Curr. Treat. Options in Oncol. (2015) 16: 47
DOI 10.1007/s11864-015-0364-2

Lung Cancer (HA Wakelee, Section Editor)

Locally Advanced Non-Small Cell Lung Cancer: Optimal Chemotherapeutic Agents and Duration

Hirva Mamdani, MD[1]
Shadia I. Jalal, MD[2]
Nasser Hanna, MD[3,*]

Address
[1]Hematology/Oncology, Indiana University Melvin and Bren Simon Cancer Center, 535, Barnhill Dr, Ste 418, Indianapolis, IN 46202, USA
[2]Division of Hematology/Oncology, Indiana University Melvin and Bren Simon Cancer Center, 980, W Walnut St, Indianapolis, IN 46202, USA
[*,3]Division of Hematology/Oncology, Indiana University Melvin and Bren Simon Cancer Center, 535, Barnhill Dr, Ste 473, Indianapolis, IN 46202, USA
Email: nhanna@iu.edu

Published online: 2 August 2015

This article is part of the Topical Collection on *Lung Cancer*

Keywords Non-small cell lung cancer · Locally advanced NSCLC · Stage III NSCLC · Unresectable NSCLC · Chemotherapy in NSCLC · Chemoradiation in NSCLC · Novel agents in NSCLC

Opinion statement

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in the USA. The treatment of locally advanced NSCLC (LA-NSCLC) is challenging and must be individualized. For patients with completely resected stage III NSCLC, adjuvant cisplatin-based chemotherapy for 4 cycles is recommended. For patients with inoperable or unresectable stage III NSCLC, chemoradiation is the preferred treatment. Patients with a good performance status, minimal or no weight loss, and adequate pulmonary function should be offered concurrent chemoradiation. The optimal chemotherapeutic agents to be used concurrently with radiation remain undefined. In the USA, cisplatin plus etoposide or carboplatin plus paclitaxel are the most commonly used regimens. In addition, the optimal duration of therapy remains undefined, including the role of consolidation chemotherapy. Thus far, randomized phase III trials have failed to identify a survival advantage for administering chemotherapy beyond that delivered during radiation therapy. Molecularly targeted agents, angiogenesis inhibitors, and immunotherapy have a defined role for patients with metastatic disease. The role, if any, of these new classes of agents is undergoing investigation for patients with earlier stage disease, including stage III disease.

Introduction

Locally advanced NSCLC (LA-NSCLC) comprises a heterogeneous group of clinical presentations. With its complex clinical and genetic landscape, the optimal treatment for all patients with LA-NSCLC remains undefined. Nevertheless, certain standards of care are well accepted. Since 1990, it has been known that the addition of chemotherapy to radiotherapy improves survival in this patient population [1]. Many other trials have provided evidence to strengthen this notion [2, 3]. Furthermore, concurrent chemoradiation has been shown to be superior to sequential chemoradiation in randomized controlled trials and a meta-analysis [4–6] and is the standard of care in patients who can tolerate such therapy (Table 1). The most commonly used chemotherapy regimens in combination with radiation are cisplatin plus etoposide or carboplatin plus paclitaxel. However, the choice of chemotherapeutic agents and optimal duration of treatment remain controversial. This article will review the evidence guiding these decisions.

Choice of Chemotherapeutic Agents

Several studies have attempted to address the optimum choice of chemotherapeutic agents in LA-NSCLC. An early indication that chemotherapy had a role in the treatment of LA-NSCLC utilized a regimen consisting of cisplatin plus vinblastine [1]. Subsequently, various other agents including etoposide (E), vinorelbine, mitomycin (M), vindesine (V), irinotecan, paclitaxel, docetaxel (D), and pemetrexed have each been studied [4–12•]. However, relatively few trials have conducted head-to-head comparisons of these agents.

A multi-arm phase II trial from the Cancer and Leukemia Group B (CALGB) by Vokes et al. comparing induction chemotherapy with cisplatin in combination with gemcitabine, paclitaxel, or vinorelbine followed by concurrent chemoradiation with the same agents reported comparable survival outcomes [7]. However, the use of gemcitabine with thoracic radiation can lead to significant toxicity and is no longer utilized. A phase III study by Yamamoto et al. comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small cell lung cancer (NSCLC) reported no significant difference in overall survival (OS) among different treatment arms [8]. In this study, patients were randomized to receive either mitomycin plus vindesine plus cisplatin (MVP), irinotecan plus carboplatin, or carboplatin plus paclitaxel, in combination with thoracic radiotherapy. The median survival time and 5-year OS rates were not statistically different among treatment arms. Moreover, the toxicity including grade 3 or 4 neutropenia, febrile neutropenia, and gastrointestinal side effects were significantly higher in the MVP arm ($p<0.001$). Another study by Segawa et al. comparing concurrent thoracic radiotherapy with either docetaxel plus cisplatin (DP) or MVP reported better 2-year OS with DP ($p=0.059$), although the rate of grade 3 or 4 radiation esophagitis was higher in docetaxel arm. There was also a trend toward improved response rate and progression free survival (PFS) in the docetaxel arm [9].

