COUNTERPOINTS

Current Controversies in Hematology and Oncology

Should EGFR Tyrosine Kinase Inhibitors Be Used in Non–Small Cell Lung Cancer in the Absence of *EGFR* Mutations?

Tyrosine kinase inhibitors (TKIs) that block epidermal growth factor receptor (EGFR) clearly work best in patients who have non–small cell lung cancer (NSCLC) with *EGFR* mutations, but are they worth using in patients without these mutations? In this month's Counterpoints, Dr Frances A. Shepherd says that there is a role for EGFR TKIs in patients with wild-type *EGFR* disease. Dr Gregory J. Riely, however, says that the level of toxicity associated with EGFR TKIs outweighs any slight chance of benefit for these patients, who have multiple other treatment options.

Yes, There Is a Role for EGFR TKIs in These Patients

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Those who say that EGFR TKIs do not work against wild-type *EGFR* NSCLC simply do not understand statistical interaction.

In statistical terms, when a treatment works differently in different subgroups, it is called *interaction*. Interaction is considered to be *quantitative* when the magnitude of the benefit from treatment differs between the subgroups, and *qualitative* when treatment results in benefit in one subgroup and harm or lack of benefit in the other. The purest way to determine true interaction is to evaluate treatment effects within subgroups of patients in studies that have a nontreatment or placebo-controlled arm. In that way, the prognostic effect in a subgroup, which may confound single-arm analyses, can be isolated in the placebo arm.

What the Studies Show

With that in mind, let us examine the effect of the *EGFR* mutation subtype on overall response rates (ORRs) and survival benefit in some of the large randomized studies that compared the EGFR TKIs gefitinib (Iressa, AstraZeneca),[1] erlotinib (Tarceva, Genentech/Astellas),[2,3] dacomitinib,[4] and afatinib (Gilotrif, Boehringer Ingelheim)[5] with placebo. These trials evaluated the use of a single-agent

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No, EGFR TKIs Should Be Reserved for Patients With *EGFR* Mutations

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Decisions about therapy for patients with metastatic NSCLC have become dramatically more complex over the last 2 years. Although EGFR TKIs are approved for use in patients with NSCLC regardless of *EGFR* genotype, the breadth of therapeutic options has expanded. We recently have learned about the role of checkpoint inhibitor immunotherapy in patients with previously treated lung cancer, and we have seen modest improvements in outcomes with chemotherapy via the addition of angiogenesis inhibitors. Whereas once we had few options for patients with NSCLC, we now can choose among a range of agents with various efficacies. It is logical to choose the treatments that we believe will have the greatest chance of shrinking cancer and improving quality of life. In this framework, the data do not support the routine use of EGFR TKIs for patients without *EGFR* mutations.

The Role of EGFR TKIs

The role of EGFR TKIs in patients with NSCLC was first established in a landmark trial by Frances Shepherd and colleagues.[1] In that study, which compared erlotinib with placebo in patients who previously had received 1 or 2

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Yes, There Is a Role for EGFR TKIs in These Patients *(cont)*

EGFR TKI as maintenance therapy following first-line and/or second-line chemotherapy[1,2] after initial response to first-line chemotherapy[3] or—in the case of the second-generation TKIs—after both chemotherapy and a first-generation EGFR TKI[4,5] (Table).

When the results of the 3 trials that reported ORRs[1,2,4] are examined according to *EGFR* mutation status, it is clear that the ORR is always higher—and frequently significantly higher—in patients whose tumors carry sensitizing *EGFR* mutations. However, every study also reported responses in the wild-type *EGFR* subgroups.

