Antiangiogenesis and Future Combinations with Anti-Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Non-Small Cell Lung Cancer

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Abstract

In the frontline setting, advanced-stage non-small cell lung cancer (NSCLC) is treated with chemotherapy; however, overall survival is low. In the past decade, advances in the treatment of NSCLC have included the approval of antiangiogenesis inhibitors such as bevacizumab and ramucirumab, and EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib. Some success has been observed in trials of antiangiogenesis inhibitors combined with EGFR TKIs in the general population, and trials are currently ongoing in the EGFR mutation-positive population. This article presents useful background on the historical development and current status of therapies for advanced NSCLC, specifically antiangiogenesis inhibitors and EGFR TKIs.

Key words: Non-small cell lung cancer, antiangiogenesis, tyrosine kinase inhibitors

Introduction

In the United States, lung cancer is the leading cause of cancer-related deaths, with approximately 158,000 expected deaths in 2015.[1] Of these, approximately 85% will be diagnosed with non-small cell lung cancer (NSCLC). Options exist for the treatment of these patients, but overall survival (OS) for patients diagnosed with late-stage lung cancer remains low, at approximately 8 months.[2]

Many US Food and Drug Administration (FDA)-approved chemotherapy options are available in the frontline setting (eg, cisplatin + paclitaxel, vinorelbine, gemcitabine, docetaxel, or pemetrexed; carboplatin + *nab*-paclitaxel). However, none of these therapies provides a substantially different survival benefit; 1-year survival ranges from 31% to 36%.[3] In the second-line setting, docetaxel, pemetrexed, and docetaxel plus ramucirumab are FDA-approved. Therapies targeting epidermal growth factor receptor (EGFR; erlotinib, afatinib), anaplastic lymphoma kinase (ALK; crizotinib, ceritinib), and immunotherapy (nivolumab) are also approved in the molecularly selected or second-line settings. Antiangiogenesis inhibitors, such as bevacizumab or ramucirumab, combined with targeted therapies, such as EGFR and ALK inhibitors, are an area of active interest.

Bevacizumab Plus Chemotherapy in the First-Line Setting

In 2006, the FDA approved the addition of bevacizumab (a monoclonal antibody to vascular endothelial growth factor) to standard chemotherapy for nonsquamous lung cancer. This was considered a paradigm change in how providers treated patients. Now histology within a NSCLC diagnosis mattered, in addition to thoughtfulness on the risk/benefit ratio. Bevacizumab was the first drug to show a survival advantage when added to doublet chemotherapy.[4,5] In 2013, Soria et al[6] published a review of phase II/III trials that added bevacizumab to platinum-based chemotherapy. Four trials (AVF-0757g, JO19907, ECOG 4599, and AVAiL) consisting of 2194 patients were evaluated. In the meta-analysis, the addition of bevacizumab to chemotherapy in the first-line setting resulted in significantly longer progression-free survival (PFS; hazard ratio [HR], 0.72; 95% CI, 0.66-0.79; P <.001) and OS (HR, 0.90; 95% CI, 0.81-0.99; P = .03).[6] Of note, when assessing each trial individually, only 1 trial (ECOG 4599) reported an improvement in OS with the addition of bevacizumab.[5] Other therapies have been approved for use in conjunction with chemotherapy that offer similar efficacy and better toxicities profiles (eg, pemetrexed in 2008), and these have been incorporated into clinical guidelines.

Treatment in the Maintenance and Second-Line Settings

New therapies and treatment approaches also have emerged in the maintenance and second-line settings. For example, pemetrexed was approved specifically as a maintenance therapy for NSCLC in 2009, based on a trial demonstrating survival advantages compared with placebo.[7] In the phase III study, 663 patients with advanced NSCLC who had not progressed after 4 cycles of platinum-based chemotherapy were randomized to receive maintenance pemetrexed plus/minus best supportive care. Median PFS and OS were improved for the pemetrexed arm (PFS, 4.3 vs 2.6 months; HR, 0.50; 95% CI, 0.42-0.61; P <.0001; OS, 13.4 vs 10.6 months; HR, 0.79; 95% CI, 0.65-0.95; P = .012). However, grade 3 and higher toxicity was ob-

served in the pemetrexed group.[7]

Erlotinib was approved in 2010 for use in the NSCLC maintenance setting, based on results from the SATURN trial.[8] A total of 884 patients were evaluated (437 erlotinib; 447 placebo). In the overall population, median PFS was significantly longer in the erlotinib group compared with placebo (12.3 vs 11.1 weeks; HR, 0.71; 95% CI, 0.62-0.82; *P* <.0001). In the *EGFR*-positive population (determined by immunohistochemistry), median PFS was also significantly longer in the erlotinib group (12.3 vs 11.1 weeks; HR, 0.69; 95% CI, 0.58-0.82; *P* <.0001). Common adverse events (AEs) included rash and diarrhea.[8]