Table 1. Clinical trials involving sequential and concurrent chemoradiation therapy in locally advanced NSCLC

Trial	Design	Comment
CALGB 8433 (1)	XRT vs. chemotherapy → XRT	Established the role of chemotherapy followed by radiation in stage III NSCLC
RTOG 8808/ECOG 4588 (2)	XRT vs. chemotherapy → XRT vs chemotherapy → hyperfractionated XRT	Further evidence of superiority of sequential chemoradiotherapy compared to XRT alone. No additional benefit of hyperfractionated XRT
Meta-analysis (3)	XRT vs. chemotherapy → XRT	Further evidence to support sequential chemoradiotherapy
WJLCG (5)	Concurrent ChemoXRT vs. sequential ChemoXRT	Concurrent chemoradiotherapy may be superior to sequential therapy, but with greater toxicity
RTOG 9410 (4)	Concurrent ChemoXRT vs. sequential ChemoXRT	Confirmed the superiority of concurrent chemoradiation over sequential therapy

CALGB Cancer and Leukemia Group B, *RTOG* Radiation Therapy Oncology Group, *WJLCG* West Japan Lung Cancer Group, *XRT* radiotherapy

No single standard chemotherapy regimen has been established for the treatment of stage III NSCLC. In the USA, cisplatin plus etoposide and carboplatin plus paclitaxel are the most commonly used regimens. While no head-to-head trials have been reported, a retrospective analysis of Veterans Health Administration data compared outcomes of 1842 patients treated with etoposide plus cisplatin (EP) or carboplatin plus paclitaxel (CP) with concurrent radiotherapy in stage III NSCLC between 2001 and 2010 [13]. This non-randomized data indicated that OS was comparable between the 2 regimens (p=0.42); but EP was associated with higher toxicity. Although patients receiving EP were younger and appeared more fit, they had more hospitalizations, gastrointestinal side effects, infectious complications, and acute kidney injury. While this study suggests these regimens may be comparable, this analysis has several limitations. Namely, this is a retrospective analysis and comparisons between these patient populations may be biased. Secondly, the patients receiving CP were more likely than those who received EP to receive consolidation chemotherapy. Although previous studies have not demonstrated a benefit from consolidation chemotherapy, the lower cumulative dose of chemotherapy in the EP arm might have obscured an advantage for EP. Thirdly, the toxicity data recorded hospitalizations only within the VA Health system and therefore hospitalizations or ED visits outside of VA systems were not included in the toxicity analysis. Finally, VA data set represents a defined patient population that may not be representative of a general patient population, including women. Despite these limitations, this is the largest retrospective analysis comparing outcomes of these two commonly used regimens. The data suggest that any difference in survival outcomes between the two regimens is likely to be small or non-existent. National Comprehensive Cancer Network (NCCN) guidelines currently recommend either regimen.

Newer Chemotherapeutic Agents

Treatment of patients with metastatic NSCLC is based upon histology. For example, pemetrexed and bevacizumab are utilized for patients with non-squamous histology only [14, 15]. Drug choice based upon histology, however, has not been integrated in the treatment of patients with stage III NSCLC undergoing chemoradiation. The two newest chemotherapeutic agents in NSCLC are pemetrexed and nab-paclitaxel. Each has been tested in patients with stage III disease.

A phase III trial (PROCLAIM) compared cisplatin plus pemetrexed with concurrent radiotherapy followed by consolidation pemetrexed versus cisplatin plus etoposide with concurrent radiotherapy followed by consolidation with cytotoxic chemotherapy of choice in stage III non-squamous NSCLC. No statistically significant difference was noted between the two arms in terms of OS, median PFS, and ORR [16, 17]. The cost of pemetrexed-containing regimen is much higher than cisplatin/etoposide combination and might preclude the routine use of pemetrexed in stage III adenocarcinoma of the lung.

Nanoparticle albumin-bound paclitaxel (nab-P) in combination with carboplatin is currently approved in the first line setting of patients with metastatic NSCLC [18]. A recently conducted phase I trial of this combination administered bi-weekly with concurrent thoracic radiation followed by 2 cycles of full dose nab-P and carboplatin reported acceptable safety profile with most common DLTs being pneumonitis, leukopenia, and treatment delays [19]. It has been suggested that this regimen may be more active in patients with squamous cell histology due to higher overall response rates reported. A clinical trial evaluating the safety and efficacy of nab-P as maintenance treatment after nab-P plus carboplatin in stage IIIB/IV squamous cell NSCLC is ongoing (NCT02027428).

