New Strategies in Non-Small Cell Lung Cancer: Improving Outcomes in Chemoradiotherapy for Locally Advanced Disease

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Abstract

The past decade has seen significant breakthroughs in our knowledge of the tumor biology of non-small cell lung cancer (NSCLC). Signaling pathways that are vital for tumor growth have been identified and have been effectively targeted for pharmacologic intervention. Furthermore, advances in imaging and treatment delivery have allowed radiation oncologists to deliver therapy more precisely to mobile tumors while minimizing the dose to surrounding critical structures. This article summarizes the implications of these advances for the patient with unresectable locally advanced NSCLC and highlights ongoing work to improve clinical outcomes in this disease.
Background

Approximately 50,000 patients are diagnosed annually in the U.S. with stage III non-small cell lung cancer (NSCLC). These patients have locally advanced disease, i.e. not surgically resectable on the basis of extent of primary disease or regional nodal involvement. Specifically their cancer has spread to lymph nodes in the mediastinum either on the same side of the tumor (N2) or on the contralateral side (N3) or they have local invasion of vital structures such as the trachea, esophagus that cannot be resected (T4 tumors). In general, N2 disease would place a patient into at least stage IIIA disease whereas N3 disease would render them IIIB. Even with aggressive therapy, these patients have an extremely poor long-term survival, on the order of 15-40%.

A. Current Standard of Care for Locally Advanced NSCLC

In the 1980’s, the standard of care for inoperable locally advanced NSCLC was radiotherapy (RT) alone; however, this changed in the early 1990s with the publication of a phase III trial performed by the Cancer and Leukemia Group B (CALGB) group.(1) This trial randomized patients with unresectable Stage III and medically inoperable stage II NSCLC to RT alone versus induction chemotherapy followed by conventional RT and showed an improvement in median survival from 9.6 months to 13.7 months. This result was duplicated in a separate phase III trial run by the Radiation Therapy and Oncology Group (RTOG) that clearly established combined modality as the standard of care in the management of locally advanced inoperable NSCLC.(2)

The trials above utilized sequential chemotherapy followed by radiotherapy; however, the idea of combining the two concurrently to take advantage of potential additive or synergistic chemosensitization has also been explored. In fact, two phase III randomized trials, one conducted by the West Japanese Lung Cancer Group(3) and another by RTOG have shown an advantage to giving chemotherapy concurrently with radiation versus the sequential approach, both showing an improvement in median survival from ~14 months to ~17 months.(4) This improvement in survival with the addition of concurrent chemotherapy does come with at a cost of increased esophageal toxicity.

In the past decade, an important technological improvement in the care of lung cancer patients has been the introduction of \(^{18}\text{F}-\text{FDG PET-CT}\) as a standard component of the staging workup in patients with lung cancer. \(^{18}\text{F}-\text{FDG PET-CT}\) can often identify patients with occult mediastinal nodal or distant metastatic disease that would otherwise go undetected on CT scans or bone scans alone.(5, 6) One study analyzed findings in 73 patients who had pathologically confirmed nodal disease identified on either CT or \(^{18}\text{F}-\text{FDG-PET}\) and determined that the PET CT scan improved the accuracy of identifying pathologically positive lymph node stations to 89% from 75% with CT alone.(7)
B. Opportunity for improving results

In spite of improvement with combined modality therapy, both local control and survival still remain poor in locally advanced NSCLC. Le Chevalier found that the 1-year local control rate was only 15% for patients with unresectable NSCLC who received 65 Gy of radiation and chemotherapy.(8) Improving local control may lead to increased survival. The Continuous Hyperfractionated Accelerated Radiotherapy (CHART) regimen without chemotherapy has been shown to improve both local control and survival when compared with standard dose radiotherapy.(9, 10) In an EORTC study for locally advanced NSCLC, the 2-year local control improved from 19% to 31% with the addition of concurrent daily cisplatin to radiation, and the 2-year overall survival increased from 13% to 26.(11) Therefore, improvement in local control represents a principal goal in designing new strategies to treat NSCLC.

