Combination of Standard Chemotherapy and Targeted Agents

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Before the introduction of novel molecularly targeted therapies, results with a wide range of chemotherapy regimens for patients with advanced non-small cell lung cancer (NSCLC) had reached a plateau beyond which improved efficacy seemed unlikely.

Multiple trials over the last several years have demonstrated the generally equivalent efficacy of a number of doublet chemotherapy regimens for first-line treatment of advanced/metastatic NSCLC. Results reported by the Eastern Cooperative Oncology Group (ECOG) 1594 study[1] and other randomized phase 3 trials of various doublets[2,3] demonstrated different toxicities with a remarkably similar efficacy and reproducible median survival results in the 8- to 10-month range and 1-year survival rates of approximately 30–40%.

Docetaxel was the first agent approved by the United States Food and Drug Administration for patients with previously treated NSCLC. This decision was based on results of 2 randomized phase 3 trials, one comparing every-3-week docetaxel vs supportive care alone,[4] and the other comparing docetaxel with single-agent vinorelbine or ifosfamide.[5] Both of these trials demonstrated a response rate for all treatments of 11% or less, no change in median survival for docetaxel, but a significant benefit in 1-year survival. A subsequent large phase 3 trial[6] compared docetaxel with pemetrexed as second-line treatment, with results revealing that both agents were associated with an identical response rate of approximately 9% and 1-year survival of approximately 30%. The hematologic toxicity profile of pemetrexed was superior in terms of risk for febrile neutropenia and need for blood product support, as well as risk of hospitalizations. Consequently, pemetrexed was approved by the Food and Drug Administration as an additional option for salvage therapy in advanced NSCLC.

However, in the last several years, new therapies targeting angiogenesis and the epidermal growth factor receptor (EGFR) axis have demonstrated survival benefits in prospective, randomized, phase 3 clinical trials. These studies have established bevacizumab and erlotinib as agents with an emerging role in the treatment of many patients with advanced NSCLC.

In light of the encouraging results achieved with EGFR tyrosine kinase inhibitors (TKIs) and other targeted approaches in the salvage setting, multiple prospective randomized clinical trials have tested platinum-based doublet chemotherapy with or without a novel targeted approach, seeking a statistically and clinically significant survival benefit. Several novel treatment approaches have generated negative results compared with standard doublet chemotherapy alone. Among these, four trials of more than 1000 previously untreated patients each evaluated gefitinib[7,8] or erlotinib[9,10] versus placebo, concurrently with standard doublet chemotherapy of carboplatin/paclitaxel or cisplatin/gemcitabine for up to six cycles. This was followed by maintenance therapy with the EGFR TKI for patients who did not experience disease progression after the planned first-line chemotherapy. Although both the EGFR TKI and chemotherapy combinations varied, the results of these trials have been consistent, clearly demonstrating no benefit in response rate, median survival, or overall survival from targeted therapy with either gefitinib or erlotinib administered concurrently with doublet chemotherapy. A subset analysis from the TRIBUTE trial[10] of carboplatin/paclitaxel with erlotinib or placebo as first-line therapy demonstrated significantly superior progression-free and overall survival in never-smokers who received the TKI.

Several clinical trials have demonstrated that mutations in the EGFR TK domain—generally observed in 5–20% of tumors in patients from North America and Europe but in greater proportion in Asian patients—are associated with a high likelihood of objective response to both gefitinib[11–14] and erlotinib.[13,14] In addition to demonstrating an association with race, recent studies have shown that the mutations are more often seen in the other clinical subgroups that have been associated with a heightened probability of response and clinical benefit, such as women,[15,16] patients with adenocarcinomas,[15,16] and never-smokers.[15–17] However, these mutations have not been clearly associated with improved survival in trials of EGFR TKIs and have yielded inconsistent results.[18–20] There has also been a lack of consensus on the predictive and prognostic value of EGFR immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). Some studies supporting a strong association between survival and/or response and EGFR overexpression by one or

