New Antiangiogenesis Agents Fight Lung Cancer

BY JANE SALODOF MACNEIL
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ATLANTA — A year after research on bevacizumab proved that angiogenesis inhibition can help patients with non–small cell lung cancer live longer, a second generation of antiangiogenesis agents is showing activity against advanced, metastatic lung cancer.

Phase II trials of sunitinib (Sutent), sorafenib (Nexavar), and an experimental drug called ZD6474 (Zactima) all reported progression-free survival rates of 11% or more at the annual meeting of the American Society of Clinical Oncology.

Because each drug hits more cellular targets than does bevacizumab (Avastin), investigators voiced hope that the new agents will be more effective. Two of the drugs—sunitinib and sorafenib—have already been approved for renal cell carcinoma. Sunitinib also has an indication for gastrointestinal stromal tumors that are refractory to imatinib (Gleevec).

Along with the possibility of better therapies, however, the three trials renewed concerns about the toxicity of antiangiogenic agents. Investigators reported cavitation and hemorrhage leading to treatment-related deaths. Rash, hand-foot syndrome, and controllable hypertension also were seen.

"More than ever, we need pulmonologists to look at the risk of bleeding and to look at cavitation," Dr. Roy S. Herbst said in an interview after presenting a review of the new drugs and the state of antiangiogenic therapy against lung cancer.

"We need to find some sort of risk factors to stratify these patients," said Dr. Herbst, of the department of thoracic/head and neck medical oncology at the University of Texas M.D. Anderson Cancer Center in Houston and the senior investigator of a series of lung cancer trials testing the combination of bevacizumab and erlotinib (Tarceva).

Dr. Herbst cited the survival advantages reported last year in a phase III trial combining bevacizumab with chemotherapy, as well as early results from his study. "Despite these advances, few, if any, metastatic patients are cured," he cautioned.

He called the three new agents "quite comparable" and noted that "signs of early activity are seen," but said that whether the new multitargeted tyrosine kinase inhibitors are more effective than single-targeted bevacizumab is "not clear yet" in non–small cell lung cancer.

Among the potential advantages of multitargeted agents, Dr. Herbst cited convenience, single-agent activity, the ability to act on both tumor and blood vessels, and the potential to lower the cost of treatment. Whether these agents can be used alone or should be combined with chemotherapy or other targeted agents still has to be worked out in clinical trials, he said.

"Angiogenesis inhibition has become a mainstay in cancer therapy, and it will be very interesting in the next few years as we figure out how to optimize its use and use it safely," Dr. Herbst said. "It is a perfect therapy to add to our existing methods."

Sunitinib

Dr. Mark A. Socinski reported that sunitinib controlled tumor growth in more than half of 63 patients who had failed previous regimens for advanced non–small cell lung cancer. Six patients (9.5%) had partial responses, and 27 patients (42.9%) had stable disease in the study. Median progression-free survival reached 11.3 weeks, and overall survival was 23.9 weeks.

Three patients died of hemorrhages, however: Two were pulmonary—only one of which was attributed to treatment—and one was cerebral. Fatigue led the list of grades III and IV toxicity. Other adverse events included myalgia, neutropenia, stomatitis, headaches, and hypertension.

Patients received 50 mg of sunitinib daily for 4 weeks followed by 2 weeks off therapy before starting another cycle in the trial. Dr. Socinski, director of the multidisciplinary thoracic oncology program at the University of North Carolina at Chapel Hill, announced that the study has been extended with a revised dosing schedule of 37.5 mg daily.

Sorafenib

Dr. Ulrich Gatzemeier reported that 30 (59%) of 51 patients with advanced non–small cell lung cancer had stable disease while they were treated with 400 mg twice a day of sorafenib. No partial responses were recorded in the study.

Another 18 patients (35%) progressed, and 3 patients died before they could be evaluated. Median progression-free survival reached 11.3 months, and median survival 29.5 weeks. Two patients have been on therapy for 2 years, according to Dr. Gatzemeier, head of thoracic oncology at Grosshansdorf Hospital in Hamburg, Germany.

Four patients, all with squamous cell carcinoma, had tumor cavitation, and four patients had bleeding events. Three hemorrhages were described as minor, but a fatal hemorrhage occurred in a cavitary lesion while the patient was receiving radiation therapy 30 days after stopping sorafenib. Other adverse events included diarrhea, hand-foot syndrome, fatigue, and hypertension.

Dr. Gatzemeier said that a phase III trial has already started. It is to randomize 900 patients to a carboplatin/paclitaxel regimen with sorafenib or a placebo.