Evaluation of progression-free survival (PFS) is arguably the best way to measure survival benefit in these randomized trials because it provides a true assessment of the effect of the treatment while the patient actually is receiving the drug. As shown in the table, every trial demonstrated a PFS benefit (when reported) from EGFR TKI therapy. All hazard ratios (HRs) were below 1.0 for both the wild-type and mutated subgroups, and only 1 trial demonstrated significant interaction based on mutation status.[3] This interaction was qualitative, however—it reflected only a difference in the magnitude of benefit between the groups. There was no evidence of harm or lack of benefit in the wild-type *EGFR* subgroup.

The results of the placebo-controlled trials are similar for overall survival (OS), with HRs all in the same direction and no significant interaction demonstrated in any trial.

The interaction based on *EGFR* mutation status is completely different when treatment with an EGFR TKI is compared with chemotherapy in the first-line[6] or second-line setting.[7,8] In randomized trials of first-line therapy,[6] patients with wild-type *EGFR* tumors who were treated with EGFR TKIs rather than chemotherapy showed significantly shorter PFS and trends for worse OS. This applied even in highly selected subgroups of patients enriched for the presence of *EGFR* mutations. In the second-line setting, OS was poorer (HR, 1.25) in patients with wild-type tumors who received erlotinib rather than chemotherapy, whereas there was a trend for benefit (HR, 0.71) in the small subset of patients with *EGFR*-mutated tumors.[7] The results of a trial comparing second-line gefitinib with docetaxel were similar, with HRs of 1.02 and 0.83 for the wild-type and mutated groups, respectively.[8] The interaction was not significant in either study.

In many jurisdictions, erlotinib and gefitinib received approval as both second- and third-line therapy, with no restrictions applied to patients who had received only 1 line of chemotherapy. However, the studies that led to these approvals specified that those patients entering the trials after only 1 line of treatment should be unfit for further chemotherapy. The mutation subgroup studies of the trials that compared a second-line EGFR TKI with chemotherapy, even in the absence of statistically significant interaction *P* values, suggest quite strongly that chemotherapy, not an EGFR TKI, should be the second-line treatment of choice in fit patients with wild-type *EGFR* tumors who are eligible to receive chemotherapy.

Returning to the question of EGFR TKIs in patients who have no proven chemotherapy options remaining, it is clear that some patients with wild-type *EGFR* cancers do respond to and derive PFS and OS benefit from EGFR TKIs vs no active treatment (ie, supportive care alone). Thus, if no further chemotherapy options are available, a trial of an EGFR TKI definitely is an option. Is there one TKI that might be preferred in this setting over others? The 798-patient LUX-Lung 8 trial (A Phase III Trial of Afatinib [BIBW 2992] Versus Erlotinib for the Treatment of Squamous Cell Lung Cancer After at Least One Prior Platinum-Based Chemotherapy),[9] which compared afatinib with erlotinib in patients who had squamous cell cancers (in which *EGFR* mutations almost never occur), is the only large randomized trial to have addressed this question. Although the response rates were low in both arms (afatinib, 6%; erlotinib, 3%; *P*=.055), afatinib was associated with significantly longer PFS (HR, 0.82; *P*=.043) and OS (HR, 0.81; *P*=.008). This suggests that in wild-type *EGFR* tumors, the irreversible binding of this pan-EGFR inhibitor may be critical. It is important to note, however, that the median differences in PFS and OS were only 0.5 and 1.1 months, respectively.

Although all of the placebo-controlled studies show only modest benefits from EGFR TKIs, the risks and toxicity levels are low.

Although all of the placebo-controlled studies show only modest benefits from EGFR TKIs, the risks and toxicity levels are low. The result is a therapeutic index that favors treatment. The studies all showed that the relative benefit of these agents usually was less in patients with wild-type *EGFR* than in those with mutated *EGFR*, and that the absolute benefit frequently was considerably less (sometimes no more

Table. Response and Survival According to *EGFR* Mutation Status in Randomized Placebo-Controlled Trials

