

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Lung Cancer in Focus

The Role of Third-Generation Epithelial Growth Factor Receptor Inhibitors in Non–Small Cell Lung Cancer



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H&O How did the discovery of *EGFR* mutations lead to the development of targeted therapies?

LS The discovery of epithelial growth factor receptor (*EGFR*) mutations a little more than 10 years ago was a defining event that changed how we think about lung cancer. Not only did it lead to treatments that targeted *EGFR*, it also paved the road for development of other targeted treatments, such as those for anaplastic lymphoma kinase (*ALK*) and *ROS1* alterations. The discovery of *EGFR* mutations was the first of numerous similar discoveries.

H&O Which first-generation and second-generation *EGFR* inhibitors are used in non–small cell lung cancer (NSCLC)?

LS The 2 first-generation *EGFR* inhibitors are gefitinib, which is currently not approved in the United States, and erlotinib (Tarceva, Genentech/Astellas). Both of these were first studied approximately 10 years ago, for general use in unselected patients with advanced NSCLC. The mutations were discovered after physicians observed that certain patients were ultrasensitive to these medications.

The only second-generation *EGFR* inhibitor that is approved by the US Food and Drug Administration (FDA) at this time is afatinib (Gilotrif, Boehringer Ingelheim). There are a couple of similar agents that are not FDA approved; one that is being developed by Pfizer is dacomitinib (PF-00299804).

H&O What is the difference between first-generation and second-generation *EGFR* inhibitors?

LS Although gefitinib and erlotinib are highly specific for *EGFR*, they are reversible inhibitors—meaning that they can be competed off the receptor by adenosine triphosphate (ATP). In contrast, later-generation *EGFR* inhibitors such as afatinib are irreversibly bound to the receptor; they form a covalent bond inside the cell between the drug and the receptor. One can think of the reversible inhibitors as being stuck to the receptors like strong magnets; they are tightly attached but can be pulled apart with some force. The bond between an irreversible inhibitor and the receptor is more like superglue.

H&O What other limitations exist?

LS As with all cancer drugs, the biggest problem with these agents is that they eventually stop working because the tumors become resistant to them. The most common time frame for resistance to occur is 9 to 15 months after the start of therapy. Through performing biopsies on patients with these drug-resistant tumors, we have learned that in 50% to 60% of cases resistance is due to a single mutation called T790M that arises in *EGFR* itself. None of the first-generation or second-generation *EGFR* inhibitors are able to work properly if the tumors acquire that mutation.

H&O How about side effects?

LS Although the drugs are fairly well tolerated, they do have some side effects, such as rash and diarrhea. Part of the reason for these side effects is that in addition to targeting the mutant EGFR that resides in the tumor cells, first-generation and second-generation EGFR drugs also inhibit wild-type EGFR that resides in normal, healthy tissues in the body such as the skin and the lining of the gut. The side effects are caused by wild-type EGFR inhibition. The second-generation drugs appear to cause slightly more problems with rash and diarrhea than the first-generation drugs, which may be related to the fact that they are irreversibly bound or that different doses are used.

H&O How good is the response rate with first-generation and second-generation drugs?

LS The majority of clinical trials in *EGFR*-mutant patients have been done with gefitinib or erlotinib, and the response rates have been quite high, approximately 70%. We know that patients who have the *EGFR* mutation ideally should be treated up front with these agents rather than with chemotherapy, because randomized trials have shown us that this strategy improves progression-free survival and quality of life.

The second-generation drug afatinib also is quite active, with a response rate of approximately 70%. It has been compared with first-line chemotherapy in 2 randomized trials. Similarly to the first-generation drugs, the strategy of starting with the genotype-specific therapy (in this case, afatinib) has been shown to improve response rate, progression-free survival, and quality of life compared with chemotherapy. When second-generation EGFR inhibitors were first being studied in the laboratory, it appeared that they might also be very useful for treating patients with resistance to first-generation EGFR inhibitors because they have *in vitro* activity against T790M. However, this was not seen in clinical trials, probably because doses sufficient to inhibit T790M were not achievable in patients. In other words, afatinib should be considered as an option for initial EGFR inhibitor therapy, not for resistance—as per its FDA-approved indication.

H&O How do the first-generation and second-generation EGFR inhibitors compare with each other in terms of efficacy?

LS Although gefitinib, erlotinib, and afatinib all have been shown to be better than chemotherapy for patients with an *EGFR* mutation, we do not yet have trials that compare these agents head-to-head. Newer data by Yang

and colleagues in *Lancet Oncology* suggest that an overall survival benefit is achieved with afatinib compared with first-line chemotherapy, which is a distinguishing factor compared with the other 2 drugs. This was seen only in the subset of *EGFR* mutation–positive patients with the exon 19 deletion mutation (the most common mutation). But in general, all of these drugs are options for first-line treatment and we are anxiously awaiting head-to-head comparisons.

H&O How is T790M-positive NSCLC treated?

LS Until recently, we did not have any treatments that successfully targeted T790M-positive disease. The third-generation EGFR inhibitors that are now being developed have the potential to be game changers because they are effective in patients who have developed resistance to the earlier EGFR inhibitor. They also have fewer side effects than previous agents.

H&O What third-generation agents are in development?

LS The two that are the farthest along are rociletinib (CO-1686), which is being developed by Clovis, and AZD9291, which is being developed by AstraZeneca. Both of these agents have received breakthrough therapy designation from the FDA. What makes these third-generation EGFR drugs different from the earlier versions is that not only do they bind to the activating *EGFR* mutations, they also bind to T790M, which is the primary cause of resistance to existing EGFR inhibitors. Another important distinction is that the third-generation drugs do not bind to wild-type EGFR. As a result, they produce much milder side effects, such as rash and diarrhea, than previous EGFR inhibitors.

H&O Could you talk about the studies that have looked at these third-generation agents?

LS Most of the studies that have been presented so far are phase 1 studies, in which small numbers of patients were treated with escalating doses. When disease activity was observed in phase 1 studies of both rociletinib and AZD9291, the studies were expanded to include a few hundred patients with *EGFR* mutations and acquired resistance to one of the existing drugs. The response rates in studies of rociletinib and AZD9291 have been approximately 60%. The follow-up is still short, so we do not yet know about the duration of response, but early data suggest that the response may last for 6 months or longer—similar to or perhaps better than what has been seen with the frontline agents.

H&O Could you talk more about the side effects with the third-generation agents?

LS We do not yet have a sense of the final prevalence of side effects, so it is a bit premature to speculate. The information that has been presented at public meetings suggests that both of these drugs are well tolerated. There seems to be much less rash and diarrhea than we have come to expect with EGFR drugs, probably because the agents do not inhibit wild-type EGFR.

Rociletinib has been found to cause elevated blood glucose, which is a side effect that has not been seen with other EGFR inhibitors. There is a lot of research right now looking at why that is, and how that interacts with the efficacy of the drug. One possibility is that this side effect is related to the insulin receptor, which is a pathway through which tumors have been known to get around EGFR drugs. As a result, we are looking into whether the drug may inhibit both EGFR and the insulin pathway. Having this information would give us a better understanding of the drug.

H&O What else would you like to say about these agents?

LS There has been a great deal of activity in the EGFR field over the last couple of years. Not only are rociletinib and AZD9291 in development, but additional third-generation EGFR inhibitors are in the pipeline. This is a very exciting time for NSCLC patients and their doctors.

Suggested Readings

Janne PA, Ramalingam SS, Yang JCH, et al. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor-resistant non-small cell lung cancer (NSCLC) [ASCO abstract 8009]. *J Clin Oncol*. 2014;32(5)(suppl).

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