Second-Line Treatment of Non-small Cell Lung Cancer: Big Targets, Small Progress; Small Targets, Big Progress?

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In the current issue of the Journal of Thoracic Oncology, Noble and colleagues provide an excellent comprehensive review of systemic treatment for patients with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy. The authors conclude that sufficient evidence exists for the routine use of either single-agent pemetrexed or docetaxel or erlotinib and that insufficient evidence exists for the routine use of other agents or combinations. I concur with these conclusions. However, whereas these agents result in prolonged survival and improved quality of life for some patients, the overall gains are modest at best. In fact, most patients still receive either no benefit or minimal benefits from treatment, and, for those who benefit, the duration of benefit is weeks to months, not months to years. We can and must do better, but how?

An ideal starting point would be to enroll all eligible, willing patients into clinical trials that test new agents, combinations, and strategies. As with the first-line treatment of NSCLC with cytotoxics, a plateau has been reached with chemotherapy in the second- and third-line settings. We must take a cue from other recent successes in oncology in which molecularly targeted agents are given to carefully selected patient populations based on disease and tumor characteristics.

In the last year, several agents have offered hope that these advances are forthcoming. I will mention just four, although there are dozens of other promising agents in the same class or others with differing mechanisms of action currently under investigation. Angiogenesis plays a vital role in tumor survival, and bevacizumab has already been proven effective in patients with NSCLC in the first-line setting. However, what is the role of continuing anti-angiogenic therapy beyond first line? Sorafenib is a multi-kinase inhibitor whose targets include the Ras signaling pathway and the vascular endothelial growth factor (VEGF) receptors. A phase II study ($n = 52$) of sorafenib in patients with previously treated NSCLC was recently reported by Gatzemeier et al.1 Of the patients, 59% were reported to have stable disease, including 31% who had objective regression of disease. The authors reported that patients with higher VEGF levels had worse outcomes and that VEGF levels declined with treatment. Sorafenib is also a multi-kinase inhibitor that targets the angiogenesis receptors of VEGF and PDGF. A phase II study ($n = 63$) by Socinski et al.2 included patients with advanced NSCLC who had received at least one prior chemotherapy regimen, including 57% who were receiving sunitinib as at least third-line therapy. Overall, 9.5% achieved a partial response, and an additional 42.9% had stable disease. Remarkably, 45 of 56 patients (80.4%) with disease evaluation reported had tumor regression at some point during treatment. These trials excluded patients treated with bevacizumab in the first-line setting. With the forthcoming, expected broad use of bevacizumab in the first-line setting, one must logically ask whether inhibition of the VEGF receptor intracellular tyrosine kinase will be effective in someone who has previously received bevacizumab.

ZD6474 is a dual kinase inhibitor that targets both the epidermal growth factor (EGFR) and VEGFR. Natale et al.3 reported the results of a randomized phase II study ($n = 168$) of gefitinib versus ZD6474. At the time of disease progression, crossover to the other agent was allowed. The hazard rate for progression-free survival (the primary
endpoint of the study) favored ZD6474 (HR 0.69, \( P = 0.025 \)). The initial disease control rate (CR + PR + SD) also favored ZD6474 (53% versus 35%), as did the disease control rate after crossover (43% versus 24%). These data suggest that dual inhibition of EGFR and VEGF may be more effective than either strategy alone. In another randomized phase II trial, Heymach et al.\(^4\) evaluated the benefits of combining ZD6474 with docetaxel versus docetaxel alone. Progression-free survival seemed superior with the combination.

If treatment with bevacizumab in the first-line setting is effective, is there any reason to think that treatment with it in the second-line setting would not be? Fehrenbacher et al.\(^5\) tested this hypothesis in a randomized phase II study in which patients received chemotherapy (docetaxel or pemetrexed) plus placebo versus chemotherapy (docetaxel or pemetrexed) plus bevacizumab versus erlotinib plus bevacizumab. Prior use of bevacizumab was not permitted. Progression-free survival seemed to favor the bevacizumab-containing regimens, although no clear differences between the erlotinib-containing and chemotherapy-containing arms were appreciated.

Despite the encouraging results with each of these new agents, survival time for most patients in the second-line setting remains poor. However, subsets of patients seem to benefit more than others, underscoring the need to determine which targets are important in an individual patient. The path to improved outcomes must first come from recognizing that the empiric treatment of an unselected patient population will offer only a continuation of the minimal gains seen during the last 10 years. The appearance of a tumor under the microscope is but one superficial piece of information about the nature of the disease. It provides no information on the genetic makeup of the cancer, the dominant driver of growth, the mechanisms of resistance, the supporting environment, or the host that harbors it. Therefore, much in the same way we would not treat someone with breast cancer with trastuzumab who has a FISH-negative, but erb-2+ tumor defined by 1+ on immunohistochemistry, we should not treat someone with a targeted agent simply because we find the target. An excellent example of this in NSCLC is the recent discovery of the EGFR mutations and the likelihood of tumor response with the EGFR inhibitors in patients harboring these mutations, but lack of response in patients who only have overexpression of the receptor.\(^6\) Furthermore, our interpretation of early trials must be carefully considered before proceeding to large phase III trials. Unfortunately, most phase III trials, which are based on “promising” phase II trials, are negative. Several clinical factors are widely known to predict better outcomes in second- or third-line phase II trials. In particular, detailed information on time since diagnosis of lung cancer, stage of original diagnosis, response to and duration of response to prior therapy, presence or absence of weight loss, number of sites of metastases, and specific sites of disease (liver, brain) must be considered. More emphasis should be given to agents active in refractory tumors, rather than only those active in patients with the most favorable disease characteristics, because it is the resistant disease that ultimately leads to the patients’ deaths.

In conclusion, the war against lung cancer continues with new agents soon to be at our disposal. These advances are coming much too slowly, however, to affect the lives of millions of people who will confront advanced lung cancer during the next few years. We must continue to encourage willing, eligible patients to participate in clinical trials and to encourage all oncologists to participate in these trials. The advances of tomorrow will only be found with this approach. Finally, as we continue to test targeted agents in the second- and third-line setting, we must not lose sight of our primary target...tobacco, which is largely responsible for this worldwide calamity.

REFERENCES


