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Clinical Implications of Chemotherapy-Induced Diarrhea in Patients with Cancer

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Summary (Abstract):

Diarrhea is one of the main drawbacks for cancer patients. Chemotherapy-induced diarrhea (CID) is a common problem, especially in patients with advanced cancer. Diarrhea is particularly problematic for some drugs which are central to the management of colorectal cancer and cancers of the gastrointestinal tract, including the fluoropyrimidines (5-FU) and irinotecan. The incidence of CID has been reported to be as high as 50–80% of treated patients (≥30% CTC grade 3–5), especially with 5-fluorouracil bolus or some combination therapies of irinotecan and fluoropyrimidines (IFL, XELIRI). However, the problem is not well recognized and frequently is not managed appropriately. The primary objectives of this report were to describe the pathophysiology of 5-FU & irinotecan in inducing diarrhea and describe the clinical consequences of CID on treatment changes.

1. Introduction:

1.1. The Definition of Diarrhea: Is the frequent passage of loose, watery, soft stools with or without abdominal bloating, pressure, and cramps commonly referred to as gas or flatulence.[1]

1.2. The Possible Etiologies of Diarrhea: Radiotherapy, chemotherapeutic agents, decreased physical performance, graft *versus* host disease and infections. Careful analysis of the causative agent can lead to a more accurate management and early intervention possibly helps to prevent severe complications that may be irreversible. In particular, chemotherapy-induced diarrhea (CID) is a common problem in patients with advanced cancer and has to be carefully differentiated from other causes of diarrhea.[2]

1.3. Chemotherapy-Induced Diarrhea: One of the most common side effects associated with cancer treatment is diarrhea. Estimates of the incidence of diarrhea suggest that 10% of patients with advanced cancer experience acute or persistent diarrhea that may range from troublesome (grade 1) to lethal (grade 5), based on National Cancer Institute–Common Toxicity Criteria (NCI–CTC). The use of chemotherapeutic regimens containing fluoropyrimidines (eg, fluorouracil [5-FU]) and irinotecan (Camptosar) has been associated with a significantly higher risk for chemotherapyinduced diarrhea (CID). As many as 80% of patients treated with these agents, alone or in combination, may experience diarrhea, and ≥ 30% of these patients may have severe diarrhea (grades 3–5).[3]

1.4. The Definition of Irinotecan: Is frequently used in first- and second-line treatment of metastatic colorectal cancer. Regardless of its schedule of administration, myelosuppression and delayed-type diarrhea are the most common side effects.[2]

1.5. The Definition of fluorouracil (5-FU) an antimetabolite drug widely used in the treatment of cancer including colorectal and breast cancer and cancers of the aerodigestive tract.[4] The severity and prevalence of diarrhea caused by 5-FU treatment is increased by the addition of leucovorin (LV) to the treatment regimen. Moreover, the severity of the diarrhea can increase when 5-FU is administered by bolus injection as opposed to intravenous infusion.[2]

2. Discussion:

A retrospective study of 378 patients who experienced diarrhea during at least one chemotherapy cycle. The most common chemotherapy regimen was 5-FU delivered via intravenous push (IVP) and leucovorin (LV),

which was taken at some point in the study by 103 patients (27%). In total, 38 patients were treated with 5-FU/LV and 35 with irinotecan alone. Other agents, used alone or in combination, included oxaliplatin (Eloxatin), docetaxel (Taxotere), paclitaxel, topotecan (Hycamtin), tegafur-uracil (UFT), cisplatin, cyclophosphamide, etoposide, gefitinib (Iressa), and gemcitabine (Gemzar). Patients with cancer undergoing chemotherapy experienced a mean of 3.9 episodes of diarrhea per patient over 1,463 cycles of chemotherapy, with approximately one third of the patients having severe diarrhea. At some point in their chemotherapy, 71% of patients experienced a delay in therapy, 45% had a dose reduction, 64% had a reduction in dose intensity, and 3% discontinued therapy.[3]

2.1. Pathophysiology of Irinotecan-Induced Diarrhea: Irinotecan can cause acute diarrhea or delayed diarrhea. Immediate-onset diarrhea is caused by acute cholinergic properties and is often accompanied by other symptoms of cholinergic excess, including abdominal cramping, rhinitis, lacrimation, and salivation. Delayed-type diarrhea is defined as diarrhea occurring more than 24 hours after administration of irinotecan and is noncumulative and occurs at all dose levels.[2]

Irinotecan is converted by hepatic and peripheral carboxylesterase to its active metabolite 7-ethyl-10-hydroxycamptothecin (SN38), which is subsequently glucuronidated by hepatic uridine diphosphate glucuronosyltransferase-1A1 (UDP-GT 1A1) to SN38-glucuronide (SN38G), which are excreted via urine and bile. Mass balance studies demonstrated that the fecal route of excretion is the major route eliminating 63.7% of the drug. SN38G, once in the intestinal lumen, is deconjugated by bacterial ß-glucuronidase to SN38. The free intestinal luminal SN38, either from bile or SN38G deconjugation, is responsible for irinotecan-induced diarrhea.[2]

2.2 Pathophysiology of Fluoropyrimidine-Induced Diarrhea: The severity and prevalence of diarrhea caused by 5-FU treatment is increased by the addition of leucovorin (LV) to the treatment regimen. Diarrhea is reported in up to 50% of patients receiving weekly 5-FU/LV combined treatment.

Although 5-FU is routinely used in the treatment of cancer and is known to cause diarrhea, very few basic research papers have attempted to elucidate the mechanisms underlying the pathophysiology. Early investigations revealed 5-FU being the causative agent for mitotic arrest of intestinal crypt cells, decrease of the relative fraction of villous enterocytes and the surface area for resorption.[2]

Conclusion:

CID is caused by changes in intestinal absorption and might be accompanied by excessive electrolyte and fluid secretion. Furthermore, this type of diarrhea may be a consequence of biochemical changes caused by chemotherapy. Depending on the chemotherapeutic regimen, rates of severe or life-threatening CID can be up to 30% (grade 3–5 diarrhea), especially with 5-FU bolus or combination therapies of irinotecan and fluoropyrimidines (IFL, XELIRI).

References:

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