Afatinib in metastatic NSCLC with mutations

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In July 2013, afatinib was approved by the US Food and Drug Administration for first-line treatment of patients with metastatic non–small-cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Quiagen's therascreen EGFR RGQ_PCR Kit for detection of EGFR exon 19 deletions (del19) and exon 21 (L858R) substitution mutations was concurrently approved. Afatinib is an oral selective ErbB family inhibitor that irreversibly blocks signaling from EGFR/ErbB1, HER2/ErbB2, and ErbB4 and has shown broad-spectrum activity against tumor cells with EGFR mutations.

The approval was based on an international phase 3 trial (LUX-Lung 3) showing significantly improved progression-free survival (PFS) for first-line afatinib compared with cisplatin plus pemetrexed.[1] In this trial, 345 patients with *EGFR*-mutant advanced lung adenocarcinoma were randomized (2:1) to afatinib 40 mg/d (n = 230) or up to 6 cycles of cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 (n = 115) given every 21 days. Patients receiving afatinib could have their dose increased to 50 mg/d after the first 21-day cycle in the absence of rash, diarrhea, mucositis, or any other drug-related adverse event higher than grade 1. Patients in the chemotherapy group received folic acid, vitamin B12, and dexamethasone.

The afatinib and chemotherapy groups were well balanced for age (median, 61.5 and 61 years, respectively), sex (64% and 67% female), race (72% East Asian in both, 26.5% and 26% white), smoking status (67% and 70% never, 30% and 28% former), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 in 100% and 99%; 0 = fully active, 5 = dead), adenocarcinoma stage (IIIB with pleural effusion in 9% and 15%, IV in 91% and 85%), and *EGFR* mutations (del19 in 49% and 59%, L858R in 40% and 41%, and other in 11% and 10%).

Afatinib was given for a median of 11.0 months (16 cycles), with a mean overall per-patient compliance of 98%. Dose reduction to < 40 mg/d was required in 52% of patients and more than 1 reduction was required in 19%; 7% had their dose increased to 50 mg/d after the first cycle. Patients in the chemotherapy group received a median of 6 cycles, with 75% receiving ≥ 4 cycles and 55% receiving 6. Dose reduction because of adverse events was required in 16% of the chemotherapy group and treatment was delayed by ≥ 6 days in 40% .

Median follow-up at the time of primary analysis was 16.4 months. Median PFS was 11.1 months in the afatinib group, compared with 6.9 months in the chemotherapy group (hazard ratio [HR], 0.58; P = .001). Median PFS among the 308 patients with del19 and L858R mutations (the most common activating *EGFR* mutations) was 13.6 months in the afatinib group and 6.9 months in the chemotherapy group (HR, 0.47; P = .001). Subgroup analyses showed generally consistent benefit of afatinib, with significant effects observed for women (HR, 0.54; 95% confidence interval [CI], 0.38-0.78), age < 65 years (HR,0.53; 95% CI, 0.36-0.76), Asian race (HR, 0.54; 95% CI, 0.38-0.76), del19/L858R *EGFR* mutation (HR, 0.47; 95% CI, 0.34-0.65), del19 *EGFR* mutation (HR, 0.28; 95% CI, 0.18-0.44), ECOG performance status of 0 (HR, 0.50; 95% CI, 0.31-0.82) or 1 (HR, 0.63; 95% CI, 0.43-0.91), and never-smokers (HR, 0.47; 95% CI, 0.33-0.67).

Objective response occurred in 56% of patients in the

What's new, what's important

With the approval of afatinib as a first-line therapy for advanced non–small-cell lung cancer with activating epidermal growth factor receptor mutations (especially exon 19 deletions and exon 21 [L858R] substitutions), oncologists in the United States now have a second option along with erlotinib for treating this disease. (Elsewhere in the world, gefitinib is a third option). The approval was based on the results of a phase 3 study that showed better progression-free survival in patients with del19 and L858R mutations who received afatinib compared with those receiving cisplatin plus pemetrexed as chemotherapy (PFS, 13.6 vs 6.9 months, respectively; 11.1 vs 6.9 months for all patients). It is worth noting that subgroup analyses showed that significant effects observed for women, being older than 65 years, Asian race, and never-smokers. Objective response occurred in 56% of the afatinib group and in 23% of the chemotherapy group, but overall survival data were still preliminary at the time of analysis. The most common treatment-related adverse events with afatinib included diarrhea, rash/acne, and stomatitis/mucositis; and with chemotherapy, nausea, decreased appetite/fatigue, and vomiting. In all, 8% of afatinib patients and 12% of chemotherapy patients discontinued treatment because of treatment-related AEs.

