Might Cigarettes Be a "Smoking Gun" to Reduce Taxane Myelotoxicity?

Lionel D. Lewis and Mark J. Ratain

In this issue of Clinical Cancer Research, de Graan and colleagues (1) describe a retrospective cohort study of patients with cancer (smokers and nonsmokers) who received either paclitaxel (n = 276) or docetaxel (n = 290) in standard doses. The authors compared differences in taxane clearance and leukopenia/neutropenia between smokers (paclitaxel, n = 62; docetaxel, n = 75) and nonsmokers (paclitaxel, n = 214; docetaxel, n = 215). Their data suggested that smokers treated with either taxane showed less myelosuppression but, somewhat incongruously, these results were not associated with any alteration in taxane clearance.

The first question is whether these results indicate a true or a false discovery. This was a retrospective study with inherent biases, the most significant of which is case selection bias. For example, the authors excluded patients if they had stopped smoking for more than 4 weeks, but chronic stimulatory effects of smoking on hematopoiesis can be observed for months or even years after smoking cessation (2). Some study patients received combination chemotherapy rather than taxane monotherapy, which could have confounded the relationship between taxane pharmacokinetics and bone marrow suppression. The categorization of patients into smokers or nonsmokers was based on information in the medical record without confirmation of smoking behavior using accepted methods for confirming cigarette smoke exposure (e.g., measurement of urine cotinine at chemotherapy administration). This raises concerns about the accuracy of this categorization. For the statistical analyses of the observed differences between smokers and nonsmokers in leukocyte and/or neutrophil cell numbers or changes from baseline in these cell numbers, the α-statistic (the probability of rejecting the null hypothesis of no difference, when in fact there is no true difference) is in many instances only marginally less than 0.05 or only trending toward this value. Given that there were multiple statistical tests for differences conducted, the nominally significant P values may be due to chance alone. On the other hand, the observed differences between smokers and nonsmokers in taxane myelotoxicity are intriguing and worthy of further study.

De Graan and colleagues (1) observed an increased baseline white blood cell and absolute neutrophil count for smokers who were treated with paclitaxel, but only a trend toward this difference was observed in the docetaxel-treated cohort. Because baseline white blood cell and absolute neutrophil count have been associated with nadir counts, this suggests that any putative protective effect of smoking is mediated by these higher baseline cell counts. The causal association between cigarette smoking and increased myeloid cell numbers, is well established (2, 3). The mechanisms for the multifaceted effects of cigarette smoke in humans, including those on hematopoiesis, are summarized in Fig. 1. Studies (4) suggest that nicotine stimulates nicotinic acetylcholine receptors (n-AChR) on neutrophils whose intracellular signaling increases superoxide production, which facilitates peroxynitrite formation from nitric oxide generated by neutrophil nitric oxide synthase. Increased intracellular peroxynitrite induces NF-κB in the neutrophils, which upregulates interleukin (IL)-8 production, thereby promoting neutrophil production and trafficking. In addition, smokers inhale small particles (<10 μm in size; PM10) into their lungs that are phagocytosed by alveolar macrophages, resulting in the release of IL-6 and granulocyte macrophage colony-stimulating factor, further stimulating proliferation of bone marrow myeloid precursors (5, 6).

Importantly, the study by de Graan and colleagues (1) provides evidence to suggest that cigarette smoking does not change the pharmacokinetic clearance of either docetaxel or unbound paclitaxel. The observed values for the population clearances of docetaxel and unbound paclitaxel in smokers and nonsmokers in this study are concordant with...
published data (7–9). The clearance of both of these drugs (in humans) is almost entirely via hepatic metabolism, mediated solely by CYP3A for docetaxel and by CYP3A and CYP2C8 for paclitaxel, with only 5% to 10% of a dose of either drug being excreted in urine (7, 8). The area under the concentration versus time curve of docetaxel (7) and time above the threshold concentration of 0.05 μmol/L for total plasma paclitaxel concentrations have been previously shown to be associated with taxane-related neutropenia (9). This leads one to conclude that the effect of smoking on leukocyte and neutrophil numbers in patients with cancer receiving taxanes in the study by de Graan and colleagues (1) was not caused by altered taxane pharmacokinetics (i.e., reduced drug exposure because of increased metabolic clearance). However, cigarette smoking clearly alters the pharmacokinetics of some drugs. The most well-established mechanism for this effect is via aromatic hydrocarbon receptor (AhR)-mediated induction of the
expression of a number of drug-metabolizing enzymes (ref. 10; Fig. 1). This is likely an important factor in the dosing and effectiveness of drugs that undergo metabolism via CYP1A2. One example of such a drug is erlotinib, which is metabolized by both CYP3A4 and CYP1A2, and may require higher doses in smokers (11). There is also evidence suggesting that phase II drug-metabolizing enzymes may be induced by cigarette smoking (10). The precise mechanism for this effect is less well established than that for CYP1A, although probably also involves nuclear receptor modulation. As one example, UGT1A1 induction probably plays some role in the putative effect of smoking on the pharmacokinetic disposition of irinotecan and its metabolites, SN-38 and SN-38 glucuronide (12).

Could the study by de Graan and colleagues (1) be proof-of-concept for a novel approach to reduce taxane myelotoxicity? Although chronic cigarette smoking is less expensive than filgastrim or pegfilgastrim in the short-term, the multiple associated negative health consequences of smoking obviously preclude such an approach (Fig 1). However, if the precise pharmacologic mechanism of the effect of cigarette smoking on the bone marrow could be elucidated, it may be possible to develop a drug, without the adverse effects of smoking, which stimulates hematopoiesis. Clearly, before such a drug development program would be embarked upon, the findings of de Graan and colleagues (1) would need to be replicated in a prospective study, as suggested by these authors.

What then is the answer to the question “Might cigarettes be a ‘smoking gun’ for reduced taxane myelotoxicity?” Taking all currently available evidence into consideration, cigarettes appear to be somewhat more of a potential rather than a definitive smoking gun in their association with reduced taxane myelotoxicity.

Disclosure of Potential Conflicts of Interest
M.J. Ratain is a Consultant/Advisory Board member of Sanofi-Aventis on matters unrelated to docetaxel. No potential conflicts of interest were disclosed by L.D. Lewis.

Authors’ Contributions
Conception and design: L.D. Lewis, M.J. Ratain
Writing, review, and/or revision of the manuscript: L.D. Lewis, M.J. Ratain
Draft sketch of Fig. 1: L.D. Lewis

Grant Support
L.D. Lewis is supported in part by P30CA23108, and M.J. Ratain is supported in part by U01GM61393 and holds a Translational Research Professorship from the Conquer Cancer Foundation.

Received June 13, 2012; accepted June 21, 2012; published OnlineFirst August 2, 2012.

References
Might Cigarettes Be a "Smoking Gun" to Reduce Taxane Myelotoxicity?

Lionel D. Lewis and Mark J. Ratain


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-1713

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2012/08/13/1078-0432.CCR-12-1713.DC1

Cited articles
This article cites 12 articles, 6 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/18/16/4219.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.