Current Standards and Clinical Trials in Systemic Therapy for Stage III Lung Cancer: What Is New?

Nasser Hanna, MD

OVERVIEW

Patients with stage III non–small cell lung cancer (NSCLC) comprise a heterogeneous group, some of whom have curable disease. Although surgery plays a role for some patients, the majority of fit patients will be treated with chemotherapy and radiation alone. The optimal therapy for all patients remains undefined, but certain principles of care are widely accepted. Specifically, concurrent chemoradiation is the standard of care for patients who are able to tolerate such therapy, namely those with a good performance status, minimal or no weight loss, and adequate end-organ function, including pulmonary reserve. The most commonly used chemotherapy regimens given in combination with radiation therapy are cisplatin/etoposide or carboplatin/paclitaxel. Studies incorporating newer agents have not improved outcomes when compared to these older regimens. The merits of chemotherapy administered beyond the conclusion of radiation therapy continue to be debated, but thus far randomized phase III trials have not provided supporting evidence for this strategy. Incorporating antiangiogenics with chemoradiation has proven to be ineffective in some cases and unsafe in others. Studies with targeted agents in unselected patient populations with stage III disease have also been disappointing. Despite these recent setbacks, however, there remains a sound rationale for incorporating molecularly targeted agents into chemoradiation regimens in select patient groups or consolidating chemoradiation with immunotherapy. Studies that incorporate drugs targeting EGFR, ALK, RAS, programmed cell death 1 (PD-1), and programmed death ligand 1 (PD-L1) into the management of patients with stage III NSCLC will be reviewed.

S
ome patients with stage III NSCLC have curable disease, although the majority will die within 3 years. This variability in outcome is a result of the heterogeneity of clinical presentations, fitness of patients, and the biology of disease. Poor prognostic variables for toxicity and/or outcomes include decreased performance status, the presence of significant weight loss, N3 disease, increased number of lymph node stations involved, and the volume of lung that will receive at least 20 Gy (V20) of radiation.1-3 Challenges in treating this patient population include advanced age (median age older than 70) and the presence of multiple comorbidities which are related to chronic tobacco exposure, including compromised cardiopulmonary function. Therapeutic decisions in the advanced-stage setting are driven by tumor histology and the presence or absence of key genetic alterations. However, the integration of this knowledge into the treatment of patients with stage III disease has lagged behind.

ADVANCES IN THE TREATMENT OF PATIENTS WITH STAGE III NSCLC

Despite these obstacles, advances have been realized over the last 30 years in the treatment of patients with stage III NSCLC (Table 1).4 For a subset of patients, surgery remains an integral part of therapy.2,3 For the majority, radiation therapy is the backbone of treatment. Beginning in the 1980s, the integration of chemotherapy with radiation therapy prolonged survival and increased the cure rate compared with radiation therapy alone.6,7 In the 1990s and early 2000s, the concurrent use of chemotherapy with radiation therapy proved modestly more effective than the sequential use of these modalities.4 In addition, the routine use of PET imaging within the last 2 decades has aided in staging and radiation planning.

For fit patients with stage III unresectable or inoperable NSCLC who have adequate end-organ function including pulmonary reserve, an absence of other substantial comorbidities or weight loss, and a V20 less than 35%, concurrent chemoradiation is a standard of care.4,8,9 However, the optimal choice of chemotherapy agents and the number of cycles to be given remains unsettled. Platinum-containing regimens are standard. Two cycles of cisplatin/vinblastine followed by radiation therapy proved to be superior to radiation therapy alone.7 Subsequent studies have tested a platinum (P) agent with etoposide (E), mitomycin (M) plus vindesine (V), vinorelbine, irinotecan, paclitaxel, docetaxel, or pemetrexed.8-13 Few trials have compared these regimens head-to-head and those that have report small therapeutic differences. The West Japan Thoracic Oncology Group (WJTOG) reported no substantial differ-

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TABLE 1. Key Historic Clinical Trials in Unresectable or Inoperable Stage III NSCLC