At the present time, histology does not play a role in selecting chemotherapeutic agents when given concurrently with radiation in stage III NSCLC. The negative results of the PROCLAIM trial suggests against histology playing a major role. Given the prospects of incorporating new targeted agents and immunotherapy in the stage III setting, it is unlikely a randomized trial will be completed to answer this question.

Duration of Chemotherapy

The optimal duration of chemotherapy in stage III NSCLC also remains unsettled. NCCN guidelines list thoracic radiation concurrently with either cisplatin plus etoposide or cisplatin plus vinblastine for 2 cycles as the preferred regimen [4, 20]. In addition, for non-squamous histology, carboplatin plus pemetrexed for 4 cycles or cisplatin plus pemetrexed for 3 cycles concurrently with radiotherapy can also be used [10, 16]. Despite several negative phase III trials evaluating the role of consolidation chemotherapy, the use of consolidation chemotherapy continues to be a part of the NCCN guidelines in the form of carboplatin plus paclitaxel concurrently with radiation followed by 2 cycles of

weekly carboplatin and paclitaxel [21]. Similarly, cisplatin plus etoposide concurrently with radiation followed by consolidation with 2 cycles of cisplatin plus etoposide is also suggested.

One compelling argument for using consolidation chemotherapy is the variation between the number of cycles recommended for patients in the adjuvant, stage III, and metastatic settings. Four cycles of adjuvant chemotherapy is recommend for stage I–III resectable disease [22, 23]. Up to 3 cycles of chemotherapy is commonly utilized in clinical trials testing the role of neoadjuvant therapy [24–26]. In the metastatic setting, maintenance therapy has become a standard in non-squamous NSCLC [27]. Therefore, utilizing only 2 cycles of EP with radiation or radiosensitizing weekly carboplatin and paclitaxel alone with radiation seems counterintuitive when treating patients with stage III disease. Despite this disconnect, randomized trials have failed to show a survival benefit for utilizing any chemotherapy beyond that given concurrently with radiation [11••, 21, 28, 29•, 30••, 31]. The proof that 2 cycles of therapy is sufficient to improve cure rates in the stage III setting comes from the landmark trials establishing the role of chemotherapy [1, 4].

Many attempts have been made to demonstrate improved outcomes with additional chemotherapy prior to (induction) concurrent chemoradiation or following (consolidation) concurrent chemoradiation. In 2005, a randomized phase II Locally Advanced Multimodality Protocol (LAMP) trial compared concurrent chemoradiation with either induction chemotherapy or consolidation chemotherapy, with sequential chemoradiotherapy. The median OS favored the consolidation arm [21]. However, an arm of concurrent chemoradiation alone was not included in this trial design. Subsequent studies utilized concurrent chemoradiation alone as a control arm. This includes a phase III study from the Hoosier Oncology Group that evaluated the role of consolidation docetaxel following concurrent EP and radiation [28]. No differences in median survival times or 3-year survival were noted between the D and O arms. Moreover, there was a higher incidence of grade 3 or 4 toxicities including pneumonia and febrile neutropenia in patients receiving docetaxel. More recently, in the GILT CT-RT trial, patients received concurrent chemoradiation with cisplatin and oral vinorelbine followed by randomization to either consolidation with cisplatin plus vinorelbine or best supportive care [29•]. No statistically significant difference was found in PFS or OS between the two arms.

As stated previously, a commonly used regimen in the USA remains weekly carboplatin plus paclitaxel with concurrent radiation. Since the weekly delivery of these agents are considered radiosensitizing, it is logical to consider the use of full doses of consolidation carboplatin and paclitaxel to treat micro-metastatic disease. Prior phase III studies testing consolidation chemotherapy did not utilize this carboplatin plus paclitaxel backbone and therefore, the role of consolidation chemotherapy following this regimen remains an open debate. At the 2014 ASCO meeting, Park et al. reported results of their phase III trial evaluating the role of consolidation chemotherapy with cisplatin plus docetaxel [11]. It is logical that weekly cisplatin and docetaxel would have similar activity to weekly carboplatin and paclitaxel, although no direct comparisons in the stage III setting have been conducted. In this phase III trial, the patients were randomized to receive either concurrent chemoradiotherapy with weekly cisplatin plus docetaxel or concurrent chemoradiotherapy followed by consolidation chemotherapy with 3 cycles of cisplatin plus docetaxel (each administered on day 1 and 8 every 3 weeks). In this study, one third (33 %) of the patients never received consolidation and among those receiving consolidation, only 67 % received all 3 planned cycles. In this study, the randomization was performed at the beginning of the treatment rather than after completion of chemoradiation, which may have led to inclusion of those patients in the consolidation arm who may have done poorly with concurrent chemoradiation and thereby were not able to receive further consolidation chemotherapy. Nevertheless, in this intention to treat analysis, the PFS and OS were not statistically different and patients receiving consolidation therapy experienced more toxicities. A pooled analysis of the literature including 41 phase II or III trials evaluating the role of consolidation (either continuation consolidation using the same drug as given during concurrent radiation or switched consolidation using different drugs) chemotherapy reported no improvement in OS with either consolidation approach (adjusted HR=0.95, 95 % CI 0.75–1.21, p=0.515) [30••].

