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Effectiveness of Parenteral Glutamine on Methotrexate-induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia

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ABSTRACT

High-dose methotrexate (HDMTX) is important for children with acute lymphoblastic leukemia (ALL). There is no effective treatment for patients with oral mucositis, which is a major side effect associated with HDMTX. Here, we reviewed the medical records of patients younger than 18 yr with newly diagnosed ALL in our hospitals from 2002 to 2013. According to the nationwide protocol (TPOG-ALL-2002), each patient received four courses of HDMTX (2.5 or 5 g/m^2) during consolidation therapy. HDMTX courses with glutamine therapy were as the glutamine group, and intravenous glutamine (0.4 g/kg/day) was started within 48 h after the initiation of HDMTX for 3 consecutive days. HDMTX courses without glutamine were as the control group. A total of 347 HDMTX courses were administrated in the 96 children with ALL during the study period. The incidence of oral mucositis was significantly lower in the glutamine group than in the control group (3.8% vs. 17.6%; $P = 0.004$). In the glutamine group, no patients suffered from severe oral mucositis. No severe adverse effects associated with glutamine administration were noted. Accordingly, parenteral glutamine appears to be feasible and safe to prevent oral mucositis in patients receiving HDMTX.

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Introduction

Chemotherapy can disrupt the integrity of intestinal epithelial cells, trigger the release of cytokines and inflammatory response, induce cellular apoptosis, and enhance colonization and invasion of opportunistic pathogens (1–4). All of these could cause a rapid loss of gastrointestinal tract structure and function. As a result, patients may experience nausea, vomiting, mucositis, diarrhea, and abdominal distention or pain. Oral mucositis can cause pain and poor nutrition, increase infection risk, prolong hospitalization, delay scheduled chemotherapy, and even compromise outcomes in patients with cancer. However, there are no effective modalities for prevention and treatment of oral mucositis (5–8).

Methotrexate (MTX), a folate antagonist, can inhibit DNA synthesis in S-phase of the cell cycle and is one of the most widely used chemotherapeutic agents with documented activity against leukemia, lymphoma, and other malignancies. High-dose MTX (HDMTX) is of vital importance in the consolidation chemotherapy for children with acute lymphoblastic leukemia (ALL), which is the most common childhood malignancy. HDMTX often results in functional and structural injury to the gastrointestinal tract (9), and oral mucositis is a major complaint of patients during HDMTX therapy.

Glutamine is regarded as an important source of energy for enterocytes, and is essential for maintenance of mucosal cell integrity and gut barrier function (10–12). Studies regarding oral supplementation of glutamine for chemotherapy-associated mucositis in adults have been reported (13–18), but the efficacy in children is variable (19–23). The safety of parenteral glutamine in human was demonstrated (24–27). However, the effectiveness of parenteral glutamine on patients receiving HDMTX has not

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been reported. The aim of this study is to determine whether parenteral glutamine is effective in reducing the incidence and the severity of oral mucositis in children with ALL receiving HDMTX chemotherapy.

Methods

Patients

We retrospectively reviewed the medical records of patients younger than 18 yr of age with newly diagnosed ALL in our hospitals from 2002 to 2013. All of these patients received chemotherapy according to the nationwide protocol (TPOG-ALL-2002) from the Taiwan Pediatric Oncology Group (28,29). According to the presenting clinical and biological features, patients with ALL were stratified to three risk groups: standard risk (SR), high risk (HR), and very high risk (VHR). Patients with T-cell ALL were classified as VHR.

HDMTX Chemotherapy

According to the TPOG-ALL-2002 protocol, each patient with achievement of complete remission after induction therapy received four courses of HDMTX chemotherapy during consolidation therapy, 2.5 g/m^2 in SR group and 5 g/m^2 in HR and VHR groups. With adequate hydration, MTX was administered intravenously for 24 h. Leucovorin rescue was started at 42 h after the initiation of MTX, until the MTX level was < 0.1 μM.