<table>
<thead>
<tr>
<th>Group</th>
<th>Design</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB</td>
<td>Chemotherapy → XRT versus XRT</td>
<td>Established the role of sequential chemotherapy followed by radiation in stage III disease</td>
</tr>
<tr>
<td>WJLCG</td>
<td>Concurrent ChemOXRT versus Sequential ChemoXRT</td>
<td>Demonstrated concurrent chemoradiation may be superior to sequential therapy</td>
</tr>
<tr>
<td>RTOG</td>
<td>Concurrent ChemOXRT versus Sequential ChemoXRT</td>
<td>Confirmed the superiority of concurrent chemoradiation over sequential therapy</td>
</tr>
<tr>
<td>CALGB</td>
<td>Chemotherapy → ChemoXRT versus ChemoXRT</td>
<td>Induction therapy prior to concurrent chemoradiation does not prolong survival compared to concurrent chemoradiation alone</td>
</tr>
<tr>
<td>HOG/USO</td>
<td>ChemoXRT versus ChemoXRT → Chemo</td>
<td>Consolidation docetaxel does not improve survival compared to concurrent chemoradiation alone</td>
</tr>
<tr>
<td>South Korea</td>
<td>ChemoXRT versus ChemoXRT → Chemo</td>
<td>Consolidation therapy utilizing cisplatin and docetaxel does not improve survival when added to weekly platinum/taxane/XRT</td>
</tr>
<tr>
<td>SWOG</td>
<td>ChemoXRT → Chemo versus ChemoXRT → Gefitinib</td>
<td>The addition of gefitinib as consolidation in an unselected patient population is potentially harmful</td>
</tr>
<tr>
<td>RTOG</td>
<td>ChemoXRT versus ChemoXRT + Cetuximab</td>
<td>The addition of cetuximab to concurrent chemoradiation does not improve survival compared with concurrent chemoradiation alone</td>
</tr>
</tbody>
</table>

Abbreviations: NSCLC, non-small cell lung cancer; CALGB, Cancer and Leukemia Group B; XRT, external beam radiation therapy; WJLCG, West Japan Lung Cancer Group; Chemo, chemotherapy; RTOG, Radiation Therapy Oncology Group; HOG, Hoosier Oncology Group; USO, US Oncology; SWOG, Southwest Oncology Group.

KEY POINTS

- Stage III non–small cell lung cancer comprises a heterogeneous group of patients.
- Concurrent chemoradiation is the standard of care for most fit patients with stage III disease.
- The optimal chemotherapy agents and duration of therapy remain undefined.
- Early results incorporating targeted agents or antiangiogenics have proven ineffective or, in some cases, unsafe.
- Newer strategies with molecularly targeted agents, including inhibitors of EGFR, ALK, RAS, and PD-1, are under investigation.

progressively conducted randomized phase III trial comparing these two regimens has not been reported.

THE ROLE OF INDUCTION OR CONSOLIDATION CHEMOTHERAPY FOLLOWING CHEMORADIATION

The initial gains in survival with the addition of chemotherapy to radiation were appreciated in phase III studies utilizing only two cycles of chemotherapy.7 This stands in contrast to the use of three cycles of chemotherapy given in the neoadjuvant setting, four cycles in the adjuvant setting, and four to six cycles of combination therapy followed by maintenance therapy in the metastatic setting. Therefore, additional attempts to improve outcomes have focused on delivering additional chemotherapy before (induction) concurrent chemoradiation or following (consolidation) concurrent chemoradiation. Each of these strategies has been extensively studied in phase II and III studies. Unfortunately, neither approach has clearly demonstrated improved survival times compared to concurrent chemoradiation alone. For example, a phase III study from the Cancer and Leukemia Group B randomly assigned patients to receive concurrent weekly carboplatin plus paclitaxel and radiation or the same therapy preceded by two cycles of full-dose carboplatin and paclitaxel.17 No difference in overall survival was reported. Investigators from the Hoosier Oncology Group and US Oncology evaluated the role of consolidation docetaxel.18 In this phase III study patients were treated with concurrent PE and 59.4 Gy of radiation and then randomly assigned (if their disease had not progressed) to receive docetaxel for three cycles or observation alone. No survival difference was seen, but patients receiving docetaxel had higher rates of pneumonitis and febrile neutropenia. More recently, Huber et al treated patients with concurrent cisplatin plus oral vinorelbine and radiation and then randomly assigned them to either consolidation cisplatin plus vinorelbine or best supportive care.19 Progression-free and overall survival times were almost identical.
At the 2014 ASCO Annual Meeting, Park et al reported the results from their phase III trial testing consolidation therapy utilizing a platinum agent and a taxane.\textsuperscript{13} All patients initially received weekly cisplatin and docetaxel with concurrent radiation followed by consolidation cisplatin and docetaxel versus observation alone. Although no survival difference was reported, patients receiving consolidation therapy experienced substantially more toxicity. A similar study design evaluating the role of consolidation carboplatin plus paclitaxel (versus observation) following weekly carboplatin and paclitaxel given concurrently with radiation has not been conducted. A pooled analysis of the literature which included 41 phase II or III studies indicated no improvement in survival (hazard ratio [HR] 0.94 for median survival time; \textit{p} = 0.4) with any consolidation strategy, including using the same drugs in consolidation as were given with concurrent radiation, switching chemotherapy agents, or incorporating novel or molecularly targeted agents.\textsuperscript{20}

