Chemotherapy for Lung Cancers: Here to Stay

Mark G. Kris, MD, Matthew D. Hellmann, MD, and Jamie E. Chaft, MD

OVERVIEW

Four decades of clinical research document the effectiveness of chemotherapy in patients with lung cancers. Chemotherapeutic agents can improve lung cancer symptoms, lengthen life in most patients with lung cancers, and enhance curability in individuals with locoregional disease when combined with surgery or irradiation. Chemotherapy’s effectiveness is enhanced in patients with EGFR-mutant and ALK-positive lung cancers and can “rescue” individuals whose oncogene-driven cancers have become resistant to targeted agents. As immunotherapies become part of the therapeutic armamentarium for lung cancers, chemotherapeutic drugs have the potential to modulate the immune system to enhance the effectiveness of immune check point inhibitors. Even in this era of personalized medicine and targeted therapies, chemotherapeutic agents remain essential components in cancer care.

When the American Society of Clinical Oncology was founded 50 years ago, no systemic therapies were proven to improve outcomes in persons with lung cancers. Clinical research conducted during the ensuing decades has identified drugs and drug combinations that can lessen symptoms, lengthen life, and, when combined with surgery or irradiation, lead to cure in more patients. The last decade of progress in lung cancers has been extraordinary. Expansion of our understanding of the biology of these illnesses, coupled with advances in agent development and a revolution in the molecular characterization of tumors, have ushered in an era of targeted therapies and precision medicine. In fact, it is now the standard approach in the treatment of lung cancers to genotype tumors at diagnosis. All agree that the optimal treatment cannot be recommended without this information. The success of this approach is obvious, so much that it has become a model for the management of all solid tumors. By grouping individuals based on the presence of oncogenic drivers found in their tumor specimens, we can reliably identify patients with a median life span measured in years, not months. The Lung Cancer Mutation Consortium (LCMC), representing 14 cancer centers across the country, has reported that the median survival from the time of diagnosis of metastatic disease for individuals with tumors with sensitizing mutations in EGFR was 4 years and with ALK-positive lung adenocarcinomas was 4.2 years. Even patients with tumors with no driver identified had a median survival of 2.1 years in this contemporary series from the LCMC. How were these remarkable results achieved even in those who did not receive a targeted therapy?

Targeted therapies like erlotinib and gefitinib for EGFR-mutant lung adenocarcinomas and crizotinib for ALK-positive lung cancers are generally credited for this huge change in outcomes. These agents routinely demonstrate major response rates of about 70% and better tolerability when compared head to head with intravenous chemotherapeutic agents. However, after a median period of 16 months on erlotinib, 10 months on gefitinib, and 8 months on crizotinib, relapse occurs in all individuals with oncogene-driven cancers. With progression-free survival on targeted therapies measured in months, how are these multiyear survivals achieved? The answer is with intravenous chemotherapies given before, after, or concomitantly with targeted therapies. In 2014, nearly all persons with lung cancers will receive and benefit from intravenous chemotherapies at some point in their illness. This being the case, it is imperative to understand how to best use and tailor chemotherapies with targeted agents.

CHEMOTHERAPY DEFINITION AND TARGETS

Chemotherapy is defined as a cytotoxic therapy that disrupts basic cellular processes such as proliferation, maintenance, metastasis, angiogenesis, and apoptosis in all cells, not just those with oncogenic drivers. Chemotherapy works because cancer cells have developed greater dependencies on these processes than normal cells. They may further have an impaired ability to survive cytotoxic stress than normal cells as well. In truth, all chemotherapies are targeted agents, we just lack a clear understanding of their targets in normal and neoplastic cells. Despite the singular success of cisplatin in the cure of metastatic germ cell cancers identified nearly 4 decades ago, we still do not understand the specific biologic processes that underlie the sensitivity of germ cell tumors to this agent. However, this knowledge gap has not impeded our
ability to use cisplatin in combination with other chemotherapies to affect a cure of most metastatic germ cell cancers and substantial benefit in other cancers as well.