ZD6474

Dr. Ronald B. Natale reported that 83 patients achieved a median progression-free survival of 11 weeks on 300 mg per day of ZD6474. In comparison, only 8.1 weeks was reached by a control arm of 85 patients treated with 250 mg of gefitinib (Iressa) daily. The response rates were 8% and 1%, respectively.

The trial allowed patients who had progressed to cross over to the other agent. There were no additional responses, but 16 of 37 patients who switched from gefitinib to ZD6474 achieved more than 8 weeks' disease control vs. 7 of 29 patients who switched to gefitinib from ZD6474.

Overall survival, however, showed a trend in favor of starting on gefitinib: The median was 7.4 months vs. 6.1 months for those who began on ZD6474.

Adverse events included diarrhea, rash, asymptomatic QTc prolongation, and hypertension, but not hemoptysis.

Dr. Natale, a medical oncologist at the Cedars-Sinai Comprehensive Cancer Center in Los Angeles, concluded that the data support further investigation of ZD6474 as monotherapy. ■

Bevacizumab-Erlotinib Combo Boosts Lung Cancer Survival

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ATLANTA — Bevacizumab (Avastin) in combination with erlotinib (Tarceva) was associated with promising preliminary results in the treatment of refractory non–small cell lung cancer in data presented at the annual meeting of the American Society of Clinical Oncology.

The 17.9% response rate with the bevacizumab-erlotinib combination was better than the 12.5% rate seen in patients treated with bevacizumab and chemotherapy and the 12.2% rate seen in those treated with chemotherapy alone.

Dr. Louis Fehrenbacher reported that 31 of 39 patients treated with bevacizumab and erlotinib were alive at 6 months. With bevacizumab and chemotherapy, 29 of 40 were still alive at 6 months.

The two bevacizumab arms also had similar progression-free survival: 4.8 months when the angiogenesis inhibitor was combined with chemotherapy and 4.4 months when it was used with erlotinib.

A control arm of 41 patients treated only with chemotherapy (either pemetrexed or docetaxel) had the worst outcomes. Only 26 of those patients were alive at 6 months. The median length of progression-free survival was just 3 months.

Dr. Fehrenbacher of Kaiser Permanente Vallejo (Calif.) Medical Center and his coinvestigators reported that about one-third of both bevacizumab arms and about one-fifth of the chemotherapy-only patients were progression-free at 6 months. The investigators calculated adjusted hazard ratios of 0.66 for bevacizumab with chemotherapy and 0.72 for bevacizumab with erlotinib, compared with the chemotherapy arm.

"Overall I think this is a very encouraging finding that the [bevacizumab-erlotinib] combination may actually work in a refractory situation," Dr. Tony Mok said in a discussion of the poster. Dr. Mok of the Chinese University of Hong Kong said the results challenge the belief that combining agents is not worthwhile for second-line treatment of non–small cell lung cancer.

The findings also raise questions, he said, about how bevacizumab works and how bevacizumab and chemotherapy work together. Instead of treating chemotherapies as interchangeable with bevacizumab, he said, clinicians need to find the best combination.

One-year data are not yet available for the trial, which enrolled patients with locally advanced or metastatic (stages IIb-IV), nonsquamous, non–small cell lung cancer. The study excluded patients with brain metastases.

Bevacizumab, a monoclonal antibody marketed by Genentech in the United States and by Roche worldwide, helps to cut off blood supply to tumors by inhibiting vascular endothelial growth factor.

Erlotinib, produced by OSI Pharmaceuticals, targets the human epidermal growth factor receptor pathway, which also plays a role in promoting tumor growth. It is approved for use as monotherapy in patients with locally advanced or metastatic non–small cell lung cancer that has progressed on chemotherapy.

Beyond the juggling of similar benefits in the two bevacizumab arms, the much-anticipated phase II trial showed less toxicity overall when patients were treated with two targeted therapies instead of chemotherapy alone or in combination.

Only four patients (10%) in the bevacizumab-erlotinib arm stopped treatment due to adverse events, compared with 10 patients in each of the chemotherapy arms. The trial reported serious events in 13 bevacizumab-erlotinib patients (33%), 16 bevacizumab-chemotherapy patients (40%), and 22 chemotherapy-only patients (54%).

One chemotherapy-only patient died of cardiopulmonary arrest. No chemotherapy-only patients had pulmonary hemorrhage, a growing concern for patients treated with angiogenic inhibitors. Two fatal pulmonary hemorrhages and a fatal gastrointestinal bleed occurred in patients treated with bevacizumab and chemotherapy. One patient in the bevacizumab-erlotinib arm died of a pulmonary hemorrhage. ■