was follows: in ALL group there were 27 (67.5%) male and 13 (32.5%) female patients; in AML – an equal proportion of males and females – 15 (50.0%); in control group 18 (69.2%) males and 8 (30.8%) females.
For MDR1 C3435T and G2677T polymorphisms analysis allele-specific real-time PCR assay was used. For detect MTHFR C677T gene polymorphism we used restriction fragment length polymorphism assay.
Results: The analysis of genotype frequencies showed that for MDR1 G2677T and MTHFR genotypes there is no statistically significant difference between groups of patients with AL and the control. But the analysis of the distribution of MDR1 C3435T gene polymorphic variations did reveal statistically significant differences between the studied groups. The TT genotype was prevalent in children with ALL 20.0% ($p = 0.008$) and AML 16.7% ($p = 0.02$) and was absent in control group. The control group was predominantly MDR1 C3435T heterozygous – 87.7% – which makes a statistically significant difference in comparison with the ALL 57.5% ($p = 0.009$) and AML 60.0% ($p = 0.02$) groups.
The analysis of the gene polymorphism distribution between male and female patients has shown no significant difference in frequency for all groups except the control one in which the majority of females had the MDR1 G2677G homozygous genotype 76.9% ($p = 0.004$), while half of males had the MDR1 T2677T homozygous mutant genotype 50.0% ($p = 0.02$). The analysis of research literature showed that the majority of studies point to the lack of correlation between gender and genotypes of investigated genes.
Conclusions: There were statistically significant differences in the distribution of MDR1 C3435T genotypes between the AL and control groups and of G2677T variations – between females and males. In the first case, the mutant TT genotype was detected only in children with leukemia, and heterozygosity was characteristic for the control group. Differences in the distribution of G2677T polymorphism between males and females may be random in nature, due to the small sample size and require further study.

9240 POSTER

Imatinib plus vincristin & prednisolone induces complete remission and prolonged survival in elderly philadelphia chromosome positive acute lymphoblastic leukemia patients

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Introduction: Acute lymphoblastic Leukemia (ALL) in elderly patients (50yrs or older) carries a poor prognosis. In survival studies using in variety of therapeutic regimens. This may be because of relatively high frequency of the Philadelphia chromosome (Ph). With the advent of dose intensive chemotherapy regimen such as hyper CVAD (Fractionated Cyclophosphamide, Vincristin, Doxorubicin, Dexamethasone) overall survival has not improved. The aim of our study was to see the effectiveness of Imatinib plus Vincristin & Prednisolone in Philadelphia Chromosome positive in elderly acute lymphoblastic leukemia patients.
Material and Methods: During period from January 2006 December 2008 we selected 30 consecutive elderly (more than 50yrs) Bcr-Abl ALL patients in the haemato-oncology department Netaji Subhash Chandra Bose Cancer Research Institute. There were 12 males & 18 females. The median age of the patient was 64 years (range 51 to 77yrs). All patients were started with Imatinib mesylate (Natco pharma) 400 mg daily. Prednisolone was given 40 mg /m^2 over 6weeks & followed by 2weeks tapering dose. Vincristin was given 2 mg/m^2 weekly for 6weeks. All patients were evaluated by bone marrow and Bcr-Abl estimation by flowcytometer every 3 months for 1 year then 6 monthly.
Result: 24 patients (80%) obtained complete haematological & partial molecular response at 3month. Nine patients (30%) achieved complete molecular response at 9month. With median follow-up of 12 months (range 4−20months) the disease free survival and overall survival were 60% & 70% respectively. Most of the induction treatment was done as OPD basis, no hospitalization required. The therapy was tolerated well.
Conclusion: We concluded that Imatinib plus Vincristin & Prednisolone is a feasible, highly active protocol for elderly Bcr-Abl positive acute lymphoblastic leukemia patients. It is well tolerated & associated with good quality of life.

