Mini-Review Article

Therapeutic integration of new molecule-targeted therapies with radiotherapy in lung cancer

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Abstract: Lung cancer is the most common form of the disease and the leading cause of cancer deaths worldwide. Non-small-cell lung cancer (NSCLC) accounts for approximately 80-85% of all lung cancers. Forty percent of all cases present with stage III, and many of them are considered inoperable (staged IIIA with mediastinal lymph node involvement) or stage IIIB disease. Concurrent platinum-based chemotherapy and thoracic radiation has demonstrated survival benefits in these patients. We review the role of new target agents in combination with radiotherapy in stage III NSCLC. Antiangiogenics improve tumor oxygenation thereby improving the therapeutic efficacy of irradiation in models. Bevacizumab in combination with thoracic radiation has shown high toxicity. However, other antiangiogenic agents are more promising. Radiation activates epidermal growth factor receptor (EGFR) pathways, inducing radioresistance, cell proliferation and enhanced DNA repair. After promising data from preclinical models and early clinical trials, cetuximab did not show any benefit in a recent phase III trial. Panitumumab and nimotuzumab are under evaluation. Gefitinib has been investigated in combination with radiotherapy for unresectable stage III NSCLC, but results in maintenance treatment after chemoradiotherapy were not encouraging. Erlotinib has also been tested in a phase II trial with chemoradiotherapy. Other new pathways and agents are being studied, such as m-TOR pathway, bortezomib, heat shock protein 90 (Hsp90) inhibition, histone deacetylase inhibitors (HDACS), aurora kinases, mitogen activated protein kinases (MARK) and PARP inhibitors.

Keywords: Non-small cell lung cancer (NSCLC); targeted therapy; chemoradiotherapy; combined modality

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Introduction

Lung cancer is the most common form of this disease and the leading cause of cancer death worldwide. Non-small-cell lung cancer (NSCLC) accounts for approximately 80-85% of all lung cancers. Forty percent of all cases presents with stage III, and many of them will be considered inoperable (staged IIIA with mediastinal lymph node involvement) or stage IIIB disease. Concurrent platinum-based chemotherapy and thoracic radiation has demonstrated survival benefits in these patients (1,2). We review the role of new agents that selectively target tumor-specific pathways used in combination with radiotherapy in stage III NSCLC. Research, which takes into consideration the tumor and toxicity profile, is focused on the identification of new cytotoxic or targeted agents that can be combined and integrate concomitantly with chemoradiotherapy to provide greater efficacy. It is important to identify potential biological targets, the blockade of which would affect multiple downstream signalling cascades. The most promising new agents for use in combination with radiotherapy to treat lung cancer are shown in *Table 1*.

Antiangiogenics

Tumor cells increase their expression of proangiogenic growth factors in response to endothelial damage and

Table 1 Mayor new agents in combination with radiotherapy

Antiangiogenics
Vandetanib
Bevacizumab
Thalidomide
Endostatin
EGFR pathway
Cetuximab
Panitumumab
Nimotuzumab
Gefinitib
Erlotinib
m-TOR pathway
Everolimus
Sirolimus
Bortezomib
Heat shock protein 90 inhibition
Celastrol
Histone deacetylase inhibitors
Vorinostat
Aurora kinases
PHA680632
AZ 1152
ZM447439
Mitogen activated protein kinase 1/2 inhibitor
Selumetinib
PARP inhibitors
Veliparib
Olaparib

EGFR, epidermal growth factor receptor.

hypoxia (3,4), and radiation induces cell death as a result of damage to cell membranes, DNA and microvascular endothelial cells within the tumor stroma (5,6). Combined antiangiogenic therapy and radiotherapy may improve tumor control (7) and targeting the VEGFR2 pathway could provide a way to overcome radioresistance. Preclinical data indicate that a hypoxic microenvironment contributes to radioresistance, and suppression of angiogenesis significantly enhances the radiosensitivity of cancer cells.

Vandetanib (ZD 6474), a potent orally available VEGFR2 and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, enhanced the therapeutic efficacy of irradiation in an orthotropic model of human NSCLC (8). Bevacizumab, in a phase II clinical trial study with chemotherapy and radiotherapy (9), showed serious adverse events including tracheobronchial fistulas. When used in combination with erlotinib (10) the principal toxicity was esophagitis but there was a lack of efficacy. Thalidomide showed significant toxicity when combined with chemotherapy and radiation but no additional efficacy (11). Endostatin in concurrent chemoradiotherapy did not show any benefit in overall response (12). Although these agents are often highly active in preclinical studies, the application of antiangiogenic therapy and radiotherapy in the clinical setting requires logical treatment schemes in an appropriate patient group to bring about any potential benefits (13).