On the Horizon

A. Exploiting tumor biology

Numerous signaling pathways are dysregulated in NSCLC (Figure 1). K-ras is mutated in 20-30% of NSCLC, the HER2/Erb-B2 receptor is overexpressed in up to 25% of cases, and the epidermal growth factor receptor (EGFR) is overexpressed in the majority of cases.(12) Nanjundan et al. performed a proteomic screen and found that markers of the PI3K/Akt and p38 MAPK pathway signaling pathways (e.g. p70S6K, S6, p38, phospho p38) as well as caveolin-1 and β-catenin were differentially expressed in lung cancer specimens compared with normal lung tissue.(13) 4-6% of NSCLC contain a chromosomal abnormality that produces a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene.(14) Patients with these mutations may respond to an oral ALK inhibitor since their cancers may be driven by the EML4-ALK fusion protein.(15) Other driver mutations found in NSCLC include those in BRAF, PIK3CA, AKT1, MAP2K1, and MET.(16) Agents have been developed for NSCLC that target the insulin-like growth factor receptor (IGF-1R), histone deacetylation acetyltransferase (HDAC), and the hedgehog (Hh) signaling pathway.(17) In this section we will focus specifically on those approaches that have been tried to improve the radiation response, namely hypoxia modifiers, anti-angiogenic agents, EGFR inhibitors, IGF-1 inhibitors, and PI3K/Akt inhibitors.

a. Hypoxia in NSCLC

Hypoxia, which exists in a variety of solid tumor types including lung, head and neck cancer, breast cancer and cancer of the cervix, may mediate tumor progression by activating genes involved in angiogenesis and metastasis.(18-23) Compared to well-oxygenated cells, severely hypoxic tumor cells require 2-3 fold the dose of radiation to achieve the same level of sterilization. (24, 25) This is likely due to the fact
that most of the DNA damage induced by radiation is indirect, mediated by the generation of free radicals, which cannot occur in the absence of oxygen. Hypoxia also upregulates the expression of hypoxia-inducible factor-1 (HIF-1), a master transcription factor, and vascular endothelial growth factor (VEGF), a potent mediator of angiogenesis. Both VEGF and HIF-1 are potential targets for increasing the radiation response in NSCLC. Zeng et al. showed that when combined with radiation, the HIF-1 inhibitor TS-1 retarded tumor regrowth of H441 NSCLC xenografts. In pre-clinical models adding anti-VEGF therapy improves the therapeutic response to radiation. The compounds YC-1 and PX-478 target HIF-1 and can increase tumor radioresponsiveness. Williams et al. showed that the combination of radiation and cediranib (RECENTIN, AZD2171), a highly potent inhibitor of VEGF receptors, cooperatively increased growth delay of Calu-6 NSCLC xenografts when given with radiation.

b. Targeting EGFR in NSCLC

The EGFR receptor (erb1/EGFR), a member of the family of receptor tyrosine kinases, is overexpressed in 80% of NSCLC and mutated in a smaller percentage. EGFR activation results in the activation of multiple intracellular signaling pathways including the Ras and PI3K pathways. EGFR inhibitors including the monoclonal antibody cetuximab (Erbitux, Imclone, New York, NY) and the small molecule tyrosine kinase inhibitors gefitinib (Iressa, AstraZeneca, London, England) and erlotinib (Tarceva, OSI Pharmaceuticals, Melville, NY) have been used in the clinic. In preclinical models, EGFR inhibition can increase radiosensitivity in NSCLC cell lines as reviewed previously. In mice bearing EGFR-expressing, NSCLC xenografts, cetuximab and radiation markedly improved tumor growth inhibition over either agent alone. Similarly, Harari’s group showed that erlotinib and radiation act synergistically to inhibit tumor regrowth of H226 NSCLC xenografts.

