Targeted Therapy and Immunotherapy for Lung Cancer

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KEYWORDS

• Molecular • Targeted therapy • Immunotherapy • Non–small cell lung cancer

KEY POINTS

- Targeted therapy and immunotherapy have had an increasing role in the management of patients with advanced non–small cell lung cancer (NSCLC).
- Therapies targeting patients with epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements have proved most successful, whereas others specific for additional genetic alterations seem promising.
- Immunotherapy in lung cancer, primarily through checkpoint inhibition, permits the activation of tumor-specific T cells often suppressed by cancer cells.
- Adverse effects of these drugs are often mild and manageable, improving quality of life and limiting cumulative toxicity seen with use of cytotoxic chemotherapy.

INTRODUCTION

The management of patients with advanced NSCLC has evolved dramatically over the past decade. Therapeutic options were previously limited to cytotoxic chemotherapy in a 1-size-fits-all approach. As more information becomes known about the driving molecular events behind tumorigenesis, however, researchers are designing drugs capable of interfering with these events in a more individualized approach. The first such drugs in NSCLC were the targeted agents, biologic compounds that interact with cell surface receptors or their downstream partners critical in cancer development. These agents have shown a monumental benefit in a small number of patients with NSCLC. The more recent addition has been the immunotherapeutic agents, which seem to have a broader benefit and are providing durable responses in NSCLC not previously seen.

The authors have nothing to disclose.
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Surg Oncol Clin N Am 25 (2016) 601–609
http://dx.doi.org/10.1016/j.soc.2016.02.011 **surgonc.theclinics.com**
1055-3207/16/$ – see front matter

TARGETED AGENTS

Background

Several genetic alterations have been identified as drivers of tumorigenesis in NSCLC. Among the most important described in lung cancer is the ERK-MAPK cascade. In this cascade, activating mutations in EGFR, RAS, and BRAF found in lung cancer lead to malignant transformation and gene expression changes.[1] Patients with KRAS-mutant tumors, accounting for 25% of cases of adenocarcinoma, are often predictive of a lack of benefit of tyrosine kinase inhibitors (TKIs)[2] and associated with poorer overall survival.[3]

The number of therapeutic targets is rapidly growing. Fortunately, the drugs being developed for these targets generally have more favorable toxicity profiles than cytotoxic chemotherapy (**Table 1**).

Epidermal Growth Factor Receptor Mutations

The cell surface receptor EGFR, when dimerized, activates tyrosine kinases. This action contributes to control of normal cell proliferation, angiogenesis, adhesion, motility, and apoptosis. Loss of this control contributes to the malignant potential of a lung cancer cell.

Mutations in EGFR account for 15% of lung adenocarcinoma in the United States, the most common of which occur in exon 19 (exon 19del) and exon 21 (L858R). Women and nonsmokers have a slightly higher likelihood of mutations. The frequency

Table 1
Select targeted biologic agents in non–small cell lung cancer

Class	Drugs	Adverse Effects
EGFR inhibitors	Erlotinib, afatinib, gefitinib, osimertinib, rociletinib	Rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, vomiting, interstitial lung disease, hepatotoxicity
ALK inhibitors	Crizotinib, ceritinib, brigatinib, alectinib	Vision disorder, diarrhea, edema, transaminase elevations, vomiting, constipation, dysgeusia, fatigue, pyrexia, pain in extremity, headache, dizziness, pneumonitis
BRAF inhibitors	Vemurafenib, dabrafenib	Other malignancies, hypersensitivity reactions, dermatologic reactions, QT prolongation, hepatotoxicity, uveitis, radiation recall/sensitivity, arthralgia, rash, alopecia, photosensitivity, nausea, pruritis
MEK inhibitors	Trametinib, cobimetinib	Hemorrhage, rash, cardiomyopathy, hepatotoxicity, retinopathy and retinal vein occlusion, rhabdomyolysis, diarrhea, photosensitivity, nausea, pyrexia, vomiting
HER2-blocking antibodies	Trastuzumab	Headache, diarrhea, nausea, chills, cardiomyopathy, infusion reactions, pulmonary toxicity
Multitargeted kinase inhibitors	Cabozantinib	Gastrointestinal perforation/fistula, hemorrhage, thrombotic events, wound complications, hypertension, hand-foot syndrome, osteonecrosis of the jaw, proteinuria, diarrhea, stomatitis, weight loss, anorexia, dysgeusia, nausea, fatigue