In summary, there is no evidence to support the use of additional chemotherapy beyond what is administered during concurrent chemoradiation. Furthermore, consolidation therapy is associated with more toxicities including treatment-related hospitalizations, neutropenic fever, and pneumonitis (Table 2). However, consolidation therapy with weekly carboplatin plus paclitaxel following concurrent chemoradiation

Table 2. Clinical trials evaluating consolidation and induction chemotherapy in locally advanced NSCLC

Trial	Design	Comment	Toxicity
LAMP (21)	Chemo → XRT vs. Chemo → ChemoXRT vs. ChemoXRT → Chemo	OS favored consolidation arm	Grade 3/4 neutropenia in induction arm, grade 3/4 esophagitis with concurrent ChemoXRT, more in consolidation arm
CALGB39801 (31)	Chemo → ChemoXRT vs. ChemoXRT	Induction chemotherapy prior to concurrent ChemoXRT does not prolong survival compared to concurrent chemoradiation alone	Grade 3/4 neutropenia in induction arm. Rate of esophagitis not different between the two groups.
HOG/USO (28)	ChemoXRT vs. ChemoXRT → Chemo	Consolidation therapy with docetaxel does not improve survival compared to concurrent chemoradiation alone	Grade 3 to 5 febrile neutropenia and pneumonitis, approximately 30 % patients hospitalized and 5.5 % died in docetaxel arm
GILT CT-RT (29)	ChemoXRT vs ChemoXRT → Chemo	Consolidation therapy with cisplatin plus vinorelbine does not improve survival compared to concurrent chemoradiation alone	Grade 3/4 anemia and neutropenia greater in consolidation arm.
South Korea (11)	ChemoXRT vs. ChemoXRT → Chemo	Consolidation cisplatin plus docetaxel does not improve survival when added to weekly platinum/taxane/XRT	Only two thirds of the patients received consolidation and among them only two thirds received all planned 3 cycles
Meta-analysis (30)	ChemoXRT vs. ChemoXRT → Chemo	Consolidation (continuation or switch) consolidation does not improve survival when added to concurrent chemoradiation	No differences between the two groups with regard to grade 3–5 toxicities in pneumonitis, esophagitis, and neutropenia
SWOG (37)	ChemoXRT → Chemo vs. ChemoXRT → Chemo → gefitinib	Addition of gefitinib as consolidation in an unselected patient population is potentially harmful	Median survival lower in gefitinib arm, toxic death rate 2 %
RTOG 0617 (12)	ChemoXRT vs. ChemoXRT → cetuximab	Addition of cetuximab to concurrent ChemoXRT does not improve survival compared to concurrent ChemoXRT alone	The use of cetuximab was associated with a higher rate of grade 3 or worse toxic effects, more treatment-related deaths in the high-dose chemoradiotherapy and cetuximab groups

CALGB Cancer and Leukemia Group B, *RTOG* Radiation Therapy Oncology Group, *XRT* radiotherapy, *HOG* Hoosier Oncology Group, *USO* US Oncology

using these agents continues to be suggested as a part of NCCN guidelines.

Role of Novel Agents

Antiangiogenic Agents

While the role of angiogenesis inhibitors in the treatment of patients with metastatic NSCLC is defined, several attempts at demonstrating a role of these agents in the treatment of stage III NSCLC have been unsuccessful, and in some cases, harmful [14, 32•]. A pilot study of EP plus radiotherapy followed by consolidation docetaxel plus bevacizumab in patients with LA-NSCLC indicated that bevacizumab was associated with fatal hemoptysis in a high-risk group of patients leading to early closure of this trial [33•]. Another phase II study was closed early because of high incidence of tracheoesophageal fistula with its associated morbidity

and mortality with use of bevacizumab in combination with chemoradiation [34]. Another antiangiogenic agent AE-941 failed to show any survival advantage in combination with chemoradiation in LA-NSCLC in a randomized phase III trial [35]. More recently, the ECOG 3598 study showed increased toxicities but no survival benefit of thalidomide in combination of chemoradiation in stage III NSCLC [36•].

