Putting Lung Cancer Clinical Trials Into Perspective

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Ganti and colleagues have provided a comprehensive overview on recent presentations involving lung cancer. However, several of the points they made in the article deserve to be put in perspective, particularly since most of the studies discussed are small phase II trials that have not yet been published. Thus, it is important to put these findings in context with the peer-reviewed and randomized phase III data published in the medical literature.

Local therapies for early-stage NSCLC
In addition to the data presented by Ganti et al, Timmerman et al recently reported the final results of a large prospective phase II RTOG (Radiation Therapy Oncology Group) trial examining the safety and efficacy of stereotactic body radiation (SBRT) in medically inoperable patients with stage I non–small-cell lung cancer (NSCLC).[1] Fifty-four patients with tumors < 5 cm received 18 Gy per fraction for three fractions (54 Gy total), which resulted in a 3-year primary tumor control rate of 97.6% and a 3-year-overall survival rate of 55.8%. The rate of local control in this study is significantly higher than rates reported in prior studies of conventional radiation in this group of patients and establishes SBRT as an accepted alternative to surgery for medically inoperable patients with stage I NSCLC. Ongoing phase III studies are comparing SBRT against surgery for operable patients with stage I disease.

Neoadjuvant chemotherapy for NSCLC
It should be noted that several phase III randomized studies have failed to show a survival advantage to neoadjuvant chemotherapy compared with either surgery alone or surgery followed by adjuvant chemotherapy.[2,3]

Adjuvant therapy for NSCLC
As pointed out by Ganti and colleagues, there is ample level I evidence to support 4 cycles of cisplatin-based chemotherapy after surgery for patients with stages II and III NSCLC. A meta-analysis of recent adjuvant trials in which cisplatin-based chemotherapy was used demonstrated a 5-year absolute survival benefit of 5.4% in favor of adjuvant chemotherapy.[4] Ongoing studies are evaluating whether the addition of biologic agents to cisplatin-based chemotherapy in the adjuvant setting will further improve survival. While the trial (NCIC BR.19) cited in the Ganti review failed to demonstrate a survival advantage with the use of gefitinib (Iressa) in the adjuvant setting, it was closed prematurely and therefore underpowered for the primary endpoint of overall survival.[5] The RADIANT trial is a randomized phase III comparison of erlotinib (Tarceva) versus placebo in patients with resected stage II and III NSCLC. It is hoped that this trial will provide a definitive answer regarding the utility of an EGFR (epidermal growth factor receptor) tyrosine kinase inhibitor (TKI) in the adjuvant setting. The Eastern Cooperative Oncology Group is also conducting a randomized trial of standard cisplatin-based chemotherapy with or without the addition of bevacizumab (Avastin, an anti-VEGF [vascular endothelial growth factor] monoclonal antibody). Eligible patients are those with completely resected stage IB (> 4 cm), II, and III NSCLC, and accrual to this study is ongoing.

Locally advanced NSCLC
One issue not touched on in the Ganti review that merits further attention is the role of surgery in locally advanced NSCLC. The Southwest Oncology Group performed a randomized phase III trial in patients with potentially resectable stage IIIA NSCLC. All patients were surgically staged and were randomized to receive cisplatin, etoposide, and radiation to 61 Gy, or the same chemotherapy regimen and radiation to 45 Gy followed by surgery. Following completion of radiation or surgery, all patients received an additional 2 cycles of cisplatin and etoposide. The final analysis showed no improvement in median overall survival with the addition of surgery,[6] although an unplanned exploratory analysis suggested that this might be due to the higher mortality rate in patients who required pneumonectomy, compared with those undergoing lobectomy following chemotherapy and radiation.
**Metastatic NSCLC**

As noted by Ganti and colleagues, a recent important advance in the treatment of patients with stage IV NSCLC is the identification of subgroups of patients whose tumors are likely to respond to specific molecularly targeted agents, notably those with activating mutations in EGFR and those with the EML4-ALK fusion gene mutation. In patients with the EGFR mutation, several large randomized trials have now demonstrated that first-line treatment with an EGFR TKI improves progression-free survival when compared with standard platinum-based chemotherapy.[7,8] Importantly, none of these trials has shown an overall survival benefit for initial treatment with an EGFR TKI, compared with chemotherapy. Given that the vast majority of patients initially treated with chemotherapy on these studies likely received an EGFR TKI as second-line treatment, this argues that exposure to an EGFR-targeted agent is the critical issue, rather than whether it is given as first-line therapy or subsequently. Equally important is the finding that patients whose tumors did not harbor an EGFR mutation had a significantly worse progression-free survival when treated with an EGFR TKI in the first-line setting, although again, no difference in survival was observed. These studies have clearly shown that single-agent EGFR TKIs are a viable alternative to first-line combination chemotherapy in patients with tumors harboring EGFR mutations. However, given that at this time, no study has shown that treatment with EGFR inhibitors has produced an overall survival benefit for patients with EGFR mutations compared with those who have wild-type EGFR, the role of EGFR mutation status in determining when these agents should be given deserves further study.

Another recent development in treatment of stage IV NSCLC is the discovery that maintenance chemotherapy is effective in selected patients following first-line chemotherapy. While it is true that the studies presented at ASCO (the American Society of Clinical Oncology) in 2010 and cited by Ganti and colleagues failed to demonstrate an overall survival benefit with maintenance treatment, it is important to recognize that two large randomized trials have led to the FDA approval of both pemetrexed (Alimta) and erlotinib (Tarceva) in this setting.[9,10] Treatment with either agent is therefore a viable option for stage IV NSCLC patients with good performance status who have responded to 4 cycles of initial platinum-based chemotherapy.

To conclude, Ganti and colleagues correctly point out that the treatment of lung cancer is evolving rapidly. There is now a successful screening modality for diagnosing the disease early. Improvements in radiation technology offer additional options for the treatment of early-stage disease, and a better understanding of the biology of the disease is moving the field away from the nonspecific treatment of advanced disease to a more personalized approach of specific molecularly targeted agents for selected patients. The hope is that this rapid evolution will continue and will lead to further improvements in survival for our patients with lung cancer.

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**References:**


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