Personalizing Therapy for Acquired Resistance to EGFR Kinase Inhibitors in Advanced NSCLC

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Abstract

The management of *EGFR* mutant NSCLC with acquired resistance to EGFR Kinase inhibitor therapy is becoming increasingly challenging. The development of multiple promising treatment strategies, including novel third-generation EGFR kinase inhibitors, has added to both treatment options and complexity. Careful assessment of the underlying mechanism of acquired resistance to initial therapy are central to selecting optimal subsequent treatment. In all cases, potential strategies for therapy must be adapted to individual patient and disease characteristics.

Introduction

The treatment of advanced epidermal growth factor receptor (*EGFR*) mutant non-small–cell lung cancer (NSCLC) has been revolutionized by continuous developments in the field of targeted therapy. First- or second-generation EGFR kinase inhibitors have become standard initial therapy for this disease.[1-4] However, the considerable clinical benefit of these agents is limited by the inevitable development of acquired resistance.[5] The evaluation and management of acquired resistance to initial therapy with EGFR kinase inhibitors has thus emerged as a key clinical challenge in the treatment of advanced *EGFR* mutant NSCLC.

Advances in the understanding of the mechanisms that underpin acquired resistance to EGFR kinase inhibitors have recently begun to yield novel targeted therapies. This is best exemplified by the recent development of third-generation EGFR kinase inhibitors capable of treating *EGFR* T790M-mediated acquired resistance.[6,7] The recent FDA approval of one agent in this class, osimertinib, has increased treatment options available to patients, but has magnified the complexity of managing acquired resistance to EGFR kinase inhibitors. Here, we review strategies for the optimal management of acquired resistance to initial EGFR kinase inhibitors in *EGFR* mutant NSCLC.

Mechanisms of Acquired Resistance to EGFR Kinase Inhibitors

Acquired resistance to EGFR kinase inhibitors inevitably occurs in advanced *EGFR* mutant NSCLC. This resistance may occur via the outgrowth of a pre-existing resistant subclone in some cases, or acquisition of a new resistance mutation in a previously sensitive cancer cell.[8] Recent data have suggested that both processes may occur in patients.[9] Regardless of its cellular origin, genetic studies of rebiopsy specimens derived from *EGFR* mutant NSCLC patients with acquired resistance have revealed multiple mechanisms underpinning resistance.[10-12] The most common mechanism of acquired resistance is the *EGFR* T790M gatekeeper mutation, which is detectable in approximately 50-60% of patients, and impairs the binding of first- and second-generation EGFR kinase inhibitors to the adenosine triphosphate (ATP)-binding pocket of mutant EGFR.[10-12] Importantly, only 65-70% of these patients will respond to the third-generation EGFR kinase inhibitor, osimertinib, implying that T790M may represent a minor subpopulation in these patients and/or that additional resistance mechanisms may be present.[13,14] An alternative genetic mechanism of resistance is acquired-*MET* amplification, which occurs in 5-10% of patients.[10-12] Rarer mechanisms such as small-cell lung cancer transformation have also been reported.[10,11] Pharmacokinetic resistance may also occur in the instance of isolated brain metastases, where sufficient concentrations of an otherwise effective EGFR kinase inhibitor cannot penetrate the blood brain barrier. The rational selection of subsequent therapy hinges upon careful selecton of the time point at which to discontinue initial EGFR kinase inhibitor therapy, as well as careful determination of the mechanism underpinning acquired resistance in a given patient.

Defining Clinically Significant Progression

The first evidence of the emergence of acquired resistance to an EGFR kinase inhibitor, is commonly, asymptomatic radiographic progression. Objective clinical and radiographic definitions of acquired resistance have been previously proposed for the purpose of defining this clinical entity to facilitate clinical trials. The majority of these definitions utilize objective radiographic progression per, Response Evaluation Criteria In Solid Tumors

(RECIST), as a key indicator of acquired resistance. This is an important tool to identify patients for clinical trials as well as an important study end point. However, the initial development of acquired resistance may manifest as subtle and indolent radiographic progression that does not necessitate an immediate change in therapy.[5] The clinical decision to change treatment in the context of acquired resistance to EGFR kinase inhibitors is nuanced and must take into consideration many important factors related to both the patient and the biology of their underlying disease.

