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Personalized targeted therapy in advanced non–small cell lung cancer

ABSTRACT

Personalized targeted therapy for advanced non–small cell lung cancer (NSCLC) primarily relies on the concept of "oncogene addiction," in which multiple genetic abnormalities are addicted to one or a few genes for tumor cell maintenance and survival. Several molecular aberrations have been identified in NSCLC, with subsequent development of drugs targeted to these aberrations; gefitinib, erlotinib, and cetuximab for the treatment of NSCLC harboring epidermal growth factor receptor mutation or overexpression, and crizotinib for the treatment of NSCLC with the EML4-ALK fusion translocation oncogene being some examples. A more recent actionable target is MET, a multifaceted receptor tyrosine kinase within the human kinome. Cellular heterogeneity within an oncogene-addicted tumor can cause resistance to targeted therapy after an initial response. As our understanding of tumor heterogeneity and tumor resistance mechanisms evolves, more rational therapies and combinations of therapies can be expected.

The efficacy of therapy targeted to a specific oncogene is convincing evidence of "oncogene addiction," or the concept that some cancers rely on or are "addicted to" a specific gene for their survival and proliferation. In the case of non–small cell lung cancer (NSCLC), drugs that target epidermal growth factor receptor (EGFR) have been proven more effective than conventional chemotherapy in patients with sensitizing *EGFR* mutations.[1]

Lung cancer oncogenes can drive oncogenic signaling pathways within tumor cells. Activation of EGFR signaling that drives cell proliferation through pathways such as RAS/RAF/MEK/ERK and the cell survival pathways P13K and AKT has been demonstrated in never-smokers. In heavy smokers, *KRAS* oncogene mutation is the dominant promoter of activation of oncogenic signaling pathways; it predicts a poor prognosis (especially for lung adenocarcinoma), and it is essentially mutually exclusive with *EGFR* mutations.

More than 50% of cases of NSCLC have known oncogene mutations for which targeted therapeutics are available.[2] For example, gefitinib and erlotinib are the effective inhibitors for the *EGFR* oncogene mutation, sunitinib for platelet-derived growth factor receptor (*PDGFR*) amplification, and lapatinib for the less common *ERBB2* insertion.

A number of molecular aberrations have been identified in NSCLC **(Table 1)**.[3] Known molecular alterations include:

- *EGFR* mutations and amplifications
- *EML4-ALK* translocation fusions
- *KRAS* mutations
- *PIK3CA* mutations
- *MET* mutations, alternative splicing, amplification, and overexpression

PLATINUM DOUBLET AS STANDARD

Multiple platinum-based combinations of chemotherapy are in use as first-line therapy for advanced NSCLC. An overall survival (OS) benefit has been established with the use of doublet regimens, but no platinum-based doublet regimen has been proven superior to another on the end point of OS in clinical trials.[4]

Adding a third agent increases the response rate in advanced NSCLC but does not improve OS; the exception is bevacizumab, a monoclonal antibody targeted to vascular endothelial growth factor (VEGF). Sandler et al[5] demonstrated a survival benefit when bevacizumab was added to paclitaxel-carboplatin in a recent study that led to US Food and Drug Adminis-

Dr. Ma reported that he has no relationships that pose a potential conflict of interest with this article.

This article was developed from an audio transcript of Dr. Ma's presentation at the "Advances in Lung Cancer Evaluation and Management" symposium held in Cleveland, Ohio, on April 30, 2011. The transcript was formatted and edited by *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness and was then reviewed, revised, and approved by Dr. Ma.

doi:10.3949/ccjm.79.s2.12

tration (FDA) approval of bevacizumab for the treatment of NSCLC.

The next oncogene target explored in advanced NSCLC was EGFR. The tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, lapatinib, and the monoclonal antibody cetuximab are all clinical inhibitory agents targeting EGFR.

Previously treated NSCLC

Several trials have demonstrated that previously treated NSCLC patients with *EGFR* mutations have a longer time to progression when treated with the TKI gefitinib compared with conventional cytotoxic chemotherapy **(Table 2)**. The first of these trials was the phase 2 Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) trial.[6] Gefitinib was eventually approved for the treatment of unselected patients with advanced NSCLC based on the phase 2 results. Gefitinib has since been replaced by erlotinib in the United States, but is still available in Asia and some European countries. The Iressa Survival Evaluation in Lung Cancer (ISEL) trial was a phase 3 study of gefitinib conducted in patients who had received one or two prior chemotherapy regimens.[7] There was no significant improvement in OS with gefitinib in the overall study population, but a subset analysis of patients of Asian origin showed a significant improvement in survival in this subgroup treated with gefitinib.

