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ORIGINAL ARTICLE

The effect of oral glutamine on 5-fluorouracil/leucovorin-induced mucositis/stomatitis assessed by intestinal permeability test

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Summary
Background & aims: Systemic chemotherapy may damage gastrointestinal epithelium. Mucositis is associated with increased intestinal permeability (IP). It is known that IP test with chromium 51-ethylene diaminetetra-acetate (^{51}Cr-EDTA) is a useful tool to assess the mucositis. Oral glutamine supplements (OGS) may have a role in the prevention of chemotherapy-induced mucositis/stomatitis. The aim of this study was to characterize the relationship between the urinary excretion of ^{51}Cr-EDTA and the severity of mucositis, and the effect of OGS on 5-fluorouracil/leucovorin (FU/LV)-induced mucositis/stomatitis.
Methods: Fifty-one patients with advanced or metastatic cancer received FU/LV chemotherapy. The control group included 18 healthy volunteers. IP was assessed via the measurement of ^{51}Cr-EDTA urinary excretion after oral challenge, on days 7 after the discontinuation of chemotherapy. Of the 51 patients, 22 patients received OGS (30 g/day) and 29 received only best supportive care (BSC). Glutamine supplementation continued for 15 days. It was initiated at least 3 days before the beginning of chemotherapy. Mucositis/stomatitis was graded according to version 3.0 of the Common Terminology Criteria for Adverse Events.
Results: In the chemotherapy group, the median (25 percentile, 75 percentile) IP test score was significantly higher than those of the control group [6.78% (4.63, 10.66) vs. 2.17% (1.38, 2.40), $P<0.001$]. The severity of stomatitis was significantly correlated with IP test

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scores ($r = 0.898$, $P < 0.001$). In the OGS group, the median IP test score was significantly lower than that of the BSC group [4.69% (3.10, 6.48) vs. 8.54% (6.48, 15.31), $P < 0.001$]. A mucositis/stomatitis of grade 2–4 was observed in two patients of the OGS group (9%), and in 11 patients (38%) in the BSC group ($P < 0.001$).
Conclusions: The IP test may be a useful tool in the evaluation of mucositis/stomatitis. OGS may exert a protective effect on FU/LV-induced mucositis/stomatitis. Further studies, however, will be necessary to define the role of glutamine supplementation in FU/LV-induced mucositis/stomatitis.

Introduction

Mucositis is one of the most common side effects of chemotherapy. Stomatitis, or a mucositis of the oral mucosa, is the best-characterized manifestation of mucositis, largely due to the fact that it results in symptoms in an area, which is amenable to examination. However, the severity of the involvement of the oral mucosa may not reflect the true extent of mucositis in distal locations. However, there is currently no tool available for the direct measurement of intestinal mucosal damage. Systemic chemotherapy produces changes in the structure of the intestinal mucosa which are associated with increases in intestinal permeability (IP).[1,2] 5-fluorouracil/leucovorin (FU/LV) induces the mitotic arrest of intestinal crypt cells, which leads to an increase in the ratio of crypt cells to villous enterocytes, and thus a reduction of the absorptive surface.[3]

In the present study, we were interested in applying non-invasive chromium 51-ethylene diaminetetra-acetate (^{51}Cr-EDTA) permeability test toward the evaluation of intestinal damage in patients receiving FU/LV chemotherapy. This test has proven to be both sensitive and reliable, and has also proved useful in a host of clinical conditions characterized by the disruption of the normal architecture of the small intestinal mucosa, including celiac disease and Crohn's disease.[4] We demonstrated that the non-invasive intestinal ^{51}Cr-EDTA permeability test was tolerated well.

Glutamine is a natural amino acid which functions as a substrate for nucleotide synthesis in most dividing cells. In some clinical situations, endogenous glutamine production may prove insufficient for the maintenance of optimal tissue structure and function, such that glutamine becomes a conditionally essential amino acid.[5] There already exist several randomized studies on the use of glutamine in chemotherapy- and radiotherapy-induced mucositis with varying results.[6–8]

We therefore examined the usefulness of the ^{51}Cr-EDTA IP test, as well as the effects of oral glutamine supplements (OGS) on FU/LV-induced mucositis/stomatitis.

Methods

Study design

Patients were randomly assigned to the OGS group or to the best supportive care (BSC) group in our open label trial. All patients received FU/LV chemotherapy and received 30 min of oral cryotherapy four times daily during chemotherapy. Healthy volunteers were placed in the control group in order to establish normal IP values. IP was assessed by the measurement of ^{51}Cr-EDTA urinary excretion after oral challenge. Our study protocol was approved by the Clinical Research Ethics Committee of the Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine in Seoul, Republic of Korea.

Eligibility criteria

Eligible patients, all of whom had histologically confirmed advanced or metastatic cancer, received FU/LV chemotherapy. Patients had not received the chemotherapy previously. Chemotherapy consisted of daily administration of 100 mg/m^2 LV over 30 min followed by 500 mg/m^2 FU continuous infusion for 5 days. All of whom did not received prior radiotherapy or concurrent radiotherapy. The inclusion criteria of our study included the following: age older than 18 years, Eastern Cooperative Oncologic Group (ECOG) performance status $\leqslant 1$, absolute neutrophil count $\geqslant 1500$/mm^3, platelet count $\geqslant 100{,}000$/mm^3, serum creatinine concentration $\leqslant 1.25$ times the upper normal limit, or creatinine clearance of more than 60 mL/min, normal liver function tests (serum bilirubin level $\leqslant 1.25$ times the upper normal limit and blood ammonia level $\leqslant 1.0$ times the upper normal limit). Healthy volunteers were place in the control group. The inclusion criteria of the control group included the following: age older than 18 years, normal function tests for hematology, renal, and liver. Patients and control subjects were all required to be free of any signs of systemic infection, and must not have taken antibiotics or consumed alcohol for at least 1 week before testing, and were not allowed to have taken non-steroidal anti-inflammatory drugs during the 2 weeks before and during the IP test. Participants gave written informed consent before entering the study.

Measurement of intestinal permeability

IP was assessed by measuring the ^{51}Cr-EDTA urinary excretion (Amersham Health, London, UK) after oral challenge, on days 7 after the discontinuation of chemotherapy. After an overnight fast (8 h), subjects drank a test solution containing 100 μCi of ^{51}Cr-EDTA in 100 mL of distilled water, followed by the ingestion of 300 mL of water.