Administration of Parenteral Glutamine

According to the protocol, each patient needed to receive four courses of HDMTX during consolidation therapy. Whether glutamine was administered or not depended on the option of the parents before each course of HDMTX chemotherapy. Dipeptiven from Fresenius Kabi Company containing N(2)-L-alanyl-L-glutamine was used. Intravenous glutamine treatment was started within 48 h after the initiation of HDMTX. N(2)-L-alanyl-L-glutamine 0.4 g/kg/day was given for 3 consecutive days. Following the suggestions from the previous reports and the manufacturer, Dipeptiven was dissolved in 0.9% NaCl to an osmolarity $<$ 800 mosmol/L, and the infusion rate was $<$0.1 g/kg/h (24,27,30,31). Patients who did not start glutamine therapy within 48 h after the initiation of HDMTX or who received glutamine orally were excluded for analysis.

Parameters for Assessment of Efficacy and Safety

The general condition and nutritional status were assessed on the day of admission in each course of HDMTX. The parameters of nutritional status included body weight, height, and serum albumin and prealbumin levels. Gastrointestinal side effects, including nausea, vomiting, diarrhea, abdominal pain, and oral mucositis, were evaluated during the period of admission. The five-grade World Health Organization Scale was used to assess the severity of oral mucositis (32). The grading parameters included symptoms (pain), functions (ability to drink and eat), and the presence of lesions (ulcers or erythema). The occurrence of any other adverse events was also recorded. Serum levels of alanine aminotransferase (ALT) and creatinine were measured at the time of admission (24 h before MTX treatment) and before discharge. The days of hospitalization and the occurrence of re-admission were recorded.

Statistical Analysis

This study was approved by the institutional review board of the China Medical University Hospital (DMR100-IRB-087), and data analysis was performed using SPSS 17.0 base/regression/advanced statistics for Windows. HDMTX courses with glutamine therapy were regarded as the glutamine group, and those without glutamine were as the control group. Patients receiving at least one course of parenteral glutamine during HDMTX therapy were regarded as the glutamine patients, and those never receiving glutamine were as the control patients. The quantitative data were presented as means $\pm$ standard deviations. The differences between groups were tested by the Student's t-test, and the categorical data were compared by the chi-square test. A value of $P < 0.05$ was considered statistically significant.

Results

From 2002 to 2013, a total of 96 patients younger than 18 yr of age with newly diagnosed ALL received chemotherapy in our hospitals. Each patient received four courses of HDMTX during consolidation therapy according to the TPOG-ALL-2002 protocol. Twenty four patients who received at least one course of parenteral glutamine during HDMTX chemotherapy were regarded as the glutamine patients. And 72 patients who never received glutamine during HDMTX were regarded as the control patients. The characteristics of these patients are summarized in Table 1. Compared with the control patients, the percentage of T-cell ALL was significantly higher among the glutamine patients (37% vs. 10%; $P = 0.002$). Patients with T-cell ALL were classified as VHR according to the criteria of risk classification, and they needed to receive higher dose of MTX during consolidation (5 g/m^2). Therefore, the percentages of VHR

Table 1. Characteristics of the enrolled children with ALL.

Number of patients	Glutamine patients $n = 24$	Control patients $n = 72$	P value
Age at diagnosis (yr)			0.105
	8.8 ± 5.2	6.9 ± 4.7	
Gender			0.077
Female	8 (33%)	39 (54%)	
Male	16 (67%)	33 (46%)	
Cell lineage of ALL			0.002*
B-cell lineage	15 (63%)	65 (90%)	
T-cell lineage	9 (37%)	7 (10%)	
Risk classification			0.118
SR	7 (29%)	36 (50%)	
HR	7 (29%)	20 (28%)	
VHR	10 (42%)	16 (22%)	
Dosage of HDMTX			0.075
2.5 g/m^2	7 (29%)	36 (50%)	
5 g/m^2	17 (71%)	36 (50%)	
Event-free survival			1.000
	21 (88%)	62 (86%)	

ALL, acute lymphoblastic leukemia; HDMTX, high-dose methotrexate; SR, standard risk; HR, high risk; VHR, very high risk. Values are expressed as a mean ± SD or *n* (%).
*$P < 0.05$.

and 5 g/m^2 HDMTX were higher among the glutamine patients, although there is no statistical significance. The event-free survival was not significantly different between the glutamine patients and the control patients (88% vs. 86%; $P = 1.000$).

