Rapid Acquisition of Alectinib Resistance in ALK-Positive Lung Cancer With High Tumor Mutation Burden

Abstract

Introduction: The highly selective ALK inhibitor alectinib is standard therapy for ALK-positive lung cancers; however, some tumors quickly develop resistance. Here, we investigated the mechanism associated with rapid acquisition of resistance using clinical samples. Methods: Autopsied samples were obtained from lung, liver, and renal tumors from a 51-year-old male patient with advanced ALK-positive lung cancer and who had acquired resistance to alectinib in only 3 months. We established an alectinib-resistant cell line (ABC-14) from pleural effusion and an alectinib/crizotinib-resistant cell line (ABC-17) and patient-derived xenograft (PDX) model from liver tumors. Additionally, we performed next-generation sequencing (NGS), direct DNA sequencing, and quantitative real-time reverse-transcription polymerase chain reaction.

Results: ABC-14 cells harbored no ALK mutations and were sensitive to crizotinib while also exhibiting MET gene amplification and amphiregulin overexpression. Additionally, combined treatment with crizotinib/erlotinib inhibited cell growth. ABC-17 and PDX tumors harbored ALK G1202R, and PDX tumors metastasized to multiple organs in vivo, whereas the third generation ALK-inhibitor, lorlatinib, diminished tumor growth in vitro and in vivo. NGS indicated high tumor mutation burden (TMB) and heterogeneous tumor evolution. The autopsied lung tumors harbored ALK G1202R (c. 3604 G>A) and the right renal metastasis harbored ALK G1202R (c. 3604 G>C); the mutation thus comprised different codon changes. Conclusions: High TMB and heterogeneous tumor evolution might be responsible for rapid acquisition of alectinib resistance. Timely lorlatinib administration or combined therapy with an ALK inhibitor and other receptor tyrosine-kinase inhibitors might constitute a potent strategy.

Keywords: NSCLC, alectinib, ALK G1202R, MET, amphiregulin