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Oral glutamine supplements in autologous hematopoietic transplant: impact on gastrointestinal toxicity and plasma protein levels

Tumor cells are major glutamine (Gln) consumers and can compete with host cells for circulating Gln. Radio- and chemotherapy increase Gln depletion. Gln supplementation could reduce mucosal injury secondary to chemotherapy in autologous hematopoietic transplantation. However, the efficacy of oral Gln is still controversial.[1-6]

Sir,

In a prospective, controlled, randomized and double-blind study, we evaluated the tolerance to and efficacy of oral Gln in decreasing gastrointestinal (GI) toxicity; and the modifications of protein and Gln plasma concentrations in patients undergoing high dose chemotherapy and autologous hematopoietic transplantation. The patients were divided into 3 groups. They received 20 g/day of a) glutamine (Gln), (Adamin Glu, SHS, Barcelona, Spain), b) whole protein (WP), (Maxipro, SHS), or c) dextrinomaltose (DXM), (Pentamalt, Nutricia, Madrid, Spain). The daily dose was dissolved in 100 mL of milk, fruit juice or water. There were no differences between groups in demographic characteristics, primary hematologic disease, initial nutritional assessment, chemotherapy (including melphalan) or infectious prophylaxis. Institutional review board approval and written informed consent to the study protocol was obtained. The study ended when neutrophil count was > 500 cells/mm^3 or when total parenteral nutrition (TPN) was required due to GI toxicity. Blood samples were obtained on the day of admission and every 7 days to measure serum concentrations of albumin, retinol-binding protein, prealbumin, transferrin (Behring Nephelometer Analyzer II) and Gln (ion-exchange chromatography method, Beckman amino acid analyzer).

Table 1. Symptom scores according to NCOG criteria for the patients included in the three groups (median; range).

	GLN	*WP*	*DXM*
Diarrhea			
Duration (days)	4;0-22	3; 0-11	4; 0-11
Patients with diarrhea %	70. 6 %	70.6 %	45.5 %
Diarrhea score (day 1-14)	3; 0-21	3; 0-23	0; 0-13
Stomatitis			
Duration (days)	4; 0-18	4; 0-12	4.5; 0-14
Patients with stomatitis	70.6 %	64.7 %	72.7 %
Stomatitis score (day 1-14)	2; 0-21	1; 0-20	4; 0-17
Vomiting			
Duration (days)	4;0-12	0;0-10	6;0-13
Patients with vomiting %	88.2 %	76.5 %	90.9 %
Vomiting score (day 1-14)	8; 0-17	4; 0-20	4; 2-22

Table 2. Evolution of plasma proteins during the study.

	GLN	*WP*	*DXM*
Albumin (g/dL)			
Day 1	4.2±0.6	4.2±0.6	4.3±0.5
Day 7	3.8±0.4	3.9±0.5	3.4±1.1
Day 14	3.7±0.5	3.8±0.4	3.6±0.6
Transferrin (mg/dL)			
Day 1	213±48	207±46	209±46
Day 7	171±62	155±71	174±34
Day 14	164 ±15	171±41	143±23
Prealbumin (mg/dL)			
Day 1	25±8	23±5	26±6
Day 7	24±6	21±5	23±6
Day 14	16±2	18±7	19±6
RBP (mg/dL)			
Day 1	4.2±1.2	3.9±1.7	4.6±1.4
Day 7	4.0±1.4	4.3±2.0	4.0±1.5
Day 14	2.9±1.0	3.5± 0.9	3.2±1.3

RBP = retinol binding protein.

Primary endpoints were GI toxicity classified according to the NCOG criteria.[7] Secondary endpoints were serum Gln and protein concentrations, and the number of patients who required TPN. Data are expressed as X±SD. One-way analysis of variance, followed by the Tukey method of multiple comparisons, was used to compare group means. A 0.05 significance level was used.

In our study, all the patients received at least 90% of the prescribed oral supplements which were well tolerated. Fifty-nine, 41 and 64% of the patients in the GLN, WP and DXM groups, needed TPN due to GI adverse events secondary

to chemotherapy. No differences were found in the length of time until TPN was started in any group. Recovery of the neutrophil count to over 500 cells/mm^3 occurred at day 16.7±3.2, 16.9±3.1 and 20.3± 2.3 in the GLN, WP, and DXM groups, respectively. There were no significant differences in the incidence, severity or duration of GI toxicity (Table 1), nor in serum proteins during this study (Table 2). Their concentration decreased significantly in the three groups from day 1 to day 14. Gln levels did not differ among the three groups, nor did they change during the treatment.

In conclusion, our results do not prove the usefulness of oral Gln for preventing GI toxicity associated with chemotherapy for autologous hematopoietic transplantation in AHT. The timing and the dosage of oral Gln should be reassessed to find more evidence of clinically significant results. After considering the results published with parenteral and oral GLn supplements, it could be argued that parenteral Gln may be more efficacious than oral Gln, but a comparative trial to test this hypothesis has not yet been performed.

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A boy with venous thrombosis, homozygous for factor V Leiden, prothrombin G20210A and MTHFR C667T mutations, but belonging to an asymptomatic family

We evaluated a 9-year old boy presenting with deep venous thrombosis who was homozygous for factor V Leiden, prothrombin 20210A and methylenetetrahydrofolate reductase C677T mutations. All of his relatives who were either triple- or double-heterozygotes were asymptomatic. This observation indicates that thrombophilia is a complex genetic disorder and there is great deal more to be learned about this disease.

Sir,

Familial thrombophilia is a complex genetic disorder often caused by the joint action of two or more mutant genes. Individuals with these combined genetic defects are at higher risk of thrombosis than those with a single gene mutation.[1] Double-heterozygosity for factor V Leiden (FVL) and G20210A in the prothrombin gene (PT 20210A) is the most common combination.[2,3] Moreover, we have recently demonstrated, by both linkage and association studies, that the C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene has a direct effect on homocysteine levels, suggesting that this polymorphism might be a genetic risk factor for thrombosis.[4] Here, we present the case of a 9-year old boy who presented with a first episode of idiopathic right popliteal deep venous thrombosis (objectively confirmed by Doppler ultrasound). This boy had never been exposed to any environmental risk factors for thrombosis. Plasma laboratory studies for thrombophilic disorders showed only a 1.3 pathologic value for resistance to activated protein C ratio (Coatest APC resistance Kit from Chromogenix) according to Dahlbäck *et al.*[5] Genetic analysis of this patient (individual IV-1 in Figures 1A and 1B) showed triple-homozygosity for FVL, PT20210 and C677T MTHFR mutations. Figure 2 shows the genetic status of these three mutations in the rest of the family members. It is important to note that the parents of the propositus were first cousins (Figure 2). Significantly, none of his relatives had a history of venous or arterial thrombosis, despite the fact that his mother and grandmother had had two and three pregnancies and deliveries, respectively, and his grandfather had died from lung cancer. Therefore, the combined carrier state in this family is apparently not associated with a high risk of venous or arterial thrombo-