– Jame Abraham, MD

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How I treat metastatic EGFR-mutated NSCLC

The US Food and Drug Administration's approval of erlotinib for use in patients with EGFR exon 19 and 21 alterations was almost an afterthought; data from multiple randomized trials supporting the activity of EGFR TKIs over chemotherapy was already well established. Thankfully, erlotinib (and gefitinib outside of the US) had already been approved for use in NSCLC some 9 years earlier, so it was available to prescribe in the front-line setting, and insurers generally approved its use in this fashion.

The years of postmarketing experience with erlotinib have given oncologists a familiarity with this drug and an expectation regarding rates of side effects associated with its use. The recent entrance of afatinib into this market provides another option for use, however it is difficult to imagine how it will supplant erlotinib in the front-line setting without a randomized comparison. This is not the first time that drugs with relatively similar mechanisms of action have been approved for the same indication in NSCLC (see paclitaxel and docetaxel), and in oncology it is a no-brainer that more treatment options are better than fewer of these.

Although the choice between the 2 drugs is not necessarily trivial, the greater current challenge lies in determining what the best approach is for EGFR-mutated NSCLC patients at the time of progression on an EGFR TKI, which typically occurs after an initial response to therapy. Larger experience with treating these very unique cancers has provided 2 common scenarios that can be approached differently:

Oligoprogression. After an initial response, progression can occur at 1 or a few sites (including the brain) and can be controlled with local therapies such as radiation while continuing the EGFR TKI and suppressing other sensitive metastatic sites. Essentially, this is a way to get as much of the treatment mileage out of the EGFR TKI as is possible before switching to another line of systemic therapy. This approach is being formally studied in a multicenter trial (NCT01573702).

Widespread progression. The EGFR TKI should be discontinued and cytotoxic chemotherapy would be the standard approach. Obtaining repeat tissue biopsy at this point is recommended to assess for the presence of T790 mutation and possibly a different type of tumor histology that may impact the selection of cytotoxic agents: multiple reports of small cell carcinoma occurring at the time of progression have been published. Retreatment with an EGFR-TKI after chemotherapy can also be considered as sensitivity can recur.

As mechanisms of resistance to EGFR TKIs have become better understood agents directed to other targets that have shown preclinical activity are being studied in current clinical trials (both alone and in combination), including inhibitors specific to mutated EGFR (CO-1686), other pan-ErbB inhibitors (dacomitinib, BMS-690514), c-Met inhibitors (LY2875358, INC280, onartuzumab), inhibitors of PI3K (BKM120), MEK (MEK162) and HSP 90 (AUY922). Given the clinical work being done in this area, the goal of further improving outcomes in EGFR-mutated NSCLC patients is likely to be realized in the near future. Efforts must be made to enroll these patients onto clinical trials whenever possible.

– James P Stevenson, MD

afatinib group and 23% in the chemotherapy group (P = .001) and median durations of response were 11.1 and 5.5 months, respectively. Overall survival (OS) data were still preliminary and median OS had not been reached in either group at the time of analysis. OS did not significantly differ between the afatinib and chemotherapy groups (HR, 1.12; P = .60; 25th percentile, 16.6 vs 14.8 months). In total, 62% of patients in the afatinib group crossed over to chemotherapy, and 65% of patients in the chemotherapy group crossed over to EGFR tyrosine kinase inhibitor treatment after progression on study treatment.

The most common treatment-related adverse events of any grade in the afatinib group were diarrhea (95% vs 15% in the chemotherapy group) , rash/acne (90% vs 6%), stomatitis/mucositis (72% vs 15%), paronychia (57% vs 0%), dry skin (29% vs 2%), and decreased appetite (21% vs 53%). The most common events in the chemotherapy group were nausea (66% vs 18% in the afatinib group), decreased appetite, fatigue (47% vs 18%), vomiting (42% vs 17%), neutropenia (31% vs 1%), and anemia (28% vs 3%). The most common grade 3 or higher adverse events were rash/acne (16% vs 0%), diarrhea (14% vs 0%), paronychia (11% vs 0%), and stomatitis/mucositis (9% vs 1%) in the afatinib group and neutropenia (18% vs < 1%), fatigue (13% vs 1%), and leukopenia (8% vs < 1%) in the chemotherapy group. Treatment was discontinued because of treatment-related adverse events in 8% of afatinib patients and 12% of chemotherapy patients. Three cases of potentially treatment-related interstitial lung disease (ILD)-like events and 4 potentially treatment-related deaths (due to respiratory decompensation in 2 patients, sepsis in 1, and unknown cause in 1) were observed among afatinib patients. There were no treatment-related fatalities in the chemotherapy group.

Afatinib is marketed as Gilotrif by Boehringer Ingelheim. It carries warnings and precautions for diarrhea, bullous and exfoliative skin disorders, ILD, hepatic toxicity, keratitis, and embryofetal toxicity.

Reference

1. Sequist LV, Yang J-CH, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31:3327-3334.