In 2014, ramucirumab was approved for use in conjunction with docetaxel in the second-line NSCLC setting. Approval was based on the large, phase III REVEL trial[9] (N = 1253) that demonstrated improved PFS and OS for those treated with ramucirumab. Median PFS for the ramucirumab/docetaxel arm was 4.5 months, whereas median PFS for the placebo/docetaxel arm was 3.0 months (HR, 0.76; 95% CI, 0.68-0.86; *P* <.0001). Overall survival also was longer in the ramucirumab/docetaxel arm (10.5 vs 9.1 months; HR, 0.85; 95% CI, 0.75-0.98; *P* = .023). Grade 3 or higher AEs included neutropenia, febrile neutropenia, fatigue, leucopenia, and hypertension; however, these AEs were manageable.[9]

Bevacizumab Plus TKIs

The administration of molecular therapies targeting EGFR, ALK, and ROS1 have changed as well. EGFR tyrosine kinase inhibitors (TKIs; eg, gefitinib, erlotinib, afatinib) and ALK inhibitors (eg, crizotinib) are now utilized in the frontline setting in patients whose tumors harbor the corresponding mutations. However, the majority of patients eventually develop resistance, and studies are testing novel therapeutics aimed at treating patients in whom resistance has occurred.[10-14]

Because patients whose tumors harbor *EGFR* mutations tend to have better prognosis and are treated with single, oral targeted agents, the need to assess these agents in combination with bevacizumab for even better survival has emerged. Combination bevacizumab and erlotinib has been explored in the first-line,[15-18] maintenance,[19] and second-line settings.[20]

Combination Bevacizumab/Erlotinib in the First-Line Setting

In the first-line setting, 154 patients with stage IIIB/IV or recurrent nonsquamous NSCLC were randomized to receive either erlotinib plus bevacizumab or erlotinib alone. Median PFS was better for those in the erlotinib/bevacizumab arm (16.0 vs 9.7 months; *P* = .0015).[15] Results of a single-arm study conducted in the United States and consisting of 50 unselected patients were comparable to that of combination bevacizumab/chemotherapy. Akerley et al[17] reported a stable disease rate of 60%, with median 1- and 2-year survivals of 50% and 21%, respectively.

In the TASK study[16] (NCT00531960), 124 patients with advanced or recurrent stage IIIB/IV NSCLC were randomized to bevacizumab plus chemotherapy versus bevacizumab plus erlotinib. No benefit in PFS was observed for the bevacizumab/erlotinib arm at the time of interim analysis, and the study was terminated. Additionally, in a small, single-arm study of 25 unselected patients (NCT00367601) who were elderly or had a performance status of 2, the bevacizumab/erlotinib combination was not encouraging.[18] No patients experienced complete response, and the rate of nonprogressive disease at 4 months was 28%. Median time to progression was 3.4 months, and OS was 5.1 months.[18]

Combination Bevacizumab/Erlotinib in the Maintenance Setting

The ATLAS trial[19] (NCT00257608) evaluated the bevacizumab/erlotinib combination in the maintenance setting. In this trial, 1145 patients received 4 cycles of chemotherapy plus bevacizumab. Following this, 743 patients without disease progression were randomized to receive bevacizumab plus/minus erlotinib. Median PFS (but not OS) was significantly better for patients in the bevacizumab/erlotinib arm (3.7 vs 4.8 months; *P* <.001).[19]

Combination Bevacizumab/Erlotinib in the Second-Line Setting

Herbst et al[20] (NCT00130728) evaluated the combination of erlotinib plus bevacizumab in the second-line setting. In the BeTa trial, 636 patients with advanced-stage NSCLC who were recurrent or refractory on standard first-line chemotherapy or chemoradiation were randomized to erlotinib plus bevacizumab or erlotinib plus placebo. Overall, no difference in OS was observed in the full study population. However, in a subgroup analysis of 355 patients with tissue available for assessment, OS trended better for the erlotinib/bevacizumab group in those patients whose tumors were *EGFR*-mutated, though this trend was not significant.[20]

Conclusion

Treatment of advanced-stage NSCLC is rapidly advancing. Combination antiangiogenesis/EGFR TKI therapy is a novel approach that has shown some early promise. A trial exploring combination bevacizumab and erlotinib is currently active in the general NSCLC population in Switzerland (NCT01116219), and updated results from a study of this combination in the general population of elderly patients with NSCLC is eagerly awaited (NCT00553800).

Recent trials of advanced NSCLC in the general population have evaluated clinical endpoints such as PFS and OS, and some have found a similar or improved PFS with combination bevacizumab/erlotinib. Overall survival results have not been as encouraging in studies of NSCLC in the general population. Further investigation of OS with this combination treatment scheme in the mutation-positive population is warranted. Results from studies currently evaluating the combination of antiangiogenic inhibitors, such as bevacizumab and ramucirumab, in combination

with targeted therapies in the *EGFR* mutation-positive patient population are expected within the next 5 years (NCT01562028, NCT01532089, NCT02411448).

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