Study	ORR, WT	ORR, Mutated[a]	PFS, WT	PFS, Mutated[a]	OS, WT	OS, Mutated[a]
BR.21[2]	6.9%	26.7%	HR, 0.59	HR, 0.41	HR, 0.74	HR, 0.55
	P=.035		Interaction *P*=0.45		Interaction *P*=0.47	
ISEL[1]	2.6%	37.5%	NR	NR	NR	NR
	P not reported					
BR.26[4]	4.3%	11.4%	HR, 0.75	HR, 0.48	HR, 0.93	HR, 0.98
	P=.02		Interaction *P*=.029		Interaction *P*=.69	
LUX-Lung 1[5]	NR	NR	HR, 0.61	HR, 0.51	HR, 1.02	HR, 1.65
			Not significant		Not significant	
SATURN[3]	NA	NA	HR, 0.78	HR, 0.10	HR, 0.77	HR, 0.83
			Interaction *P*<.001		Not significant	

HR, hazard ratio; ISEL, Iressa Survival Evaluation in Lung Cancer; LUX-Lung 1, BIBW 2992 Versus Placebo and BSC in Non-small Cell Lung Cancer Patients Failing Erlotinib or Gefitinib; NA, not applicable; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SATURN, Sequential Tarceva in Unresectable NSCLC; WT, wild-type.

Note: All hazard ratios compare EGFR TKI treatment with placebo.

[a] Sensitizing *EGFR* mutations in exon 19 or exon 21.

than 1 month at the median), which can be explained by the poorer prognosis of patients with wild-type *EGFR* tumors. This raises the question of what constitutes a "clinically meaningful" survival benefit. For some patients and oncologists, a 1-month survival benefit might not be considered meaningful. Although it is nearly impossible to apply science and statistics to value judgments of what is meaningful to patients, it is possible to calculate the financial cost of such treatment. Interestingly, in BR.21 (A Randomized Placebo Controlled Study of Erlotinib [OSI-774, Tarceva] Versus Placebo in Patients With Incurable Non-Small Cell Lung Cancer Who Have Failed Standard Therapy for Advanced or Metastatic Disease), the cost of treating patients with *EGFR*-mutated tumors actually was higher ($138,168 per life-year gained) than treating those with wild-type tumors ($87,994). The most important reason for this was the cost of drug acquisition; patients with mutated tumors stayed on treatment longer than did those with wild-type tumors.[10] In many countries, this cost would fall within what is considered an acceptable cost per life-year gained.

Conclusion

In summary, when chemotherapy options have been exhausted, a trial of an EGFR TKI is indicated in patients with wild-type *EGFR* tumors. The risk-to-benefit ratio favors such treatment, and the costs are acceptable in many jurisdictions.

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lines of chemotherapy, the ORR for erlotinib was 9% and the HRs for PFS and OS were 0.66 and 0.7, respectively. Although these results were better than those seen in patients given placebo and led to the approval of erlotinib by the US Food and Drug Administration, it is fair to point out that the median PFS was just 2 months in the erlotinib-treated population. Much has been made of the subsequent analyses of patients with squamous cell lung cancer, as well as the efficacy in patients with wild-type *EGFR* tumors.[2,3] But, at the time BR.21 was designed, conducted, and initially analyzed, *EGFR* mutations had not been discovered in people with lung cancer. Moreover, the relevance of tumor histology was not appreciated in the way it is today. These subsequent analyses only highlight the challenges of performing a subset analysis after dramatic changes in our knowledge of a disease, and they emphasize the value of data from trials in which mutation status and histology are prospectively assessed.