Role of Molecularly Targeted Therapies

The role of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in metastatic NSCLC harboring activating EGFR mutations is well established. However, the results of initial studies incorporating molecularly targeted agents in the treatment of locally advanced NSCLC have been disappointing. In a phase III study from the Southwest Oncology Group (SWOG), Kelly et al. treated patients with stage III NSCLC (irrespective of EGFFR status) with EP plus thoracic radiation followed by docetaxel consolidation [37]. The patients without progressive disease were then randomized to receive either gefitinib or placebo. OS favored placebo in this unselected patient population. More recently, in a phase III from the Radiation Therapy Oncology Group (RTOG), Bradley et al. randomized patients with stage III NSCLC, irrespective of EGFR status, to receive chemoradiation (60 versus 74 Gy) followed by consolidation chemotherapy with carboplatin plus paclitaxel with or without cetuximab, a monoclonal antibody to EGFR [12•]. Median OS was better for patients receiving 60 Gy radiation. The addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no additional benefit in overall survival for these patients. The results of these studies are not surprising as cetuximab has limited activity in NSCLC and significant efficacy of EGFR TKIs is by far limited to patients harboring sensitizing EGFR mutations [38, 39].

Despite the failure of initial studies to show a survival advantage in unselected patient population, further studies are underway to evaluate the role of EGFR and ALK inhibitors in combination with radiation in stage III NSCLC (NCT01822496). These studies are based on preclinical data showing increased sensitivity of tumor cells to these targeted agents after treatment with radiation [40, 41, 42•]. These studies allow patients with EGFR mutations or ALK translocations to receive induction therapy with erlotinib or crizotinib (respectively) prior to initiation of concurrent chemoradiotherapy and compare that to outcomes of patients with the corresponding mutation who are receiving concurrent chemoradiotherapy alone. This induction phase is up to 12 weeks with patients not demonstrating a response at 6 weeks initiating chemotherapy and radiotherapy immediately. The delay in initiation of chemoradiotherapy in patients on the experimental arm can possibly render it difficult to interpret results of these studies if negative as the standard therapy arm initiate treatment on day 1. In addition, this study does not address the combination of targeted agents with radiotherapy alone.

In addition, preclinical studies have shown potential role of RAS oncogene in radiation resistance [43]. Although attempts at targeting the RAS pathway have been unsuccessful, inhibition of the downstream pathway with MEK inhibitors may increase sensitivity to radiation in NSCLC. Incorporation of a MEK inhibitor, trametenib, is currently being evaluated in combination with concurrent chemoradiation in KRAS mutant LA-NSCLC (NCT 01912625).

Role of Immunotherapy

Immunotherapy is a promising emerging modality in cancer therapeutics. Recently, the Program Death Receptor-1 (PD-1) inhibitor, nivolumab, was approved in second line treatment of squamous cell lung cancer after demonstrating a significant survival advantage when compared with docetaxel (ASCO 2015 Annual Meeting, Abstract 8009, Clinical Trial NCT01642004).

Ionizing radiation damages DNA within tumor cells, leading to tumor-cell apoptosis/necrosis. Tumor antigens released from the dying tumor cells can potentially provide antigenic stimulation that induces antitumor-specific immune responses [44, 45••]. Ionizing radiation also induces a local inflammatory response that enhances the infiltration of tumor-specific T cells and simultaneously upregulates the PD-1/PD-L1 pathway in the tumor microenvironment which is a potent inhibitor of immune activation. This upregulation decreases some of the radiation-induced toxicities but at the same time markedly weakens radiation-induced antitumor immunity. Therefore, combination therapy with radiation and PD-L1 blockade could potentially enhance antitumor immune response. Another intriguing phenomenon related to radiation-induced antitumor immunity is the abscopal effect. The abscopal effect refers to the ability of radiation delivered to a local site to minimize or eradicate metastases at distant sites, potentially through antitumor immune response mounted as a result of release of tumor antigens from radiation induced cellular damage [46, 47]. It has been shown in preclinical studies that abscopal effect is potentiated by

PD-1 blockade [48]. Furthermore, a positive correlation has been shown between tumor response and the presence as well as number of tumor infiltrating lymphocytes (TLIs) after chemoradiation in several solid tumors, indicating that enhancement of immune response after radiation contributes to increased tumor response and improved outcomes [49–51].

