Crizotinib — Latest Champion in the Cancer Wars?

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Three articles in this issue of the Journal report on the therapeutic potential of a new kid on the kinase inhibitor block: crizotinib, an ATP-competitive inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase.

Kwak et al. summarize a study involving patients with non–small-cell lung cancer who were enrolled in a phase 1 trial, starting in 2008, hot on the heels of a study in which cell lines derived from non–small-cell lung tumors were shown to be sensitive to NVP-TAE684 and crizotinib (PF-02341066). From a cohort of 1500 patients with non–small-cell lung cancer, 82 (5.5%) were found to carry an ALK rearrangement on fluorescence in situ hybridization (FISH). The authors note that not all of these genetic rearrangements were confirmed as EML4-ALK, which suggests that other ALK fusions may be present, such as TFG-ALK and KIF5B-ALK. Although the best-studied ALK fusion is the nucleophosmin (NPM)-ALK protein found in lymphoma, it is reasonable to expect that a number of the signaling pathways activated by NPM-ALK will also be involved in transformation by variants such as EML4-ALK (Fig. 1).

Most of the patients with non–small-cell lung cancer who carried the EML4-ALK translocation were nonsmokers and had adenocarcinomas. Even though more than 90% of these patients had undergone at least one previous line of therapy, the investigators observed a 57% response rate to crizotinib, according to Response Evaluation Criteria in Solid Tumors (RECIST), with a rate of disease control of 87% at 8 weeks. Although a control group was lacking in this study, these results compare very favorably with the reported 10% response with second-line chemotherapy. At a mean treatment duration of 6.4 months, 27 patients had stable disease, 46 had a partial response, and 1 had a complete response. All patients tested negative for amplification of MET, another target for crizotinib, which suggested that the therapeutic effect is through inhibition of ALK.

These results raise the question of whether crizotinib will yield equally strong responses as the first therapeutic intervention or whether a combined approach will be more beneficial. At a rate of approximately 5% positivity for the ALK rearrangement, the number of potential patients for crizotinib therapy is substantial, approaching 10,000 annually in the United States alone. Clearly, with mutant epidermal growth factor receptor (EGFR), K-RAS, and ALK as important clinical determinants in this type of lung cancer, the use of genotyping as standard practice must be considered as a move toward personalized therapy.

As with the kinase inhibitors already in use, such as imatinib and EGFR inhibitors, kinase inhibition frequently leads to the appearance of drug-resistance mutations within the target kinase itself. Although Kwak et al. do not address this issue, it is possible that in a number of ALK-positive patients who had a limited response in this study, such mutations may have developed either before or during treatment with crizotinib. This factor is clearly illustrated in a study by Choi et al., who describe mutations in EML4-ALK that confer resistance to crizotinib. Their data support the independent appearance of mutations leading to C1156Y and L1196M coding changes in a patient with non–small-cell lung cancer who had an initial strong clinical response to
On the basis of structural considerations of the crystal structure of the ALK kinase domain, L1196M represents a mutation of the gatekeeper residue, similar to the T790M gefitinib-resistance mutations observed in EGFR and T315I mutations in ABL, and it would be predicted to prevent crizotinib binding to ALK. The effect of the C1156Y mutation is unclear, since it appears unlikely to have a direct effect on crizotinib binding. Further studies will be required to establish the mechanism of action behind C1156Y resistance. Choi et al. found that these EML4-ALK mutants are less sensitive to crizotinib than is wild-type EML4-ALK when expressed in Ba/F3 cells, in agreement with the loss of clinical response in this patient. The resistance of the C1156Y variant to crizotinib was not as great in vitro as in vivo, suggesting that this mutation may require interaction with additional factors in the cell to have strong drug sensitivity.

The appearance of crizotinib-resistance mutations in this patient indicates that additional ALK inhibitors will be required to target EML4-ALK mutants that are insensitive to crizotinib in a clinical setting. This brings clinical reality to the predictions from a recent prospective mutagenesis study on NPM-ALK in which strong...
tance to ALK inhibitors in mouse tumor models was observed with the NPM-ALK mutant L256M, which is in the same residue as L1196M of EML4-ALK.\textsuperscript{13} Thus, a familiar story line emerges, highlighting the need for basic scientists and clinicians to work together to plan a step ahead of the evolving tumor. It is encouraging that some progress in this area has already been made, and a number of such drugs are in the pipeline, including a new ALK inhibitor.\textsuperscript{14}

Although patients with ALK-positive non–small-cell lung cancers make up the largest group of patients who may benefit from crizotinib, other patients with rarer diseases, such as those with ALK-positive non-Hodgkin’s lymphoma or inflammatory myofibroblastic tumor (IMT), also stand to benefit. This is illustrated in a study by Butrynski et al.,\textsuperscript{15} in which the authors describe two patients with IMT, one of whom carried the RANBP2-ALK fusion protein. Both patients were treated with crizotinib, with the ALK-positive patient having a strong response for several months. However, there was subsequent identification of growth in three lesions, which were resected before resumption of crizotinib postoperatively. A complete radiographic remission was reported in June 2010. It will be interesting to understand more about the nature of the masses that were surgically removed, since it is possible they carried crizotinib-insensitive RANBP2-ALK variants. Therefore, ALK-positive IMT, like non–small-cell lung cancer, appears to have an Achilles’ heel when it comes to inhibition of ALK signaling.

One major problem for cancer drugs, including kinase inhibitors, is toxic effects. Both Kwak et al. and Butrynski et al. report that crizotinib produced only grade 2 side effects in patients when used at the therapeutic dose of 250 mg twice daily. This is good news for patients facing the prospect of long-term cancer therapy.

Together, these three studies provide an optimistic view of the successful treatment of ALK-positive cancers. One positive offshoot is the potential use of crizotinib in treating neuroblastoma, a devastating childhood cancer, in which ALK gain-of-function mutations have been reported in approximately 10% of patients.\textsuperscript{10} Clearly, in groups of patients with cancers in which ALK is implicated, a standard genotyping approach will be important for a more personalized therapeutical protocol. Future clinical studies of crizotinib and other ALK inhibitors will tell us whether they will be the latest champions in the cancer wars.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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