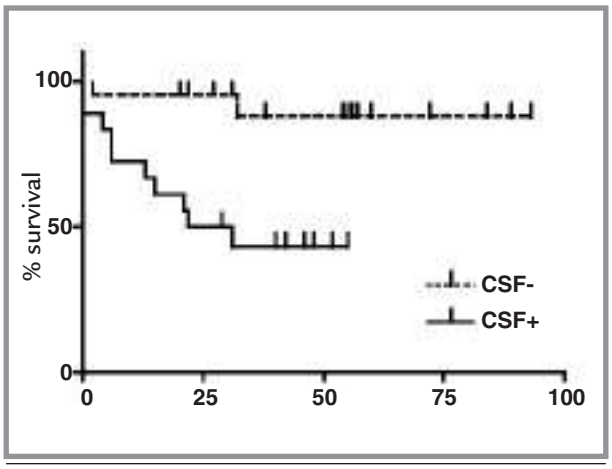

Figure 1. Kaplan-Meier analysis of event-free survival (EFS) according to the presence (CSF^+) or absence (CSF^-) of molecularly detected CSF involvement.

0.74 (0.82 and 0.61 in standard and high risk groups respectively). When molecular CNS detection at diagnosis was analyzed as a prognostic factor in association with age, white cell count and immunophenotyping by multivariate analysis using a Cox proportional model, no statistical significance was observed ($p = 0.38$).

Controversies exist about the prognosis of the children with low cell counts in CSF.[3,4,6,7] Our data suggest that molecular detection of blast cells in CSF at diagnosis could be associated with a poor prognosis in children with ALL in univariate analysis, in accordance with results described by some authors in patients with low CSF blast cell counts at diagnosis.[3,4] Although these data were not confirmed in multivariate analysis and need to be viewed with caution due to the relative small number of cases, the short follow-up of the study and the selected group of patients analyzed. From a clinical point of view, the present study supports the identification of a new level of CNS involvement and could suggest a revision of the standard definition of CNS leukemia. To confirm these initial data and analyze the real prognostic impact of molecularly detected CNS leukemia involvement a prospective study with a greater number of patients and a longer follow-up will be necessary.

Carlos A. Scrideli, Rosane P. Queiroz,* Osvaldo M. Takayanagui,# Jose E. Bernardes,* Enaldo V. Melo,* Luiz G. Tone**

*Departments of *Pediatrics and #Neurology, Ribeirao Preto Medicine School, University of Sao Paulo, Ribeirao Preto-SP, Brazil*

Funding: supported by grants from Fundaçáo de Apoio ao Ensino, Pesquisa e Assistància do HC-FMRP-USP (FAEPA) and the Federal Brazilian financial support agencies CAPES and CNPq.

Key words: ALL, cerebrospinal fluid, PCR, CNS leukemia.

Correspondence: Prof. Dr. Luiz Gonzaga Tone, Departamento de Pediatria e Puericultura, Faculdade de Medicina de Ribeirao Preto, USP, Av. Bandeirantes, 3900, 14049-900 Ribeirao Preto, SP, Brazil. Phone: international +55.16.602-2573. Fax: international +55.16.602-2700. E-mail: lgtone@fmrp.usp.br

References

1. Mastrangelo R, Poplack D, Bleyer A, Riccardi R, Sather H, D'Angio G. Report and recommendations of the Rome workshop concerning poor-prognosis acute lymphoblastic leukemia in children: biologic bases for staging, stratification, and treatment. Med Ped Oncol 1986;14:191-4.
2. Chessells JM. Pitfalls in the diagnosis of childhood leukaemia. Br J Haematol 2001;114:506-11.
3. Mahmoud HH, Rivera GK, Hancock ML, Krance RA, Kun LE, Behm FG, et al. Low leukocyte counts with blast cells in cerebrospinal fluid of children with newly diagnosed acute lymphoblastic leukemia. N Engl J Med 1993;329:314-9.
4. Odom LF, Wilson H, Cullen J, Bank J, Blake M, Jamieson B. Significance of blasts in low-cell-count cerebrospinal fluid specimens from children with acute lymphoblastic leukemia. Cancer 1990;66:1748-54.
5. Gajjar A, Harrison PL, Sandlund JT, Rivera GK, Ribeiro RC, Rubnitz, JE, et al. Traumatic lumbar puncture at diagnosis adversely affects outcome in childhood acute lymphoblastic leukemia. Blood 2000;96:3381-4.
6. Gilchrist GS, Tubergen DG, Sather HN, Coccia PF, O'Brien RT, Waskerwitz MJ, et al. Low numbers of CSF blasts at diagnosis do not predict for the development of CNS leukemia in children with intermediate-risk acute lymphoblastic leukemia: a Children Cancer Group report. J Clin Oncol 1994;12:2594-600.
7. Tubergen DG, Cullen JW, Boyett JM, Gilchrist GS, O'Brien RT, Coccia PF, et al. Blasts in CSF with a normal cell count do not justify alteration of therapy for acute lymphoblastic leukemia in remission: a Children's Cancer Group study. J Clin Oncol 1994;12:273-8.
8. Scrideli CA, Kashima S, Cipolloti R, Defavery R, Bernardes JE, Tone LG. Minimal residual disease in Brazilian children with acute lymphoid leukemia: comparison of three detection methods by PCR. Leuk Res 2002;26:431-8.
9. Scrideli CA, Queiroz RP, Takayanagui OM, Bernardes JE, Tone LG. Polymerase chain reaction on cerebrospinal fluid cells in suspected leptomeningeal involvement in childhood acute lymphoblastic leukemia: comparison to cytomorphological analysis. Diagn Mol Pathol 2003;12:124-7.
10. Scrideli CA, Queiroz RG, Kashima S, Sankarankutty BO, Tone LG. T cell receptor γ (TCRG) gene rearrangements in Brazilian children with acute lymphoblastic leukemia: analysis and implications for the study of minimal residual disease. Leuk Res 2004;28:267-73.