Based on these preclinical data, a number of immune checkpoint inhibitors in combination with radiotherapy are currently being evaluated in clinical trials. MED14736, an antibody to PDL-1, will be tested in a multinational multicentric phase 3 pharmaceutical trial (PACIFIC Trial, NCT 02125461) involving 702 patients. In this study, patients with unresectable stage III NSCLC will be treated with concurrent chemoradiation with at least 2 cycles of platinum-based chemotherapy. Patients without progressive disease will then be randomized to receive either MED14736 or placebo for up to 1 year. The primary endpoint of this study is overall survival.

Another phase II single-arm study conducted by Hoosier Cancer Research Network is evaluating pembrolizumab (NCT 02343952) as consolidation therapy after concurrent chemoradiation. In this trial, approximately 83 patients with unresectable stage III NSCLC will receive either weekly carboplatin plus paclitaxel or cisplatin plus etoposide with 59.4–66 Gy radiation. Patients with non-progressive disease will then receive pemborlizumab every 3 weeks for up to 1 year. After the initial 10 patients receive this treatment, a safety analysis will be conducted. The primary endpoint of this trial is to assess the time to distant relapse. In addition, a randomized trial with nivolumab after chemoradiation is under development. Of particular importance while combining radiation with immune checkpoint inhibitor is the possibility of increased incidence of pneumonitis and esophagitis in the radiated field because of radiation-induced damage combined with activation of T cells. The optimum duration of immune therapy is unknown but up to 1 year or treatment is being evaluated in these trials.

The role of other agents targeting different immunotherapy antigens has also been evaluated in patients with stage III NSCLC. Tecemotide (L-BLP25), a MUC1 antigen-specific cancer immunotherapy, was evaluated as consolidation therapy after chemoradiation in a phase III randomized trial by Butts et al. [52•] Patients were allowed to receive either concurrent or sequential chemoradiation followed by tecemotide. Although overall survival was not statistically different between the two groups, a subset analysis of patients treated with concurrent chemoradiation showed improved overall survival with tecemotide. Another trial from the Eastern Cooperative Oncology Group, combining tecemotide with bevacizumab after chemoradiation, has recently completed accrual (NCT 00828009).

Conclusion

Multiple factors render the management of locally advanced NSCLC to be challenging. These include patient factors and comorbidities as well as the heterogeneity of both the clinical presentation and disease biology. Therefore, the optimal choice of drug and duration of therapy remain undefined. Several chemotherapeutic agents have been studied in this setting but very few trials have conducted head-to-head comparisons between different regimens. With the discovery of newer therapeutic agents and ongoing trials incorporating these agents into the treatment of LA-NSCLC, it seems improbable that further attempts will be made at defining the best chemotherapy regimen in this setting. Currently available evidence suggests that the difference between currently used chemotherapy regimens is likely to be small, if any. In contrast to metastatic setting, currently tumor histology does not play a role in choice of chemotherapy agents. However, it is logical to limit the use of pemetrexed to non-squamous NSCLC. Available data does not support the use of additional chemotherapy in the form of either induction or consolidation beyond concurrent chemoradiation, although the NCCN guidelines list consolidation

therapy as an option. Despite demonstration of improved outcomes with antiangiogenic agents in metastatic NSCLC, their use in stage III disease has been proven to be harmful. The role of EGFR TKIs, ALK inhibitors, and immune checkpoint inhibitors in the paradigm of treatment of stage III NSCLC remains to be determined. A number of clinical trials evaluating novel targeted agents and immunotherapy in this setting are underway, and the results are eagerly awaited. As the upcoming years promise to bring new discoveries, we remain hopeful that increased cure rates can be achieved for patients with stage III NSCLC.

Compliance with Ethics Guidelines

Conflict of Interest

Hirva Mamdani declares that she has no conflict of interest.
Shadia I. Jalal declares that she has no conflict of interest.
Nasser Hanna has received research support from Merck.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med. 1990;323(14):940–5.
2. Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, et al. Radiation Therapy Oncology Group (RTOG) 88–08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst. 1995;87(3):198–205.
3. Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis. Ann Intern Med. 1996;125(9):723–9.
4. Curran Jr WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103(19):1452–60.
5. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol. 1999;17(9):2692–9.
6. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181–90.
7. Vokes EE, Herndon 2nd JE, Crawford J, Leopold KA, Perry MC, Miller AA, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. J Clin Oncol. 2002;20(20):4191–8.
8. Yamamoto N, Nakagawa K, Nishimura Y, Tsujino K, Satouchi M, Kudo S, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol. 2010;28(23):3739–45.
9. Segawa Y, Kiura K, Takigawa N, Kamei H, Harita S, Hiraki S, et al. Phase III trial comparing docetaxel and

cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. J Clin Oncol. 2010;28(20):3299–306.