The *EGFR* genotype has been prospectively evaluated as a determining factor in both the first- and second-line treatment of patients. IPASS (Iressa Pan-Asia Study) compared gefitinib with carboplatin/paclitaxel as initial therapy in patients with untreated NSCLC.[4] The patients without *EGFR* mutations had a rate of response to gefitinib of less than 1%. In comparison, the patients with *EGFR* mutations had a response rate of 71%. TAILOR (Tarceva Italian Lung Optimization Trial) explored whether erlotinib or docetaxel is the preferred second-line treatment in patients with previously treated wild-type *EGFR* lung cancer.[5] In this population, treatment with docetaxel led to a longer OS than treatment with erlotinib (HR, 0.71; median OS, 8.2 vs 5.4 months). The radiographic response rate was 15% for patients who received docetaxel vs 3% for those who received erlotinib. This 3% response rate was very similar to the 1% response rate observed in IPASS. These 2 trials make it clear that in the first- or second-line setting, patients with wild-type *EGFR* lung cancer should be treated with conventional chemotherapy, whether that means a platinum-based doublet as first-line treatment or docetaxel as second-line treatment.

The addition of angiogenesis inhibitors to docetaxel as second-line treatment was recently explored in a trial that compared treatment with docetaxel and treatment with docetaxel plus ramucirumab (Cyramza, Lilly), an antibody to vascular endothelial growth receptor 2 (VEGFR-2).[6] In this trial, combination therapy was found to be superior to docetaxel alone, with an HR of 0.86 in the overall population. Importantly, the HR was 0.83 in the group of patients who were known to have wild-type *EGFR*, suggesting that this patient population benefitted equally from the addition of ramucirumab.

In 2015, nivolumab (Opdivo, Bristol-Myers Squibb) was added to the group of agents with clear benefit in patients having wild-type *EGFR* NSCLC. In 2 practice-changing randomized trials in which patients with either squamous cell or non–squamous cell NSCLC were randomly assigned to receive either docetaxel or nivolumab, nivolumab treatment led to prolongation of OS, improving median OS by approximately 3 months.[7,8] Similarly, the response rates were better with nivolumab treatment (the response rate went from 9% to 20% in patients with squamous cell NSCLC, whereas it went from 12% to 19% in patients with non–squamous cell NSCLC). Exploring *EGFR* mutations in the subset analysis, the authors observed that patients with wild-type *EGFR* disease appeared to benefit even more than the overall population. The HR for OS was 0.75 in the overall population of patients with non–squamous cell NSCLC, whereas it was 0.66 for those patients with no *EGFR* mutations detected. These data make it clear that nivolumab is superior to docetaxel for patients with wild-type *EGFR* lung cancer, in whom we know that docetaxel is superior to erlotinib.

In the first- or second-line setting, patients with wild-type *EGFR* lung cancer should be treated with conventional chemotherapy.

The data that most clearly define the relative inactivity of EGFR TKIs in patients with wild-type *EGFR* disease, as well as the toxicity of these agents, come from a trial comparing afatinib with erlotinib in patients having squamous cell NSCLC.[9] In this trial, an improvement in OS and PFS was noted in the patients treated with afatinib. The ORR was disappointing, with just 6% of patients in the afatinib arm and 3% of patients in the erlotinib arm having a partial response to therapy with an EGFR TKI. In this contemporary trial of patients treated with an EGFR TKI, grade 3 or higher adverse events occurred in 57% of patients in the afatinib group and 57% of patients

in the erlotinib group. Grade 3 diarrhea occurred in 10% of patients, grade 3 stomatitis in 4%, and grade 3 rash in 10%. In cross-trial comparisons, the magnitudes of the response rate, PFS, and OS with both of the EGFR TKIs were numerically inferior to those observed for patients with squamous cell NSCLC in trials of nivolumab, single-agent docetaxel, or docetaxel and ramucirumab.

Conclusion

When we have a choice of available therapies, we must select those with the best overall outcome, taking into account both toxicity and disease control. The data described here demonstrate that multiple therapeutic options are available for patients with wild-type *EGFR* NSCLC, with efficacy significantly greater than that observed with single-agent EGFR TKIs. Given the real toxicities of EGFR TKIs and the multiple other available therapies with significantly better outcomes, EGFR TKIs should not be used routinely in patients who do not have *EGFR* mutations.

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