

Chemotherapy-Induced Mucositis: Focusing on Diarrhea

Kari Wisinski, MD, and Al Benson III, MD, FACP

Dr. Wisinski is an oncology fellow and Dr. Benson is Professor of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Commentary on “Chemotherapy-Induced Mucositis: The Role of Gastrointestinal Microflora and Mucins in the Luminal Environment” by Stringer et al (page 259).

Mucositis, or inflammation of the mucous membranes lining the alimentary tract, is a potential adverse effect of chemotherapeutic agents, and diarrhea is the symptomatic result of mucositis of the large bowel. Understanding the mechanism of mucosal injury that leads to chemotherapy-induced diarrhea may have important clinical implications. Diarrhea can limit the maximal dose of an agent that can be delivered safely. For some chemotherapy regimens, like 5-fluorouracil (5-FU) and IFL (irinotecan [CPT-11; Camptosar], 5-FU, and leucovorin), diarrhea has been linked to excess hospitalizations and death.^{1,2} Even at recommended doses, significant diarrhea can occur in some individuals, causing dose reductions or treatment delays that can result in less effective chemotherapy delivery. Moreover, diarrhea is an uncomfortable, intrusive, and embarrassing symptom for many patients. An improved understanding of this side effect's etiology may lead to better care of the cancer patient.

In this issue of *The Journal of Supportive Oncology*, Stringer et al systematically review the normal histology and physiology of the gastrointestinal tract, specifically focusing on the role of the intestinal microflora and the mucin-producing goblet cells. The proposed mechanism of chemotherapy-induced diarrhea related to irinotecan is discussed in detail. The authors focus on the relationship between the intestinal microflora and mucin production in the large bowel and the diarrhea induced by irinotecan and other chemotherapy agents.

Correspondence to: Al Benson III, MD, FACP, Northwestern University, Division of Hematology/Oncology, 676 N. St. Clair, Suite 850, Chicago, IL 60611; telephone: (312) 695-6180; fax: (312) 695-6189; e-mail: a-benson@northwestern.edu

J Support Oncol 2007;5:270-271

© 2007 Elsevier Inc. All rights reserved.

Irinotecan and 5-Fluorouracil

Grade 3 or higher diarrhea occurs in $\geq 30\%$ of patients on single-agent irinotecan.^{3,4} This review by Stringer et al discusses the well-described metabolism of irinotecan to SN-38, a more potent compound, and the subsequent conversion to the inactive SN-38 glucuronide. This article also discusses recent publications supporting the role of bacterial β -glucuronidase produced by intestinal microflora in the pathogenesis of irinotecan-induced diarrhea. There is evidence in rats demonstrating that bacterial β -glucuronidase leads to increased intestinal SN-38. Furthermore, β -glucuronidase inhibitors, or antibiotics that decrease β -glucuronidase activity, improved irinotecan-induced diarrhea in these rats.⁵ Another study showed that germ-free mice treated with irinotecan were found to have less intestinal damage and diarrhea than normal mice, again implicating the role of the intestinal microflora.⁶ A study published in 2004 demonstrated that saccharic acid 1,4-lactone, an inhibitor of β -glucuronidase, led to decreased irinotecan-induced mucosal damage in mice.⁷

In humans, a small study indicated that neomycin reduced the amount of β -glucuronidase produced by the microflora and reduced fecal concentrations of SN-38.⁸ However, a larger, randomized study in subjects being treated with irinotecan did not find a significant difference in diarrhea when neomycin was used.⁹ Although Stringer et al present several studies that demonstrate alterations in the mucin-producing goblet cells secondary to irinotecan therapy, the correlation between this histopathologic finding and diarrhea is still unclear and needs further investigation. More detailed understanding of the human intestinal microflora and its β -glucuronidase activity, as well as the role of goblet cells in chemotherapy-induced diarrhea, may lead to the development of pharmacologic agents aimed at reducing the diarrhea caused by irinotecan and other chemotherapeutic agents.

Another agent frequently associated with diarrhea is 5-FU, with some studies indicating that diarrhea occurs in nearly 50% of patients receiving this drug.^{2,10,11} 5-FU induces mitotic arrest of intestinal crypt cells, resulting in an increased ratio of crypt cells to villous enterocytes and thus a reduction of the absorptive surface.^{12,13} The diarrhea from 5-FU has not been related to the intestinal microflora or mucin production in the large intestine.