A total of 347 HDMTX courses were administrated in these 96 patients (Table 2). Of them, 80 eligible courses of parenteral glutamine during HDMTX in the 24 patients were regarded as the glutamine group, and the remaining 267 courses of HDMTX without glutamine treatment were regarded as the control group. There were no significant differences in the general condition and nutritional status of the patients between the two groups. Among the 80 courses in the glutamine group, the mean time to start glutamine administration was 36 h after the initiation of HDMTX. Intravenous administration of glutamine was well-tolerated without additional side effects. There was a significantly higher percentage of patients receiving 5 g/m^2 of HDMTX in the glutamine group than that in the control group (70% vs. 49%; $P = 0.001$). No significant differences in ALT and creatinine levels at the time of admission and before discharge were noted between the two groups.

Of note, the incidence of oral mucositis was significantly lower in the glutamine group than in the control group (3.8% vs. 17.6%; $P = 0.004$). Furthermore, we investigated the efficacy of parenteral glutamine on HDMTX-induced oral mucositis by grading the severity of mucositis with the World Health Organization Scale. As can be seen in Table 3, the incidence of grade 1 to grade 4 oral mucositis was lower in the glutamine group. No patients in the glutamine group suffered from severe oral mucositis (i.e., grade 3 and grade 4). These findings suggested that parenteral glutamine could reduce the incidence and the severity of oral mucositis after HDMTX chemotherapy.

Whereas the incidence of vomiting was significantly higher in the glutamine group (28% vs. 14%; $P = 0.006$) as shown in Table 2, this is probably because the percentage of patients receiving 5 g/m^2 of HDMTX in the glutamine group was higher. There were no significant differences in the incidence of other gastrointestinal side effects, including nausea, diarrhea, and abdominal pain. Although there were no significant differences in the days of hospitalization and the occurrence of re-admission between the two groups, further analysis of the relation between days of hospitalization and gastrointestinal side effects after HDMTX revealed that vomiting, diarrhea, abdominal pain, and oral mucositis were associated with a longer hospital stay (Table 4). This may be why the beneficial effects on alleviation of oral mucositis from parenteral glutamine did not lead to a shorter hospital stay in the glutamine group.

Table 2. Comparison between glutamine group and control group after HDMTX.

Number of HDMTX courses	Glutamine group $n = 80$	Control group $n = 267$	P value
Dosage of HDMTX			0.001*
2.5 gm/m^2	24 (30%)	135 (51%)	
5 gm/m^2	56 (70%)	132 (49%)	
Side effects of gastrointestinal tract due to HDMTX			
Nausea	9 (11.3%)	24 (9.0%)	0.545
Vomiting	22 (28%)	38 (14%)	0.006*
Diarrhea	4 (5%)	11 (4.1%)	0.979
Abdominal pain	5 (6.3%)	13 (4.9%)	0.841
Oral mucositis	3 (3.8%)	47 (17.6%)	0.004*
ALT levels			
Admission (U/L)	40 ± 38	50 ± 57	0.12
Discharge (U/L)	91 ± 114	112 ± 150	0.264
Creatinine levels			
Admission (mg/dL)	0.41 ± 0.19	0.37 ± 0.16	0.327
Discharge (mg/dL)	0.33 ± 0.19	0.37 ± 0.19	0.117
Days of hospitalization	8.8 ± 4.4	7.9 ± 4.0	0.077
Re-admission	1 (1.3%)	15 (5.6%)	0.183

HDMTX, high-dose methotrexate; ALT, alanine aminotransferase. Values are expressed as a mean ± SD or *n* (%).
*$P < 0.05$.

Table 3. Grading of oral mucositis after HDMTX.

Number of HDMTX courses	Glutamine group $n = 80$	Control group $n = 267$
Oral mucositis		
Grade 1	2 (2.5%)	19 (7.1%)
Grade 2	1 (1.3%)	21 (7.7%)
Grade 3	0	6 (2.2%)
Grade 4	0	1 (0.4%)

HDMTX, high-dose methotrexate. Values are expressed as *n* (%).

Table 4. Analysis of the relation between days of hospitalization and gastrointestinal side effects after HDMTX.