Anti-EGFR

EGFR induces receptor homo- or hetero-dimerization and results in the activation of an intracellular tyrosine kinase domain. Receptor activation causes downstream signalling events through activation of the Ras/Raf/MEK/MAPK and PI3K/AKT/mammalian target of rapamycin (mTOR) pathways and has been involved in cellular proliferation, inhibition of apoptosis, angiogenesis, metastasis and chemoradioresistance (14). Radiation activates EGFR autophosphorylation increasing the activity of protein tyrosine kinase, and initiates downstream processes leading to radioresistance. In preclinical studies, NSCLC cells with *EGFR* mutations have increased radiation-induced apoptosis (15).

The monoclonal antibody cetuximab combined with radiotherapy (16) has shown synergistic activity in preclinical models. However, the addition of cetuximab to a combination of pemetrexed, carboplatin, and thoracic radiotherapy did not confer any benefit to NSCLC patients in a phase II randomized study (17). Similarly, no benefits in overall or progression free survival were shown when cetuximab was added to radiotherapy in a phase III trial (18). The safety of the cetuximab combination with radiotherapy was established in the SCRATCH (19) study, where synchronous cetuximab with radical RT were administered to patients with stage III NSCLC, and the results suggest that the early and late toxicities of synchronous cetuximab and radical RT are acceptable. The NEAR trial (20) was designed to evaluate the toxicities and feasibility of combined treatment with cetuximab and intensity-modulated radiation therapy (IMRT) locoregional irradiation in patients unfit for chemoradiation regimens. With an overall response rate of 63% and median

locoregional, distant, overall progression-free survival of 20.5, 10.9, and 8.5 months, respectively, the median overall survival was 19.5 months and only mild toxicity was reported. Combined radioimmunotherapy with cetuximab is both safe and feasible, especially in elderly patients with multiple comorbidities.

Panitumumab, a fully human monoclonal antibody specific to the EGFR, has been tested in preclinical models. RTOG 0839 is a phase II study of preoperative chemoradiotherapy with or without panitumumab in potentially operable, locally advanced stage IIIA NSCLC (21). Nimotuzumab is a humanised monoclonal antibody specific to the EGFR with similar preclinical and clinical activity to other anti-EGFR monoclonal antibodies, and characterized by a lack of severe skin toxicity. *In vitro* studies have demonstrated that nimotuzumab increases the radiosensitivity of NSCLC cell lines (22). Nimotuzumab in combination with palliative radiotherapy has been studied in two phase I trials which showed low toxicity and absence of rash (23,24). A phase II trial in combination with carboplatin/docetaxel and radiotherapy is awaiting final results (25).

Gefitinib, an EGFR-TKI, has a radiosensitizing effect that was confirmed in cell lines (26). It was studied in combination with radiotherapy in unresectable stage III NSCLC and showed a median overall survival of 16 months with esophagitis (19.5%) being the main toxicity (27). Erlotinib has been shown to enhance radiation response at several levels (cell cycle arrest, apoptosis, induction, accelerated cellular repopulation, and DNA damage repair) (28). In lung cancer cell lines, the radiosensitizing effects of erlotinib differed when the drug was administered using different administration schedules. The highest lethal effect was obtained when radiation was administered after erlotinib, which may be related to PI3K signal transduction (29). A phase II trial (30) investigated concurrent erlotinib, carboplatin, and paclitaxel with radiotherapy in 48 patients, followed by two cycles of chemotherapy. No grade 4 toxicities were reported. Median progression free survival and overall survival were 13.6 and 25.8 months, respectively, and 1-year overall survival was 84%. *EGFR* mutation analysis was performed on 41 tumor samples and only detected in 5; the local control rate was significantly higher among patients with an *EGFR* mutation. In a prospective randomized phase II study (31), RT with or without concurrent erlotinib was administered to unresectable stage I to IIIA NSCLC patients who were not candidates for chemotherapy. The toxicities associated to erlotinib were skin rash (61.5%) and diarrhea (23%), however, erlotinib did not increase the toxicity associated to radiotherapy. The response rate was 55.5% in the radiotherapy arm and 83.3% in the concomitant arm.

m-TOR pathway

The PI3 kinase/AKT pathway is activated by mutation of *Ras* or pathway components, and by deregulated growth factor receptor signalling to *Ras*. The activation of Ras signalling increases the survival of tumor cells exposed to agents that cause DNA damage. mTOR is a critical downstream effector of the PI3K/Akt pathway. In xenograft models of human NSCLC, everolimus plus radiotherapy produces significant tumor growth suppression by increasing the antitumor activity of radiation (32). Sirolimus has been tested with thoracic radiation therapy (60 Gy) and weekly cisplatin in a phase I trial and has demonstrated a safe profile (33).

