Relationship of serum selenium to tumor activity in acute non lymphocytic leukemia (ANLL) and chronic lymphocytic leukemia (CLL)

Y. Beguin*, V. Bours*, J.M. Delbrouck, G. Robaye, I. Roelandts, G. Fillet*, G. Weber

Departments of Hematology* and Experimental Nuclear Physics, University of Liège, IPNE, Sart Tilman B15, 4000 Liège, Belgium
VB is «Aspirant» and GW «Chercheur Qualifié» of the National Fund for Scientific Research (FNRS), Belgium. Supported in part by grant 4450865 of the Institut Interuniversitaire des Sciences Nucléaires (ISSN), Belgium

Pharmacologic doses of selenium (Se) can reduce tumorigenesis and retard progression of established tumors (Ip, 1986). Several geographic studies have shown an inverse relationship between Se status and cancer mortatility (Clark, 1985) and nested case-control studies have found an inverse relationship between prediagnosis serum Se and the subsequent risk of cancer (Willett et al., 1983). Reduced Se levels have been observed in a variety of cancer patients (Shamberger et al., 1973), but the significance of this finding as a cause or consequence of cancer is poorly understood. We therefore decided to study two groups of leukemic patients to examine the relationships between serum Se, tumor activity, and chemotherapy.

Patients and methods

We studied 70 patients with ANLL who received high-dose induction chemotherapy, consisting of a combination of cytarabine and daunorubicin, mitoxantrone, amsacrine, or etoposide. Complete remission (CR) was defined as a normocellular marrow with < 5% blasts, and a peripheral blood with hemoglobin > 10gr/dl, platelets (PLT) > 100000/μl, and neutrophils > 1500/μl. Partial remission, failure, and death were all classified as failures. Day E refers to the day of evaluation of response to the first course of chemotherapy. Day F refers to the day of final evaluation, i.e. after 2 courses in patients not entering CR after one. Serum samples were obtained before chemotherapy (day 0), and thereafter twice weekly for five weeks. We also studied 47 patients with CLL. Patients were classified into clinical stages 0 through 4 as described (Rai et al., 1975). There were 21 stage 0, 15 stage 1, 12 stage 2, 1 stage 3, and 9 stage 4 patients. For further analysis, stage 3 or 4 patients were assembled in a stages 3-4 group. Eight patients were studied on two occasions, in different stages. Serum selenium was measured by PIXE (Proton-Induced X-Ray Emission) as described previously (Johansson et al., 1970). Normal serum Se levels were determined in 100 healthy subjects. Student's t-test were used to compare two groups, paired Student's t-tests to compare pre- to post-treatment values and ANOVA to compare more than two groups.

Results

Table 1 - Serum Se levels (M±SD) in ANLL patients during induction chemotherapy

Time	Se(μg/ml)		
	All patients (N=70)	CR (N=41)	Failures (N=19)
Pre-treatment	0.082±0.033	0.085±0.032	0.074±0.034
Day 7	0.108±0.037	0.100±0.037	0.131±0.027
Day 21	0.105±0.041	0.105±0.041	0.104±0.041
Day E	0.099±0.032	0.099±0.029	0.100±0.039
Day F	0.100±0.031	0.102±0.029	0.093±0.037
Relapse		0.073±0.027	

ANLL

Pre-treatment serum Se levels were lower in patients than is controls (0.082 ±0.033 μg/ml vs 0.097±0.035 μg/ml, $P<0.01$). Se correlated negatively with the peripheral absolute blast cell count ($R = -0.62$, $P<0.001$) and WBC count ($R = -0.58$, $P<0.001$), bone marrow blast + promyelocyte percentage ($R = -0.41$, $P<0.01$), and serum LDH ($R = -0.53$, $P<0.001$). There was no correlation between serum Se and sex, cytologic sub-typ, infection, age, serum protein, albumin, alkaline phosphatase, fibrinogen, hemoglobin, or platelet count. In multivariate analysis, no other variable added predictive value to the peripheral blast cell count.

On day 7 after chemotherapy (Table 1), Se levels increased significantly ($P<0.01$). The difference between day 7 and day 0 (in μg/ml) correlated with the initial peripheral blast cell count ($R = 0.44$, $P<0.01$). Mean serum Se levels on days 14, 21, 28, E, and F remained comparable to the levels observed in controls. CR was achieved in 49/70 (71%) patients. Failures tended to have higher WBC and blast cell counts and lower pretreatment serum Se levels than CRs (Table 1). However, day 7 Se levels were significantly higher in failures ($P<0.005$). Thereafter Se levels remained stable in CRs while decreasing in failures (Table 1).