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both of these techniques,[19,20] whereas others have failed to demonstrate such an association.[11,21] The population of never-smokers comprises approximately 10% to 15% of those diagnosed with lung cancer and has recently emerged as a distinct clinical entity with unique epidemiology, natural history, and response to treatment.[22] Never-smokers almost exclusively develop NSCLC (in particular adenocarcinomas with or without bronchoalveolar carcinoma [BAC] features), they are disproportionately female and often older than other patients at diagnosis. Early studies of underlying tumor biology demonstrated that lung adenocarcinomas in nonsmokers are genetically much simpler than those that arise in smokers[23] and are extremely unlikely to harbor k-ras mutations[24] but more likely than other lung cancers to possess HER-2/*neu* mutations.[25] Pao and colleagues[14] showed that never-smokers are especially likely to have tumors with an activating mutation of the EGFR and that these mutations are associated with a strong possibility of objective response to EGFR TKIs gefitinib and erlotinib. As already noted, a particularly high proportion of EGFR mutation-positive tumors has consistently been seen among never-smokers by United States-based investigators[17] and in Asian populations.[15,16] Thus, smoking status has consistently emerged as a clinical variable predictive of significant clinical benefit with these agents in therapeutic trials. As previously noted, the never-smoker population derived the largest survival benefit among the clinical subsets on the BR.21 trial of erlotinib versus placebo as monotherapy for previously treated patients with NSCLC.[26] In addition, a recent post hoc analysis of data from the BR.21 trial demonstrated that never-smoking status was more predictive of survival benefit from erlotinib than EGFR expression by IHC in a multivariate model.[27] Although the overall survival results of the ISEL trial were negative, the study demonstrated a significant benefit in never-smokers.[28] As previously observed, the never-smoker subset in the TRIBUTE trial (i.e., first-line chemotherapy and concurrent erlotinib)[10] showed significantly better overall and progression-free survival compared with chemotherapy alone in an otherwise negative trial. Finally, in EGFR TKI monotherapy trials[29] of the BAC population, gefitinib was associated with significantly superior survival among lifelong non-smokers compared with former or current smokers, whereas the response rate in a similar trial of erlotinib in BAC[30] was more than twofold higher in never-smokers compared with smokers. At this point, erlotinib treatment of patients with BAC or no smoking history in the first-line setting has a compelling rationale but requires additional study before it can be routinely recommended. Erlotinib as single agent has been tested as first-line therapy in 53 patients affected by advanced NSCLC.[31] This treatment induced a 23% response rate and a 55% non-progression rate at 6 weeks; median time to progression was 3 months, and median survival was 13 months. Such results can be considered encouraging in the first-line setting. Therefore, the activity of erlotinib as single agent, given in first-line therapy of NSCLC patients, provides the rationale of the TORCH study. This is a phase 3 protocol investigating whether erlotinib as first-line therapy until progression followed by chemotherapy with cisplatin and gemcitabine (PG) will be inferior to the standard arm, consisting of first-line PG for 6 cycles, followed at progression by erlotinib until progression in terms of overall survival.

Monoclonal antibodies targeting EGFR, such as cetuximab and panitumumab, have not been studied extensively in NSCLC. A randomized phase 2 trial by Rosell and colleagues[32] administered first-line cisplatin/vinorelbine alone or in combination with cetuximab. Although there was a suggestion of a potential efficacy benefit with the addition of cetuximab from this trial, as well as encouraging results from other trials combining first-line chemotherapy doublets with cetuximab,[33,34] the merit of this approach will ultimately be determined by the randomized phase 3 FLEX trial. In this trial, cisplatin/vinorelbine with or without cetuximab will be administered to previously untreated patients with advanced NSCLC. Another prospective randomized phase 3 trial is being conducted in the second-line setting; patients may receive standard chemotherapy (previously, randomization to docetaxel or pemetrexed, now amended to pemetrexed only) with or without cetuximab.

The Southwest Oncology Group (SWOG) reported the results of SWOG 0342,[35] a randomized phase 2 study of cetuximab administered concurrently with first-line carboplatin/paclitaxel and followed by maintenance cetuximab in non-progressors after four cycles of chemotherapy, or an alternative approach of chemotherapy alone followed by sequential maintenance therapy in non-progressors after four cycles of the same chemotherapy. The concurrent arm with maintenance had a median overall survival of 10 months, meeting the prespecified target for further study.

Other monoclonal antibodies against EGFR, including panitumumab and matuzumab, have also completed early clinical trials, generally in combination with chemotherapy. Early clinical trials have demonstrated no unexpected safety concerns and efficacy results—findings encouraging enough to move ahead with later clinical trials in the phase 2 and 3 settings.

Bevacizumab is an antibody to the vascular endothelial growth factor (VEGF) ligand and has antiangiogenic activity in multiple preclinical models and clinical settings.[36] Active in a range of solid tumors, bevacizumab has also been the subject of considerable interest for treatment of advanced NSCLC. A randomized phase 2 trial[37] demonstrated a very encouraging potential survival benefit, especially for the dose of 15 mg/kg IV every 3 weeks when combined with standard carboplatin and paclitaxel. This trial reported a concerning risk for life-threatening or fatal hemoptysis, which was associated with squamous-type tumors, in a minority of patients. Consequently, the subsequent phase 3 trial with bevacizumab excluded patients with squamous tumors, as well as those with prior hemoptysis, brain tumors, and/or those patients on therapeutic anticoagulation because of concerns about the potential risk of clinical bleeding in these settings.

In contrast to the negative findings from studies of chemotherapy and EGFR-based therapies, the ECOG 4599 trial[38] of carboplatin/paclitaxel along with either the anti-VEGF antibody bevacizumab or placebo reported a survival benefit in the first-line NSCLC setting. There was a signifi-

cant benefit for the combination of carboplatin/paclitaxel every 3 weeks for up to six cycles, along with bevacizumab 15 mg/kg on the same schedule, compared with placebo. Bevacizumab or placebo was continued until disease progression. Despite the eligibility restrictions already described, there were a few cases of fatal hemoptysis or other bleeding complications in bevacizumab-treated patients, although at about half the rate reported in the phase 2 study. The investigators concluded that the combination of carboplatin/paclitaxel/bevacizumab should be the new standard first-line approach within ECOG for patients with non-squamous NSCLC, no prior hemoptysis, no brain metastases, and not receiving therapeutic anticoagulation. The National Comprehensive Cancer Network now endorses the combination of concurrent chemotherapy and bevacizumab as first-line treatment for patients with advanced NSCLC, no prior chemotherapy, performance status of 0-2, and none of the aforementioned exclusion criteria in its treatment guidelines[39] for this setting.

