Use of Probiotics for Treatment of Chemotherapy-induced Diarrhea: Is It a Myth?

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Chemotherapy-induced diarrhea (CID) is the most common chemotherapy-related toxicity resulting in dose reduction or cessation. Probiotics are increasingly being examined as a means to prevent or treat CID. It is thought that probiotic administration may both alleviate symptoms and improve chemotherapy tolerability and effectiveness.

Discussion

Mucositis (inflammation of the mucous membranes) is a major gastrointestinal (GI) complication following cancer chemotherapy.\(^1\,^2\) Because mucositis may affect any portion of the GI tract, patients may exhibit any number of symptoms including abdominal pain, heartburn, nausea, bloating, vomiting, and diarrhea. CID, however, is the most common chemotherapy-related toxicity. It is estimated that 20%–45% of all chemotherapy patients experience severe diarrhea during their treatment.\(^3\,^4\) CID may worsen patients’ quality of life, resulting in treatment interruptions or discontinuation, more frequent clinical visits, and longer hospital length of stay.\(^5\) Although yet to be fully characterized, CID is generally classified as an osmotic or secretory diarrhea. The osmotic component is believed to be attributable to cytotoxic agent-induced damage to colonic crypts, thereby reducing chloride absorption and causing water to be released into the intestinal lumen, resulting in diarrhea. While the secretory component is through cytotoxic agents’ alteration of bowel content transit time and eventually diminishes water absorption. Furthermore, chemotherapy changes the composition of the native intestinal microflora, which is critical for metabolism of various intestinal enzymes and regulation of intestinal angiogenesis and immune functions. Other factors that appear to be associated with an increased incidence of CID include older age, female gender, an Eastern Cooperative Oncology Group performance status of \(\geq 2\), underlying bowel pathology (eg, colitis, lactose intolerance), and bowel-associated tumor.\(^4\) In addition, certain therapy-related variables are associated with increased incidence of CID. These may include treatment with irinotecan and 5-fluorouracil (5FU), weekly chemotherapy regimens, intravenous chemotherapy, history of CID, and simultaneous abdominal radiation and chemotherapy.\(^4\)

Because CID can lead to many serious complications, management usually requires prompt assessment to rule out other or concomitant causes of diarrhea. In addition, diet modification and antidiarrheal medications such as loperamide, diphenoxylate/atropine, octreotide, and even antibiotics may be helpful.

Few animal studies have advocated the utility of probiotics for CID resistant to the above management strategies.\(^6\,^7\) Early animal data sparked multiple human studies designed to examine the effect of probiotics in cancer patients with CID. Österlund et al\(^8\) assessed the role of \textit{Lactobacillus rhamnosus} GG with guar gum in preventing grade 3 or 4 diarrhea induced by adjuvant chemotherapy (5FU) in patients with Dukes’ B or C colorectal cancer (\(n = 126\)) or metastatic cancer rendered free from all overt metastases by surgery (Dukes’ D, \(n = 24\)). Patients on \textit{Lactobacillus} during their chemotherapy reported less grade 3 or 4 diarrhea (22% vs 37%, \(P = .027\)), had less abdominal discomfort, suffered fewer chemotherapy dose reductions attributable to bowel toxicity, and required less in-hospital care.\(^8\) The authors concluded that \textit{Lactobacillus} GG supplementation is well
tolerated and may reduce the frequency of severe diarrhea and abdominal discomfort related to 5FU-based chemotherapy in colorectal cancer patients. Similar findings were supported with other human studies.7

Probiotics may lessen CID through several mechanisms. For instance, following oral administration, probiotics modulate the composition of intestinal microflora and form a protective physical barrier, thereby interfering with the attachment of pathogenic bacteria. Probiotics may also bind and degrade carcinogens.9 Other proposed effects are through exerting trophic and anti-inflammatory effects on bowel mucosa and producing lactic acid, thereby creating an acidic environment that is unfavorable for pathogens. However, there are no clear dosing recommendations for probiotic use in managing CID. Hence, most of the current data were generated through administering probiotics for irritable bowel syndrome and chronic ulcerative colitis.

In this issue of JPEN, Abd El-Atti and colleagues report the case of a patient with metastatic breast cancer and CID whom they treated with probiotics.10 Initial attempts to manage the patient’s CID through hydration, oral loperamide, and chemotherapy dose reduction or even discontinuation were unsuccessful. The authors recommended that probiotics be considered in treating patients with GI disturbances, particularly CID, regardless of the chemotherapy regimen.

The Abd El-Atti et al report highlights a CID-related challenge. However, a few caveats should be considered when analyzing the conclusions by Abd El-Atti and colleagues. First, they did not account for other possible unrecognized or unappreciated cofactors that may account for the improvement in that patients’ diarrhea. For example, administration of various chemotherapeutic agents may increase the risk of mucositis, which in turn may trigger severe diarrhea. The possible reduction in oral intake secondary to the mucositis may result in declining diarrheal symptoms with subsequent improvement in abdominal complaints. Second, given many possible mechanisms of CID, Abd El-Atti et al did not consider an infectious etiology for the patient’s diarrhea; hence, no fecal test results were reported. Furthermore, the authors did not report the duration of time between the discontinuation of initial chemotherapeutic agents and the initiation of capecitabine and lapatinib. It is possible that the improvement in the diarrhea was secondary to the secision of the initial chemotherapeutic agents and not the effect of the probiotics. Furthermore, the authors did not

report which specific probiotics were prescribed to their patient, the dosing regimen, and whether adjunctive therapies such as loperamide were continued during probiotic administration.

**Conclusion**

Although the relationship between chemotherapy-induced diarrhea and the beneficial effects of probiotics administration is extremely complex, there is limited information regarding the response of CID to specific probiotic administration. Further research is warranted to elucidate any interrelationships that may exist. Such information may provide clues as to whether a direct connection or merely a causal association exists between probiotics administration and CID cessation. In addition, such information can be a platform for targeted therapies for CID.

**References**