Updates in the Treatment of Lung Cancer

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Overview

The International Lung Cancer Congress® was held July 31 to August 2 in Huntington Beach, CA. The meeting serves as an update on advances in the lung cancer field with a focus on the clinical implications of the rapid changes in treatment options--novel agents, strategies, and improved regimens. The State of the Art segment of the agenda focused on the key treatment areas--novel agents, molecular testing, and maintenance therapy. This article reviews anti-angiogenetic therapy, next-generation EGFR TKIs, ALK inhibitors, acquired resistance, and maintenance therapy, providing physicians who could not attend the live meeting the opportunity to engage in the education.

Target Audience

This activity is directed toward medical oncologists and hematologists who treat patients with solid tumors and hematologic malignancies. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers may also participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

1. Discuss strategies to improve care for patients with lung cancer
2. Review current standards and emerging data regarding systemic therapies for the treatment of advanced non-small cell lung cancer

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From July 31 through August 2, 2014, the 15th Annual International Lung Cancer Congress® convened clinicians responsible for the care of patients with lung cancer to help them stay up to date regarding the latest lung cancer data, and to learn what will impact practice in the near future. Highlights are provided here of 5 of the presentations from the meeting, covering updates on antiangiogenesis, epidermal growth factor receptor (EGFR) inhibition, anaplastic lymphoma kinase (ALK) inhibition, acquired resistance, and maintenance therapy.

Current Status of Antiangiogenic Therapy

Roy S. Herbst, MD, PhD

Dual Inhibition

At this year's annual meeting of the American Society of Clinical Oncology, data were presented from a randomized phase 2 trial in Japan. The results revealed that dual pathway inhibition of EGFR with erlotinib and vascular endothelial growth factor receptor (VEGFR) with bevacizumab resulted in an improvement in median progression-free survival (PFS): 16.0 months versus 9.7 months in the erlotinib monotherapy group (hazard ratio [HR] = 0.54; *P* <.0015). The combination was well tolerated but resulted in more grade 3+ toxicities than erlotinib alone (91% vs 53%), especially involving hypertension and proteinuria. Also, 41% of patients discontinued bevacizumab because of adverse events (AEs).[1] This combination, which Dr Herbst indicated is his preferred regimen moving forward for patients with *EGFR* mutations, is being studied currently in the United States in the ACCRU trial.[2]

Investigational VEGFR Inhibitors

Researchers are searching for a small-molecule VEGFR inhibitor that can provide a survival benefit with chemotherapy in second-line treatment of lung cancer. Vandetanib (ZD6474), which is a dual EGFR/VEGFR2 inhibitor, showed marginal PFS improvement in a phase 2 trial.[3] Results of the LUME-Lung 1 trial, which studied nintedanib plus docetaxel versus docetaxel alone for patients with stage IIIB/IV or recurrent (after chemotherapy) non–small-cell lung cancer (NSCLC), offered potential benefit in both adenocarcinoma and squamous cell carcinoma. The primary end point of prolonged PFS was met regardless of histology (HR = 0.79; *P* =.0019). Although overall survival (OS) generally was not significantly better in the combination-therapy group than in the chemotherapy-alone group, the improvement was statistically significant in the adenocarcinoma subgroup (12.6 vs 10.3 months; HR = 0.83; *P* =.0359). These benefits, along with a manageable safety profile and no unexpected safety findings, provided the impetus to test the combination in another phase 3 trial, which is under way.[4]

Ramucirumab is an anti-VEGFR2 monoclonal antibody that is currently approved in the United States as second-line treatment for advanced gastric cancer. Data from the large phase 3 REVEL trial showed that second-line ramucirumab-docetaxel combination therapy in stage IV disease of all histologies improved overall response rate (ORR; 22.9% vs 13.6%; *P* <.001) and median PFS (4.5 vs 3.0 months; HR = 0.762; *P* <.0001) compared with docetaxel alone, and this benefit was seen across all patient subgroups. The OS benefit seen with the combination was not statistically significant. There were no major bleeding issues and no increase in the incidence of serious AEs in the combination group.[5,6]

In Dr Herbst's opinion, ramucirumab might have some potential in combinations, such as with immunotherapies, and antibodies such as ramucirumab will probably combine better than small molecules, with fewer off-target toxicities. Truly predictive biomarkers are still needed, however, for antiangiogenic therapy to move forward.

