Effects of Cigarette Smoking on Metabolism and Effectiveness of Systemic Therapy for Lung Cancer

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Introduction: Cigarette smoke associated polycyclic aromatic hydrocarbons can induce key drug-metabolizing enzymes of cytochrome P450 and isoforms of the glucuronyl transferases families. These enzymes metabolize several systemic therapies for lung cancer. Induction of these enzymes may lead to accelerated clearance with resultant impact on systemic therapy efficacy and toxicity in smokers compared with nonsmokers. This article reviews published literature regarding the influence of smoking as it relates to alteration of metabolism of systemic therapy in lung cancer.

Methods: A structured search of the National Library of Medicine's PubMed/MEDLINE identified relevant articles. Data were abstracted and analyzed to summarize the findings.

Results: Studies that analyzed pharmacokinetic data were prospective. Smokers receiving erlotinib exhibited rapid clearance, requiring a higher dose to reach equivalent systemic exposure compared with nonsmokers. Smokers receiving irinotecan also demonstrated increased clearance and lower systemic exposure. There was no difference in clearance of paclitaxel or docetaxel in smokers. Chemotherapy-associated neutropenia was worse in nonsmokers compared with smokers in patients treated with paclitaxel, docetaxel, irinotecan, and gemcitabine.

Conclusions: Systemic therapy for lung cancer has a narrow therapeutic index such that small changes in plasma concentrations or exposure in smokers may result in suboptimal therapy and poor outcomes. Smoking cessation must be emphasized at each clinical visit. However, prospective trials should take into consideration the effects of smoking history on drug pharmacokinetics and efficacy. The metabolizing enzyme phenotype in smokers may require individualized dose algorithms for specific agents.

Key Words: Pharmacokinetics, Pharmacodynamics, Smoking, Chemotherapy metabolism, Nicotine, Response, Toxicities, Lung cancer

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Cigarette smoking is a significant source of morbidity and mortality. According to the National Health Interview Survey, approximately one in five (20.2%) of US adults currently smoke.[1] In addition, there is an estimated 49.9 million former smokers in the United States.[2] Smoking is the greatest risk factor for lung cancer, which continues to be the leading cause of cancer-related death for both sexes.[3] Outcomes in lung cancer for both current and former smokers are dismal, with a 5-year relative survival rate of approximately 15%.[4] It is also evident that nonsmokers have an improved survival from therapy for advanced lung cancer compared with smokers.[4–6] The recent Surgeon General Report highlights 50 years of progress in tobacco control and prevention and presents new data on the health consequences of smoking. This may relate to a multitude of factors ranging from intrinsic differences in lung cancer biology, host associated medical comorbidities[7] and polymorphisms in drug-metabolizing enzymes[8] leading to reduced efficacy of therapies.

In addition to the carcinogenic effects of tobacco products, the components of cigarette smoke can induce drug-metabolizing enzymes, which have been demonstrated in both in vitro and animal models.[9–11] Induction of these metabolizing enzymes resulting in accelerated clearance may reduce drug efficacy in smokers and impact clinical outcomes. Smoking is associated with reduced beta blocker effectiveness, in terms of lowering blood pressure and heart rate, and reduced sedation from benzodiazepines.[12] Several often used chemotherapeutic drugs and many of the newer targeted therapies are metabolized by the hepatic cytochrome P450 enzymes, in addition to the uridine 5′-diphosphate-glucuronyl transferases. Although the exact mechanism behind the accelerated drug metabolism has not yet been clearly elucidated, there is emerging evidence that compounds in cigarette smoke may epigenetically modify these enzymes that result in persistently elevated activity, even after smoking cessation.[13] In addition, there may be a direct effect of nicotine on molecular effectors of cellular apoptosis induced by several chemotherapies for lung cancer.[14]

Several studies have reported the effects of cigarette smoking on the ,pharmacokinetic (PK) and pharmacodynamic (PD) effects of systemic for lung cancer. The goal of this article is to review the effects of cigarette smoke as it relates to metabolism and efficacy of systemic therapies for lung cancer. We searched PubMed/MEDLINE to identify relevant articles published between 2000 and January 2014. The search strategy included Medical Subject Headings (MeSH) and keywords representing the concepts of smoking status, smoking cessation or nicotine replacement combined with MeSH and keywords for lung cancer, chemotherapy, and selected

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chemotherapeutic agents (docetaxel, gemcitabine, etc.). Citations were filtered to exclude citations solely on "never smokers," and then filtered again using MeSH, subheadings, and keywords to identify articles that focused on molecular rather than metabolic or pharmacokinetic responses to chemotherapy. Data were abstracted from 171 publications and summarized below.

EFFECTS OF CIGARETTE SMOKE ON PHASE I AND II METABOLIZING ENZYMES

Cigarette smoke is known to contain more than 7000 chemicals, of which more than 60 possess carcinogenic properties.[2] Smoke is composed of both volatile and particulate phases that comprise approximately 95% and 5%, respectively. The volatile phase is composed primarily of nitrogen, oxygen, and carbon dioxide.[15] Excluding the alkaloid and the water content, the remaining particulate mass is referred to as tar, which is composed of carcinogens including polycyclic aromatic hydrocarbons (PAHs), *N*-nitrosamines, and aromatic amines.[16] PAHs are compounds with two or more aromatic and cyclic rings that can induce DNA mutations.[17,18] More than 500 PAHs have been identified in cigarette smoke.[19] PAHs are oxidized by cytochrome P450 enzymes and the resultant metabolites exert mutagenic effects on DNA. The same PAHs have also been shown to induce members of the P450 enzyme family, which normally process xenobiotics.[15,20,21] The P450 enzymes are responsible for phase I drug metabolism by oxidizing the parent compound to a more readily excreted metabolite.[22] The most common isoforms as relates to metabolism of often used systemic therapy for lung cancer include CYP1A1/2, CYP2D6, and CYP3A4. Herein, we will review how tobacco smoke interacts with these enzymes either through increased induction or increased degradation.