CLL

Serum Se levels in CLL patients (0.107±0.034 μg/ml) did not differ from levels in controls (0.097±0.035 μg/ml). Selenium levels were 0.103±0.041 μg/ml, 0.124±0.031μg/ml, 0.105±0.035 μg/ml, and 0.079±0.035 μg/ml, respectively in stages 0, 1, 2, and 3-4 ($P<0.04$). There was a steady decrease in hemoglobin ($P<0.0001$) and PLT count ($P<0.0001$), and an increase in lymphocyte count ($P<0.03$) and LDH ($P<0.04$), from stage 0 to stage 3-4. Serum Se correlated positively with the PLT count ($P<0.01$), and inversely with the lymphocyte count in patients with lymphocytes >20000/mm^3 ($P<0.05$).

Discussion

Reduced Se levels have been reported in patients with solid tumors (Shamberger et al., 1973) but normal levels have been described in a limited number of patients with leukemia (Calautti et al., 1980; McConnell et al., 1975). In patients with ANLL we found decreased Se levels as compared to controls. This could mean that individuals with a low Se status are at increased risk ANLL or that leukemia causes a decline of serum Se. In ANLL patients, nutrition was greatly impaired but Se levels normalized at the time of maximum nutrition impairement.

Several studies reported a trend towards reduced Se levels in more advanced cancer (Dworkin et al., 1988). In ANLL patients, Se levels correlated inversely with measurements of the tumor burden i.e. marrow blast + promyelocyte, LDH, and blood WBC and blast cells. Se increased after chemotherapy, and the increment was proportionnal to the initial burden. Thereafter, Se remained stable in patients who will eventually enter CR. In patients with resistant disease, Se was lower before and increased more after chemotherapy, to fall gradually later on. In CLL patients, serum Se correlated inversely with the lymphocyte count and was significantly reduced in stages 3-4. All these findings are in favor of an inverse relationship between Se levels and disease activity in leukemia. Evidence that some tumors can accumulate Se have been reported (Di Ilio et al., 1987) but this remains to be demonstrated in ANLL and CLL. However, in view of the close relationship between tumor burden and serum Se, as well as the rapid modifications induced by chemotherapy, such a sequestration mechanism appears to be likely. Because of this effect, no conclusion on the relationship between Se status and cancer can be derived from data obtained in patients with active cancer.

References

Calautti, P., Moschini, G., Stievano,B.M., Tomio, L., Calzavara, F. & Perona, G. (1980) : Serum selenium levels in malignant lymphoproliferative diseases. Scand.J.Haematol., 24, 63-66

Clark, L.C. (1985) : The epidemiology of selenium and cancer. Fed.Proc. 44, 2584-2589

Di Ilio C., Del Boccio, G., Casaccia, R., Aceto, A., Di Giacomo, F. & Federici, G. (1987) : Selenium level and glutathione-dependent enzyme activities in normal and neoplastic human lung tissues. Carcinogenesis 8, 281-284

Dworkin, B.M., Rosenthal, W.S., Mittelman, A., Weiss, L., Applebee-Brady, L. & Arlin, Z. (1988) : Selenium status and the polyp-cancer sequence : a colonoscopically controlled study. Am.J.Gastroenterol. 83, 748-751

Ip, C. (1986) : Selenium and experimental cancer. Ann.Clin.Res. 18, 22-29

Johansson, T.B., Akselsson, R., Johansson, S.A.E. (1970) : Elemental trace element analysis at the 10^{-12} level. Nucl.Instrum.Meth. 84, 141-143

McConnell, K.P., Broghamer, W.L., Jr, Blotcky, A.J. & Hurt, O.J. (1975) : Selenium levels in human blood and tissues in health and in disease. J.Nutr. 105, 1026-1031

Shamberger, R.J., Rukovena, E., Longfield, A.K., Tytko, S.A., Deodhar, S. & Willis, C.E. (1973) : Antioxidants and cancer. 1. Selenium in the blood of normals and cancer patients. J.Natl.Cancer Inst. 50, 863-870

Willett, W., Polk, B., Morris, S., Stampfer, M.J., Pressel, S., Rosner, B., Taylor, J.O. Schneider K. & Hames, C.G. (1983) : Prediagnostic serum selenium and risk of cancer. Lancet, ii, 130-134