	Courses of HDMTX $n = 347$	Days of hospitalization	*P* value
Nausea			0.083
No nausea	314 (90.5%)	8.0 ± 4.0	
Nausea	33 (9.5%)	9.3 ± 4.4	
Vomiting			0.002*
No vomiting	287 (82.8%)	7.7 ± 3.9	
Vomiting	60 (17.2%)	9.8 ± 4.6	
Diarrhea			0.022*
No diarrhea	332 (95.7%)	8.0 ± 3.9	
Diarrhea group	15 (4.3%)	11.7 ± 5.7	
Abdominal pain			0.006*
No abdominal pain	329 (94.8%)	8.0 ± 4.0	
Abdominal pain	18 (5.2%)	10.7 ± 4.4	
Oral mucositis			0.001*
No oral mucositis	297 (85.6%)	7.8 ± 4.0	
Oral mucositis	50 (14.4%)	10 ± 4.2	

HDMTX, high-dose methotrexate. Values are expressed as a mean ± SD or *n* (%).
*$P < 0.05$.

Discussion

ALL is the most common malignancy in children, and HDMTX is the mainstay during consolidation for children with ALL. Oral mucositis is a major complaint during HDMTX therapy, but there are no effective modalities for prevention and treatment of oral mucositis (5–8). The efficacy of oral glutamine for chemotherapy-associated mucositis is variable in children (19–23). Many modalities were used to alleviate the severity of oral mucositis in children receiving HDMTX in our hospitals, including oral glutamine. However, a proportion still had severe mucositis even with oral glutamine. Besides, decreased appetite is usually noted during HDMTX therapy and the compliance of oral medication is related poor during this period of time. The safety of parenteral glutamine in human has been demonstrated (24–27), but the effectiveness of parenteral glutamine on patients receiving HDMTX has not been reported. Therefore, it is valuable to evaluate the effectiveness of parenteral glutamine in children with ALL receiving HDMTX. In the present study, our results showed that parenteral glutamine could significantly reduce the incidence and the severity of oral mucositis in these patients.

In this study, we found that the incidence of vomiting was higher in the glutamine group. To our knowledge, no evidence shows intravenous administration of glutamine leading to vomiting. It is possible that the percentage of patients receiving 5 g/m^2 HDMTX was higher in the glutamine group and the likelihood of vomiting is higher in patients with higher dose of MTX. Of interest, the incidence and the severity of oral mucositis were reduced in the glutamine group despite the higher percentage of patients receiving 5 g/m^2 HDMTX, indicating the efficacy of parenteral glutamine on HDMTX-induced oral mucositis.

Several animal studies provided evidence for mechanisms of glutamine in MTX-induced mucositis (33–36). In a rat model of MTX-induced mucositis, the glutamine group showed greater intestinal mucosal weight, villus height and crypt depth, and proliferation index compared with the control group (34), indicating that glutamine supplementation could improve mucosal recovery. The increased intestinal permeability in the rats treated with MTX could be reversed by administration of glutamine, and the mechanism of glutamine supplementation for the prevention of MTX-induced gut barrier disruption was via regulating occludin and claudin-1, which are the tight junction proteins altered in MTX-treated rats (33). In animal models, administration of glutamine with high doses or rapid infusion rates may result in cramps, increased salivation, and ataxia (37). When correctly administered, there were no known adverse reactions in humans. All patients in the present study were treated during hospitalization with monitoring adverse reactions closely, and they tolerated well without additional side effects.

Due to the early in vitro knowledge that cancer cells preferably consume glutamine, there is a concern about glutamine supplementation associated with stimulation of tumor growth (25,36). In animal models, the provision of supplemental glutamine in the diet increased MTX concentrations in tumor tissues (38,39), suppressed tumor glutaminase activity (38,40), and decreased systemic clearance of MTX (41). These studies suggested that glutamine supplement may enhance the tumoricidal effectiveness of MTX. Many clinical studies found that glutamine supplementation in cancer patients could improve host metabolism and clinical situation without increasing tumor growth (26). Here, the event-free survival was not significantly different between patients receiving glutamine and those never receiving glutamine during HDMTX. Additionally, patients in the present study always received HDMTX after achievement of complete remission, and thus with minimal tumor burden. They needed to receive additional 2-yr maintenance chemotherapy after consolidation. Therefore, the adverse influence of glutamine on disease control, if any, may not impact on them.

Conclusion

This is the first report to demonstrate the effectiveness of parenteral glutamine on HDMTX-induced oral mucositis in children with ALL. Parenteral glutamine appears to be feasible and safe to prevent oral mucositis without compromising the prognosis, and can be considered in patients with ALL undergoing HDMTX chemotherapy. Further randomized controlled studies on more patients are needed to provide more solid conclusions.

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