There are various other antiangiogenic agents in clinical trials of advanced NSCLC, with several distinct mechanisms of action. AZD 2171 is an oral small-molecule TKI of the VEGF receptor that has demonstrated safety and encouraging activity in a phase 1 combination trial with carboplatin/paclitaxel.[40] This result has led to an ongoing phase 2/3 trial run by NCIC (BR.24) of chemotherapy alone or in combination with AZD 2171 that will include a broad range of advanced NSCLC patients rather than the narrower subset identified by the E4599 eligibility criteria. Safety of this alternative antiangiogenic strategy will be carefully monitored. Other antiangiogenic agents, including soluble VEGF receptors, are used in earlier stages of clinical trials for lung cancer treatment. It is not clear whether the bleeding complications identified in the bevacizumab trials are a class effect or are specific to bevacizumab.

An alternative to combining two or more molecular therapies with distinct targeted pathways is to inhibit more than one target with a single agent. One of the agents exemplifying this strategy is vandetanib (AZD 6474), an orally available tyrosine kinase that can inhibit both VEGF and EGFR. This agent was compared in a randomized phase 2 trial with gefitinib as salvage therapy for advanced NSCLC and showed an improved progression-free survival, although overall survival was not superior.[41] Crossover from one agent to the other was permitted after progression on the initially assigned agent. Another randomized phase 2 trial[42] with 127 patients compared second-line docetaxel alone against the combination of docetaxel with placebo or vandetanib at 100 mg or 300 mg daily. Combination with the 100-mg dose was associated with a strong trend toward improved progression-free survival (12 vs 18.7 weeks, HR = 0.64, $p = 0.074$), but there was no difference in overall survival (13 months in both). No improvements were noticed when vandetanib was administered at a higher dose of 300 mg daily. There is no clear explanation for the lack of a dose-response relationship, but the unfavorable results may have emerged from a detrimental interaction of docetaxel with EGFR inhibitory effects that are seen only at the higher dose. Based on the favorable results of the latter trial, a prospective randomized phase 3 trial that compares docetaxel alone with docetaxel/vandetanib in the setting of second-line advanced NSCLC is being initiated.

Finally, other multikinase inhibitors, such as sunitinib and sorafenib, have been studied in single-arm trials of patients previously treated with advanced NSCLC. Sunitinib, which inhibits VEGFR1, 2 and 3, PDGF-alpha/beta, Ret, Kit, and Flt3, was tested in 63 patients and had a very encouraging response rate of 10%, a median progression-free survival of 11 weeks, and a median overall survival of 24 weeks.[43] This degree of efficacy was promising, but toxicity was high, with considerable fatigue, myalgias, and stomatitis, as well as bleeding complications in three patients, although the relationship between the bleeding events and sunitinib was weak in two of these cases. Another multikinase inhibitor, sorafenib, which inhibits the VEGF family of receptors as well as PDGFR-beta and RAF, was also administered in a single-arm phase 2 trial to 51 patients as salvage therapy for advanced NSCLC.[44] Although no objective responses were seen, 59% of patients experienced stable disease, and the median progression-free survival was a very encouraging 12 weeks. Modest diarrhea, hand-foot syndrome, stomatitis, and hypertension were seen, and there was one fatal bleeding event in a patient who had not received sorafenib for a month. A randomized phase 3 trial of carboplatin/paclitaxel with or without sorafenib as first-line treatment of NSCLC is currently being initiated.

CONCLUSIONS

EGFR TKI therapy, such as erlotinib, has produced an overall survival benefit in the salvage setting and has led to such consistent and profound improvements in the clinical outcomes of never-smokers, patients with BAC, and patients who have tumors with EGFR mutations or gene amplification that first-line use is being actively studied and considered a strong possibility outside the trial setting. We await results of other agents targeting the EGFR axis in first-line and salvage treatment. Antiangiogenic therapy with bevacizumab has demonstrated a survival benefit in first-line therapy and is being actively studied with multiple chemotherapy combinations, as well as other targeted therapies. Many other targeted therapies against these pathways, as well as very distinct mechanisms of action, remain in clinical testing but provide hope that we will continue to see ongoing evolutionary improvements in clinical outcomes in advanced NSCLC and a growing armamentarium of new options for this setting. Targeted therapies are now being integrated with standard chemotherapy as single agents and in combination with each other to provide survival benefits beyond what we have been able to achieve with chemotherapy so far, or as a less toxic alternative to chemotherapy-based approaches.

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