Malignant Lymphomas

Effect of interleukin-1β and glutathione S-transferase genotypes on the development of gastric mucosa-associated lymphoid tissue lymphoma

We tested whether polymorphic variations in glutathione S-transferase genes (*GSTM1*, *GSTT1*, *GSTP1*) and inyterleukin-1 (IL-1β and IL-1RN) genes confer susceptibility to mucosa-associated lymphoid tissue lymphomas (MALT) in a Chinese population. The rates of *GSTM1*, *GSTP1*, *IL-1β* and *IL-1RN* genotypes did not differ between patients and controls. However, *GSTT1* null genotypes were significantly more common in patients with MALT lymphomas (43/75 vs. 138/321, p=0.029; OR=1.8, 95% CI: 1.1~3.0) than in controls. Our results suggest that a glutathione S-transferase defect plays a role in MALT lymphoma.

haematologica 2004; 89:1015-1017
(*http://www.haematologica.org/2004/8/1015*)

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is the most commonly encountered extranodal marginal-zone B-cell lymphoma. Accumulating evidence has indicated that *H. pylori* infection induces the formation of MALT and the subsequent occurrence of lymphoma.[1-3] *H. pylori* infection is also involved in the pathogenesis of gastritis, peptic ulcer, and gastric adenocarcinoma.[4] The factors determining why *H. pylori* can lead to different gastroduo-

Table 1. Distribution of interleukin(IL)-1β, IL-1 receptor antagonist (IL-1RN) and glutathione-S-transferase (GST) genotypes in controls and cases with gastric mucosa-associated lymphoid tissue lymphoma (MALT lymphoma).

Genotype	*MALT lymphoma (n=75)*	*Controls (n=321)*	*P value*
IL-1β -511			
C/C	21 (28.0%)	86 (26.8%)	
C/T	41 (54.7%)	174 (54.2%)	0.94
T/T	13 (17.3%)	61 (19.0%)	
IL-1 RN			
11	67 (89.3%)	280 (87.2%)	
12	8 (10.7%)	33 (10.3%)	0.75
13	0 (0%)	3 (9.3%)	
15	0 (0%)	2 (6.2%)	
22	0 (0%)	3 (9.3%)	
GST-M1			
Non-null	30 (40.0%)	154 (48.0%)	
Null	45 (60.0%)	167 (52.0%)	
GST-T1			
Non-null	32 (42.7%)	183 (57.0%)	0.029
Null	43[a] (57.3%)	138 (43.0%)	
GST-P1			
Ile/Ile	53 (70.7%)	214 (66.7%)	
Ile/val	18 (24.0%)	83 (25.9%)	0.72
val/val	4 (5.3%)	24 (7.4%)	

[a]: odds ratio for cases versus control was 1.8 (95% confidence interval 1.1~3.0).

denal disorders and why only some infected patients develop MALT lymphoma are still under intensive investigation. Genetic factors are likely to play a fundamental role in the different clinical outcomes after *H. pylori* infection.[1-4] Recently, Rollinson *et al.* demonstrated that *GSTT1* and *IL-1* genotypes have a strong impact on the risk of gastric MALT lymphoma.[5] However, previous epidemiologic studies of glutathione S transferase (GST) and interleukin (IL)-1 in gastric adenocarcinoma implied that results of genotypes vary among different populations.[6,7] Therefore, the effect of these genotypes on MALT lymphomas must be replicated in other ethnic populations.

