Editorial

Is T790M mutation the key in development of resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)?

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Over the last 2 decades, a number of new approaches were proposed in diagnosis and treatment of non-small cell lung cancer (NSCLC), which comprises about 80 to 85% of all lung cancers. For its diagnosis, gene expression profiling has recently been suggested as a predictive and prognostic biomarker in early-stage NSCLC (1). For its treatment, multiple modalities have been developed and introduced into clinical practice.

Due to the advances in laparoscopic equipment and the use of single-lung ventilation techniques, video-assisted thoracoscopic surgery (VATS) is rapidly gaining popularity (2). VATS is beginning to be practiced globally in a large number of cases (3-5) and multiple institutions are announcing technical modifications to meet their needs. For instance, Zhao et al. reported that robot-assisted VATS is a safe and feasible approach (6). Our group proposed the use of a "hybrid technique" which involves VATS with a small thoracotomy to help community hospitals perform VATS more safely and easily (7). Our group has performed 1,170 cases of hybrid-VATS in the last 8 years, and recently reported our outcome in our Journal (8). In specialized centers, investigations and clinical trials are looking at the perioperative care of VATS with interventions such as prophylactic use of noninvasive positive pressure ventilation (9, 10), and feasibility of adjuvant chemotherapy post-VATS (11). Local treatment such as surgery, however, is limited to Stage I or II of NSCLC and approximately 30% of patients have locally advanced disease that is surgically unresectable at the time of presentation.

Despite the advances in cytotoxic chemotherapy, the survival for patients with advanced NSCLC remains poor with a median survival of 8-10 months (12). In fact, the 5-year survival rate for all patients diagnosed with NSCLC is about 15%, only 5% better than that of 40 years ago (13). Therefore, new modalities of treatment, such as specific molecular-targeted approaches to treat different aspects of tumor progression and metastasis, are of particular interest to NSCLC patients.

Two signaling pathways in particular have been exploited, the vascular endothelial growth factor receptor (VEGFR), and the epidermal growth factor receptor (EGFR) pathways. VEGF is the primary survival factor of vascular endothelial cells that activate tyrosine kinase after binding to VEGF receptors. VEGFR2 is the key mediator of VEGF-mediated angiogenesis, and VEGFR1 and VEGFR3 are involved in embryonic vessel development (vasculogenesis), and lymphangiogenesis, respectively (13). Therefore, compounds that target the VEGF pathway are expected to inhibit them. EGFR is a transmembrane receptor tyrosine kinase that transduces downstream signaling by various pathways including Raf1, PI3K/Akt, and STAT factors upon

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binding of specific ligands such as EGF or TGF-alpha, which leads to cancer cell proliferation or inhibition of apoptosis depending on the pathway (14). It has been shown that EGFR expression is associated with frequent lymph node metastasis, poor chemosensitivity, and reduced survival in NSCLC patients (14).

Currently two tyrosine kinase inhibitors (TKIs), gefitinib (Iressa) and erlotinib (Tarceva), that block the EGFR signaling pathway are approved and used for NSCLC. The results of clinical trials using these compounds have been thoroughly reviewed by Voon et al (15). Despite the fact that approximately 10-20% of NSCLC patients initially respond positively to these TKIs, most of them inevitably acquire resistance after a progression-free period of about 10 months due to acquired resistance to TKIs.

In this issue of the Journal of Thoracic Disease, multiple comprehensive reviews on this topic are published in an attempt to overview and update the recent results of these molecular targeted therapies for NSCLC (13, 16-18). Shash et al. reviewed the role of predictive bio-markers in patient selection for EGFR TKIs to optimize its use (16). Mendez et al. provides a comprehensive review on the number of compounds targeting not only the EGFR pathway, but also the VEGF pathway as well (17). Korpanty et al. summarized the clinical efficacy of multi-targeted therapies and the results of clinical trials (13).

Ma et al. addressed the issue of acquired resistance to these TKIs (18). Even if patients with NSCLC initially respond to EGFR-TKIs, inevitably they will acquire resistance, which is the major contributor to poor outcomes. Ma et al. conducted a systematic review of current literature on the impact of T790M mutations in development of resistance to EGFR-TKIs. T790M is a secondary mutation of EGFR at exon 20 involving substitution of methionine for threonine at 790 (15). Based upon their inclusion and exclusion criteria, 157 articles were identified and 22 reports were analyzed. This systematic review is particularly useful since most of the currently available studies on T790M in NSCLC are small in size and heterogenous, thus, accumulation of studies will provide us with more reliable data to make clinical decisions. In this study, they report that T790M mutations are found in about half of TKI acquired-resistant patients but in only a few TKI-naïve patients. In addition they found that T790M-harbored patients may benefit from "switch therapy", which is treating the T790M-acquired patient who developed gefitinib-resistance with erlotinib, or irreversible TKIs. They also advocated the use of high-sensitivity analytical techniques that may aid in finding suitable individualized therapy for patients based on their mutational status.

They conclude in this review that a better understanding of the mechanisms leading to TKI resistance is crucial in the development of effective treatments to overcoming this problem. It is convincing from this paper that T790M is one of the major players in TKI resistance, but the question remains, are there any other signaling mechanisms involved when it is acquired? For instance, we have recently published that there is crosstalk between EGFR and lysphosphatidic acid signaling that mediates upregulation of sphingosine kinase 1 (SphK1), which is one of the critical factors of cancer progression (19). Sphingosine-1-phosphate, a lipid mediator that promotes cell growth, migration and angiogenesis, is generated by SphK1 (20). SphK1 is overexpressed in cancer, and it is associated with tumor angiogenesis and resistance to radiation and chemotherapy (21). We have also found that upregulation of SphK1 transcription is dependent on ERK1 activation, although both ERK and Akt pathways are activated by lysophosphatidic acid-mediated transactivation of EGFR (22).

Another vastly underappreciated mechanism is lymphangiogenesis, generation of new lymphatic vessels, compared from angiogenesis (23). As is pointed out by Korpanty et al, activation of VEGFR3 will cause lymphangiogenesis (13), but its role in TKI resistant tumors has not yet been investigated. Better understanding of the circumvent mechanism of TKI resistance should lead us to discovery of new treatments to overcome this acquired resistance.

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