c. Targeting the IGF-1 pathway in lung cancer

The IGF axis, which consists of the IGF-1 receptor (IGF-1R), a range of stimulatory ligands (insulin, IGF-1, and IGF-2), and various IGF-binding proteins, has been implicated in the development and maintenance of many cancers including NSCLC. Agents that inhibit this pathway including monoclonal antibodies are available for clinical use. Targeted disruption of the insulin-like growth factor 1 receptor (IGF-1R) has been shown to enhance the in vitro radiosensitivity of some lung cancer cell lines. Therefore, there is some potential for using anti-IGF agents in combination with radiation therapy for patients with NSCLC.
d. Targeting the PI3K pathway in lung cancer

Approximately 50-83% of NSCLC tumors exhibit activation of the PI3K pathway, which plays a key role in controlling cell proliferation, growth and survival. (36, 37) Activation of this pathway has further been associated with radioresistance in many cell types.(38) Gupta et al. showed that three NSCLC cell lines with high P-Akt levels were radiosensitized in vitro using the inhibitor LY294002.(36) A dual PI3K/mTOR inhibitor developed by Novartis, NVP BEZ-235, has been shown to sensitize xenografts of K-ras mutated NSCLC tumors to radiation.(39) This agent is currently being tested in the clinic, but not in combination with radiation.

Our group and others have demonstrated that the HIV protease inhibitor nelfinavir (Viracept, Agouron Pharmaceuticals, La Jolla, CA) can interfere with PI3K-Akt signaling and radiosensitize a variety of tumor types including NSCLC.(40-42)We are currently testing nelfinavir in a phase I/II trial with concurrent chemoradiotherapy for locally advanced NSCLC. The final results are still pending but the initial clinical response data are promising.(43)

e. The impact of the tumor microenvironment and relevance for imaging

Despite elucidation of the intracellular mechanisms regulating radiation resistance, clinical trials targeted at radiosensitization through inhibition of components of these pathways have yielded disappointing results.(44) One possible explanation for these poor outcomes is the inability to deliver adequate drug to the tumor bed due to an extrinsic mechanism of tumor radiation resistance. One postulated mechanism of extrinsic radiation resistance in NSCLC is that abnormal tumor vasculature and increased interstitial fluid pressures lead to impairment of tumor perfusion resulting in inadequate drug and oxygen delivery.(45) Theoretically, targeted anti-angiogenic therapy aimed at vascular normalization through pruning of immature and abnormal blood vessels could abrogate this mechanism of extrinsic radiation resistance through increased oxygen and drug delivery to the tumor.(45) Indeed, it has been demonstrated in preclinical models that inhibition of vascular endothelial growth factor (VEGF) signaling results in pruning of immature tumor vasculature and reduction of interstitial hypertension thereby improving tumor hemodynamics and oxygenation in animal models.(46-48) An added benefit to vascular normalization would be to enhance the delivery of chemotherapy to the tumor bed. Although provocative, this theory has not yet been confirmed in patients and it is unclear what impact vascular normalization has on sensitivity to chemoradiotherapy in NSCLC. The hemodynamic characteristics of tumor microvasculature can be noninvasively assessed by dynamic contrast enhanced imaging. DCE-CT has been shown to be a useful method for monitoring lung tumor
vascularity,(49-52) confirming the general value of tumor vascular assessment in this population.

B. Advances in concurrent chemoradiotherapy for locally advanced NSCLC

a. Functional Imaging
The ability of radiotherapy to locally control cancer is also dependent upon how well the tumor can be delineated. $^{18}$F-FDG-PET scanning has helped greatly in this regard; however, other novel tracers are also being developed. $^{18}$F-3-deoxy-3fluorothymidine (FLT), a marker that images cellular proliferation, shows promise. One study of 34 patients with NSCLC reported that $^{18}$F-FLT-PET showed better specificity, positive predictive value and accuracy for N staging on a per-patient basis than did $^{18}$F-FDG-PET.(53) However, $^{18}$F-FDG-PET was found to have higher sensitivity for identification of the primary tumor than $^{18}$F-FLT-PET.