We conducted a case-control study consisting of 75 MALT lymphoma (43 low grade, 32 high grade; 52 stage IE 20 stage IE and 3 stage IE) and 321 controls. The genotypes of *IL-1RN*, *GSTT1*, and *M1* were typed by polymerase chain reaction (PCR) while those of *GSTP1* and *IL-1β -511* (C/T) were determined by PCR with restriction fragment length polymorphisms as described previously.[6-8] The distribution of gender and age among cases and controls were not statistically different. The mean age was 56.7±14.6 years (range, 21~80) for cases and 57.8±10.9 years (range, 20~80) for controls. The rate of seropositivity for *H. pylori* was significantly higher among patients with MALT lymphoma (68/75, 90.7%) than among controls (168/321, 52.3%; $p<0.001$). The distribution of genotypes was similar between *H. pylori* positive and –negative controls. Table 1 summarizes the investigated genotypes in patients and controls. A significant difference in the distribution of *GSTT1* genotypes was observed, with the null genotype being associated with an increased risk of MALT lymphoma (43/75 vs. 138/321, $p=0.029$; OR=1.8, 95% CI: 1.1~3.0). Stratification of the MALT lymphomas according to tumor histology and stage revealed no statistical difference with respect to the distribution of genotypes.

The relationship between genetic determinants and clinical outcomes of *H. pylori* infection has recently received considerable attention. Before our study, Rollinson *et al.* first reported the influence of the *GSTT1* null type and IL-1 *RN* 2/2 genotypes on the risk of MALT lymphoma.[5] These researchers studied 66 Caucasian cases and 163 controls and noted a 9.5-fold increased risk associated with the *GSTT1* null type. We, however, only detected a 1.8-fold increase (95%CI:1.1~3.0). Such discrepancies may arise from ethnic variations in the incidence of *GSTT1* gene deletions. The frequencies of *GSTT1* null type in MALT lymphomas were almost identical (57.6% and 57.3%, respectively) in these two studies while those in control populations were very different (13.5% and 42.9%, respectively). These results were in accordance with previous reports showing that approximately 10~20% of Caucasians lack the *GSTT1* gene and a relatively high frequency (40~60%) of Chinese have the *GSTT1* null type.[9]

The precise mechanism by which *GSTT1* is responsible for the development of gastric MALT lymphoma remains ill-defined. It is worth noting that the *GSTT1* null type has already been reported to predispose to the development of other lymphoproliferative disorders such as lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphomas.[9] Furthermore, Rossi *et al.* have demonstrated that inactivation of GST through promoter methylation occurs in 50% of MALT lymphomas.[10] Collectively, these observations argue for a role of GST defects in the pathogenesis of lymphoid malignancies.

In conclusion, *GSTT1* deletions increase the risk for MALT lymphoma in a Chinese population although the influence of this factor is smaller than that seen in a Caucasian population due to interethnic variations of genotype frequencies in controls. Further larger studies to improve the understanding of associations of host genetic variants in MALT lymphomas are mandatory and should take into account ethnic differences as well as genetic heterogeneity.

Ming-Shiang Wu, Chia-Tung Shun, Shih-Pei Huang, Ann-Li Cheng, Li-Tzong Chen, Jaw-Town Lin

Departments of Internal Medicine, Pathology, Surgery and Oncology, National Taiwan University Hospital, and Division of Cancer Research, National Health Research Institute, Taipei, Taiwan

Key words: MALT lymphoma, Helicobacter pylori, interleukin-1, glutathione-S-transferase, genetic susceptibility.

Funding: Supported by grants from the National Science Council (NSC-2314-B002-122, 123, 124) and the National Health Research Institute (NHRI-90A1CAQO0005) of Taiwan.

Correspondence: Jaw-Town Lin, No. 7, Chung-Shan S. Rd., Department of internal Medicine, National Taiwan University Hospital, Taipei, Taiwan. E-mail: jawtown@ha.mc.ntu.edu.tw

References

1. Isaacson PG. Gastric MALT lymphoma: From concept to cure. Ann Oncol 1999;10:637-45.
2. Zucca E, Bertoni F, Roggero, E, Cavalli F. The gastric marginal zone B-cell lymphoma of MALT type. Blood 2000;96:410-9.
3. Du MQ, Isaacson PG. Gastric MALT lymphoma: from etiology to treatment. Lancet Oncol 2002;3:97-104.
4. Peek RM, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinoma. Nat Rev Cancer 2002;2:28-37.
5. Rollinson S, Levene AP, Mensah FK, Roddam PL, Allan JM, Diss TC, et al. Gastric marginal zone lymphoma is associated with polymorphisms in genes involved in inflammatory response and