Regardless of the drugs used, doses of radiation, or duration of chemotherapy, it appears we have reached a plateau in survival with current strategies in stage III NSCLC. Although the median survival time has improved in contemporary studies, the 3-year survival rates (a surrogate for long-term survival or even cure) are only 15% to 25%. Improvements in median survival may be attributed to better patient selection, stage migration, improved radiation techniques and supportive care, and greater experience by clinicians in treating this population of patients with concurrent chemoradiation.\textsuperscript{21}

### INITIAL ATTEMPTS AT INCORPORATING NOVEL AGENTS INTO CHEMORADIATION REGIMENS

Initial attempts to incorporate molecularly targeted therapies into chemoradiation have been disappointing thus far. A phase III study from the Southwest Oncology Group treated patients (irrespective of EGFR status) with PE plus radiation followed by consolidation docetaxel. Patients without progressive disease were randomly assigned to receive further therapy with gefitinib or placebo.\textsuperscript{22} Overall survival favored placebo. More recently, a study led by the Radiation Therapy Oncology Group randomly assigned patients with stage III NSCLC to receive chemoradiation (60 Gy vs. 74 Gy; MST 28.7 vs. 20.3 months, HR 1.38, \textit{p} = 0.004). with or without cetuximab. Survival times favored 60 Gy, and the addition of cetuximab provided no additional benefit.\textsuperscript{12} Furthermore, attempts at incorporating antiangiogenic agents have proven to be ineffective or unsafe.\textsuperscript{23–26}

### NEWER STRATEGIES INCORPORATING MOLECULARLY TARGETED AGENTS INTO STAGE III NSCLC

Despite these early failures incorporating molecularly targeted agents into chemoradiation regimens, the scientific rationale to do so remains sound (Table 2). The initial trials evaluating EGFR targeting agents did not require patient selection based on the tumor molecular profile. Continued efforts to target the EGFR in stage III disease are underway. Radiation is known to increase the expression of EGFR, resulting in radiation resistance.\textsuperscript{27} Proposed mechanisms for this include EGFR interaction with DNA repair enzymes; EGFR activation of PI3K/AKT signaling which suppresses DNA damage-induced apoptosis; and activation of downstream signaling through the RAS and STAT pathways to promote cancer cell repopulation. Furthermore, tumors with activating EGFR mutations appear to be more sensitive to radiation than their \textit{ALK} wild-type counterparts.\textsuperscript{27,28} This may be because mutated EGFR fails to bind to a key enzyme in DNA repair. Similarly, in vitro studies suggest that cell lines that harbor \textit{ALK} fusion proteins may be more sensitive to \textit{ALK} inhibition combined with radiation.\textsuperscript{29} In one experiment, the combination of crizotinib with radiation resulted in greater tumor growth inhibition than either treatment alone in a cell line with an \textit{ALK} fusion protein. Similar effects were not seen in a cell line without the \textit{ALK} fusion protein.