10. Govindan R, Bogart J, Stinchcombe T, Wang X, Hodgson L, Kratzke R, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol. 2011;29(23):3120–5.

11.•• Park K, Ahn YC, Ahn JS, Ahn M-J, Kim J-H, Cho EK, et al. A multinational phase III randomized trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small cell lung cancer (CCheIN). ASCO Meeting Abstracts. 2014;32(15):7500.

A phase III trial evaluating the role of consolidation chemotherapy with cisplatin plus docetaxel after concurrent chemoradiotherapy with weekly cisplatin plus docetaxel. The PFS and OS were not statistically different and patients receiving consolidation therapy experienced more toxicities.

12.• Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187–99.

A randomized phase III trial of standard dose versus high dose radiotherapy in combination with concurrent and consolidation chemotherapy with or without cetuximab. Median OS was better with 60Gy radiation and the addition of cetuximab provided no additional survival benefit.

13.•• Santana-Davila R, Devisetty K, Szabo A, Sparapani R, Arce-Lara C, Gore EM, et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. J Clin Oncol. 2015;33(6):567–74.

This is the largest retrospective analysis comparing etoposide plus cisplatin or carboplatin plus paclitaxel with concurrent radiotherapy in stage III NSCLC from Veterans Health Administration. The data suggest that any difference in survival outcomes between the two regimens is likely to be small or non-existent.

14. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542–50.

15. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543–51.

16. Vokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non-small-cell lung cancer of other than predominantly squamous cell histology. Clin Lung Cancer. 2009;10(3):193–8.

17. Senan S, Brade AM, Wang L, Vansteenkiste JF, Dakhil SR, Biesma B, et al. Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC). ASCO Meeting Abstracts. 2015;33(15):7506.

18. Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol. 2012;30(17):2055–62.

19. Hasegawa Y, Miura D, Ota T, Yokouchi J. Phase I study of bi-weekly nab-paclitaxel and carboplatin with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer. ASCO Meeting Abstracts. 2015;33(15):7529.

20. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi 3rd AT, Weick JK, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol. 1995;13(8):1880–92.

21. Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol. 2005;23(25):5883–91.

22. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552–9.

23. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7(9):719–27.

24. Pass HI, Pogrebniak HW, Steinberg SM, Mulshine J, Minna J. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. Ann Thorac Surg. 1992;53(6):992–8.

25. Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canto A, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone

in patients with non-small-cell lung cancer. N Engl J Med. 1994;330(3):153–8.

26. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam Jr JB, Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst. 1994;86(9):673–80.

27.• Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2013;31(23):2895–902.

A phase III trial of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous NSCLC showing improved OS with maintenance therapy compared to placebo.

28. Hanna N, Neubauer M, Yiannoutsos C, McGarry R, Arseneau J, Ansari R, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol. 2008;26(35):5755–60.

29.• Huber RM, Engel-Riedel W, Kollmeier J, Andreas S, Staar S, Klautke G, et al. GILT study: Oral vinorelbine (NVBo) and cisplatin (P) with concomitant radiotherapy (RT) followed by either consolidation (C) with NVBo plus P plus best supportive care (BSC) or BSC alone in stage (st) III non-small cell lung cancer (NSCLC): final results of a phase (ph) III study. ASCO Meeting Abstracts. 2012;30(15):7001.

A phase III GILT CT-RT evaluating role of consolidation chemotherapy with cisplatin plus vinorelbine following chemoradiation with cisplatin and oral vinorelbine No statistically significant difference was found in PFS or OS with consolidation chemotherapy.

30.•• Tsujino K, Kurata T, Yamamoto S, Kawaguchi T, Kubo A, Isa S, et al. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. J Thorac Oncol. 2013;8(9):1181–9.

A pooled analysis of the literature including 41 phase II or III trials evaluating the role of consolidation (either continuation consolidation or switched consolidation) chemotherapy reported no improvement in OS with either consolidation approach.

31. Vokes EE, Herndon 2nd JE, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol. 2007;25(13):1698–704.

32.• Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384(9944):665–73.

A randomized phase 3 trial of ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV NSCLC after disease progression on platinum-based therapy showing improved survival with ramicirumab based therapy.