In the phase 3 National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) BR.21 trial, erlotinib demonstrated significant superiority over placebo as second- or third-line chemotherapy on PFS and OS in unselected patients with NSCLC. The results led to its approval as treatment for advanced NSCLC in patients who have received at least one prior chemotherapy regimen.[8]

Patient survival in NCIC CTG BR. 21 was evaluated in a series of patient subsets in exploratory univariate analyses. The effect of erlotinib on survival was similar across most subsets. A greater effect on survival by erlotinib was observed in patients who had never smoked (hazard ratio [HR] = 0.42). In the subgroup of patients who never smoked, EGFR status was predictive of erlotinib survival benefit. Patients who never smoked and were EGFR-positive had a survival benefit with erlotinib (HR = 0.27). There were too few EGFR-negative patients who never smoked to reach a conclusion.

Sensitizing mutations lead to better response

With the approval and clinical use of EGFR-TKIs came knowledge of EGFR kinase mutations that sensitize the mutated RTK to EGFR-TKI; this mechanism translates into dramatic tumor responses.[9,10] Certain *EGFR* mutations contribute to sensitivity to EGFR-TKI treatment. The most common sensitizing mutations are the Exon 21 L858R mutation and the Exon 19 short in-frame deletions. The Exon 20 tends to yield resistant alterations (eg, prototypical T790M mutation and some Exon 20 Dup/Ins) in patients who initially derived benefit from targeted therapeutics. Although advances have been made in targeted therapeutics in lung cancer and other cancers, clinical resistance, particularly acquired or secondary resistance, remains the rule rather than the exception, which inherently limits the long-term clinical success of targeted therapeutics. A higher level of

TABLE 1
Molecular aberrations in non–small cell lung cancer

Molecular aberration	Frequency in NSCLC (%)	Comment
EGFR mutation	10–16.6	Indicates sensitivity to EGFR inhibitors
EGFR amplification	30.8–59.2	May be associated with response to EGFR inhibitors
EML4-ALK fusion	5–7	Indicates sensitivity to ALK inhibitors (eg, PF-02341066, crizotinib)
KRAS mutation	19–21	Usually in smokers; associated with poor prognosis irrespective of therapy; conflicting data with respect to resistance to EGFR inhibitors
PIK3CA mutation	2	May be involved in EGFR resistance
PIK3CA amplification	12–17	May be involved in EGFR resistance
MET mutation	12–14	Contributes to EGFR resistance
MET amplification	11.1–21	Contributes to EGFR resistance

EML4 = echinoderm microtubule-associated protein-like 4; *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; *KRAS* = GTPase *KRAS*; *MET* = hepatocyte growth factor receptor; NSCLC = non–small cell lung cancer; *PIK3CA* = phosphatidylinositol 3-kinase p110 alpha catalytic subunit isoform

TABLE 2
Phase 2 and 3 studies of epidermal growth factor receptor tyrosine kinase inhibitors in previously treated non–small cell lung cancer

Study	No. patients	Drug	Dose (mg)	RR (%)	CB (%)	PFS (mo)	OS (mo)
Phase 2							
IDEAL I[6]	104	Gefitinib	250	18.4	54.4	2.7	7.6
	106		500	19	51.4	2.8	8
IDEAL II[25]	102	Gefitinib	250	12	NR	NR	7
	114		500	9	NR	NR	6
Phase 3							
NCIC CTG BR.21[8]	488	Erlotinib	150	8.2	45	2.2[a]	6.7[a]
	243	Placebo		0.7	NR	1.8	4.7
ISEL[7]	1,129	Gefitinib	250	8	40	3[b]	5.6
	563	Placebo		1.3	32	2.6[b]	5.1

[a]Significant difference in progression-free survival (PFS) or overall survival (OS).

[b]Time to treatment failure.

CB = clinical benefit (response + stable disease); NR = not reported; RR = response rate

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understanding of the mechanisms of resistance could have a substantial impact in maintaining the clinical efficacy of these targeted therapies.

The Iressa Pan-Asia Survival Study (IPASS) was a phase 3 study in which patient selection was based on clinical factors that predict a higher probability of harboring sensitizing *EGFR* mutations, thus enriching the mutant population, rather than screening for mutation status.[11] Patients selected for participation were East Asians with advanced lung adenocarcinoma who were never smokers or former light smokers. They were randomized to treatment with platinum-based doublet chemotherapy (carboplatin-paclitaxel) or the EGFR-TKI gefitinib.

The primary end point—PFS—favored gefitinib over the chemotherapy doublet in the overall patient population. Of the 1,217 patients enrolled, *EGFR* mutation data for 35.9% could be evaluated. Sixty percent of the patients' tumors harbored sensitizing *EGFR* mutations and, in this subset, the benefit of gefitinib was greater than it was in the overall population. In patients without an *EGFR* mutation, particularly those without Exon 19 deletions or Exon 21:L858R mutations (sensitizing mutations), platinum-based doublet chemotherapy performed better than gefitinib on the PFS end point. Of the mutation-positive patients, 4.2% had T790M mutations, which confers resistance to TKIs; this finding underscored the observation that all mutations cannot be treated the same.