#### TABLE 2. Key Ongoing or Planned Clinical Trials in the United States in Unresectable or Inoperable Stage III NSCLC

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Schema</th>
<th>NCT Registry Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized phase II</td>
<td>Arm 1: Erlotinib → ChemoXRT</td>
<td>01822496</td>
</tr>
<tr>
<td></td>
<td>Arm 2: ChemoXRT (EGFR mut cohort)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 3: Crizotinib → ChemoXRT</td>
<td></td>
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<tr>
<td></td>
<td>Arm 4: ChemoXRT (ALK+ cohort)</td>
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</tr>
<tr>
<td>Randomized phase II</td>
<td>Following definitive ChemoXRT, consolidation with:</td>
<td>01909752</td>
</tr>
<tr>
<td></td>
<td>Arm 1: Dribbles vaccine and HPV vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2: Dribbles vaccine and HPV vaccine and imiquimod</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 3: Dribbles vaccine and HPV vaccine and GM-CSF</td>
<td></td>
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<tr>
<td>Single-arm phase II</td>
<td>Following definitive ChemoXRT, consolidation with: tecemotide and bevacizumab</td>
<td>00828009</td>
</tr>
<tr>
<td>Randomized phase II</td>
<td>Arm 1: ChemoXRT followed by consolidation chemo</td>
<td>02186847</td>
</tr>
<tr>
<td></td>
<td>Arm 2: Metformin X 14 d followed by ChemoXRT with metformin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>followed by consolidation with chemotherapy and metformin</td>
<td></td>
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<tr>
<td>Phase I</td>
<td>ChemoXRT with trametinib followed by consolidation chemotherapy</td>
<td>01912625</td>
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<tr>
<td>Single-arm phase II</td>
<td>ChemoXRT followed by pembrolizum</td>
<td>02343952</td>
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<tr>
<td>Randomized phase III</td>
<td>Following definitive ChemoXRT, consolidation with:</td>
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<tr>
<td></td>
<td>Arm 1: MED14736</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2: Placebo</td>
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</tbody>
</table>

Abbreviations: NSCLC, non-small cell lung cancer; NCT, National Clinical Trial; Chemo, chemotherapy; XRT, external beam radiation therapy; mut, mutated; GM-CSF, granulocyte macrophage colony-stimulating factor; d, days.
Based on this preclinical data, a study of erlotinib or crizotinib as induction therapy in patients with stage III NSCLC is ongoing (NCT 01822496). Approximately 234 patients with nonsquamous NSCLC will be stratified based on EGFR mutation and ALK gene-rearrangement status and randomly assigned to one of four arms. Patients on arm 1 and 3 receive erlotinib or crizotinib, respectively, as induction therapy for up to 12 weeks. Those who have no disease response after 6 weeks will undergo immediate chemoradiation. After 2 weeks of completion of induction therapy, patients receive concurrent chemoradiation with cisplatin and etoposide or carboplatin and paclitaxel. Patients on arm 2 (EGFR mutation cohort) or arm 4 (ALK gene-rearranged cohort) receive concurrent chemoradiation beginning on day 1. The primary objective is to assess whether patients treated with targeted agents based on molecular characteristics have a longer progression-free survival than those treated with chemoradiation alone.

The RAS oncogene has also been proposed to play a role in radiation resistance. Although targeting RAS activation directly has yielded disappointing results, downstream targets of RAS, including MEK, may be feasible. In vitro studies demonstrate an increased radiosensitization when such downstream pathways are inhibited. It has also been proposed that PI3K is a mediator of RAS-induced radiation resistance. Efforts are underway within the National Cancer Institute to incorporate trametinib (NCT 01912625), a MEK inhibitor, into chemoradiation in patients with KRAS mutations. Approximately 30 patients with any histology NSCLC with a KRAS mutation in exons G12, G13, or G61 will receive daily oral trametinib with concurrent carboplatin, paclitaxel, and radiation for 6 weeks followed by two cycles of consolidation carboplatin and paclitaxel alone. The primary objective is to determine the maximum tolerated dose of trametinib when combined with chemoradiation. Future efforts with PI3K inhibitors may also be worth testing.