Next-Generation EGFR Inhibitors

Fred R. Hirsch, MD, PhD

Afatinib—a second-generation tyrosine kinase inhibitor (TKI) that irreversibly blocks the HER/ErbB family: EGFR, human epidermal growth factor receptor 2 (HER2), and ErbB4—has been compared as monotherapy with platinum-based chemotherapy as first-line treatment of *EGFR*-mutant lung adenocarcinoma as part of the LUX-Lung 3 and LUX-Lung 6 trials. An OS benefit was shown for patients with common mutations (exon 19 deletion and exon 21 point mutation *L858R*); this benefit was significant in the exon 19 deletion subgroup (HR = 0.54; *P* =.0015 and HR = 0.64; *P* =.0229, for trials 3 and 6, respectively).[7]

Third-Generation EGFR TKIs

The third-generation EGFR TKIs target the resistance mechanism T790M without targeting the wild-type receptor, sparing patients the typical side effects of EGFR inhibitors such as rash and diarrhea. One of these agents, CO-1686, which was recently named rociletinib, has had an ORR to date of 58% among *T790M+* patients, with a PFS curve that is encouraging even though the PFS has not yet been reached. The TIGER program is enrolling patients this year in 3 separate trials to study this agent as both first- and second-line therapy.[8]

Another irreversible mutant-selective TKI is AZD9291. It has shown a significant response rate (68%) among patients with *T790M+* tumors who received first-line treatment with an EGFR TKI. The responses were of long duration, and there is a large difference so far, although it is still early, between the PFS curves for patients with *T790M+* tumors and those with *T790M* wild-type tumors.[9] Similarly, HM61713 has shown efficacy against resistant tumors while sparing wild-type tumors preclinically. In a Korean clinical trial, the maximum tolerated dose of HM61713 has not been reached, although data are still preliminary.[10] All 3 of these third-generation EGFR TKIs so far have demonstrated much lower rates of diarrhea and rash than those normally seen with erlotinib or afatinib.

EGFR Antibodies

Necitumumab, an anti-EGFR monoclonal antibody, was studied in stage IV squamous cell NSCLC in combination with gemcitabine and cisplatin versus gemcitabine and cisplatin alone in the phase 3 SQUIRE trial.[11] An exploratory analysis of EGFR expression by immunohistochemistry (H-score) in tumor tissue used a cutoff score of 200 based on the response-driven threshold determined in a subanalysis of the FLEX study.[12] In SQUIRE, OS was superior in the necitumumab combination therapy group (HR = 0.84; *P* =.012). Patients in the combination-therapy group with H-scores of at least 200 experienced an OS benefit, meaning that high levels of EGFR expression correlated with survival. The necitumumab combination-therapy group had an HR of 0.75 for OS compared with 0.84 in the non-necitumumab group in the intent-to-treat population.[11]

First- and Second-Generation ALK In hibitors

Sai-Hong Ignatius Ou, MD, PhD

Progression of disease during crizotinib therapy can be caused by a variety of mechanisms, such as brain metastases, acquired resistance in the *ALK* gene, loss of ALK, or activation of secondary pathways.

First-Generation ALK Inhibitors: Crizotinib and Brain Metastases

In the PROFILE 1014 study of treatment-naïve patients, 92 patients with brain metastases were treated with crizotinib or chemotherapy with pemetrexed plus either cisplatin or carboplatin. The PFS HR favored crizotinib for these patients, but it was not as high as that of patients without brain metastases (n=251).[13] The PROFILE 1007 trial showed that crizotinib has limited activity in patients with brain metastases.[14] Approximately half of all patients with *ALK+* NSCLC for whom crizotinib treatment fails have brain metastases.[15]

Second-Generation ALK Inhibitors: Effect on Brain Metastases

Several second-generation ALK inhibitors have been able to improve brain metastases. Alectinib had an impressive treatment duration among patients who were ALK inhibitor-naïve but who had baseline brain metastases.[16] In a small study (N=21), the central nervous system ORR with alectinib was 52% (11/21).[17] Treatment with another second-generation ALK inhibitor, AP26113, led to regression of brain metastases in 69% (9/13) of patients. The ORR with AP26113 was 72% and increased to 100% (6/6), including 1 complete response, among TKI-naïve patients.[18]

Ceritinib is also active in brain metastasis.[15] In a subset analysis, patients with baseline stable brain metastases had a median duration of response to ceritinib of 7 months.[19] The majority of patients treated with ceritinib had at least a 30% decrease in the sum of the longest diameter of all target lesions, and the PFS was high for patients who were ALK inhibitor-naïve (61.3% at 12 months).[19]

Inhibition of brain metastasis has been seen with both X396 (phase 1 trial), as well as preclinically with RXDX-101 (in preclinical animal models). Tumor response was observed with X396 in both ALK inhibitor-naive and experienced patients as well, and partial responses have been seen with RXDX-101 in patients with *ALK+* tumors.[20,21] PF-06463922, which is a dramatically reengineered version of crizotinib, has also demonstrated good penetration to the brain in preclinical models.[22]

Acquired Drug Resistance in Oncogene-Driven Cancers

Karen Kelly, MD

All patients ultimately develop resistance to TKIs, whether from tumor adaptation or, as in the case of brain metastases, from pharmacokinetic failure. For EGFR TKIs, the major mechanism of resistance is caused by *EGFR T790M* mutations,[23] whereas for ALK agents, many patients have bypass track activation, and a large percentage of resistance among these patients is due to still unknown causes.[24] In situations of tumor heterogeneity, where resistance clones are already present in the tumor milieu and become dominant as drug-sensitive cells die, drug-combination strategies could work. In situations in which tumors adapt their biology to resist cell death, both sequential and combination therapy could be viable treatment strategies.