The important message from the IPASS results is that even in a population preselected for *EGFR* mutation occurrence, the actual presence of the alteration of the target (*EGFR* mutations) leads to better survival with gefitinib. Molecular profiling of the tumor, therefore, is ultimately superior to profiling by patient phenotype or ethnicity. Thus, molecular selection trumps clinical selection.[12]

On the basis of IPASS and four similar phase 3 randomized controlled trials, the American Society of Clinical Oncology issued a clinical opinion that "patients with NSCLC who are being considered for first-line therapy with an EGFR-TKI (patients who have not previously received chemotherapy or an EGFR-TKI) should have their tumor tested for *EGFR* mutations to determine whether an EGFR-TKI or chemotherapy is the appropriate first-line therapy."[13]

Monoclonal antibody against EGFR

The First-Line Erbitux in Lung Cancer (FLEX) phase 3 worldwide study demonstrated that cetuximab, a monoclonal antibody directed against EGFR, as add-on therapy to a platinum-based doublet (cisplatin and vinorelbine) can extend median OS in patients with advanced EGFR-expressing NSCLC (stage wet IIIB or stage IV).[14] As a result, the use of cetuximab combined with cisplatin-vinorelbine has been endorsed by a National Comprehensive Cancer Network (NCCN) guideline as a first-line option for the treatment of advanced NSCLC.

EML4-ALK fusion gene as target for crizotinib

The *EML4-ALK* fusion translocation oncogene was first identified in 2007 in a small proportion of

patients with NSCLC,[15,16] and a targeted therapy (crizotinib, an inhibitor of the ALK tyrosine kinase) has been developed. A single-arm phase 1 trial of crizotinib in patients selected for the *EML4-ALK* fusion gene has been completed.[17] Of the approximately 1,500 NSCLC patients screened for the trial, 82 were identified as having advanced ALK-positive disease and were entered. These patients tended to be younger than those with ALK-negative disease, most had little or no exposure to tobacco, and all had adenocarcinoma.

The mean treatment duration was 6.4 months. Most treatment-related side effects were grade 1 or grade 2 gastrointestinal adverse events. The overall response rate was 57%. The disease control rates were 87% at 8 weeks and 66% at 16 weeks. Crizotinib has since moved to phase 2 and phase 3 trials and received FDA approval on August 26, 2011, for treatment of EML4-ALK–positive patients as assayed by a simultaneously approved companion molecular diagnostic test.

Crizotinib-resistant mutations of the ALK-kinase domain have recently been identified; L1196M and C1156Y mutations have been found to confer resistance to crizotinib in initially responsive patients.[18]

MET: An emerging molecular target

An emerging molecular target being tested in clinical trials is MET, a multifaceted receptor kinase that, when activated, induces tumor cell activities such as cell proliferation and angiogenesis, epithelial-mesenchymal transition, and cell scattering, leading to tumor cell invasion and metastasis.[19]

MET receptors and EGFR in lung cancer often are coexpressed and coactivated. Dual targeting of MET and EGFR pathways simultaneously is an attractive combined targeted strategy and is being studied in the hope of overcoming secondary resistance to EGFR-TKI as well as enhance the primary response to targeted therapy. A number of MET targeting agents, including both small molecular inhibitors and monoclonal antibodies, are currently undergoing various stages of clinical development.[20,21]

In a phase 2 study, erlotinib plus the MET inhibitor ARQ197 was compared with erlotinib plus placebo in 117 previously treated EGFR-inhibitor–naïve patients with advanced NSCLC.[22] In the population of patients with nonsquamous NSCLC, both PFS and OS were extended incrementally by the use of combined inhibition that targeted both the EGFR and MET pathways. Interestingly, the benefit on PFS appears to be more significant in *EGFR* wild type and *KRAS*-mutant molecular subgroups. A phase 3 global trial using a similar design, with a goal of enrolling 1,000 patients, has been activated in an attempt to validate the findings from the phase 2 study.

UNDERSTANDING RESISTANCE MECHANISMS WILL OPEN DOORS

Other than novel and more rational combined TKI in lung cancer, a deeper understanding of the resistance mechanisms in the context of oncogene addiction targeting would ultimately have a large impact on the long-term clinical success in lung cancer targeted therapy.

Resistance arises because of cellular heterogeneity within an oncogene-addicted tumor. Tumor shrinkage indicates a response to a molecularly targeted therapy, but residual tumor may be a source of slow-growing drug-tolerant "persistor" cells that promote tumor regrowth, regeneration, and heterogeneity.[23,24] Coaddiction, reversible resistance, and addiction-switching models have been proposed to explain resistance, but it is unlikely that a single mechanism can fully explain tumor cell maintenance.

FUTURE OF TARGETED THERAPY IN LUNG CANCER

Technologic advances provide hope for the future of targeted therapy in lung cancer. Some of these advances are cancer genome deep sequencing and tumor molecular profiling. A greater understanding of tumor heterogeneity at the molecular level and tumor-resistant mechanisms, both intrinsic and acquired, should provide further therapeutic opportunity. In the modern era of targeted cancer therapy, identification of novel "druggable" driver oncogene targets can lead to swift development of inhibitors of those targets and adoption of improved and rational combinations of drugs. It is hoped that a better tumor response and more durable responses can be achieved with targeted therapy.

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