

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## Managing Chemotherapy-Induced Diarrhea

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### **H&O** With what cancer-treating agents is diarrhea most commonly associated?

**LS** Diarrhea has been most commonly associated with fluoropyrimidine chemotherapy and with irinotecan. More recently, it has been observed as a side effect of some of the newer tyrosine kinase inhibitors. The gastrointestinal malignancies are the most common cancer setting in which this side effect occurs.

### **H&O** What are the mechanisms behind chemotherapy-induced diarrhea?

**LS** There has been a great deal of effort to understand the mechanisms that lead to diarrhea as a side effect of chemotherapy, but the search has not been very rewarding thus far; we do not have a good mechanistic approach to management.

### **H&O** What is the approximate rate of occurrence of diarrhea with patients undergoing chemotherapy?

**LS** The question of diarrhea frequency is drug-specific, regimen-specific, disease-specific, and dependent on many individual patient baseline factors. Chemotherapy-induced diarrhea must be graded from the baseline, measuring the change from the starting point. If a patient already has semi-formed stools multiple times per day before starting chemotherapy, this cannot be considered a toxicity; this is the baseline. It can be difficult to measure this change, and likewise difficult to measure the incidence rate.

### **H&O** Are the mortality rates associated with chemotherapy-induced diarrhea known?

**LS** Again, this is a broad question, and it can't be answered with a general number. Patients experiencing therapy-related diarrhea almost always have other toxicities, and it can be very difficult to identify a specific cause of death. Diarrhea occurring simultaneously with neutropenia is a very dangerous combination, but how often this combination or diarrhea on its own is fatal is not well characterized.

### **H&O** How is therapy-related diarrhea quantified?

**LS** The most common grading system is the National Cancer Institute Common Toxicity Criteria 3.0. This system has limitations but is as good as anything else we have. One of the challenges in grading the severity of diarrhea is that while the number of bowel movements can be counted, volume cannot be easily quantified. Thus, a patient experiencing multiple periods of cramping and making several visits to the bathroom but ultimately having a small volume output may be considered equal to a patient having three large voluminous movements per day. The science behind attributing grades of severity is not very exact and entails more subjectivity than would be desired.

### **H&O** Are preventive measures recommended?

**LS** The only confirmed effective measure for preventing chemotherapy-induced diarrhea is to use less-toxic drug regimens. Prophylactic dietary changes are not recommended because there is no evidence that such changes are appropriate. In addition, there is also no evidence that taking antidiarrheal medication in advance is advisable, and this is also generally not recommended; in fact, taking prophylactic antidiarrheal medication may lead to constipation, which can also be problematic. In those patients who have true rapid onset cholinergic diarrhea from irinotecan, prophylactic atropine can be effective.

**H&O** Could you discuss some of the less toxic drug regimens now being used?

**LS** In recent years, oncologists have learned how to use the agents associated with diarrhea in ways that cause less of this toxicity. For example, the 4-week-on, 2-week-off schedule of irinotecan has been fairly difficult for patients to tolerate in terms of diarrhea and is not used very commonly anymore. An every-other-week schedule, or a schedule of 2 weeks on followed by 1 week off appears to be better tolerated. Interestingly, the 4-week-on, 2-week-off schedule was the first irinotecan schedule developed in the United States, and during the 1990s was the only schedule that was developed in this country. However, more recent data have shown that the alternative schedules seem to give the bowel a better chance to recuperate and are somewhat better tolerated.

With 5-fluorouracil, infusional schedules are becoming increasingly utilized as they appear less likely to cause diarrhea than some of the older bolus schedules. For years, oncologists in the United States preferred to use the bolus formulations, and high-dose intermittent schedules were adopted much earlier in Europe. Especially when 5-fluorouracil is combined with other agents, the infusional approach seems to be much better tolerated. When bolus schedules are used, low-dose leucovorin appears to reduce the diarrhea rate substantially compared to higher doses.

**H&O** How is loperamide used to treat chemotherapy-induced diarrhea?

**LS** If a patient develops significant diarrhea, particularly as a result of irinotecan therapy, the general recommendation is two tablets of loperamide (Imodium, McNeil) immediately, followed by one tablet every two hours if they are experiencing large volumes of diarrhea, until the problem subsides. Patients may take up to 12 tablets per day, substantially more than the over-the-counter recommended daily limit of four tablets per day. Loperamide can significantly diminish diarrhea. Patients may still experience cramping and discomfort, but the toxicity is kept at a more controlled level.

**H&O** When is octreotide used?

**LS** Octreotide (Sandostatin, Novartis) is very active in the treatment of carcinoid or islet cell-related diarrhea. Here, a specific hormone is involved, and this agent turns off that hormone. Octreotide has been investigated in the setting of severe chemotherapy-related diarrhea, where it

is added after 3 or 4 days of aggressive loperamide therapy. However, when diarrhea resolves, it is not clear whether this is due to octreotide or not. I'm not convinced that octreotide has a major role in the management of chemotherapy-related diarrhea. In general, this agent may be used when the patient does not respond to other therapy. It can also be used to treat mild diarrhea, but it is usually not necessary in this setting.

**H&O** Is pharmacologic treatment always necessary?

**LS** For mild diarrhea, fluids may be sufficient, and of course are necessary regardless of whether other therapies are employed. The key to treating diarrhea is to maintain hydration and electrolyte balance. Diarrhea may resolve on its own, with fluid supplementation alone, but there is usually no good reason to not treat and thereby solve the problem sooner rather than later.

**H&O** What dietary changes are recommended when this side effect occurs?

**LS** While preventive dietary changes are not recommended, diet does become an issue once diarrhea occurs. Patients are recommended to avoid greasy and spicy foods, and to focus their diet on foods that are easy to digest. Diarrhea may cause a transient lactose intolerance, so it is often advisable to avoid milk products during and shortly after severe diarrhea.

**H&O** Is it possible to conduct clinical studies of treatments for chemotherapy-induced diarrhea?

**LS** It is very difficult to conduct a clinical trial for treatment of a side effect. In general, people prefer to focus on efficacy in clinical trials, and this is one reason why solid data are not available on the incidence and mortality rates associated with chemotherapy-induced diarrhea. Both patients and doctors would prefer to focus on finding better treatments for cancer, rather than making a marginally effective treatment less toxic. Therefore, it is unlikely that diarrhea control would ever be seen as a major endpoint in a large clinical trial.

**Suggested Reading**

Abigeres D, Armand J-P, Chabot GG, et al. Irinotecan (CPT-11): high-dose loperamide to control diarrhea. *J Natl Cancer Inst.* 1994;86:446-449.

Wadler S, Benson AB, Bengelking C, et al. Recommended guidelines for the treatment of chemotherapy-induced diarrhea. *J Clin Oncol.* 1998;16:3169-3178.