LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Neoadjuvant and Adjuvant Approaches in Surgically Resectable NSCLC

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H&O Which patients with non–small cell lung cancer (NSCLC) are eligible for surgical resection?

JC Surgical resectability, which is determined by the thoracic surgeon, is based on the technical question of whether the surgeon can adequately remove all visible disease. The other factor that plays a role in the surgical decision is medical operability, also called functional operability, which refers to the patient's fitness to withstand medically the surgery needed to remove the entire tumor. Medical operability depends on functional status, cardiac status, and pulmonary status, as well as the specific surgical procedure required to remove the tumor. For example, the medical fitness required for a lobectomy is substantially different from that required for a pneumonectomy.

Surgery remains the preferred treatment modality for all patients with stage I or II NSCLC. Surgery in stage III NSCLC remains a bit controversial, in part because the staging system has evolved to the point at which some patients with stage IIIB NSCLC are considered to have resectable disease. The data regarding surgery in patients with stage III disease are rather poor and outdated, so the decision is very much a multidisciplinary one.

H&O What is the risk for recurrence after resection?

JC The risk is as low as 8% in patients with stage IA disease to as high as 60% in patients with stage III disease.

H&O What is the role of adjuvant therapy in NSCLC?

JC Adjuvant cytotoxic chemotherapy has been shown to improve survival in patients with stage II or III NSCLC according to the current staging system, so all of these patients should be offered this treatment. One of the challenges we face as medical oncologists is that the staging system has migrated twice since the collection of the data that led to the establishment of adjuvant chemotherapy. As a result, decisions regarding stage IB NSCLC can be confusing. However, the current National Comprehensive Cancer Network (NCCN) guidelines recommend at least a discussion of adjuvant chemotherapy for patients with higher-risk stage I disease.

H&O What adjuvant regimens are used?

JC All of the level 1 data for adjuvant chemotherapy are based on cisplatin-based doublets. The reality, however, is that the data that established cisplatin doublets as the standard of care were derived from studies in which vinorelbine and etoposide were used; neither of these is used in NSCLC anymore. Therefore, I think that the chemotherapy regimens used in the E1505 trial, which examined chemotherapy with or without bevacizumab, are our standard arsenal. These regimens are cisplatin with vinorelbine, gemcitabine, docetaxel, or—for those with nonsquamous histology—pemetrexed (Alimta, Lilly).

The average age of patients with newly diagnosed lung cancer at my institution is 76 years, however, and cisplatin

is not safe for patients in this age group. As a result, we often substitute carboplatin for cisplatin, despite the lack of level 1 evidence.

H&O What is the evidence for these adjuvant regimens?

JC The randomized studies that compared preoperative or postoperative chemotherapy and surgery vs surgery alone were conducted several decades ago. The absolute improvement in survival was 5%, but these studies included patients with stage I disease, who are already at low risk and therefore less likely to benefit. Looking just at patients with stages II and III disease, the absolute improvement in survival is significantly better—closer to 10% to 15%.

H&O What have newer studies found?

JC The newer data we have include subsets of patients selected for personalized therapy based on biomarker selection. The most striking data to date have been from the ADAURA study, which looked at adjuvant osimertinib (Tagrisso, AstraZeneca) in endothelial growth factor receptor (EGFR)–positive NSCLC. Only the classical activating and sensitizing *EGFR* mutations were examined. Patients with resected NSCLC as small as 3 cm—this was stage IB according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system—were randomly assigned to 3 years of osimertinib or placebo with or without adjuvant chemotherapy. At 24 months, the researchers found that osimertinib dramatically improved disease-free survival in the overall population, with a hazard ratio of 0.2 ($P<.001$). That was a truly remarkable finding. The data are fairly immature, and we all await longer-term data to see if the curves come back together, but so far they are striking enough that I consider adjuvant osimertinib to be a new standard of care.

More recently, at the 2021 annual meeting of the American Society of Clinical Oncology (ASCO), Dr Heather Wakelee presented results from the IMpower010 study, which evaluated 1 year of adjuvant atezolizumab (Tecentriq, Genentech) after cisplatin-based therapy. IMpower010 is unique among studies of adjuvant immunotherapy in that it required the use of cisplatin-based therapy. Thus far, the study has demonstrated encouraging disease-free survival with the use of adjuvant atezolizumab in patients who have stage II or III NSCLC according to the old staging system, so the tumors were 5 cm or larger. The most notable improvements were seen in the programmed death ligand 1 (PD-L1)–positive and PD-L1–high subsets. So far, it appears that patients with PD-L1–low tumors do not benefit, although we still need to see more information. We may soon have a new standard of care for patients with PD-L1–high resected tumors, however.

Medical oncologists and thoracic surgeons in the United States have begun to use next-generation sequencing routinely to screen patients for oncogenic driver mutations. We now understand that EGFR testing is absolutely essential in the postoperative setting, and it appears that PD-L1 testing will be, too, as soon as atezolizumab has an indication.