Bortezomib

Bortezomib, a proteasome inhibitor, disrupts homeostatic mechanisms within the cell and leads to cell death. The ubiquitin-proteasome pathway is essential in the degradation of intracellular proteins and regulates the cell cycle, neoplastic growth, and metastasis. Bortezomib has demonstrated *in vitro* chemotherapy- and RT-sensitizing properties (34), but a phase I (35) trial with carboplatin and paclitaxel with concurrent radiotherapy was halted because of postoperative deaths in patients who underwent right pneumonectomy.

Heat shock protein 90 (Hsp90) inhibition

Hsp90 is a molecular chaperone that mediates the refolding of denatured proteins, such as AKT, HER2, Bcr-Abl, c-KIT, EGFR and PDGFR-α (36). Hsp90 inhibition results in substantial cell death in both chemosensitive and chemoresistant small-cell lung cancer cell lines. Clinically, the geldanamycin compounds are the most mature with manageable toxic effects (37). Celastrol inhibits the ATP-binding activity of Hsp90, and it is considered an effective radiosensitizer acting as a Hsp90 inhibitor and a p53 activator in lung cancer cell lines (38).

Histone deacetylase inhibitors (HDACS)

HDACS play a role in cell motility and are involved in the regulation of many transcription factors. Vorinostat and other HDACs have shown successful results in a wide range

of cancers, including NSCLC (39).

Aurora kinases

Aurora kinases are a family of serine-threonine kinases that control chromosome assembly and segregation during mitosis and are expressed in a broad range of cancers (40,41). Most Aurora-selective small-molecule inhibitors are currently undergoing preclinical assessment (42-46).

Mitogen activated protein kinase (MARK) 1/2 inhibitor

The MAPK/extracellular signal-regulated kinase (ERK) signalling pathway is involved in proliferation and survival of tumor cells.

Selumetinib, a selective inhibitor of MAPK1/2 (MEK1/2), inhibits tumor hypoxia in human lung and colon carcinoma xenograft models (47) and is currently in an ongoing phase I trial in combination with RT (48).

Parp inhibitors

Poly (ADP-ribose) polymerases are critical in the repair of DNA strand breaks. Ionizing radiation induces DNA strand breaks, and PARP-1 inhibition may sensitize tumor cells to radiation. Veliparib (ABT-888), a PARP-1 inhibitor, with radiation in lung cancer models is effective in enhancing tumor sensitivity to radiation (49), and is being tested in a phase I trial with chemoradiotherapy (50). A trial with another PARP-1 inhibitor, olaparib, in combination with high dose radiotherapy with or without daily dose cisplatin in locally advanced NSCLC, is ongoing (51).

Conclusions

In the development of novel targeted radiation enhancers, some recommendations have to be followed in relation to the determination of agent activity, preclinical testing of radiation enhancement effects, prioritizing agents when biomarker-based patient selection is available, understanding the proper sequencing of combining targeted agents with radiation together with determining early and late safety of the combination in phase I studies as well as regulatory issues. Angiogenic therapies have been shown to enhance radiotherapy in preclinical models. Antiangiogenics reduce vascular density, but improve tumor oxygenation, therefore, it is reasonable to suppose that a combination of antiangiogenic therapy and radiotherapy may improve tumor control. Radiation activates EGFR signalling, leading to radioresistance by inducing cell proliferation and enhanced DNA repair. Numerous clinical trials are currently exploring this combination.

Combining new drugs and concomitant chemoradiation has become an attractive therapeutic option for locally advanced NSCLC, but the addition of targeted therapies to concomitant chemoradiotherapy is still under investigation. Caution has to be exercised with respect to compliance with treatments as this is not always reported in clinical trials. Furthermore, large volume radiotherapy plus targeted drugs should be avoided and especially in hypo-fractionated regimens where high toxicities have been observed (52).

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