Lung Cancer: Targeted Therapy No Help in Chemo Combo

BY ED SUSMAN

MADRID—The IMPRESS non-small-cell lung cancer trial failed to achieve its primary objective, but nevertheless the results appear to be practice changing. That was the surprising conclusion of the study as reported here as a late-breaking abstract at the European Society for Medical Oncology Congress.

The trial was designed to show a benefit in continuing treatment with the tyrosine kinase inhibitor gefitinib even when patients diagnosed with epidermal growth factor receptor (EGFR)-positive cancer have disease progression on the drug by combining gefitinib with standard platinum-based doublet chemotherapy. Instead, as reported by Tony Mok, MD, Professor of Clinical Oncology at Chinese University, the trial determined that gefitinib added little to treatment with chemotherapy, and should be discontinued if that patient requires a second-line therapy.

"Overall, the IMPRESS trial was not very impressive," he said at an ESMO news briefing. Treatment with gefitinib plus chemotherapy following disease progression had similar outcomes as for chemotherapy alone—and there is a hint that adding gefitinib in this patient population might even be harmful to patients, he said.

Progression-free survival—the primary endpoint of the study—among the 133 patients on gefitinib plus chemotherapy was 5.4 months, the same as for the 132 patients who received placebo and chemotherapy. After 14 months, about 72 percent of the patients on gefitinib had disease progression or had died, compared with 81 percent of patients on chemotherapy without gefitinib. In the progression-free survival analysis, a total of 98 events occurred in the gefitinib arm, compared with 107 in the placebo arm.

Mok said that when the researchers scrutinized the overall survival results, they were distressed to note that median overall survival among the gefitinib-plus-chemotherapy patients was 14.8 months compared with 17.2 months among the patients given placebo plus chemotherapy arm, noting, though, that the overall survival data are still immature.

There were 50 deaths among the gefitinib-plus-chemotherapy patients compared with 37 in the placebo plus chemotherapy arm. He said that only about 33 percent of the deaths required for completed statistical analysis of overall survival have occurred.

TONY MOK, MD: "What we have shown with this study is clinically important. Patients do not need to take gefitinib after there is progression with gefitinib."

"IMPRESS results do not support the continuation of gefitinib after disease progression by RECIST [Response Evaluation Criteria In Solid Tumors] criteria when a platinum-based doublet is used as second-line therapy," Mok

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of a CVC care clinical bundle that includes optimal catheter site selection and assessment of the need for a CVC, among other interventions like hand hygiene.

"The catheter can be a patient's best friend, but since there are side effects associated with placement and longer-term use, obviously you have to figure out who needs a catheter and who doesn't," said the Chair of the panel that wrote the guideline, Charles A. Schiffer, MD, Professor of Medicine and Oncology and Interim Chair of the Department of Oncology and Head of the Multidisciplinary Leukemia/Lymphoma Group at the Barbara Ann Karmanos Cancer Institute.

In an interview for this article, Schiffer said the findings for the new study are interesting but not unpredictable for an older Medicare population. For the elderly, there are a number of other factors that could influence whether people get infected or not, independent of catheter use.

"In patients who have catheters and develop infections, it's actually a minority where the infections are related to the catheter," he said. "As an example, patients with lung cancer sometimes develop pneumonia with bacteremia—that's not related to the catheter, and it is not totally clear how this was assessed in this paper."

CHARLES SCHIFFER, MD, noted that there is little information available about how oncologists actually use long-term catheters, how long they are typically used, and for what treatments—"More research addressing these questions would be of considerable interest."

But, he said, the fact that elevated risk was seen across a variety of cancers does give credibility to the overall results and the methodology used.

Schiffer also stated that there is little information available about how oncologists actually use long-term catheters, how long they are typically used, and for what treatments. For example, as a lymphoma specialist, he said, he uses ports only infrequently: "We only do so if the veins are inadequate. I have no idea what the world does, although I suspect that more people put in ports than we do. More research addressing these questions would be of considerable interest."

Inpatient/Outpatient

Another author of the ASCO guidelines, Diane G. Cope, PhD, ARNP-BC, AOCNP, an oncology nurse practitioner at Florida Cancer Specialists and Research Institute, listed the inclusion of both inpatient/outpatient settings and the large population cohort as definite pluses of the study.

But like Schiffer, she said using data from the elderly could easily skew the results. "This is definitely a limited study population of older adults, which place a person in already high risk of infection. You have to factor in all these other comorbidities: chemotherapy, stress of cancer, surgical or radiation procedures, and age."

Lipitz-Snyderman said that as a next step, to find out whether the results remain true for a younger population, the team is currently working on another retrospective analysis using a commercially insured population.

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IMPRESS

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said. "What we have shown with this study is clinically important. Patients do not need to take gefitinib after there is progression with gefitinib."

He said that he believed his data would apply to other tyrosine kinase inhibitors as well as gefitinib.

