

## Meeting Abstracts

Abstract Category

- Oral presentation; Leukemia; Lymphoma; Myeloma; Transplant; Miscellaneous

### Oral Presentations:

#### Abstract 001

**Total body irradiation using in hematopoietic stem cell transplantation detrimentally induces cytogenetic abnormalities of bone marrow-derived mesenchymal stem cells.** Su-Peng Yeh. China Medical University Hospital, Taiwan. Email: supengyeh@gmail.com

Purpose: Total body irradiation (TBI) is routinely used before allogeneic transplantation to kill the leukemic cells as well as to suppress the immunity of recipient. Nevertheless, TBI is associated with a lot of long-term adverse effects on normal cells, including radiation-induced sarcoma. Mesenchymal stem cells (MSCs) are the stromal stem cells in the bone marrow (BM) and other mesenchymal tissue and are extensively studied in the clinical application as cell therapy for tissue repair. However, some in vitro and animal studies had pointed out that sarcoma could be derived from cultured or in vitro manipulated MSCs. We therefore conduct this study to see whether irradiation using the dosing schedule similar to TBI can induce malignant transformation of BM-MSCs. Materials & Methods: Ex vivo expanded (passage 3 to 5) BM-MSCs from three normal adults were irradiated with 1200 cGy (200cGy twice a day for consecutive 3 days, mimicking TBI clinically). Each of them was kept ex vivo culture for 6 and 12 passages respectively. The cells were then subjected to investigate morphology, phenotype, differentiation potential, and cytogenetic analysis using traditional G-banding technique and also spectral karyotyping (SKY). Ex vivo expanded (passage 3 to 5) BM-MSCs from five leukemic patients obtained before and after TBI (1200cGy)-conditioned allogeneic transplantation were also examined in the same way. The differences in the characteristic of BM-MSCs before and after irradiation (or TBI) were evaluated and the effects of TBI on MSCs were determined. Results: BM-MSCs from normal adults or transplant patients after receiving irradiation or TBI are still fibroblast-like and are CD29+, CD44+, CD73+, CD90+, CD105+, CD166+, CD14-, CD34-, and CD45-, which are just the same to normal BM-MSCs. However, the proliferation and multi-differentiation ability are markedly decreased in BM-MSCs after irradiation or TBI. Of the three BM-MSCs obtained from normal adults and having normal karyotype, cytogenetic abnormalities can be easily identified on G-banding and SKY after irradiation. Besides, the same cytogenetic abnormality can be detected in both passage 6 and passage 12 MSCs. Interestingly; cytogenetic clonal evolution was detected in 1 of them. In sex-mismatched allogeneic transplant, the cytogenetic studies showed all the BM-MSCs remain recipient-origin after transplant. Nevertheless, of the five BM-MSCs isolated from transplant patients who had received TBI conditioning, cytogenetic abnormalities were detected in all of them. More importantly, cytogenetic clonal evolution was also found in 1 of them. Conclusions: BM-MSCs cannot be eradicated by myeloablative, TBI-based conditioning chemoradiotherapy and they remain recipient-origin after transplant. The cellular morphology and surface antigen expression did not differ significantly after irradiation. However, TBI significantly reduced the proliferation and differentiation potential of BM-MSCs. Most important of all, TBI induced clonal cytogenetic abnormality on BM-MSCs, which is evident not only from ex vivo irradiation study but also from clinical patients' specimens. Besides, cytogenetic clonal evolution, a unique feature of malignant process, was found in some of them. TBI is known to be an important risk factor for soft tissue sarcoma in transplant survivors, our study further provides the direct evidence showing that TBI-exposed BM-MSCs may have clonal cytogenetic abnormality and the tumorigenic potential of these cells merits extensive study. Taking together, the BM-MSCs isolated from patients who had received TBI have defective proliferation and

differentiation potential. Moreover, because of cytogenetic abnormality, these cells should not be considered for any clinical application. Keywords: TBI, Transplant, MSCs

#### **Abstract 002**

**Risk of hepatitis B virus reactivation in multiple myeloma patients with HBV Infection.** Hae Tha Mya, Shuting Han, Daryl Tan. Singapore General Hospital, Singapore. Email: [mhtha2004@yahoo.com](mailto:mhtha2004@yahoo.com)