The rate and pattern of progression observed in *EGFR* mutant advanced NSCLC with acquired resistance is variable and potentially related to the underlying mechanism of acquired resistance. *EGFR* T790M-positive disease has, in particular, been reported to exhibit a more indolent course than other subtypes.[15] Patients with more indolent disease may benefit from remaining on EGFR kinase inhibitor therapy after the emergence of acquired resistance with the rationale that acquired resistance is a heterogeneous process, and that the need for initiating second-line therapy may be delayed by continuing initial therapy.[16] The distinction between the identification of acquired resistance and clinically significant progression necessitating treatment change is, therefore, key (**Table 1**).

The ASPIRATION study recently reported on the feasibility of continuing EGFR kinase inhibitor therapy beyond initial radiographic progression. This single-arm phase II study of *EGFR* mutant advanced NSCLC treated with first-line erlotinib and allowed patients to continue erlotinib, after initial progression, at the discretion of the treating physician. The patients in this study who continued on erlotinib post-progression were more likely to have good performance status, longer initial duration of response, greater depth of response, and possess isolated brain metastases compared to those who discontinued treatment at initial progression. Those who continued on erlotinib were able to remain on therapy for a median of an additional 3.1 months before discontinuing therapy due to symptomatic disease progression necessitating a change of therapy.[16] However, caution must be exercised in interpreting the results of this study, particularly given the lack of a comparator arm and the high potential for selection bias, as well as confounding by indication and disease severity inherent in the study design.[17] Previous retrospective studies have also found that post-progression therapy, with an EGFR kinase inhibitor can prolong survival compared to immediately switching to second-line therapy, and that the use of locally ablative therapy with EGFR kinase inhibitor therapy can delay the need for second-line therapy in the context of acquired resistance.[18-20] However, no added benefit has been observed in combining EGFR inhibition with subsequent second-line combination chemotherapy.[21] These studies underscore the feasibility of postprogression therapy in patients who have good performance status and asymptomatic indolent progression of minimal residual disease.

Resistance Biopsy and the Emerging Role of Plasma Genotyping

The selection of systemic therapy for acquired resistance now hinges on identifying the molecular mechanism that is driving disease progression.[5] This may be assessed by a repeat biopsy and molecular testing for *EGFR* T790M, as well as *MET* amplification and histological analysis for evidence of small-cell transformation. Repeat biopsies are inherently limited by their invasive nature, risk of complications, and potential for delaying subsequent therapy. Acquired resistance to EGFR kinase inhibitors is also increasingly recognized as a heterogeneous process across metastatic sites in a given patient.[22] Therefore, the resistance biopsy of a single metastatic site may not be representative of the resistance mechanism at work in other metastatic sites and, in particularly unlucky situations, could hypothetically miss the resistance mechanism present at the majority of sites.

Plasma genotyping of cell-free DNA (cfDNA) allows for the rapid and noninvasive detection of *EGFR* T790M while avoiding many of the inherent limitations of repeat tissue biopsy.[23] Various platforms for plasma genotyping exist with variable levels of validation. A prospective validation of plasma genotyping utilizing a droplet digital polymerase chain reaction (ddPCR)-based platform has recently been completed demonstrating that this assay exhibits high specificity for the detection of *EGFR* and *KRAS* driver mutations. Interestingly, the assay detected some *EGFR* T790M mutations missed by tissue genotyping that is likely secondary to heterogeneity of resistance mechanism across metastatic sites.[24] Plasma genotyping may be particularly useful in patients where repeat tissue biopsy is not feasible at resistance, while also having the potential to detect *EGFR* T790M mutations that are missed by standard tissue genotyping. Although a positive result from these assays is actionable, caution should be exercised in interpreting negative plasma results. A negative result may imply the absence of a mutation or merely that a patient's tumor is not shedding cfDNA at detectable levels, thus necessitating a confirmatory tissue biopsy to rule out a false negative plasma result.