EGFR-Driven Tumors

Afatinib and cetuximab was the first combination to show a benefit for patients whose disease was resistant to EGFR TKIs (diseaes control rate of 75%).[25] Recently, however, it was shown that patients can develop resistance to this combination by way of activation of mammalian target of rapamycin complex 1 (mTORC1).[26] Overcoming this bypass track may require the addition of a third agent.

PFS curves with AZD9291 reflect improvements in both *T790M*+ and *T790M*-negative NSCLC, but the curves do decline, indicating that patients develop resistance,[9] as is the case with CO-1686 as well.[8] The pan-HER inhibitor dacomitinib is active in *T790M*. In a phase 2 trial, the HR was 0.46 in favor of dacomitinib versus erlotinib in the *EGFR*-mutant subpopulation,[27] so there is reason to believe that the ongoing ARCHER 1050 study may have positive results.

Another mechanism of resistance in patients who have been treated with EGFR TKIs is the MET pathway. Clinical efficacy has been seen with the combination of INC280 and gefitinib among patients with *EGFR*-mutant tumors and MET amplification for whom EGFR TKI therapy has failed.[28]

ALK-Driven Tumors

Patients with *ALK*+ disease fared better with pemetrexed therapy than with docetaxel, suggesting that pemetrexed is active in this population. Furthermore, low thymidylate synthase levels, which were associated with response to pemetrexed, were found in *ALK*+ tumors.[14,29]

The heat-shock protein inhibitor ganetespib has demonstrated potent activity against *ALK*-driven tumors in both in vitro and in vivo models.[30] A phase 2 clinical trial of ganetespib monotherapy resulted in a partial response rate among 4 of the 8 patients who had *ALK*+ tumors.[31] Clinical trials evaluating ganetespib alone and in combination with crizotinib are ongoing.

Maintenance Therapy: Current Status

Heather Wakelee, MD

Continuation Maintenance

Strong data now exist to support the use of pemetrexed as continuation maintenance therapy despite past skepticism.[32] Bevacizumab, which has long been given as maintenance therapy, has not undergone a prospective clinical trial to demonstrate that it should be used for continuation maintenance therapy. For the first time, however, a trial is being conducted (ECOG 5508) to determine whether bevacizumab maintenance therapy is warranted. It will comprise 3 arms: continuation of bevacizumab, a switch to pemetrexed, and continuation of bevacizumab with the addition of pemetrexed.[33]

Additional trials studying continuation maintenance strategies are being conducted with *nab*-paclitaxel, necitumumab, and immune checkpoint inhibitors.[11,34]

Switch Maintenance

All of the switch maintenance regimens studied to date have shown improvements in PFS, and most have shown a trend toward OS improvement as well. SATURN studied erlotinib maintenance after 4 cycles of first-line platinum-based doublet therapy. The PFS rate was higher for erlotinib than for placebo at both 12 weeks (53% vs 40%) and 24 weeks (31% vs 17%), with an HR of 0.71 (P <.0001). There was also an OS benefit, with an HR of 0.81 (P =.0088).[35] The ATLAS trial was similar, but patients received bevacizumab with their platinum doublet, and the maintenance arms studied were bevacizumab plus erlotinib versus bevacizumab plus placebo. There was a PFS benefit with the bevacizumab/erlotinib combination, with an HR of 0.722 (P =.0012), but this advantage was not statistically significant.[36]

Another study looked at the difference in benefit between im-

mediate and delayed docetaxel maintenance therapy. The PFS was lower in the delayed-therapy group than in the immediate-therapy group (2.7 vs 5.7 months; *P* =.0001); however, only 63% of patients in the delayed arm received treatment, as opposed to 95% in the immediate arm. If one looks at only the patients in the delayed arm who actually received docetaxel, their OS was about the same as patients in the immediate arm (12.5 vs 12.3 months). Thus, patients who receive delayed second-line treatment may live as long if they eventually receive the effective agent, but chemotherapy holidays may cause about a third of patients to be lost to follow-up, and they may never receive their second-line treatment.[37]

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