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Review

Biomarkers and targeted systemic therapies in advanced non-small cell lung cancer

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ABSTRACT

The last decade has witnessed significant growth in therapeutic options for patients diagnosed with lung cancer. This is due in major part to our improved technological ability to interrogate the genomics of cancer cells, which has enabled the development of biologically rational anticancer agents. The recognition that lung cancer is not a single disease entity dates back many decades to the histological subclassification of malignant neoplasms of the lung into subcategories of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While SCLC continues to be regarded as a single histologic and therapeutic category, the NSCLC subset has undergone additional subcategorizations with distinct management algorithms for specific histologic and molecular subtypes. The defining characteristics of these NSCLC subtypes have evolved into important tools for prognosis and for predicting the likelihood of benefit when patients are treated with anticancer agents.

Contents

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1. Introduction

The last decade has witnessed significant growth in therapeutic options for patients diagnosed with lung cancer. This is due in major part to our improved technological ability to interrogate the genomics of cancer cells, which has enabled the development of biologically rational anticancer agents. The recognition that lung cancer is not a single disease entity dates back many decades to the histological subclassification of malignant neoplasms of the lung into subcategories of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While SCLC continues to be regarded as a single histologic and therapeutic category, the NSCLC subset has undergone additional subcategorizations with distinct management algorithms for specific histologic and molecular subtypes. The defining characteristics of these NSCLC subtypes have evolved into important tools for prognosis and for predicting the likelihood of benefit when patients are treated with anticancer agents.

A discrete and measurable factor, whether in the whole patient or within the neoplastic cancer cells, that provides information on the likelihood of treatment efficacy is termed a predictive biomarker (Biomarkers Definitions Working Group, 2001; Oldenhuis et al., 2008). In contrast, a measurable factor that provides information on the overall patient outcome irrespective of treatment intervention is classically considered a prognostic biomarker (Biomarkers Definitions Working Group, 2001; Oldenhuis et al., 2008). Various biomarkers have emerged as predictive and prognostic markers in NSCLC patients and are now employed as part of their standard management. Putative biomarkers employed in clinical trials of investigational agents in SCLC, none of which have led to a management-defining paradigm, will be outside the scope of this review. This review will therefore focus on the clinical, histologic and molecular factors that are currently employed to guide the selection of therapeutic options for NSCLC patients.

2. Tumor histology as a biomarker in NSCLC

The WHO/IASLC classification of NSCLC includes various subtypes characterized by distinct morphology and immunophenotype (Brambilla et al., 2001; Travis et al., 2011). The squamous and adenocarcinoma categories represent the two major histologic subtypes of NSCLC. The utility of tumor histology as a biomarker for selecting therapeutic intervention is therefore relevant to this review. The impact of squamous histology as a poor prognostic factor is supported by various retrospective and prospective studies (Clark, 2008; Hirsch et al., 2008). This strategy became an established paradigm following retrospective analysis of outcome data from prospective studies of pemetrexed in unselected NSCLC patients, where a differential efficacy was noted between patients with squamous and non-squamous tumors (Langer et al., 2010; Scagliotti et al., 2011). Prospective comparison of the efficacy of pemetrexed-containing and gemcitabine-containing platinum doublet chemotherapy regimens as first line treatment of advanced NSCLC confirmed the differential efficacy of a pemetrexed-containing doublet by histology (Scagliotti et al., 2008).

Histology has also served as a surrogate biomarker for increased risk of treatment-related toxicity leading to the avoidance of specific therapeutic agents. The notable example is the increased propensity for squamous tumors, which are more likely to be cavitary and centrally located in close proximity to major blood vessels, to hemorrhage following treatment with agents targeting angiogenesis such as bevacizumab (Langer et al., 2010). Squamous histology has thus become a biomarker to exclude patients who are unsuitable for anti-angiogenesis therapies. The main drawback with the use of tumor histology as a predictive biomarker in NSCLC is the significant discordance even among expert pulmonary pathologists in establishing a pathologic diagnosis of squamous NSCLC (Grilley-Olson et al., 2013). Nonetheless, an algorithm that couples cell morphology and immunophenotype in the hands of an experienced pathologist can overcome this challenge in most cases.

3. Genetic alterations as biomarker

The major advance in the treatment of NSCLC in the last decade grew from the recognition that specific genetic alterations define subsets of NSCLC (Berge and Doebele, 2014). This paved the way for the development of an array of effective agents to specifically counteract the biological consequences of such genetic aberrations. Thus, NSCLC went from a disease defined primarily by tumor histology to an amalgam of molecular subtypes, of which the subsets characterized by alterations in the epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) genes are the most dominant.

3.1. Epidermal growth factor receptor (EGFR) gene mutations as a biomarker

The EGFR is a 170-kDa plasma membrane glycoprotein consisting of a large extracellular region, a single transmembrane domain, and an intracellular domain with tyrosine kinase activity and a C-terminal tail. The EGFR family consists of 4 closely related receptors, HER-1/ErbB1, HER-2/neu/ErbB2, HER-3/ErbB3 and HER-4/ErbB4 with significant homology in their kinase domains, but differences in the coding regions for the extracellular domain and the C-terminal tails (Normanno et al., 2006). Dimerization of ErbB receptors upon ligand binding to the extracellular domain results in activation of their intrinsic tyrosine kinase activity. Activation of the EGFR receptor via phosphorylation relays downstream signals to the phosphatidylinositol 3-kinase (PI3K)/AKT and RAS/RAF/ mitogen-activated protein kinase (MAPK) pathways. These intracellular signaling pathways that are responsible for the normal regulation of essential cellular processes such as proliferation and apoptosis are coopted by neoplastic cells harboring *EGFR* mutation (Grandis and Sok, 2004; Normanno et al., 2006). Mutations in the *EGFR* gene occurring in NSCLC are commonly localized within the tyrosine kinase domain of the gene. Well established mutations include deletions in exon 19 (60%), missense mutation (L858R) in exon 21 (25%), point mutations in exons 18, 20 or 21, and insertion in exon 20 (Lynch et al., 2004; Paez et al., 2004; Pao et al., 2004). These