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Clinical Response to Crizotinib Retreatment After Acquisition of Drug Resistance

Case Report

A 39-year-old Japanese male former smoker presented at our hospital with several months of history of an occasional dry cough. He was found to have stage IV (cT4, N2, M1b) adenocarcinoma of the lung with bone metastasis. He received six courses of first-line chemotherapy with cisplatin and pemetrexed. His best response was a partial response, and after 7 months of first-line treatment, he showed evidence of progressive disease, with an increase in the size and number of pulmonary metastases as well as pleural fluid accumulation (Fig 1A). Mutation analysis of biopsied tumor tissue revealed that the tumor was wild type for the epidermal growth factor receptor (*EGFR*) gene. However, fluorescent in situ hybridization analysis with break-apart probes for the anaplastic lymphoma kinase gene (*ALK*) revealed the presence of an *ALK* rearrangement. As a second-line treatment, therefore, crizotinib was administered orally at a dose of 250 mg twice per day. Marked tumor regression became apparent (Fig 1B), and this response persisted for 4 months. Given that crizotinib toxicities were mild and manageable, the drug was administered without pause or dose reduction. After this time, however, pulmonary metastases again developed, and crizotinib was discontinued. The patient was enrolled onto a phase I clinical trial of new agents, but treatment was withdrawn after 4 weeks because of disease progression. Docetaxel was then administered as fourth-line chemotherapy, but the patient was hospitalized again after 8 weeks with obstructive pneumonitis as a result of disease progression (Fig 2A). Retreatment with crizotinib (500 mg daily) commenced at the patient's request 5 months after completion of the initial crizotinib treatment. One month later, a significant response had been achieved (Fig 2B), and this response persisted for 2.5 months.

Discussion

Despite the great benefits of crizotinib treatment for *ALK* rearrangement–positive non–small-cell lung cancer (NSCLC), all such treated patients ultimately develop drug resistance, which has been observed with other effective small-molecule tyrosine kinase inhibitors (TKIs) such as those for *EGFR*. Although multiple clinical trials have studied therapies for acquired TKI resistance, no published results have led to a change in clinical practice.[1] The current standard practice for such patients is to switch to conventional cytotoxic chemotherapy. We now describe a pronounced antitumor effect of crizotinib retreatment in a patient with *ALK* rearrangement–positive NSCLC who initially responded to this drug but subsequently showed tumor progression. A recent study found that NSCLC cells that harbored an activating *EGFR* mutation and acquired resistance to

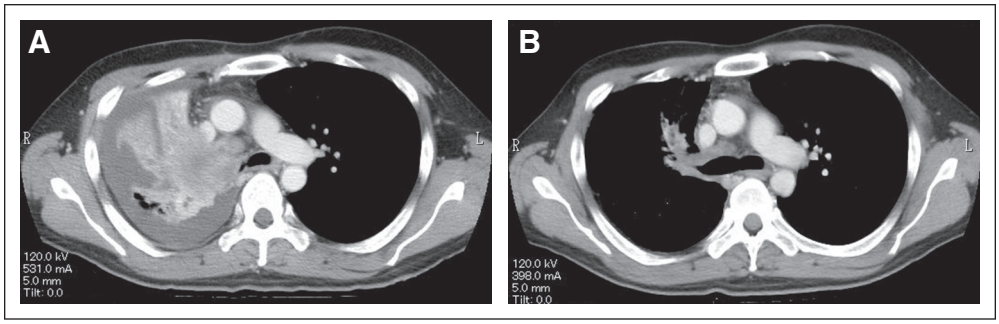

Fig 1.

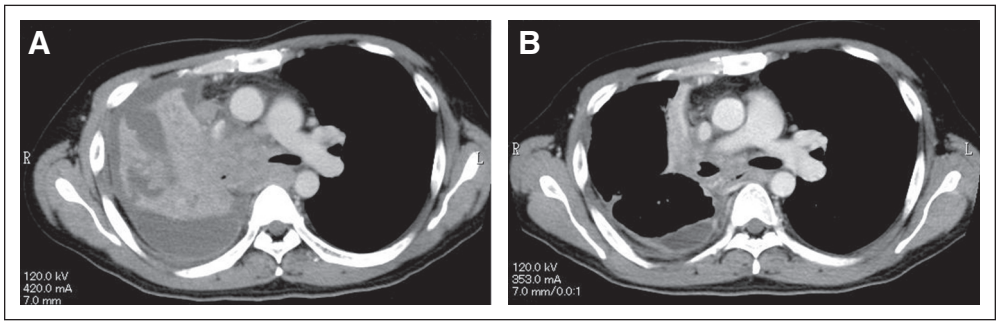

Fig 2.

EGFR-TKIs as a result of a secondary *EGFR* mutation (T790M) regained sensitivity to these drugs after drug withdrawal, with this renewed sensitivity being associated with a reduction in the proportion of cells harboring the T790M mutant allele.[2] Similar to these in vitro findings, withdrawal of treatment with an EGFR inhibitor after the development of drug resistance in patients with *EGFR* mutation–positive NSCLC resulted in the restoration of tumor sensitivity to subsequent treatment with either the same or a different *EGFR* inhibitor.[3-5] We recently established an ALK-TKI–resistant NSCLC cell line positive for the echinoderm microtubule-associated protein–like 4 gene (*EML4*) –*ALK* transforming fusion gene by exposing the parental H3122 cells to increasing concentrations of ALK-TKI, and we found that the resistant cells regained sensitivity to ALK-TKI treatment after culture in drug-free medium.[6] These observations may be explained by a selection process in which the withdrawal of a TKI results in a reduction in the fraction of TKI-resistant tumor cells, rendering the tumor sensitive to retreatment with the TKI. Taken together, they provide a rationale for temporary cessation of treatment after the development of ALK-TKI resistance in patients with *EML4-ALK*–positive NSCLC to allow the tumor to regain drug sensitivity. Our experience with the present case further supports such a strategy. Additional clinical evaluation of such an approach is thus warranted.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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