**USE OF CHEMOTHERAPY IN DRIVER-POSITIVE LUNG CANCERS**

An important observation of the randomized trials comparing targeted agents with chemotherapy is the increase in the activity of chemotherapy in patients with oncogene-driven lung cancers. For example, in the IPASS trial comparing gefitinib with the combination of carboplatin and paclitaxel, individuals with EGFR-mutant adenocarcinomas had a response rate with chemotherapy that was double that of EGFR wild-type patients (47% vs. 24%). In the trial comparing crizotinib with either pemetrexed or docetaxel in patients with ALK-positive lung cancers, partial responses were seen in 65% of patients treated with crizotinib and 20% in the group receiving any chemotherapy. The 29% single-agent rate of response seen with pemetrexed is triple that observed in an earlier trial of the same agent in patients enrolled without molecular section. The reasons for these increased responses for chemotherapeutic agents in patients with oncogene-driven lung cancers are not known. This observation may provide clues for future research into mechanisms of chemotherapy sensitivity.

**CAN CHEMOTHERAPY COMBINED WITH TARGETED THERAPIES IMPROVE OUTCOMES?**

Despite more than a decade of research combining gefitinib or erlotinib with chemotherapy, we still do not know if this approach improves response or survival. In a cohort of patients with EGFR-mutant lung adenocarcinomas, it was observed that the median survival was improved by 7 months in patients assigned erlotinib plus carboplatin plus paclitaxel (38 months) compared with erlotinib alone (31 months). This observation will require further follow-up. There is no question that these combinations are well-tolerated based on the trial just mentioned and earlier large randomized trials combining gefitinib or erlotinib with chemotherapy. Giving erlotinib at high doses immediately before chemotherapy has been shown to improve the anticancer effects of chemotherapy or erlotinib alone. When this observation was tested in patients with EGFR wild-type lung cancers, improved survival was demonstrated in those individuals receiving daily doses of 1,500 mg of erlotinib for 2 days before carboplatin plus paclitaxel compared with the same chemotherapy alone or the same high dose of erlotinib given for 2 days after chemotherapy. In the FAST ACT trial, where chemotherapy was intercalated with erlotinib again in patients without molecular selection, progression-free survival was improved compared with individuals receiving erlotinib alone. These results continue to support the hypothesis that combining, sequencing, or intercalating chemotherapy with EGFR tyrosine kinase inhibitors may be effective strategies to improve outcomes for all persons with lung cancers and provide even greater benefit in patients with EGFR-mutant cancers.

**CHEMOTHERAPY IMPROVES SURVIVAL IN CURABLE LUNG CANCERS**

Multimodality therapy is recommended for all but the earliest stages of lung cancers. Although it is not surprising that integrating chemotherapy into the multimodal treatment of limited-stage small cell lung cancer, an exquisitely chemotherapy-sensitive disease, improves survival, it also significantly improves cures rates in adenocarcinomas and squamous cell lung cancers when compared with surgery or radiotherapy alone.

Small cell lung cancers are well known for their rapid cell death when treated with chemotherapy, as well as their likelihood of recurrence. In limited-stage small cell lung cancers, it was initially the role of radiotherapy that was difficult to establish. A meta-analysis of 16 randomized trials solidified the role of radiotherapy in limited-stage small cell lung cancers. Since that time, cisplatin (or carboplatin) and etoposide have been established as the initial regimen of choice for small cell lung cancers, and radiation techniques have been honed to safely and effectively deliver potentially curative concurrent chemoradiotherapy to patients with limited-stage disease.

Adenocarcinomas and squamous cell lung cancers are a more heterogeneous group of diseases and, as a whole, not as sensitive to chemotherapy as small cell lung cancers; yet, here too a multimodal approach including chemotherapy increases cure rates in stages IB-IIIA lung cancers treated with surgery and in stage IIIA and B disease treated with concurrent radiotherapy.

**ADJUVANT AND NEOADJUVANT CHEMOTHERAPY FOR ADENOCARCINOMAS AND SQUAMOUS CELL CANCERS**

Unlike small cell lung cancers, the mainstay of treatment for early-stage adenocarcinomas and squamous cell carcinomas
is surgical resection, although outcomes with surgery alone are disappointing in all stages of disease with 5-year overall survival percentages ranging from 73% for stage IA lung cancers to 24% for stage IIIA. To date, no modern trials have been adequately powered to address the question of whether chemotherapy can produce a survival advantage in stage IA disease compared with surgery alone. In completely resected pathologic stages IB-III, adjuvant (postoperative) cisplatin-based chemotherapy has repeatedly demonstrated survival improvements. The best estimates of the added benefit of chemotherapy compared with surgery alone are derived from the LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis, demonstrating a remarkably low number needed to treat to save a life as presented in Table 1. 