When we compare meta-analyses of neoadjuvant and adjuvant therapy, these approaches appear to be equivalent.

H&O What is the role of neoadjuvant therapy in these patients?

JC Neoadjuvant therapy has been a bit of an underdog in NSCLC during the last couple of decades, and we are largely stuck with small, underpowered studies, along with meta-analyses based on these same studies. However, when we compare meta-analyses of neoadjuvant and adjuvant therapy, these approaches appear to be equivalent.

We did see game-changing data from CheckMate 816, however, which Dr Patrick Forde presented at the most recent annual meeting of American Association for Cancer Research (AACR) and Dr Jonathan Spicer presented at the most recent annual meeting of ASCO. CheckMate 816 was a 3-arm study, but the third arm closed early, so data from only 2 of the arms have been presented: neoadjuvant chemotherapy with nivolumab (Opdivo, Bristol Myers Squibb) and without nivolumab. The primary endpoints of the study were pathologic complete response and event-free survival. The event-free survival data have not yet been presented, but the presented data showed a striking improvement in pathologic complete response after the addition of nivolumab to chemotherapy, with an odds ratio of 13. It was eye-opening to realize that chemotherapy alone induced a pathologic complete response in only 2% of tumors, which is pretty pathetic.

The other interesting information from this study thus far is that the complete resection rate was higher in

patients who had a good response to chemotherapy, which allowed more lung-sparing surgeries and fewer pneumonectomies, than in those who did not. Historically, the multidisciplinary discussion regarding the patient's fitness for surgery took place at diagnosis. However, this study demonstrates that when systemic therapy produces a robust response, we may be able to remove the tumor completely with a lesser surgery, which is an approach we never before used in NSCLC. I can also see neoadjuvant chemoimmunotherapy playing a role in higher-stage tumors, particularly stage III—although I would argue that anyone who is a potential candidate for adjuvant therapy should be considered for neoadjuvant therapy.

H&O What are the neoadjuvant regimens that are used?

JC Right now, the neoadjuvant regimens are the same ones used in adjuvant therapy. Unfortunately, we do not have any approvals or indications at this time for more advanced regimens. So, despite all the exciting data we have seen in the past year, the only change beyond platinum doublet chemotherapy either pre- or postoperatively has been adjuvant osimertinib in the subset of patients with EGFR-positive disease.

H&O What studies are being conducted of neoadjuvant regimens in NSCLC?

JC Multiple ongoing studies are looking at neoadjuvant chemoimmunotherapy in NSCLC. Several are also looking at neoadjuvant targeted therapy. The largest of these is the phase 3 NeoADAURA study, which is evaluating neoadjuvant osimertinib, chemotherapy, and a combination of them in patients with EGFR-positive NSCLC (NCT04351555). This study is currently enrolling patients. Another example is the phase 2 NAUTIKA1 study, which is examining the use of various targeted therapies in patients with mutations in *ALK*, *ROS1*, *NTRK*, *BRAF*V600, or *RET* (NCT04302025) and is also enrolling patients.

H&O What do you see happening in the future regarding the approach to adjuvant and neoadjuvant therapy?

JC Many chemoimmunotherapy induction and adjuvant immunotherapy studies are ongoing, so we are going to have a dizzying amount of data to dissect in the next 2 years. We know that adjuvant therapy will remain important, and I do think that patients with PD-L1–high tumors will be receiving adjuvant immunotherapy. The follow-up question will be whether patients with PD-L1–high tumors need chemotherapy—I expect to see newer studies look at de-escalation of treatment. In the meantime, the standard of care is likely to remain chemotherapy plus immunotherapy, although it has yet to be determined whether immunotherapy should be used in all PD-L1–positive patients or just those with PD-L1–high tumors. I think that targeted therapy will be used increasingly in the adjuvant setting—and I hope in the neoadjuvant setting—because we know that oncogene-driven tumors are less likely to respond to immunotherapy.

I also expect that chemoimmunotherapy will find its way into the preoperative setting. Uptake is going to depend on surgical enthusiasm, however, because we depend on surgeons to refer eligible patients to the medical oncologist preoperatively. Some surgeons are concerned that systemic therapy will lead to pulmonary inflammation and fibrosis, which could make surgery more difficult. Although the concern that systemic therapy will make surgery riskier has been largely debunked with data, medical oncologists still cannot treat these patients preoperatively unless we see them.

We have very little to offer our patients with NSCLC beyond platinum-based chemotherapy, so we must continue to enroll them in the available studies to obtain the data we need.

Disclosure

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Suggested Readings

Forde PM, Spicer J, Lu S, et al. Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIA) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial [AACR abstract CT003]. *Cancer Res.* 2021;81(13)(suppl).

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