antioxidative capacity. Blood 2003;102:1007-11.
6. Wu MS, Chen CJ, Lin MT, Wang HP, Shun CT, Sheu JC, et al. Genetic polymorphisms of cytochrome p450 2E1, glutathione S-transferase M1 and T1, and susceptibility to gastric carcinoma in Taiwan. Int J Colorectal Dis 2002;17:338-43.
7. Wu MS, Wu CY, Chen CJ, Lin MT, Shun CT, Lin JT. Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese. Int J Cancer 2003;104:617-23.
8. Watson MA, Stewart RK, Smith GB, Massey TE, Bell DA. Human glutathione S-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. Carcinogenesis 1998;19:275-80.
9. Strange RC, Fryer AA. The glutathione S-transferases: influence of polymorphism on cancer susceptibility. In: Vineis P, Malatus N, Lang M, editors. Metabolic polymorphisms and susceptibility to Cancer. IARC Scientific Publications No. 148. Lyon, France: International Agency for Research on Cancer. 1999. p. 231-49.
10. Rossi D, Capello D, Gloghini A, Franceschetti S, Paulli M, Bhatia K, et al. Aberrant promoter methylation of multiple genes throughout the clinicopathologic spectrum of B-cell neoplasia. Haematologica 2004;89:154-64.

Thrombosis

Treatment of heparin-induced thrombocytopenia with fondaparinux

Anticoagulation of patients with heparin-induced thrombocytopenia (HIT) may be limited by cross-reaction of HIT antibodies with danaparoid and generation of antibodies during therapy with lepirudin. We used fondaparinux to treat 6 patients with a history of HIT with thromboembolism and 2 patients with thrombocytopenia during low-molecular-weight heparin administration.

haematologica 2004; 89:1017-1018
(*http://www.haematologica.org/2004/8/1017*)

Thrombocytopenia is a potentially serious side effect following administration of heparins. In type I heparin-induced thrombocytopenia (HIT) there is a temporary decrease of platelets following heparin administration. Type II HIT is an immune-mediated reaction which usually develops 5 to 10 days after heparin administration but can manifest earlier in cases of re-exposure to heparin. It is mediated by antibodies against a neoantigen of platelet factor 4 formed by complexing with heparin. In the presence of HIT antibodies, thromboembolic complications develop in up to 50% of patients, producing a thrombotic risk ratio of more than 30.[1] Discontinuation of heparin and alternative anticoagulation is required. Lepirudin,[2] danaparoid[3] and argatroban[4] are effective anticoagulants for continuing anticoagulation in these patients, although anticoagulation of patients may be limited by cross-reaction of HIT antibodies with danaparoid and generation of antibodies during therapy with lepirudin.[5]

The linear, polysulfated glycosaminoglycan heparin contains a unique pentasaccharide sequence that binds to antithrombin. This pentasaccharide does not bind to platelet factor 4[6] and does not react with heparin-induced antibodies in the presence of platelet factor 4 and platelets. The synthetic compound, fondaparinux has been proven to be more effective than enoxaparin for post-operative prophylaxis of thromboembolism at a once daily dose of 2.5 mg subcutaneously.[7] Given that fondaparinux does not bind to platelet factor 4 or HIT antibodies,[8] we used it to treat 8 patients with an acute episode or a history of type II HIT. The once daily subcutaneous administration of 2.5 mg for 7-14

Table 1. Clinical features of type II HIT patients treated with fondaparinux.

Initials	*Age (y)*	*Height (cm)*	*Weight (kg)*	*episode, year, heparin, indication*	*HIPA*	*Indication for TEP with fondaparinux, duration*	*VKA*
M-G	82	152	91	HIT II, DVT, 1997, UFH post-operative TEP	pos	pneumonia, atrial fibrillation 14 days	yes
D-K	31	207	135	HIT II, DVT 1995, UFH post-operative TEP	pos	cerebro-abdominal shunt operation, 15 days	yes
M-K	73	160	75	HIT I, thrombocytopenia, 2003, LMWH, non-operative TEP	n.a.	cerebral infarction, 14 days	no
A-S	74	147	57	HIT I, thrombocytopenia, 2003, LMWH, non-operative TEP	neg	cerebral infarction 7 days	no
*K-L 1	65	178	82	HIT II, PE, 1998, UFH post-operative TEP	pos	cholecystitis 12 days	yes
*K-L 2	65	178	82	HIT II, PE, 1998, UFH post-operative TEP	pos	cholecystectomy 15 days	yes
E-E	75	170	64	HIT II, PE, 1999, LMWH post-operative TEP	pos	pancreatitis 13 days	yes
S-H	74	174	80	HIT II, MI , 1997, UFH post-operative TEP	pos	cerebral infarction 14 days	no

*HIPA: heparin-induced platelet aggregation assay; HIT: heparin-induced thrombocytopenia; DVT: deep vein thrombosis; PE: pulmonary embolism; MI: myocardial infarction; UFH: unfractionated heparin; LMWH: low-molecular-weight heparin; TEP: thromboembolic prophylaxis; VKA: current therapy with vitamin-K antagonist. *Patient K-L was treated twice on different occasions.*