33.• Wozniak AJ, Moon J, Thomas CR, Jr., Kelly K, Mack PC, Gaspar LE, et al. A pilot trial of cisplatin/etoposide/radiotherapy followed by consolidation docetaxel and the combination of bevacizumab (nsc-704865) in patients with inoperable locally advanced stage iii non-small-cell lung cancer: SWOG S0533. Clin Lung Cancer. 2015. A pilot study evaluating the role of bevacizumab plus docetaxel as consolidation therapy after initial chemoradiation in locally advanced non-small cell lung cancer. Bevacizumab was associated with fatal hemoptysis in a high-risk group of patients

34. Spigel DR, Hainsworth JD, Yardley DA, Raefsky E, Patton J, Peacock N, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol. 2010;28(1):43–8.

35. Lu C, Lee JJ, Komaki R, Herbst RS, Feng L, Evans WK, et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. J Natl Cancer Inst. 2010;102(12):859–65.

36.• Hoang T, Dahlberg SE, Schiller JH, Mehta MP, Fitzgerald TJ, Belinsky SA, et al. Randomized phase III study of thoracic radiation in combination with paclitaxel and carboplatin with or without thalidomide in patients with stage III non-small-cell lung cancer: the ECOG 3598 study. J Clin Oncol. 2012;30(6):616–22.

A randomized phase III study evaluating the role of thalidomide in combination with chemoradiation in stage III NSCLC which showed increased toxicities but no survival benefit with addition of thalidomide to chemoradiation.

37. Kelly K, Chansky K, Gaspar LE, Albain KS, Jett J, Ung YC, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol. 2008;26(15):2450–6.

38. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet. 2009;373(9674):1525–31.

39. Pirker R, Pereira JR, von Pawel J, Krzakowski M, Ramlau R, Park K, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol. 2012;13(1):33–42.

40. Chen DJ, Nirodi CS. The epidermal growth factor receptor: a role in repair of radiation-induced DNA damage. Clin Cancer Res. 2007;13(22 Pt 1):6555–60.
41. Das AK, Chen BP, Story MD, Sato M, Minna JD, Chen DJ, et al. Somatic mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) abrogate EGFR-mediated radioprotection in non-small cell lung carcinoma. Cancer Res. 2007;67(11):5267–74.
42.• Sun Y, Nowak KA, Zaorsky NG, Winchester CL, Dalal K, Giacalone NJ, et al. ALK inhibitor PF02341066 (crizotinib) increases sensitivity to radiation in non-small cell lung cancer expressing EML4-ALK. Mol Cancer Ther. 2013;12(5):696–704.
This paper provides pre-clinical data indicating that ALK inhibitor crizotinib acts as a radiosensitizer in cells harboring the EML4-ALK fusion, providing a rationale for a clinical trial combining ALK inhibitor with radiation in the NSCLCs harboring ALK gene rearrangement.
43. McKenna WG, Muschel RJ, Gupta AK, Hahn SM, Bernhard EJ. The RAS signal transduction pathway and its role in radiation sensitivity. Oncogene. 2003;22(37):5866–75.
44. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124(2):687–95.
45.•• Tang C, Wang X, Soh H, Seyedin S, Cortez MA, Krishnan S, et al. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer Immunol Res. 2014;2(9):831–8.
This paper explains the concept of combining radiotherapy and immunotherapy, especially immune checkpoint inhibitors in the treatment of solid tumors along with currently available preclinical and clinical data to support this approach.
46. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med. 2012;366(10):925–31.
47. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res. 2013;1(6):365–72.
48.• Park SS, Dong H, Liu X, Harrington SM, Krco CJ, Grams M, et al. PD-1 Restrains Radiotherapy-Induced Abscopal Effect. Cancer immunology research. 2015. This paper highlights the important phenomenon of PD-1 mediated blunting of heightened anti-tumor immune response after radiotherapy in preclinical models, thereby indicating that combination of radiotherapy and PD-1 blockade may be a potential treatment strategy for malignant tumors.
49. Lim SH, Chua W, Cheng C, Descallar J, Ng W, Solomon M, et al. Effect of neoadjuvant chemoradiation on tumor-infiltrating/associated lymphocytes in locally advanced rectal cancers. Anticancer Res. 2014;34(11):6505–13.
50. Balermpas P, Michel Y, Wagenblast J, Seitz O, Weiss C, Rodel F, et al. Tumour-infiltrating lymphocytes predict response to definitive chemoradiotherapy in head and neck cancer. Br J Cancer. 2014;110(2):501–9.
51. Denkert C, von Minckwitz G, Brase JC, Sinn BV, Gade S, Kronenwett R, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol. 2015;33(9):983–91.
52.• Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(1):59–68.
This is a phase III randomized trial evaluating the role of Tecemotide (L-BLP25), a MUC1-antigen specific cancer immunotherapy, as consolidation therapy after chemoradiation in locally advanced NSCLC. In this study, a subset analysis of patients treated with concurrent chemoradiation showed improved overall survival with tecemotide.