

# Cigarette Smoking and the Personalization of Irinotecan Therapy

Neal L. Benowitz, *Division of Clinical Pharmacology and Experimental Therapeutics, Departments of Medicine, Psychiatry, and Biopharmaceutical Sciences, Medical Service, San Francisco General Hospital Medical Center, San Francisco, CA*

Lifelong cigarette smokers have a 50% chance of dying prematurely due to their addiction.<sup>1</sup> Nearly one third of these deaths are due to cancer. Smokers who develop cancer are often highly addicted and many continue to smoke after the diagnosis of cancer.<sup>2</sup> Smoking-induced cancers that are treated with irinotecan include colon cancer, lung cancer, and others.

Irinotecan is a topoisomerase I inhibitor, with dose-limiting toxicity that includes leukopenia and severe diarrhea. Irinotecan is a prodrug, which is metabolized primarily by carboxylesterase enzymes to an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38).<sup>3</sup> Irinotecan is also metabolized by the enzyme CYP3A4, and one of the metabolites via the CYP3A4 pathway can be metabolized further by carboxylesterase to SN-38. SN-38 is in turn detoxified by glucuronide conjugation via the enzyme uridine diphosphate glucuronosyltransferase (UGT) 1A1.

The disposition kinetics and related safety and efficacy of irinotecan are influenced to a considerable degree by genetic and environmental factors. A variant genotype in the promoter region of the UGT enzyme, *UGT1A1\*28*, is associated with a remarkably reduced rate of SN-38 glucuronidation, and a higher risk of irinotecan toxicity with standard dosing.<sup>4,5</sup> This variant also causes the Gilbert syndrome. Clinical diagnostic tests for the *UGT1A1\*28* variant have been developed and promoted as a way to individualize irinotecan dosing and to prevent serious toxicity.<sup>3</sup>

Environmental factors such as the use of other drugs and cigarette smoking also influence response to irinotecan. Antiepileptic drugs such as phenytoin and carbamazepine accelerate irinotecan and SN-38 metabolism substantially, resulting in decreased levels of SN-38.<sup>6</sup> As a consequence, higher doses of irinotecan are recommended in patients receiving antiepileptic drugs as part of treatment of malignant glioma. Another major environmental modulator of irinotecan response, cigarettes smoking, has been shown to decrease the risk of hematologic toxicity from irinotecan, as described by van der Bol et al in this issue.<sup>7</sup> The risk of irinotecan-induced neutropenia in this study was 6% for smokers compared with 38% for nonsmokers. There was a trend toward a lesser incidence of delayed-onset diarrhea (6% v 15%), but this difference was not significant.

Cigarette smoking is well known to interact with a variety of drugs, both by pharmacokinetic and pharmacodynamic mechanisms.<sup>8</sup> Pharmacokinetic interactions are related primarily to the effects of cigarette smoking to induce many drug-metabolizing

enzymes and to inhibit some drug-metabolizing enzymes. Polycyclic aromatic hydrocarbons in cigarette smoke are responsible for the induction of lung and liver enzymes, including CYP1A1 and CYP1A2. Smoking-induced induction of CYP1A2 accounts for well-known interactions of smoking with drugs such as caffeine, clozapine, haloperidol, fluvoxamine, olanzapine, tacrine, and theophylline. Recently, smoking has been shown to accelerate the metabolism of erlotinib, another drug metabolized by CYP1A1 and 1A2, which likely explains the poorer response of smokers compared with nonsmokers with non-small-cell lung cancer.<sup>9</sup> Cigarette smoking also induces the enzyme CYP2E1 and inhibits CYP2A6, effects that may be mediated by nicotine.<sup>10,11</sup> There are conflicting data on the effects of cigarette smoking on the induction of CYP3A4. Cigarette smoking also induces the glucuronidation of some drugs, including mexiletine, propranolol, and codeine, although interestingly in the context of the present study, not morphine or bilirubin.<sup>8</sup>

Cigarette smoking has many other physiologic effects that could affect drug response, including effects on the hematopoietic system, including an increase in neutrophil count.<sup>12</sup> Smoking seems to stimulate the bone marrow by releasing proinflammatory factors from macrophages. A direct effect of cigarette smoking on neutrophil count must be considered as a possible mechanism by which smoking reduces neutropenia due to irinotecan.