As discussed above, tumor hypoxia is believed to be a significant contributor to radiation resistance. Hence, there is a great deal of interest in imaging tumor hypoxia. $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO), a radioactively labeled version of a well-studied nitroimidazole, was one of the initial tracers to be developed for this purpose. However, the results NSCLC have been mixed using this isotope.(54) A recent study reported poor correlation between $^{18}$F-FMISO uptake, $^{18}$F-FDG uptake, and tumor markers of hypoxia and angiogenesis.(55) However, other markers of hypoxia have been developed that could have broader applicability in NSCLC. The 2-nitroimidazole $^{18}$F-EF5 has also been used to image glioblastomas, but its use in NSCLC remains to be evaluated.(56)

Although biological imaging has proven valuable in staging and improving the accuracy of tumor identification for target delineation, its role in assessing response to therapy still remains largely unexplored. In a recent pilot study from the University of Michigan, Kong et al. found that $^{18}$F-FDG uptake during radiotherapy in NSCLC correlated with post-treatment scans, suggesting that tumor metabolic response during therapy may serve as an early predictor of outcome.(57) While intriguing, these results must be validated in larger studies in order to firmly establish the utility of $^{18}$F-FDG-PET scanning as a predictive imaging biomarker for response to radiotherapy.

b. Proton beam therapy
Particle beams, such as protons and heavy ions, due to their physical properties offer improved dose distributions when compared with photon beam radiation. Chang and co-workers reported that proton beam radiotherapy significantly reduced dose to critical normal structures including the esophagus, spinal cord, and heart, even with dose escalation, when compared with photon therapy for patients with early
stage lung cancers.(58) For locally advanced NSCLC in which the mediastinum is generally treated, the critical normal structures include the spinal cord, heart, esophagus, and normal lungs. In order to meet dose constraints for the spinal cord the radiation oncologist must use oblique beams that avoid this structure, which results in radiation dose being spread to the surrounding normal lungs. There are no prospective data to date comparing proton beam radiotherapy to photons. However, a recently completed retrospective comparative analysis of 678 NSCLC patients (primarily stage III) treated at M.D. Anderson with proton beam radiotherapy to IMRT photon or 3D-conformal radiotherapy revealed a significant decrease in esophageal toxicity with proton beam radiotherapy.(59) A prospective phase III randomized trial of IMRT photon (74Gy) vs proton beam radiotherapy (74CGE) with concurrent chemotherapy for patients with unresectable locally advanced NSCLC is currently underway. The results of this trial are eagerly anticipated.

**c. Accounting for Tumor Motion: IGRT and 4D-CT based treatment planning**

In NSCLC, the radiation oncologist is faced with the challenge of delivering radiation dose to a moving target embedded within an exquisitely radiosensitive poorly functioning vital organ. Respiratory motion can result in significant intrafraction variability in the location of the gross tumor volume (GTV).(60, 61) Stevens et al. found that lung tumors move 5-10 mm during quiet breathing and often as much as 4.5 cm and that movement cannot be predicted based on tumor size, location, or pulmonary function. (62) One approach to account for this is to create a treatment margin around the GTV that accounts for the entirety of tumor excursion through the respiratory cycle. Modern multislice spiral computed tomography scanners permit a fourth dimension, time, to be added to a 3D CT scan, which can image the tumor throughout the respiratory cycle. This allows the radiation oncologist to expand the treatment margin appropriately. (63) However, this is achieved at a cost of increased toxicity to normal lung tissue due to the larger treatment volume.