Current cancer treatments often involve combination chemotherapy, which can lead to increased toxicity when side effects overlap. For colorectal cancer, diarrhea is a shared side effect of many of the agents used. For example, in clinical trials, the incidence of diarrhea with FOLFOX (5-FU, leucovorin, and oxaliplatin [Eloxatin]) is 56%, with 11% having grade 3 or 4 toxicity.¹⁴ Off trial, that number has been reported as high as 64%, with 21% at grade 3 or 4.¹⁵ Studies with IFL and FOLFIRI (5-FU, leucovorin, and irinotecan) reported grade 3 or 4 diarrhea in 23% and 11% of cases, respectively.^{1,16}

Management

Given the frequency with which chemotherapy-induced diarrhea occurs, oncologists need to be knowledgeable of the management of this problem. It is important to evaluate patients for disorders that may predispose them to diarrhea, such as surgical shortening of the bowel, non-malignant bowel disorders, or prior bowel irradiation. The patient's baseline bowel routine must be understood. When a patient is started on a chemotherapy agent or regimen that can cause diarrhea, the physician should educate him or her to monitor the frequency, volume, and consistency of his or her stools.¹³

Current guidelines for chemotherapy-induced diarrhea start with early, rigorous assessment of symptoms. Evaluation for any other medications that induce diarrhea (ie, antibiotics) should also be done. Complicated diarrhea is defined as grade 3/4 diarrhea or grade 1/2 diarrhea with the presence of any of the following: moderate to severe cramping, \geq grade 2 nausea/vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration. Management of complicated cases should involve intravenous fluids, octreotide dose escalation, and antibiotics. Uncomplicated diarrhea can be initially managed with dietary modifications and loperamide every 4 hours, increased to every 2 hours if diarrhea persists after 24 hours of treatment. If uncomplicated diarrhea continues despite 24 hours of high-dose loperamide, a second-line antidiarrheal agent (eg, octreotide, tincture of opium, or oral budesonide [Rhinocort]) should be added.¹⁷

In summary, chemotherapy-induced diarrhea is an important side effect of several chemotherapy agents, particularly 5-FU and irinotecan. Diarrhea can limit the effective dosing of these agents, as well as have a significant effect on the patient's quality of life. As more is understood about the mechanisms

of mucosal injury induced by these agents, directed pharmacologic interventions to prevent diarrhea may be developed. Furthermore, as cancer care migrates to individualized, targeted regimens based on tumor biology and gene activation, both clinicians and patients can hope that side effects like diarrhea will be avoided.

References

PubMed ID in brackets

1. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000;343:905–914. [11006366]
2. Petrelli N, Herrera L, Rustum Y, et al. A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. *J Clin Oncol* 1987;5:1559–1565. [2443619]
3. Conti JA, Kemeny NE, Saltz LB, et al. Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. *J Clin Oncol* 1996;14:709–715. [8622015]
4. Rothenberg ML, Eckardt JR, Kuhn JG, et al. Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. *J Clin Oncol* 1996;14:1128–1135. [8648367]
5. Takasuna K, Hagiwara T, Watanabe K, et al. Optimal antidiarrhea treatment for antitumor agent irinotecan hydrochloride (CPT-11)-induced delayed diarrhea. *Cancer Chemother Pharmacol* 2006;58:494–503. [16437251]
6. Brandi G, Gabard J, Raibaud P, et al. Intestinal microflora and digestive toxicity of irinotecan in mice. *Clin Cancer Res* 2006;12:1299–1307. [16489087]
7. Fittkau M, Voigt W, Holzhausen HJ, Schmoll HJ. Saccharic acid 1,4-lactone protects against CPT-11-induced mucosa damage in rats. *J Cancer Res Clin Oncol* 2004;130:388–394. [15160289]
8. Kehrer DF, Sparreboom A, Verweij J, et al. Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. *Clin Cancer Res* 2001;7:1136–1141. [11350876]
9. de Jong FA, Kehrer DF, Mathijssen RH, et al. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for UGT1A1*28 genotype screening: a double-blind, randomized, placebo-controlled study. *Oncologist* 2006;11:944–954. [16951398]
10. Grem JL, Shoemaker DD, Petrelli NJ, Douglass HO Jr. Severe life-threatening toxicities observed in study using leucovorin with 5-fluorouracil. *J Clin Oncol* 1987;5:1704. [3309201]
11. Leichman CG, Fleming TR, Muggia FM, et al. Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group study. *J Clin Oncol* 1995;13:1303–1311. [7751875]
12. Milles S, Mugia A, Spiro H. Colonic histological changes induced by 5-fluorouracil. *Gastroenterology* 1962;43:391.
13. Kornblau S, Benson AB, Catalano R, et al. Management of cancer treatment-related diarrhea: issues and therapeutic strategies. *J Pain Symptom Manage* 2000;19:118–129. [10699539]
14. André T, Boni C, Mounedji-Boudiaf L, et al. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343–2351. [15175436]
15. Jirillo A, Cairo G, Pasetto LM, Lonardi S, Monfardini S. FOLFOX as adjuvant treatment in colon cancer—safety data: a monoinstitutional experience. Presented at the 2007 Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology. January 19–21, 2007. Orlando, Florida. Abstract 457.
16. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229–237. [14657227]
17. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004;22:2918–2926. [15254061]