapy.

unacceptable toxicities such as esophagitis and pneumonitis, while not offering significant enhancements in outcome. At present, the use of bevacizumab in concurrent use with RT cannot be recommended for routine clinical use. While newer anti-angiogenic agents such as endostatin, sunitinib and sorafenib are now available, it must be stressed upon that they are yet unproven for safety and efficacy in the scenario of concurrent use with RT (71-73).

RT with other targeted agents

While anti-EGFR therapies have been the mainstay of effective targeted therapies for NSCLC, there are new novel agents in consideration for trials. Bortezomib is a proteasome inhibitor, already approved for use in multiple myeloma. Though was found to have demonstrated radio-sensitizing properties *in vitro*, it was found un-safe for clinical use in a phase-I trial combining bortezomib with RT and chemotherapy (74,75). Sirolimus, a MTOR inhibitor has been tested in a phase I trial involving RT & concurrent cisplatin (76). Though safety has been evaluated, definitive results on response and survival is awaited. Finally, trials in early phases are evaluating celastrol (HSP90 inhibitor), vorinostat (HDAC inhibitor), selumetinib (MAPK inhibitor) and olaparib (PARP inhibitor) for concurrent use with RT (77-80). Though many novel agents (*Table 3*) have demonstrated radio-sensitizing properties *in vitro*, it needs to be seen if the results can be translated clinically.

Conclusions

At present, it can be concluded that the use of anti-EGFR monoclonal antibodies for concurrent use with RT may be

beneficial, and is an attractive option for NSCLC patients who are unable to tolerate concurrent chemotherapy for any reason. At the same time, it may be remarked that the addition of cetuximab when concurrent chemotherapy is already being provided with RT may not lead to any benefit. The use of EGFR tyrosine kinase inhibitors offers the convenience of the oral route of administration. However the use of EGFR tyrosine kinase inhibitors with RT is feasible only in adenocarcinoma patients with specific mutations. Anti-angiogenic therapy with RT may lead to more harm than benefit, and must be avoided at the present time. There are many newer agents against newer targets which are under investigation for concurrent use with RT. With painstaking and time consuming efforts, there will be hope for better results in the future.

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Footnote

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