Several methods have been used to reduce intrafraction variability during normal breathing. First, radiation can be synchronized to be delivered at specific points during the patient’s respiratory cycle. The linear accelerator is turned on and off accordingly while the patient breathes freely. An initial study by Mageras et al. found that tumor motion (as defined by average diaphragmatic excursion) was reduced from 1.4 cm to 0.3 cm with this technique, more commonly known as respiratory gating. (64)

While the respiratory gating technique permits the patient to breathe freely, Active Breathing Control (ABC) relies on the patient’s voluntary control of breathing via the use of an occlusive valve. This was originally described by Wong et al. and has been utilized in NSCLC. (65) Wilson et al. found that with ABC the tumor location showed no significant variation
in tumor location over several weeks and the volume of normal lung irradiated was reduced by a median of 6.4% and the median spinal cord dose was reduced by a median of 6.4% in 80% of the patients. (66) A variation on the ABC technique is the deep inspiration breath hold (DIBH) technique. Patients are simulated at deep inspiration and then treated as such with port films for verification. Hanley et al found an intra breath-hold reproducibility of 1.0 (+/- 0.9) mm and inter breath-hold reproducibility of 2.5 (+/- 1.6) mm as determined from diaphragm position. They found that the volume of normal lung irradiated could be reduced on average by 30% with DIBH versus 18% with respiratory gating. (67)

With the advent of techniques such as respiratory gating that allow the radiation oncologist to shrink the treatment volume, there is a critical need for accurate tumor localization on the treatment machine. Image-guided RT (IGRT) utilizing cone beam CT (CBCT) technology now permits imaging and re-alignment of the patient at every treatment to help reduce interfraction variability. Hugo et al. found that a larger margin is required with gating or breath-hold when CBCT-based IGRT is not used than when it is (9-10 mm vs. 2-3 mm). (68)

The 4D and IGRT techniques can be combined into 4D online adaptive RT (ART) technique where inter-and intrafraction variability is accounted for either on a daily basis or after a given number of fractions. (7) Harsolia et al. performed a comparative study examining 3D-conformal, 4D-union, 4D-offline adaptive with a single correction (offline ART), and 4D-online adaptive with daily correction (online ART) and found that 4D ART with daily correction was optimal. This approach yielded a decrease in treatment volumes (44% reduction) and a decrease in volume of normal lung irradiated (31% reduction) and reduction of mean lung dose (31% reduction). (69) Although more labor intensive, 4D-ART with daily correction may allow radiation oncologists to treat patients with extremely poor baseline lung function who otherwise could not have received definitive therapy for their disease.

d. Summary

The past decade has seen significant advancements in treatment planning, imaging, and delivery of therapeutic radiation in locally advanced NSCLC. The overall goal of these advances being the improvement of local control without an excessive increase in toxicity to the patient. As local control improves, the importance of systemic sterilization of disease is amplified.

C. Concurrent chemotherapy

Given the knowledge that distant relapse represents the most common type of recurrence in patients with locally-advanced NSCLC, the use of more efficacious systemic therapies in this setting should produce better outcomes. However, efforts to improve relapse-free and overall survival in these patients through the incorporation of modern cytotoxic
and/or targeted agents have had minimal impact on clinical practice to date. Strategies have included applying the agent of choice concurrently with radiotherapy or as consolidation therapy after chemoradiation.

Concurrent use of the taxoids paclitaxel and docetaxel, or the vinca alkaloid vinorelbine with radiotherapy proved feasible but showed no gain in efficacy when compared to the historical benchmark results produced in studies of concurrent etoposide and cisplatin (EP), agents that first appeared in the clinic approximately 40 years ago.(70-73) One caveat put forth was the need to use the concurrent agent at full-dose to maximize systemic sterilization, but toxicity has limited the ability to do so with the newer cytotoxics and was prohibitive in the instance of the antimetabolite gemcitabine.(74) Consolidation full-dose docetaxel for three cycles following concurrent EP produced a promising median survival of 26 months in the SWOG 9504 study.(75) However, when this regimen was studied by the Hoosier Oncology Group in a randomized trial vs. concurrent EP alone, the docetaxel-containing arm failed to show an improvement in survival and significantly increased toxicity, including pneumonitis.(76) The West Japan Thoracic Oncology Group recently published their phase III results indicating that full-dose consolidation paclitaxel and carboplatin following low-dose weekly paclitaxel/carboplatin concurrent with radiation produced similar survival with significantly less toxicity than WJTOG standard concurrent regimen of mitomycin/vindesine/cisplatin without consolidation.(77)