The article by van der Bol et al<sup>7</sup> explores the mechanism of the smoking effect on irinotecan toxicity. Key observations in smokers include lower levels of irinotecan and SN-38 in the plasma, and no significant change in SN-38 glucuronide levels. As an important control, *UGT1A1\*28* genotype prevalence was not different in smokers versus nonsmokers, eliminating genetic predisposition as a confounder for differential risk of toxicity. The data in this article suggest that cigarette smoking accelerates the metabolism of irinotecan to SN-38, and based on the higher ratios of SN-38 glucuronide to SN-38, also accelerates the glucuronidation of SN-38. Given that the levels of SN-38 were substantially lower in smokers compared with those in nonsmokers, the effects of smoking to induce SN-38 glucuronidation seem to far exceed the effects of smoking to accelerate the conversion of irinotecan to SN-38.

As the authors of this informative study mention, although cigarette smoking may reduce the toxicity of irinotecan, it does so by lowering the levels of the active metabolite SN-38. Lower levels of circulating SN-38 might be expected to reduce the therapeutic

effect of irinotecan, although carboxylesterase is present in tumors, so irinotecan may also be activated to SN-38 locally.<sup>13</sup> In the study by van der Bol et al,<sup>7</sup> the number of patients was too small to detect such an effect. The possibility that smoking will reduce the efficacy of irinotecan by lowering irinotecan and/or SN-38 levels has potential implications for personalizing the dose of irinotecan—that is, dosing differently in smokers compared with nonsmokers. Higher doses of irinotecan may need to be administered to smokers, as they are for patients receiving antiepileptic drugs.<sup>14,15</sup> In the latter studies, doses of irinotecan were escalated in successive courses, from initial doses of 300 to 350 mg/m<sup>2</sup> up to doses as high as 1,700 mg/m<sup>2</sup>, as limited by the development of toxicity. Given that the SN-38 levels averaged 40% lower in smokers compared with nonsmokers, one would predict that 40% higher doses of irinotecan are needed in smokers. Other recent studies suggest that many patients can tolerate higher than usual starting doses of irinotecan, and that dose escalation to toxicity might be more generally applied as a way to improve outcome.<sup>16</sup>

Thus there is good reason to consider personalized dosing of irinotecan. Genetic screening can predict individuals who are more susceptible to toxicity and who should be started on lower than usual doses. Cigarette smoking or the use of antiepileptic drugs suggests the need for upward dose titration to toxicity.

What if cigarette smoking does reduce the toxicity of irinotecan without affecting its efficacy? Should oncologists be less aggressive in counseling and helping their patients to stop smoking? The answer is unequivocally no. Smoking is highly detrimental to cancer patients in many ways. Smoking reduces overall survival, decreases the efficacy of radiation therapy, and increases the risk of second primary malignancies in cancer patients.<sup>17</sup> Smoking substantially increases the risks and severity of infection, particularly pulmonary infections.<sup>18</sup> For example, cigarette smoking is a very strong risk factor for the development of invasive pneumococcal disease.<sup>19</sup> Smoking substantially increases the risk of cardiovascular events and markedly increases surgical risks, both of which are important concerns with older cancer patients.<sup>20,21</sup> Just as is the case for smokers with coronary heart disease or chronic obstructive lung disease, assisting the cancer patient to stop smoking is one of the most important interventions for improving morbidity and mortality that an oncologist can provide.<sup>17</sup>

The article by van der Bol et al<sup>7</sup> sends another message to cancer clinical trialists. Information on tobacco use should be collected routinely and analyzed as part of all cancer chemotherapy trials. Irinotecan has been in use for many years and many patients who have received the drug have undoubtedly been smokers. Yet it is not until 2007 that the very impressive interaction between smoking and irinotecan, affecting safety and possibly efficacy, has been discovered. Guidelines for collecting tobacco use data have been published and are highly recommended for inclusion both in clinical trials and clinical practice.<sup>22</sup>

## AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author indicated no potential conflicts of interest.

## REFERENCES

- Peto R, Lopez AD, Boreham J, et al: Mortality from tobacco in developed countries: Indirect estimation from national vital statistics. *Lancet* 339:1268-1278, 1992
- Walker MS, Vidrine DJ, Gritz ER, et al: Smoking relapse during the first year after treatment for early-stage non-small-cell lung cancer. *Cancer Epidemiol Biomarkers Prev* 15:2370-2377, 2006
- Innocenti F, Ratain MJ: Pharmacogenetics of irinotecan: Clinical perspectives on the utility of genotyping. *Pharmacogenomics* 7:1211-1221, 2006
- Ando Y, Saka H, Ando M, et al: Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: A pharmacogenetic analysis. *Cancer Res* 60:6921-6926, 2000
- Innocenti F, Undevia SD, Iyer L, et al: Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 22:1382-1388, 2004
- Kuhn JG: Influence of anticonvulsants on the metabolism and elimination of irinotecan: A North American Brain Tumor Consortium preliminary report. *Oncology (Williston Park)* 16:33-40, 2002 (suppl 7)
- van der Bol JM, Mathijssen RH, Loos WJ, et al: Cigarette smoking and irinotecan treatment: Pharmacokinetic interaction and effects on neutropenia. *J Clin Oncol* 25:10.1200/JCO.2006.09.6115
- Zevin S, Benowitz NL: Drug interactions with tobacco smoking: An update. *Clin Pharmacokinet* 36:425-438, 1999
- Hamilton M, Wolf JL, Rusk J, et al: Effects of smoking on the pharmacokinetics of erlotinib. *Clin Cancer Res* 12:2166-2171, 2006
- Benowitz NL, Peng M, Jacob P III: Effects of cigarette smoking and carbon monoxide on chlorzoxazone and caffeine metabolism. *Clin Pharmacol Ther* 74:468-474, 2003
- Howard LA, Micu AL, Sellers EM, et al: Low doses of nicotine and ethanol induce CYP2E1 and chlorzoxazone metabolism in rat liver. *J Pharmacol Exp Ther* 299:542-550, 2001
- van Eeden SF, Hogg JC: The response of human bone marrow to chronic cigarette smoking. *Eur Respir J* 15:915-921, 2000
- Guichard S, Terret C, Hennebelle I, et al: CPT-11 converting carboxylesterase and topoisomerase activities in tumour and normal colon and liver tissues. *Br J Cancer* 80:364-370, 1999
- Prados MD, Yung WK, Jaeckle KA, et al: Phase 1 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: A North American Brain Tumor Consortium study. *Neuro-oncol* 6:44-54, 2004
- Cloughesy TF, Filka E, Kuhn J, et al: Two studies evaluating irinotecan treatment for recurrent malignant glioma using an every-3-week regimen. *Cancer* 97:2381-2386, 2003
- Ychou M, Raoul JL, Desseigne F, et al: High-dose, single-agent irinotecan as first-line therapy in the treatment of metastatic colorectal cancer. *Cancer Chemother Pharmacol* 50:383-391, 2002
- Gritz ER, Fingeret MC, Vidrine DJ, et al: Successes and failures of the teachable moment: Smoking cessation in cancer patients. *Cancer* 106:17-27, 2006
- Arcavi L, Benowitz NL: Cigarette smoking and infection. *Arch Intern Med* 164:2206-2216, 2004
- Nuorti JP, Butler JC, Farley MM, et al: Cigarette smoking and invasive pneumococcal disease: Active Bacterial Core Surveillance Team. *N Engl J Med* 342:681-689, 2000
- Moller AM, Villebro N, Pedersen T, et al: Effect of preoperative smoking intervention on postoperative complications: A randomised clinical trial. *Lancet* 359:114-117, 2002
- Vaporciyan AA, Merriman KW, Ece F, et al: Incidence of major pulmonary morbidity after pneumonectomy: Association with timing of smoking cessation. *Ann Thorac Surg* 73:420-426, 2002
- Gritz ER, Dresler C, Sarna L: Smoking, the missing drug interaction in clinical trials: Ignoring the obvious. *Cancer Epidemiol Biomarkers Prev* 14:2287-2293, 2005

## Acknowledgment

Supported by US Public Health Service Grants No. DA020830 and DA02277 from the National Institute on Drug Abuse and the University of California San Francisco Comprehensive Cancer Center.