11

CNS PROPHYLAXIS WITH HIGH DOSE METHOTREXATE IN HIGH RISK CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

I.J. Cohen, R. Zaizov, Y. Matoth

Pediatric Hematology-Oncology, Beilinson Medical Center, Tel Aviv University Medical School, Israel.

In an attempt to reduce CNS involvement in high risk childhood acute lymphocytic leukemia, 500 mg/m^2 methotrexate (MTX) as a 4-hour infusion was added to the skull irradiation of 2400 rads and sixth intrathecal MTX injection, followed by Leucovorin rescue at 24 hours. MTX levels were measured by an I^{125} MTX competetive enzyme binding technique (New England Enzyme Center, Boston). In 8 children with high risk acute lymphocytic leukemia very high CSF levels, 2.5×10^{-4} and 1.6×10^{-6} at 4 and 23 hours respectively were found, as compared with parallel serum levels of 9.9×10^{-4} and 7.3×10^{-7}. In contrast, a 5 gm/m^2 MTX 6-hour infusion without intrathecal MTX failed to achieve "therapeutic" levels of 10^{-6} at 24 hours. Higher CSF levels were observed in CNS and marrow relapse 1.76×10^{-3} and 3.3×10^{-5} at 4 and 29 hours respectively. In two cases toxicity was associated with transient increased serum creatinine and correlated with toxic MTX levels. It is concluded that this additional therapy resulted in sustained therapeutic CSF MTX levels by preventing MTX eflux from CSF, thus giving more effective brain penetration and preventing CNS leukemia.

12

VITAMIN E AND ERYTROCYTE GLUTATHIONE-PEROXIDASE IN NEWBORN INFANTS WITH HYPERBILIRUBINEMIA.

M.Dettori, G.Falciani, L.Ciccoli, M.De Donno, C.De Simone, R. Bracci. Inst. Clinica Pediatrica and Inst. Patologia Generale--University of Siena, Italy.

Plasma vitamin E and erytrocyte G-6-PD, GR, PK and GSH-Px activities have been measured in 43 newborn infants one to two weeks old, out of which 25 had jaundice probably due to increased hemolysis presumed on the basis of increased serum haptoglobin content or appreciable decrease of erythrocyte count in the first weeks of life. G-6-PD, GR and PK were within the normal adult range and no differences between jaundiced and healthy newborn infants were found. Plasma vitamin E was 7.1±3.6µg/ml in the jaundiced newborn infants, 5.2±1.5µg/ml in the healthy newborn infants and 11.5±2.7µg/ml in the adults.GSH-Px activity was 9.97±1.52 I.U. in the newborn infants with jaundice and 11.3±1.64 I.U. in the healthy newborn infants; the latter difference was significant (P<0.05).The data may indicate that during the first two weeks of life, when the vitamin E deficiency is a common feature, low GSH-Px activity may be a factor predisposing to the oxidative hemolysis.However the presence of jaundice probably due to increased hemolysis in cases with normal vitamin E and normal GSH-Px suggests that possible moderate decrease of both these antioxidative agent must be considered nothing more that predisposing factor.

13

DISSOCIATED RECOVERY OF LYMPHOCYTE FUNCTIONS AFTER CESSATION OF LONG-TERM INTENSIVE COMBINATION CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA (A.L.L.)

R. Eife*, G. Janka*, B. Lau*, R. Haas*, and F. Lampert+. Universitäts-Kinderkliniken München (*) and Gießen (+). D-8 München 2, Lindwurmstr.4, W-Germany.

This study was designed to investigate the effect on the cellular immunocompetence of long-term intensive combination chemotherapy (ICC). In 28 patients with A.L.L. in continuous complete remission the PHA-induced lymphocyte blast cell proliferation (PHA-CP) and the lymphotoxin production (LT PROD) by peripheral blood lymphocytes was investigated during the initial 18 months following cessation of 2 1/2 years of ICC. PHA-CP was estimated by measuring 3H-thymidine incorporation into lymphocyte DNA during a three hour pulse on day three of culture. LT PROD was estimated by measuring (1) cell lysis (51-Cr-release) and (2) reduction of cell metabolism (DNA synthesis) in target cell cultures exposed to cell-free medium from PHA-stimulated leukocyte cultures. At the time when ICC was stopped one third of the patients showed impaired PHA-CP and two thirds showed impaired LT PROD. During the initial three months following cessation of ICC the number of patients with impaired LT PROD significantly increased. After 12 months off therapy all patients showed a normal PHA-CP while the LT PROD was still impaired in some of them.

In contrast to healthy individuals, a considerable number of the A.L.L. patients showed a dissociation between PHA-CP and LT PROD: defective LT PROD by lymphocytes with elevated proliferative capacity.

