4110 POSTER

Prognostic Significance of Mediastinal Involvement in Childhood Lymphoblastic Lymphoma

S.V. Semochkin[1], S.S. Kulikova[1], D.V. Litvinov[2], E.V. Inyushkina[2], N.V. Myakova[2], K.L. Kondratchkik[2], L.V. Baydun[3], D.M. Konovalov[4], D.A. Peregudov[2], E.V. Samochatova[2]. *[1]Federal Scientific Clinical Center of Pediatric Hematology Oncology and Immunol, Adolescent and Young Adult Hematology, Moscow, Russian Federation; [2]Federal Scientific Clinical Center of Pediatric Hematology Oncology and Immunol, Pediatric Hematology, Moscow, Russian Federation; [3]Federal Scientific Clinical Center of Pediatric Hematology Oncology and Immunol, Laboratory Hematology, Moscow, Russian Federation; [4]Federal Scientific Clinical Center of Pediatric Hematology Oncology and Immunol, Pathology, Moscow, Russian Federation*

Lymphoblastic lymphoma (LBL) is an uncommon malignancy accounting for approximately 2% of all non-Hodgkin's lymphomas (NHL). Most of the studies carried out on a small number of patients (pts) and the significance of prognostic factors is poorly understood. The purpose of this study was to investigate the effect of individual features on the outcome.
Methods: 58 patients (m − 40, f − 18) were enrolled from May 1991 to August 2008. Fifty-two (90%) patients were treated with NHL-BFM 90 or 95 protocols for non-B-NHL (leukemia-type) and 6 (10%) − NHL-BFM 90 (NHL-type).
Results: Median age at time of presentation was 11.0 (range 1.5–21.6) years. 45 (90%) patients have a T-cell immunephenotype. 53 (91%) had advanced (III, IV) stage. The presenting sites of T-LBL included mediastinal mass − 35 (78%) and lesion of bone marrow − 13 (29%). The complete response (CR) rate was 94 and 83% for non-B-NHL and B-NHL treatment respectively. 5-years event free survival (5 y-EFS) was 0.80±0.06 (median of observation 4.1 years) and 0.67±0.19 (5.1 years) respectively ($p > 0.05$). 5-years overall survival (5 y-OS) was 0.85±0.05 and 0.80±0.06 respectively ($p > 0.05$). The situation without mediastinal involvement was a factor unfavorable prognosis for T-LBL: 5 y-EFS − 0.56±0.17 vs. 0.90±0.05 ($p = 0.036$). Sex, age, increased LDH, slow or fast therapy response, involvement of the central nervous system or bone marrow did not affect the prognosis ($p > 0.05$).
Conclusions: The absence of mediastinal involvement is a factor unfavorable prognosis for childhood T-LBL treated with BFM protocols.

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Clinical Importance of Methotrexate Pharmacokinetics and Pharmacogenetics in Pediatric Osteosarcoma

M.Z. Hegyi[1], A. Gulacsi[1], A.F. Semsei[2], E. Cságoly[2], D. Erdelyi[2], C.S. Szalai[2], G.T. Kovacs[1]. *[1]Semmelweis University, II. Department of Peadiatrics, Budapest, Hungary; [2]Semmelweis University, Department of Genetics Cell- and Immunobiology, Budapest, Hungary*

Introduction: High-dose methotrexate (HD-MTX) with leucovorin rescue is widely used to treat osteosarcoma, which predominantly affects children. The human gamma-glutamyl hydrolase (GGH) is important in the antifolate-resistance in the tumour cells. The reduced folate carrier(RFC1)gene encodes the major methotrexate transporter. Our objectives were to analyze the relationship between exposure to HD-MTX and toxicity, and to assess correlations between pharmacokinetic parameters, toxicity and polymorphisms of the GGH promoter (**GGH −401C>T**) and the the reduced folate carrier **(RFC1 G(80)A)** in children with osteosarcoma.
Methods: Pharmacokinetic data of 112 patients treated with 1029 HD-MTX courses were evaluated. Pharmacokinetic parameters (MTX clearance and AUC) were calculated based on methotrexate serum levels measured at 6, 24, 36, 48 hours after the initiation of the infusion by high pressure liquid chromatography (HPLC) technique. Clinical data (the highest serum GPT, GGT, bilirubin values and the lowest number of granulocyte, thrombocyta and serum protein levels in the first two weeks after methotrexate treatments) were collected by retrospective chart review. Toxicity parameters were categorized according to Common Toxicity Criteria. Data were analysed by Student's t-test, Mann-Whitney U test and chi square test (StatSoft's STATISTICA v8.0). The polymorphisms were determined by a PCR-RFLP method using DNA extracted from peripheral blood of 72 children among the 122 patients.
Results: Patients with serious hepatotoxicity had significantly higher peak MTX concentrations ($p = 0.002$), 48 h MTX serum levels ($p = 0.0034$) and AUC_{0-48} ($p = 0.00001$), and significantly lower MTX clearance ($p = 0.0001$). Patients with serious bone marrow toxicity had significantly higher 24 h MTX serum levels ($p = 0.000012$). Nephrotoxicity was associated with higher 24 and 48 h MTX serum levels and higher AUC_{0-48} ($p < 0.00001$). The incidence of serious acute hepatotoxicity was less frequent ($p = 0.0033$) and drug serum levels were significantly lower in the cellular elimination phase ($p = 0.0003$ at 48 hours) in patients homozygous for the GGH −401T allele than in the group with −401CC or CT genotypes. The frequency of serious acute hepatotoxicity was significantly higher ($p = 0.001$) in patients with RFC1 80AA genotype than in those who carried the G allele. This difference was even higher between patients with RFC1 80AA plus GGH-401CC+CT genotypes and patients with other genotypes ($p = 0.00005$).
Conclusion: Higher MTX exposure leads to more frequent occurence of toxicity. Patients homozygous for the GGH −401T allele had less hepatotoxicity and faster methotrexate elimination compared to those with −401CC or CT genotype. The hepatotoxicity was more frequent in patients homozygous for the RFC1 80A allele than in those who carried the G allele and the difference was intensified without the protective effect of GGH −401TT genotype.