In the news briefing, he conceded that determining when a patient has reached definite progression can be challenging, and there may be some cases in which treatment with gefitinib or other tyrosine kinase inhibitors may be acceptable therapy.

Commenting on the study and its impact on patient care, Floriana

Morgillo, MD, PhD, Assistant Professor of Internal Medicine at Seconda Universita degli Studi di Napoli in Italy, explained at the news conference, "RECIST is very strict. When we treat patients with a tyrosine kinase inhibitor we sometimes see slow progression. If a patient receiving a TKI first-line and according to RECIST has minimal progression, maybe this patient can still respond to the tyrosine kinase inhibitor.

"But when we are in front of a patient with progressive disease affecting several organs—severe, disseminating progression—IMPRESS demonstrates that when you shift from a tyrosine kinase inhibitor to chemotherapy, there is no advantage to continuing the tyrosine kinase inhibitor."

'Greatly Debated'

Mok noted that the study, which was supported by AstraZeneca, was designed to resolve the greatly debated issue of whether TKIs should be continued beyond progression: "I suspected the inhibition of tyrosine kinase inhibitor-sensitive cancer cells with continuation of gefitinib and inhibition of resistant cells with chemotherapy would optimize the treatment outcome. However, the study has proved otherwise."

IMPRESS—which stands for Iressa Mutation Positive Multicentre Treatment Beyond ProgRESsion Study—enrolled 265 patients from 71 centers in Europe and the Asia Pacific region. "EGFR tyrosine kinase inhibitors are the standard first-line therapies for patients with EGFR mutation-positive, non-small cell lung cancer," Mok said in explaining the rationale for the trial. "However, almost all patients with an initial response to EGFR TKI therapy eventually develop 'acquired resistance.'"

'Still, Not Necessarily the End of Gefitinib for These Patients'

In an interview, the meeting's Scientific Chair, Johann de Bono, MD, PhD, commented: "Even though IMPRESS is classified as a failed trial, the results are very important and may well impact clinical practice by telling us when not to use gefitinib in these patients. But it is not necessarily the end of gefitinib use in these patients."

He suggested that while patients are being treated with chemotherapy it is possible that wild-type EGFR-positive cells will re-emerge and then will again be susceptible to gefitinib or other tyrosine kinase inhibitors. He said he anticipated that blood test monitoring will be able to detect the return of these susceptible cells and trigger re-administration of the TKIs.

> "The results were very robust and reliable, and will help clinicians in their daily clinical practice. When possible, however, it is important to re-biopsy patients when their tumors progress after treatment with TKIs to understand the mechanism that underlies the resistance."

Study Details

For the study, eligible adults were enrolled following cytological or histological confirmation of non-small-cell lung cancer other than predominantly squamous cell histology with an activating EGFR tyrosine kinase mutation.

Patients were required to be diagnosed with documented "acquired resistance" on first-line gefitinib. They also had to be suitable candidates to undergo cisplatin/pemetrexed combination chemotherapy.

The researchers did not enroll patients who had previously been treated with chemotherapy or other systemic cancer therapy aside from gefitinib. Palliative bone radiotherapy had to have been completed at least two weeks before the start of study treatment with no persistent radiation toxicity. Patients with a past medical history or clinically active interstitial lung disease were also excluded.

Patients were treated with a gefitinib dose of 250 mg/day or placebo, plus cisplatin at 75 mg/m^2 and pemetrexed at 500 mg/m^2.

This was the first randomized study to explore the question of what to do when progression occurs. The median number of days in which patients were treated with chemotherapy was 117 in the gefitinib arm and 122 in the placebo arm. The median number of days gefitinib was administered was 152.5 days, and in both groups the median number of cycles of chemotherapy completed was five.

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A total of 31.6 percent of patients continuing with gefitinib and adding chemotherapy achieved a response, compared with 34.1 percent of the placebo-plus-chemotherapy patients.

Adverse Events

The adverse events seen with the combination of gefitinib plus the chemotherapy of cisplatin and pemetrexed did not appear to raise any new or unexpected safety issues, Mok reported.

The most common adverse events were nausea, reported by 64 percent of the gefitinib patients and 61 percent of the placebo arm patients, and decreased appetite, reported by 49 percent of the gefitinib patients and 34 percent of the placebo arm patients.

No interstitial lung disease noted was observed. Gefitinib was associated with increased grade 1/2 gastrointestinal toxicities. There were two treatment-related deaths in the gefitinib-plus-chemotherapy patients and one in the placebo-plus-chemotherapy group.

Also commenting on the study, Marina Garassino, MD, of the National Cancer Institute of Milan, called the results "very robust and reliable," and said they should help clinicians in their daily clinical practice.

"However, when possible," she added, "it is important to re-biopsy patients when their tumors progress after treatment with tyrosine kinase inhibitors to understand the mechanism that underlies the resistance."