Changing Therapy

Patients with clinically significant disease progression and evidence of an *EGFR* T790M mutation are good candidates for treatment with the third-generation EGFR kinase inhibitor, osimertinib. A recent single-arm study of 253 patients with acquired resistance to EGFR kinase inhibitors treated with osimertinib demonstrated an impressive objective response rate (ORR) of 61% and progression-free survival (PFS) of 9.6 months among *EGFR* T790M-positive patients.[6] The results of this study have led to the accelerated regulatory approval of osimertinib, while a randomized phase III study is ongoing. The ease of initiating second-line therapy with a highly active oral kinase inhibitor, such as osimertinib, renders it a more appealing option than moderately active systemic chemotherapy. Therefore, practitioners may opt to utilize it earlier in patients

TABLE 1. Potential Challenges in Personalizing Management of Acquired Resistance

Clinical challenge	Potential strategy
Isolated progression of CNS metastases	Consider radiotherapy if symptomatic or concerning features. Consider osimertinib if small, asymptomatic and T790M-positive. Trials of high-dose osimertinib ongoing (BLOOM).
Repeat biopsy reveals SCLC transformation	Consider immediate platinum-based chemotherapy; do not await T790M testing.[10]
Indolent disease progression	Consider repeat biopsy or plasma genotyping. May continue initial EGFR kinase inhibitor in the interim if asymptomatic and no new concerning sites of disease.
Disease progression not amenable to tissue biopsy	Consider plasma genotyping to assess for EGFR T790M. If positive, consider treatment with osimertinib. If negative, will need confirmatory tissue biopsy when feasible.
Liquid biopsy shows T790M without any clinical evidence of resistance	Unclear clinical meaning at present, would continue therapy and retest when there is clinical evidence of progression on therapy.

CNS indicates central nervous system, SCLC indicates small–cell lung cancer, EGFR indicates epidermal growth factor receptor.

with T790M-mediated acquired resistance and perhaps even in the instance of indolent asymptomatic progression.

Treatment in patients with non-T790M mediated acquired resistance requires careful consideration of individual patient and disease characteristics. Patients with localized disease progression or isolated brain metastases could be considered for local radiotherapy and possible continuation of initial EGFR kinase inhibitor therapy.[19] Isolated progression of central nervous system (CNS) metastases may also be amenable to treatment with osimertinib, a strategy currently being investigated in the BLOOM trial which contains an arm examining high-dose osimertinib in CNS metastases regardless of tumor T790M-status (NCT02228369). Any T790M-negative disease progression should prompt consideration of standard second-line therapy with intravenous platinum-based chemotherapy, especially in the instance of small cell transformation (**Table 1**).[5,10] Patients with *MET*-amplified tumors may benefit from combination treatment with an EGFR and MET inhibitor.[25] This strategy is currently under investigation in multiple clinical trials, although anecdotal evidence exists of clinical responses to standard inhibitors such as the combination of erlotinib and crizotinib. Strong consideration should be given to available clinical trial options in *EGFR* T790M-negative patients.

Conclusion

Acquired resistance is a predictable and unavoidable waypoint in the initial treatment of *EGFR* mutant NSCLC. The natural history of resistant disease is variable and presents multiple options for treatment based on clinical parameters and the molecular mechanism underpinning resistance in a given patient. Strong consideration should be given to postprogression EGFR kinase inhibitor therapy in asymptomatic patients with indolent disease. Careful analysis of resistance mechanisms at the time of clinically significant disease progression will allow for the smooth transition to approved therapies in the instance of T790M-mediated resistance or the consideration of clinical trials in *MET*-amplified tumors. Standard chemotherapy, locally ablative therapies, and clinical trials are options for the patients with T790M-negative tumors.

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