**IMMUNOTHERAPY IN STAGE III NSCLC**

Targeting immune regulatory pathways has proven to be a successful strategy in NSCLC. A phase III study comparing nivolumab with docetaxel in patients with NSCLC was recently closed based on the recommendations of a Data and Safety Monitoring Board citing evidence of superior overall survival favoring nivolumab (CheckMate-017 trial, Bristol Myers Squibb press release January 11, 2015). Consolidating chemoradiation with an immunotherapy has been studied in 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. In this trial, patients were allowed to receive either concurrent or sequential chemoradiation. Although overall survival did not statistically differ between the two groups (HR 0.88, 0.75–1.03; p = 0.123), a subset analysis of 829 patients treated with concurrent chemoradiation favored the tecemotide arm (median survival, 30.8 vs. 20.6 months, HR 0.78; p = 0.016). Another trial from the Eastern Cooperative Oncology Group, combining tecemotide with bevacizumab after chemoradiation, has recently completed accrual (NCT 00828009). Patients with stage III nonsquamous NSCLC received concurrent chemoradiation using weekly carboplatin and paclitaxel for 6.5 weeks. Patients with non-progression receive two additional cycles of consolidation chemotherapy. On completion of consolidation chemotherapy, patients receive a single dose of cyclophosphamide 3 days before the first tecemotide and bevacizumab treatment. Patients then receive bevacizumab on day 1 and tecemotide subcutaneously on days 1, 8, and 15 for cycles 1 and 2 and then every other cycle beginning in course 4. Treatment continues every 21 days for up to 34 cycles. The primary endpoint is to determine the safety of bevacizumab plus tecemotide as maintenance therapy in this setting.

Evidence indicates radiation therapy induces tumor antigen release from the dying tumor cells that can be recognized by the immune system. Therefore, radiation is an immune stimulator that enhances T-cell activation and infiltration. Furthermore, radiation has been shown to increase the expression of PD-L1, an immune checkpoint. Combining radiation with checkpoint inhibitors, such as PD-1 or PD-L1 inhibitors, including MED14736, pembrolizumab, and nivolumab, are being investigated. MED14736, an antibody to PD-L1, will be tested in a phase III industry-sponsored trial (PACIFIC) involving 702 patients across 100 sites around the globe (NCT 02125461). Patients with unresectable stage III NSCLC will be treated with concurrent chemoradiation utilizing at least two cycles of platinum-based chemotherapy. If no evidence of progression is seen, patients will then be treated with MED14736 or placebo (2:1 randomization) for up to 1 year. The primary endpoint is overall survival. A phase II single-arm study evaluating pembrolizumab as consolidation therapy after concurrent chemoradiotherapy will be conducted by the Hoosier Cancer Research Network (NCT 02343952). In this trial, approximately 83 patients will receive either weekly carboplatin/paclitaxel or cisplatin/etoposide with 59.4 to 66 Gy radiation. Patients with nonprogressive disease will then receive pembrolizumab every 3 weeks for up to 1 year. A safety analysis will take place after the initial 10 patients have been treated and received at least three cycles of pembrolizumab. Given the possibility of pneumonitis after chemoradiation and the expected activation of T cells with pembrolizumab, the incidence of delayed or severe pneumonitis and/or recurrent esophagitis in the irradiated field will be of special importance. The primary endpoint is to assess the time to distant relapse. Secondary analyses will evaluate the effect of PDL-1 status on outcomes. In addition, a randomized trial with nivolumab after chemoradiation is under development (personal communication, Jeffrey Bradley, February 2015).

**CONCLUSION**

Therapeutic advances in the treatment of stage III NSCLC are difficult to achieve. Many factors contribute to the diffi-


faculty of this task. Valuable lessons have been learned from research over the last 3 decades. Namely, further manipulations of existing chemotherapy drugs are unlikely to provide substantial survival gains. The path forward will follow new science and new drugs. The recent success with targeted agents and immunotherapy in the metastatic setting provides encouragement that similar success is possible in the stage III setting, where cures are still possible.

Disclosures of Potential Conflicts of Interest


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23. Wozniak AJ, Moon J, Thomas CR, et al. SWOG 50533: a pilot trial of cisplatin (C)/etoposide (E)/radiotherapy (RT) followed by consolidation docetaxel (D) and bevacizumab (B) (NSC-704865) in three cohorts of patients (pts) with inoperable locally advanced stage III non-small cell lung cancer (NSCLC). J Clin Oncol. 2012;30 (suppl; abstr 7018).