Although publication of these adjuvant chemotherapy trials established adjuvant cisplatin-based chemotherapy for patients with resected stage IB-III lung cancers, these data also forced early closure of many concurrent neoadjuvant chemotherapy trials creating a lack of randomized trial data supporting the neoadjuvant approach already supported by strong phase II data, especially in patients with stage IIIA disease. A meta-analysis of these data suggests that neoadjuvant chemotherapy has an equivalent benefit to adjuvant chemotherapy in stages IB-III adenocarcinomas and squamous cell carcinomas, with an equivalent hazard ratio of 0.84 (95% CI 0.77– 0.92). Neoadjuvant chemotherapy has an established role in patients with resectable stage IIIA lung cancers involving the ipsilateral mediastinal lymph nodes (N2), demonstrated in randomized studies showing a striking survival advantage over surgery alone. Although some institutions offer neoadjuvant chemotherapy and radiation in this setting, the outcomes of a randomized trial revealed increased toxicity and no benefit over neoadjuvant chemotherapy alone followed by radiation therapy tailored to pathologic results. The sole exception to this rule is treatment of apical (Pancoast) tumors, where preoperative concomitant chemotherapy and irradiation remains the standard of care.

It is well established that the addition of chemotherapy—given neoadjuvantly or adjuvantly—to surgical resection can improve the potential for cure in patients with stage IB-III lung cancers. Several meta-analyses have demonstrated that neoadjuvant or adjuvant chemotherapy similarly improves survival for patients with resectable lung cancers. However, the neoadjuvant approach offers several advantages, beginning with improved tolerability and greater dose delivery. Perhaps most importantly, neoadjuvant chemotherapy uniquely permits assessment of the in vivo response to chemotherapy, both during treatment and again after resection, by determining the pathologic response in the resection specimen. These determinations can be used to stop ineffective therapies, change to potentially more effective therapies, or continue effective therapies. Additionally, several studies have demonstrated that greater than 90% response to chemotherapy is associated with improved survival and this outcome, termed "major pathologic response," may serve as a surrogate outcome for clinical trials.

As an example, pathologic response is now an accepted outcome in patients with resectable breast cancers, and an improvement in pathologic response was the basis for recent U.S. Food and Drug Administration approval of neoadjuvant pertuzumab for HER2-amplified breast cancers. Incorporation of major pathologic response into care and trials of neoadjuvant chemotherapy has the potential to improve efficiency, spur innovation, and expedite advances for patients with resectable lung cancers.

**COMPARISON CHEMOTHERAPY AND IRRADIATION**

An alternative curative approach can be offered to those with unresectable stages IIIA and stage IIIB adenocarcinomas and squamous cell carcinomas combining definitive thoracic radiation therapy with chemotherapy. Many randomized studies have shown that chemotherapy improves survival when added to definitive thoracic radiation. The best timing of chemotherapy, either sequentially administered before radiation or concurrently with radiation, was demonstrated in a randomized trial showing an approximate 6% absolute 5-year survival advantage in patients receiving concurrent therapy. Therefore, concurrent irradiation with cisplatin-based chemotherapy is recommended for those with sufficient performance status; whereas, sequential therapy is administered when toxicity is a concern. Newer chemotherapy regimens (including pemetrexed for patients with adenocarcinomas) administered with concurrent radiation has been demonstrated to be safe with intriguing single-arm survival data.