CYP1A1 and CYP1A2 are the most common CYP1 family isoforms that metabolize some systemic therapies used to treat lung cancer such as erlotinib, an epidermal growth factor (EGFR) inhibitor. PAHs in tobacco smoke can induce isoenzymes CYP1A1 and CYP1A2.[20] Zhu et al.[23] theorized that the process of selective induction of a CYP isoform by PAHs is primarily determined by the following three core elements: each inducible CYP isoform has a corresponding intracellular receptor that interacts with the inducer chemicals, each isoform and its receptor may share highly similar steric structures, and each inducible *CYP* gene may have a distinct genomic response element that interacts selectively with the corresponding receptor. The CYP1A1 enzyme, an aryl hydrocarbon hydroxylase, is involved in the activation of procarcinogens, such as PAHs, and can be transcriptionally induced by PAHs.[24,25] Binding to the aryl hydrocarbon receptor, a basic helix-loop-helix transcription factor, leads to heterodimerization and binding to the aryl hydrocarbon-responsive elements in the *CYP1A1* gene,[26] as detailed in Figure 1*A*. These events then lead to increased expression of the *CYP1A1* gene and potentially accelerated drug metabolism.[27,28] Anttila et al.[29] observed smoking-related alterations of the *CYP1A1* promoter methylation status in lung tumor samples. DNA from resected lung tumors demonstrated complete or partial

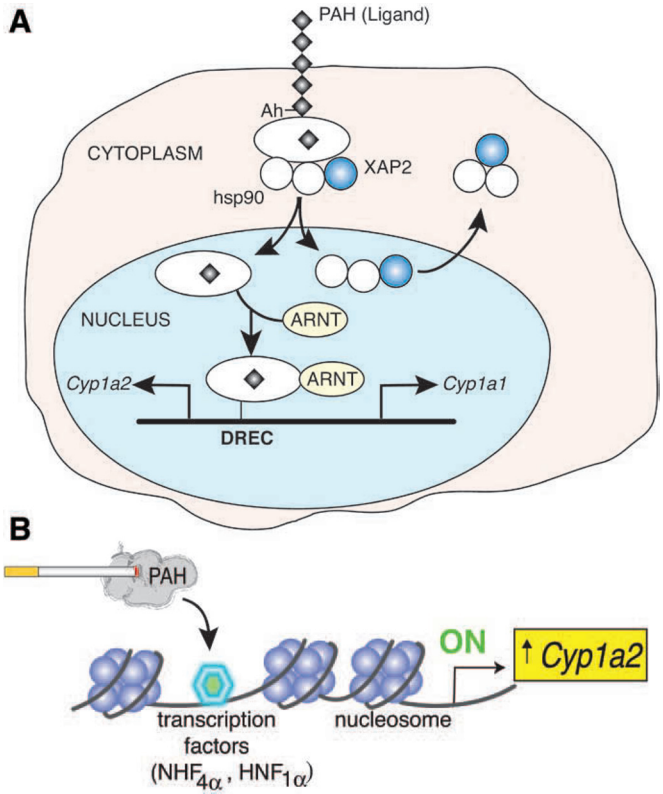

FIGURE 1. PAH-induced direct (*A*) transcriptional and (*B*) epigenetic regulation of cytochrome P450 enzymes, CYP1A1, and CYP1A2. PAH, polycyclic aromatic hydrocarbon; Ah, aryl hydrocarbon; ARNT, aryl hydrocarbon receptor nuclear translocator; Hsp90, heat shock protein 90; XAP2, X-associated protein.

CYP1A1 promoter methylation in 33% of heavy smokers, 71% of light smokers, and 98% of nonsmokers.[29]

Similarly, CYP1A2 is a hepatic enzyme that is responsible for the metabolism of several often used medications, such as theophylline, caffeine, and acetaminophen.[12] Induction of CYP1A2 may be mediated through binding of PAHs similar to CYP1A1, which leads to transcriptional activation of the *CYP1A2* gene.[30] Alternatively, as detailed in Figure 1*B*, PAH can epigenetically modify transcription factors such as $NHF_{4\alpha}$ and $HNF_{1\alpha}$, which leads to the upregulation of CYP1A2.[31,32] Cigarette smoke induces chromatin remodeling by acetylating lysine residues on histone proteins to facilitate gene expression.[33] In Addition, the activity of histone deacetylases, which remove acetyl groups to repress transcription were reduced activity in bronchial biopsies from smokers compared with nonsmokers ($p < 0.01$).[34] Induction of CYP1A2 is linked to increased activity of the enzyme which in turn leads to reduced serum concentrations and reduced efficacy of the substrates.[35]

CYP2D6, the most common isoform of the CYP2 family, is involved in metabolism of opiates used in supportive care for lung cancer patients. The gene encoding this enzyme has been reported to have multiple single nucleotide polymorphisms (SNPs) that can lead to varying expression among the