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Treatment Outcome of Children With Hepatoblastoma

K. Josip[1], M. Anicic[1]. *[1]Clinical Hospital Centre Zagreb, Pediatric Hematology and Oncology, Zagreb, Croatia*

Background: Hepatoblastoma is the most common malignant primary tumour of the liver in children. The prognosis of hepatoblastoma in children has significantly improved over the last 20 years. This is attributable to improved multidisciplinary input including specialist pediatric hematology-oncology and surgery.
Objective: To review our institutional experience with hepatoblastoma.
Patients and Methods: Files of children treated at our hospital between 1995–2010 with the diagnosis of hepatoblastoma were reviewed for clinical characteristics and treatment results. All patients presented a palpable abdominal mass. Ultrasound, CT and/or MRI were used to assess site and resectability of tumours. All patients underwent diagnostic biopsy. 9 children (5 male and 4 female, median age at diagnosis was 2.3/ 1−3.5 y) with hepatoblastoma (3 had lung metastases) have been treated according to SIOPEL protocol with pre-operative chemotherapy, surgery and post-operative chemotherapy. One was treated only with chemotherapy (surgery wasn't possible).
Results: The remission has been achieved in all patients; 2 patients died in relapse. 7 patients are still alive in the first remission (also 3 with lung metastases and 1 treated only with chemotherapy). Serious side effects were not noticed (only 1 cardiomyopathy). Secondary malignancies did not occur in any of patients.
Conclusion: Combined modality therapy is optimal treatment for the majority of children with hepatoblastoma. New treatment strategies using innovative approaches are still needed to further improve treatment results.

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Pharmacokinetics and Toxicity of 5 G/m^2 MTX Treatments in Children With ALL

K. Csordas[1], M. Hegyi[1], O. Eipel[1], M. Csoka[1], J. Muller[1], G.T. Kovacs[1]. *[1]Semmelweis University, 2nd Department of Pediatrics, Budapest, Hungary*

High-dose methotrexate (MTX) is the part of treatment for different childhood malignancies. It has been used for many years, however the exact dose is not clearly defined.
The aim of our study was to analyse the pharmacokinetic data and toxicity of 5 g/m^2 MTX treatments in children with acute lymphoblastic leukemia (ALL) treated according to BFM 1995 and 2002 protocols at the 2nd Department of Pediatrics at Semmelweis University between 1998–2006.
Patients and Methods: 43 patients were treated with 5 g/m^2/24h intravenous MTX. Mean age of the patients was 7.02 years (0.45–17.95). 147 MTX infusions were analysed. Serum MTX and 7-OH-MTX levels were measured with HPLC at 24, 36, 48 hours. Delayed elimination was registered. We calculated AUC and half-life time at the first and at the terminal phase of elimination. Considering the toxicity we measured the serum ALAT, ASAT, bilirubin, creatinine, protein levels before therapy and one day, two days and one week after treatment. Correlations between pharmacokinetics and toxicity were calculated using Mann-Whitney-test and Chi squre-test after testing normality.
Results: MTX elimination showed two-compartment model, with a fast phase between 24. and 36. hours, and a slow phase between 36. and 48. hours. Mean half-life time in the first phase (T1) was at 30 hours (SD: ±0.4), in the terminal phase (T2) it showed greater difference: the mean time was at 45 hour (SD: ±3.1). There was no significant correlation between AUC, T1, T2, 24.h, 36.h MTX and 24.h, 36.h, 48.h 7-OH-MTX and the toxic parameters. We found significant correlation between 48.h MTX and serum ALAT ($p = 0.029$), serum bilirubin ($p = 0.006$) levels elevation. Delayed elimination correlated with serum bilirubin level elevation ($p = 0.032$).
Conclusion: Serum MTX levels show great inter- and inpatient differences. Higher 48. hour plasma concentration and delayed elimination show strong