**COMBINING CHEMOTHERAPY WITH IMMUNOTHERAPIES**

Historically, there has been general reluctance to combine any cytotoxic chemotherapy with immunotherapies. Concerns included that the lymphopenia associated with many cytotoxic chemotherapies may be antagonistic with immunotherapies and that chemotherapy-induced cell death may be either nonimmunogenic (via organized apoptosis) or immune inhibitory (via massive antigen release leading to tolerance and exhaustion). However, these concerns have been replaced by a more nuanced understanding of the potential ways in which cytotoxic chemotherapy can synergize with immunologic responses to cancers. Mechanisms of synergy have been reviewed in several articles and include chemotherapy-induced:

### Table 1. Summary of Impact of Adjuvant Chemotherapy for Patients with Stage IB-III NSLCCs

<table>
<thead>
<tr>
<th>Stage</th>
<th>Hazard Ratio</th>
<th>Dead at 5 Years</th>
<th>Alive at 5 Years</th>
<th>Saved by Chemotherapy</th>
<th>Number Needed to Treat to Save One Life</th>
</tr>
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<tr>
<td>IB</td>
<td>0.92</td>
<td>33</td>
<td>63</td>
<td>3</td>
<td>33</td>
</tr>
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<td>II</td>
<td>0.83</td>
<td>51</td>
<td>39</td>
<td>10</td>
<td>10</td>
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<td>III</td>
<td>0.83</td>
<td>61</td>
<td>26</td>
<td>13</td>
<td>8</td>
</tr>
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• release of tumor-specific antigens for processing and presentation by professional antigen-presenting cells;
• upregulation of major histocompatibility complex expression on the surface of tumor cells;
• upregulation of immunostimulatory cytokines and chemokines to direct T-cell infiltration and enhance effector function;
• destruction of immunosuppressive cells in the tumor microenvironment; and
• expression of danger/death signals that promote and facilitate effector T-cell response.

Recent studies have also demonstrated that specific chemotherapies commonly used to treat patients with lung cancers—including cisplatin, paclitaxel, and gemcitabine—can augment immunologic responses to cancers. In mice, paclitaxel and cisplatin sensitized tumor cells to killing by tumor-specific cytotoxic T-cells. T-cell–mediated destruction of tumor cells was increased without an associated increase in T-cells directed toward neighboring normal tissue. Consistent with this preclinical observation, one study of patients with breast cancers treated with paclitaxel demonstrated significant increases in tumor-infiltrating lymphocytes after treatment, and the degree of increase correlated with clinical response to treatment. Other studies have shown that gemcitabine can increase T-cell responses to tumors by selectively depleting immunosuppressive cells in the tumor microenvironment (including myeloid-derived suppressor cells and regulatory T cells) and by enhancing effector T cells.

Based on results from these studies, two clinical studies have evaluated the effect of combining cytotoxic chemotherapy with T-cell checkpoint inhibitors in patients with lung cancers. Lynch et al treated 204 patients with advanced lung cancers randomly assigned to carboplatin and paclitaxel with or without ipilimumab (anti-CTLA-4). Ipilimumab was given either concurrently with chemotherapy or in a phased fashion, starting after two cycles of chemotherapy. Median progression-free survival was significantly longer in the phased group compared with chemotherapy alone (progression-free survival 5.6 vs. 4.6 months, HR 0.72, \( p = 0.05 \)); whereas, the progression-free survival in the concurrent treatment arm was numerically longer (5.5 vs. 4.6 months, HR = 0.81, \( p = 0.13 \)). A second study combined platinum-based chemotherapies with nivolumab (anti-PD-1). Overall responses ranged from 30% to 40%, which was not significantly better than response rates seen in previous studies of initial chemotherapy. Long-term follow-up data are awaited to evaluate if the addition of nivolumab may increase the duration of response or survival compared with chemotherapy alone.

CONCLUSION
Chemotherapy shrinks lung cancers, improves cancer symptoms, lengthens life, and enhances curability when combined with local therapies. Chemotherapy can be safely combined with targeted agents in patients with oncogene-driven lung cancers and may improve outcomes when combined or sequenced with targeted drugs in all patients with lung cancers. Responses to chemotherapy are nearly doubled when given to individuals with EGFR-mutant and ALK-positive lung cancers. Chemotherapy can effectively treat patients who develop acquired resistance to tyrosine kinase inhibitors. Today, chemotherapy is the only modality proven to enhance curability when given before or after complete surgical resection or with definitive irradiation in patients with small cell lung cancers, adenocarcinomas, and squamous cell carcinomas. Chemotherapy has important immunomodulatory effects that may complement or supplement emerging approaches to enhance the anticancer activity of cytotoxic T cells. With proven success and substantial potential in this era of targeted therapies, chemotherapy is here to stay.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and uncompensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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