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Plasma levels of brain natriuretic peptide in children with solid tumors treated by anthracycline chemotherapy

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Background. Plasma levels of circulating natriuretic peptides are elevated in left ventricular (LV) dysfunction and heart failure and have therefore been suggested as noninvasive markers for asymptomatic LV dysfunction. The objective of this study is to evaluate the diagnostic value of plasma brain natriuretic peptide (BNP) as early indicator of cardiac dysfunction in patients treated with anthracycline drugs for childhood solid tumors.

Material and Methods. Thirty-four patients (11 girls) with an age range between 5 and 20 (mean age 12.2 ± 3.44) were included in the study. All patients were clinically asymptomatic and without evidence of residual malignancy. Cardiac function was assessed by ECG, exercise ECG and ecocardiography with both systolic and diastolic functions. BNP was measured before (BNP1) and after (BNP2) exercise testing. Sixteen healthy children (6 girls) with an age range between 6 and 17 (mean age 11.3 ± 3.64) were used as control group.

Results. Mean plasma concentrations of BNP1 and BNP2 were 10,56 ± 10,22 pg/ml and 15,70 ± 14,06 pg/ml, respectively. Mean plasma concentrations of BNP in the control group were 4,09 ± 2,26 pg/ml. BNP1 plasma levels was significantly increased when compared with BNP plasma levels of the control group ($p<0.016$). Although mean BNP2 plasma levels (after exercise testing) were higher than mean BNP1 plasma levels (resting), this increase was not statistically significant ($p>0,05$).

Conclusion. None of the patients developed overt congestive heart failure and all except one had normal shortening fraction but various systolic and diastolic abnormalities were found. Elevated plasma BNP levels can be considered as an early indicator of myocardial damage.

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Elevated blast glutathione levels are associated with decreased sensitivity to prednisolone and to proliferative rate in the in vitro t-cell lymphoblatic leukaemia model CCRFCEM

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Background: Raised blast glutathione (GSH) levels in childhood lymphoblastic leukaemia (ALL) are correlated with high presenting white cell counts (WCC) and an increased risk of relapse but the relationship to drug resistance remains unclear. Using the T lineage leukaemia cell line CCRF-CEM C7, we demonstrate that increased total GSH is associated with resistance to prednisolone and that GSH levels are related to proliferation rates *in vitro*.

Materials and Methods: Total GSH levels were measured using the recycling assay of Tietze. *In vitro* cytotoxicity was assessed using the sulforhodamine B (SRB) colorimetric assay and proliferation was measured using incorporation of ^{3}H thymidine.

Results: Cells grown in the absence of serum had 2-fold higher GSH levels (34.9 v 17.6; $p<0.001$). Higher GSH content resulted in decreased sensitivity to prednisolone ($p<0.05$) and peak GSH concentrations were related to peak rate of incorporation of ^{3}H thymidine. Reducing GSH levels in serum-free culture using buthionine sulfoximine resulted in partial restoration of prednisolone sensitivity ($p<0.05$ at effective dose combinations). Paradoxically, increasing total GSH levels with 10 mM *N*-acetylcysteine under standard (serum-containing) culture conditions, increased the sensitivity to prednisolone.

Conclusions: Our data lends support the concept that redox status is one of the molecular determinants of prednisolone sensitivity in childhood ALL and as such suggests another mechanism that might be exploited therapeutically. Furthermore, microenvironment may also be an important determinant of blast sensitivity to glucocorticoids. The correlation of total GSH with rate of proliferation offers an explanation for its association with high WCC at presentation in children with ALL.

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The impact of infectious events in morbidity and mortality in children with ALL treated with ALL-BFM-90 Protocol

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Leukemia is the most prevalent cancer in children in R. Macedonia; 37% of all children with malignancies presented acute leukemia, and 82% of them were diagnosed as Acute Lymphoblastic Leukemia (ALL). Since the 1997 the German protocols for treatment of children with ALL (ALL-BFM-90, ALL-REZ-BFM-90) have been introduced into University Children's Hospital in Skopje.

Objective of this study was to explore the characteristics of Infective Episodes-IE (as judged by length, timing, leucopoenia, fever, CRP elevation and length of antibiotic treatment) and there impact in morbidity and mortality in children with ALL treated with ALL-BFM-90 protocol.

Methods and Results: We retrospectively evaluated data of 64 patients treated with ALL-BFM-90 protocol between Jan 1997 and Jan 2003 with the minimum follow up of 6 months. The percentage of patients treated by age were <1 year: 1,5%; 1-10 years: 74,5%; 11-16 years: 24%. The rate male:female was 1:0,88. Patients were selected in three risk groups according to the protocol: SR (Standard risk) 23,8%, IR (Intermediate risk) 68,2% and HR (High risk) 7,9%. In SR and IR, Protocol I and Protocol II gave most events (Febrile Neutropenia FN, raised CRP). In HR the second course of cytosine arabinoside gave the highest event frequency. Lungs and upper airways were the more frequent sites of infection. They were detected as a focus of infection in 56,5% of patients (pts). The IE were associated with FN in 86,3% of pts. Mean duration of antibiotic treatment was 15 days during Protocol I, 18 days during Protocol II, 7 and 5 days during Protocol M and Maintence therapy. The follow microorganisms were found as the most frequent causes of the IE: Streptococcus pneumonia, Haemophilus influenza, Staphylococcus aureus, herpes simplex virus, varicella- herpes zoster virus and hepatitis B virus. CRP elevation was seen prior to antibiotic treatment and duration of CRP elevation was 3-4 days shorter than treatment with antibiotics. At the end of antibiotic treatment 40% of pts with IE were current, 59% had association with other complications, two of them died.

Conclusion: Protocol I and Protocol II were the periods with more frequency of IE and FN. Lungs and upper airways were the most frequent focus of infection. Antibiotic treatment combined with therapy against virus infections, prophylaxis of fungal infections and supportive therapy, gave the best results in the treatment of IE.

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Treatment results and prognostic factors in osteosarcoma relapse in children

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Background. Osteosarcoma relapse has a poor prognosis. The aim of the study was to evaluate results of treatment and significance of prognostic factors in pediatric patients with the relapse of osteosarcoma.

Patients and Methods. From 1990 to 2000, we treated 24 patients (pts) with osteosarcoma relapse, median age 15 years (range 9 to 18 years). All patients received aggressive multimodal therapy (chemotherapy/surgery) in previous treatment for classic high-grade nonmetastatic osteosarcoma.

Pulmonary metastases were detected in 21 pts (7 solitary), while 3 pts had local relapse of the disease. Disease-free interval (DFI) was more than 1 year in 9 pts.

Surgery was performed in 18 pts (thoracotomy in 16, amputation in 3 pts). Chemotherapy regimens were administered in all patients: 1. IFO, VP 16 (11 pts); 2. HDMth/IFO VP 16 (7 pts); 3. HDMth/Carbo VP 16 (6 pts).

Results. During 10 to 132 months follow-up period (Me=42 months) overall survival rate in all patients was 41%, DFS was 39%. In the subgroup with pulmonary meta, the overall survival rate was 32%, DFS was 30%. The most significant prognostic factors influencing survival were: presence of solitary pulmonary meta ($p=0.035$), DFI longer than 1 year ($p=0.013$), completeness of resection ($p=0.03$), local relapse of the disease ($p=0.039$) and tumor necrosis over 90% in previous treatment ($p=0.046$).

There were no significant differences in survival in relation to the chemotherapy regimen applied.