9241 POSTER

Arsenic trioxide induces apoptosis in NB-4, an acute promyelocytic leukemia cell line, through up-regulation of p73 via suppression of nuclear factor kappa B-mediated inhibition of p73 transcription

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Background: Acute promyelocytic leukemia (APL) is characterized by t(15;17). Although Arsenic trioxide (ATO) is the treatment of choice in APL, the molecular mechanisms underlying its anti-proliferative effects are not fully understood. p73 is a new member of p53 family capable to transactivate p53-responsive promoters to induce cell cycle arrest and apoptosis. NF-κB contributes to ubiquitin-dependent proteasomal degradation of p73, inhibits its transcription and proapoptotic functions. Given this, therapeutic disabling of NF-κB might promote apoptosis in tumor cells through triggering p73-mediated apoptosis. This study was aimed to evaluate the effects of ATO on transcriptional activity of p73 through preempting NF-κB.
Material and Methods: MTT assay, BrdU-proliferation assay, Caspase 3 assay, Cell-based NF-κB phosphorylation assay by ELISA and real time PCR array were employed to assess the effect of ATO on proliferation of NB-4 cells, activation of pro-caspase 3, phosphorylation of NF-κB cascade and expression of genes involved in survival as well as stabilization and degradation of p73.
Results: ATO suppressed proliferation of NB-4 cells, activated pro-caspase 3, hindered phosphorylation of p65 subunit of NF-κB and caused an increase in transcriptional activity of p73 and its targets p21 and TP53INP1. Considerable reduction in transcriptional levels of IKK2 and Nemo, subunits of IKK complex, and ATM (which activates NF-κB) and TIP60 (which represses p73 message) was observed. Moreover, ATO repressed mRNA levels of XIAP, BCL-XL, IAP1, Bcl-2 and survivin. No inhibitory effect of ATO on mRNA expression of IAP2, cyclin D1 and BFL2 was obtained. ATO exerted no inductionary effect on promoter activity of CYLD and ING4, repressors of NF-κB, neither Kpm nor CD145 and YAP1 which stabilize p73. No inhibitory effect of ATO on Itch (which governs p73 proteasomal degradation as well as reduces its mRNA message)was obtained.
Conclusions: The results of the present study imply for the first time that ATO could inhibit proliferation and executes apoptosis in NB-4 cells through trammeling NF-κB-mediated suppression of p73 transcription. These results are the ones to indicate that the inhibitory effect of ATO on NF-κB is through suppression of p65 phosphorylation and cramping the mRNA expression of IKK2, Nemo and ATM. Quelling NF-κB by ATO caused significant reduction in mRNA levels of its target genes including XIAP, BCL-XL, IAP1 and survivin. Our outcomes show for the first time that the preventive impacts of ATO on proliferation of NB-4 cells might be through transcriptionally stimulation of WNK2 and Lipocalin 2.

9242 POSTER

Pharmacogenetic factors in metabolism, transport and toxicity of cytarabine treatment in patients with AML

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Background: Cytarabine is commonly used in the treatment of acute myeloid leukemia (AML). However, therapy associated side effects like neutropenia are often leading to severe infections, which are the most frequent cause for therapy associated mortality. Polymorphisms in genes encoding for cytarabine biotransformation or transport are considered to be an important factor contributing to individual drug toxicity in patients undergoing chemotherapy with cytarabine. For a suitable drug response cytarabine has to be actively transported into the cell via the human concentrative nucleoside transporter 1 (hCNT1) and the equilibrative nucleoside transporters 1 and 2 (hENT1, hENT2), activated by deoxycytidine kinase (dCK) and not extensively inactivated by cytidine deaminase (CDA).
Material and Methods: We analysed genetic polymorphisms in cytarabine biotransformation, transport and genes involved in cytarabine toxicity using PCR-RFLP and RealTime PCR in 322 adults younger than 60 years of age with cytogenetically normal AML. Patients participated in one of four clinical trials on drug therapy of AML. All trials used double-induction therapy with idarubicin, cytarabine and etoposide and several cycles of consolidation therapy with high-dose cytarabine. Cytarabine toxicity was measured as reconstitution time of total white blood cells (WBC) and neutrophils.
Results: The hCNT1 1561 C>T variant influenced the reconstitution time of WBC and neutrophils significantly ($p = 0.02$ and 0.03, respectively),