Our data suggest that upon cessation of ICC the peripheral blood of patients with A.L.L. is repopulated by lymphocytes with a normal or even elevated proliferative capapacity but with a defective (or immature) lymphokine producing capacity. This defect of the cellular immune function in vitro may persist as long a 1 1/2 years after cessation of ICC.

This work was supported by grants from the "Kind-Philipp-Stiftung für Leukämie-Forschung" and the "Deutsche Forschungsgemeinschaft (SFB 37, B7)".

14

DISTINCTION BETWEEN ACUTE LYMPHOCYTIC LEUKEMIA AND MALIGNANT LYMPHOMA WITH LEUKEMIC TRANSFORMATION

A.Feldges, M. Westerhausen and U. Schmid

Children's hospital and Kantonsspital, 9000 St. Gallen

Malignant lymphoma with leukemic conversion is characterized by a rapid tumor progression and poor prognosis. In acute lymphocytic leukemia however the outlook has improved markedly in the last years. Many children exhibit complete remission for a long time and cure is even possible. In order to differentiate between this two diseases and to treat patients separately, we analyzed the clinical data of 8 children, aged 2 to 12 years, who entered the children's hospital of St. Gallen in the last year. Based on clinical findings and with the aid of a biopsy (EM), cytochemical and immunological studies, we interpreted 4 patients as stage IV non Hodgkin lymphoma with leukemic transformation and 4 patients as acute lymphocytic leukemia.

Of the 4 patients with malignant lymphoma, diffuse lymphoblastic, the new entity "convoluted type" was seen in 2 patients. One was a 3 months old baby with probably congenital malignant lymphoma.

The distinction between acute lymphocytic leukemia and non Hodgkin lymphoma with bone marrow involvement is made on clinical criterias. These criterias are discussed.

15

ERYTHROCYTE METABOLISM IN PROTEIN-ENERGY MALNUTRITION ANAEMIA.
I. GLUCOSE METABOLISM AND REDUCTION OF THE ACTIVATED OXYGEN.

P. Fondu, J. Nève, C. Heyder-Bruckner, F. Vertongen and I.M. Mandelbaum.

Cemubac Medical Mission to IRS, Lwiro, Zaïre, Departments of Pediatrics and of Clinical Chemistry, and Institute of Pharmacy, Free Universities of Brussels, Belgium.

The anaemia of protein-energy malnutrition (PEM) observed in Kivu is a distinct syndrome, characterized a.o. by a slight hemolysis and by surprisingly normal 2,3-DPG and P50 levels for age and altitude.

In an attempt to define the mechanisms of these phenomenons, the following parameters have been studied in large numbers of untreated, treated and healthy children : glycolytic rate, enzymatic activities (HK, PK, G6PD, 6PGD, GSSG-red, GSH-Px and SOD), glycolytic metabolites, adenine nucleotides, glutathione, and Heinz body formation. The plasma and erythrocyte selenium levels were also determined.

It appears :

1) that there exists in PEM an erythrocyte glycolytic abnormality limiting the 2,3-DPG increase on hypoxia;
2) that the reduction of the activated oxygen is decreased because, firstly of a GSH-Px activity reduction attributable to a selenium deficiency, and secondly of decreased GSH levels.

16

ERYTHROCYTE METABOLISM IN PROTEIN-ENERGY MALNUTRITION ANAEMIA. II. THE ERYTHROCYTE MEMBRANE.

P. Fondu, N. Mozes, P. Nève, L. Sohet-Robazza and I.M. Mandelbaum.

Cemubac Medical Mission to IRS, Lwiro, Zaïre, Departments of Pediatrics and of Clinical Chemistry, and Laboratory of Pathology, Free Universities of Brussels, Belgium.

The existence of an erythrocyte membrane abnormality in PEM anaemia is indicated by morphological examinations (increased mean red cell diameter, presence of target cells under optical microscopy and codocytes under scanning electronic microscopy) and by the study of the red cell osmotic resistance. The last parameter is increased but normalizes when patients' labelled red cells are transfused into healthy adults.

The study of the erythrocyte lipids discloses high cholesterol and phosphatidylcholine levels. The turnover of the membrane cholesterol is decreased on incubation with isolated patients' LDL. The incorporation of a labelled fatty acid in the membrane is accelerated. No increased cation leak is evident. The plasma vitamin E levels are low. An abnormality of the LDL composition is evident.

These studies show :

1) that the increase in membrane phosphatidylcholine and cholesterol levels is due to a qualitative lipoprotein disturbance;
2) that the main cause of hemolysis in PEM might be a peroxidation of the erythrocyte membrane, leading to an increased formation of lysophospholipids.