The multi-targeted antifolate pemetrexed has proven to be one of the most active agents in nonsquamous NSCLC and shows radiosensitizing properties as would be expected with this drug class.(78, 79) Phase I/II trials reveal that pemetrexed can safely be administered at full-dose in combination with cisplatin and concurrent radiation in Stage III NSCLC.(80) The ongoing Phase III PROCLAIM trial will provide definitive data on concurrent and consolidation pemetrexed/cisplatin vs. standard concurrent EP with consolidation platinum-based doublets in locally advanced nonsquamous patients and may produce a new standard of care if the primary endpoints are met. Enrollment of 600 patients is planned.

Limited data with molecularly targeted agents are available, the majority with EGFR inhibitors. The largest trial, SWOG 0023, was closed early when it was found that the addition of maintenance daily gefitinib following EP/radiation and consolidation docetaxel produced inferior survival when compared to placebo following EP/radiation and docetaxel (23 vs. 35 months, P=.013).(81) Concurrent strategies to take advantage of the radiosensitizing properties of EGFR-interactive agents may be more attractive, and have already become a standard approach in locally-advanced head and neck cancer.(82) Blumenschein et al. reported a median survival of 22.7 months and 50% 2-year survival in RTOG 0324, adding weekly cetuximab to low-dose weekly paclitaxel/carboplatin with radiotherapy followed by consolidation cetuximab/paclitaxel/
carboplatin. Based on these results the current intergroup phase III trial (RTOG 0617) compares this regimen to paclitaxel/carboplatin alone, as well as two doses of radiotherapy, 60 vs 74 Gy. Erlotinib appears to be safe when given daily at full dose alone or in combination with chemotherapy concurrent with full-dose thoracic radiation however efficacy data are lacking at present. Given the rapidly expanding knowledge of molecular predictors of response to these agents in the metastatic disease setting it can be expected that these markers will eventually prove useful in selecting stage III patients for the optimal use of EGFR-targeted therapies with radiation.

Multiple trials of bevacizumab given concurrently and as maintenance with chemoradiation in small cell lung cancer and NSCLC were halted early due to enhanced toxicity, chiefly in the form of tracheoesophageal fistula formation, leaving the future of this strategy in doubt. The Eastern Cooperative Oncology Group recently launched a novel trial of maintenance bevacizumab plus the MUC1 vaccine L-BLP25 following chemoradiation with weekly paclitaxel/carboplatin and two cycles of consolidation paclitaxel/carboplatin.

Conclusion

The past decade has seen significant advances in our understanding of the biology of NSCLC and its role in tumor resistance to radiation. Additionally, we have significantly improved our ability to deliver radiation to the tumor while sparing surrounding vital structures. It is through coupling of these advances with targeted approaches that clinical outcomes will improve in this disease.
Numerous signaling pathways are dysregulated in human cancers, including NSCLC. K-ras is mutated in 20-30% of NSCLC. The epidermal growth factor receptor (EGFR) is overexpressed in the majority of NSCLC and mutated in a smaller subset. Other tyrosine kinase receptors that are overexpressed in NSCLC, although to a lesser extent, are the insulin-like growth factor-1 receptor (IGF1-R) and HER2/Erb-B2. Overexpression of these receptor kinases leads to activation of multiple downstream signaling pathways including the Erk1/2 MAP kinase pathway, the p38 MAP kinase pathway, and the PI3K/Akt/mTOR pathway. Inhibitors are available that target various molecules in these pathways. Several EGFR inhibitors, including erlotinib, gefitinib, and cetuximab, and PI3K inhibitors including the Novartis compound NVP-BEZ235, which also inhibits mTOR, have been used to radiosensitize NSCLC cells. The HIV protease inhibitor nelfinavir, which inhibits Akt phosphorylation, also radiosensitizes cells.
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