Introduction Patients with hepatitis B virus (HBV) infection, defined by the presence of HBV surface antigen (HBsAg), have an increased risk of HBV reactivation when they are on immunosuppressive treatment for multiple myeloma (MM). Although there is no guideline for MM patients with HBV infection, current lymphoma guidelines do recommend that these patients should receive antiviral prophylaxis during and after chemotherapy. Of late, the advent of bortezomib in the management of MM has resulted in a high reported incidence of varicella-zoster reactivation. The risk of HBV reactivation in MM patients with HBV infection undergoing treatment has not been previously studied. As HBV infection is endemic in Asia, we sought to evaluate the prevalence of HBV infection in our patients, the incidence of its reactivation especially in patients receiving bortezomib and the role of anti-viral prophylaxis. Methods Previously untreated MM patients diagnosed from 2000-2008 who were tested for HBsAg in our institution were included. Hepatitis attributable to HBV reactivation was defined as an increase in HBV DNA levels of tenfold, or an absolute increase greater than 10<sup>5</sup> copies/ml in the HBV DNA level. HBV infected patients were prospectively followed. 33% of all patients have been exposed to bortezomib, while 26% received high dose therapy with autologous stem cell transplantation (HDT/ASCT). Results 244 untreated MM patients were identified. The prevalence of HBV infection is 6.1% (15/244). 7 (47%) HBV infected patients had detectable HBV DNA viral load (>3 log) at baseline. All 7 patients had normal baseline liver function tests and received lamivudine prophylaxis. All 15 HBV infected patients went on to receive systemic therapy for MM, with continual monitoring of HBV DNA viral load and liver enzymes for viral reactivation. 4 patients with undetectable HBV DNA load did not receive anti-viral prophylaxis. Of these 15 patients, 3 (21%) who had been on lamivudine prophylaxis had reactivation of the virus, with 1 dying from it, and 1 having emergence of a mutant viral strain. Two of them had no detectable viral load at presentation. Two patients reactivated 3 and 5 months after HDT/ASCT, while 1 reactivated immediately after a bortezomib/ doxil salvage regimen. Conclusion The risk of HBV reactivation appeared to be commonest during the immune reconstitution phase after HDT/ASCT. Although the majority of patients with HBV infection and not receiving HDT/ASCT do not reactivate, the risk may not be negligible when bortezomib is used (7%). Undetectable HBV DNA and the use of anti-viral prophylaxis do not appear to preclude reactivation. The optimal use of anti-viral prophylaxis, particularly if bortezomib is given, should be further evaluated. This is particularly relevant in the current era where bortezomib plays a dominant role in the treatment of MM, and especially in endemic regions where the incidence of HBV infection is high. Keyword: myeloma, hepatitis B, bortezomib

#### **Abstract 003**

**T-regulatory cells in Multiple Myeloma and their response to immunomodulatory therapy.** Prasanth Ganesan, Mrinali Hakim, Ritu Gupta, Atul Sharma, Lalit Kumar. All India Institute of Medical Sciences, New Delhi, India. Email: [pg1980@gmail.com](mailto:pg1980@gmail.com)

Introduction: T-regulatory (Treg) cells suppress anti-tumor immunity and are increased in most cancers. Studies, using varying definitions for Treg cells and involving heterogeneous populations of patients, in Multiple Myeloma (MM), however, show conflicting results. There is paucity of data regarding the impact of immunomodulatory therapies on Treg cells in MM. We studied the Treg cell numbers in newly diagnosed MM and in the same patients after treatment with thalidomide, an immunomodulatory drug and in a cohort of patients undergoing high dose chemotherapy and autologous stem cell transplant (ASCT). Methods: Treg cells (defined as CD4+CD25+FoxP3+ T cells by sequential gating) were assayed using Flow cytometry. Assessment was done at the time of diagnosis (n=30), and after 4 months treatment with Thalidomide and Dexamethasone (n=15). Treatment naïve Salmon Durie stage IIIA MM patients were included to negate the effect of renal failure per se on Treg cell numbers. In a second cohort (n=6), assessment was done pre-transplant and at 1 month and 6 months after ASCT. Treg cells were expressed as percentages of the total CD4+ T cell population (mean ± standard error of mean). The Mann-Whitney U test and Wilcoxon log rank test were used to test for differences in Treg cell numbers between patients and controls and after therapy. Results: Treg cell numbers in newly diagnosed MM patients (5.9±2.5%) were significantly decreased when compared with those in healthy controls (9.6%± 2.7%; P=0.002). Baseline Treg cell

numbers were not associated with age, sex, light chain subtype, or the ISS stage. After 4 months of therapy, there was a significant increase in Treg cell numbers (post treatment:  $9.7\pm 3.1\%$ ;  $p=0.02$  as compared to baseline). In patients undergoing ASCT, Treg cell values increased at 6 months post transplant (pretransplant:  $6.5\pm 1.02\%$ ; 1 month post-transplant:  $5.9\pm 5.2\%$ ; 6 months post-transplant:  $10.7\pm 4.7\%$ ). This rapid increase in the CD4+CD25+Foxp3+ fraction contrasted the recovery of CD4+ population as a whole, which remained low at diagnosis, post therapy as well as in the post-transplant period. Conclusions: We found decreased Treg cell numbers in newly diagnosed MM patients which increased after therapy with thalidomide. In patients undergoing ASCT, the Treg cell fraction of the CD4+ T cells recovered within 6 months. The rapid reconstitution of Treg cells may have implications on disease outcome. Keyword: Multiple myeloma, T-regulatory cells, Thalidomide

#### **Abstract 004**

**Molecular Characterization of Normal Karyotype Acute Myeloid Leukemia in Korean Patients.** Je-Hwan Lee, Yunsuk Choi, Jung-Hee Lee, Dae-Young Kim, Sung-nam Lim, Sung-Doo Kim, Eun-Hye Hur, Mee Seol, Eul-Ju Seo, Seongsoo Jang, Chan Jeoung Park, Hyun Sook Chi, Kyoo-Hyung Lee. Asan Medical Center, University of Ulsan, College of Medicine, Seoul, Korea. Email: jhlee3@amc.seoul.kr

Recent advances in molecular characterization of acute myeloid leukemia (AML) have led to molecular classification of normal karyotype (NK) AML. Mutations of the NPM1 gene showed a good response to induction therapy and had a favorable prognosis, especially in the absence of a FLT3-ITD mutation, in the studies of NK AML. However, most studies regarding the NPM1 gene mutations have come from the Western countries. Thus we investigated clinical implications of the NPM1 mutations as well as other gene alterations in Korean patients with NK AML. Inclusion criteria of this retrospective study were the followings: a new patient (1) with NK AML, (2) receiving standard induction chemotherapy ('7+3' regimen), and (3) with DNA from leukemic blasts at diagnosis being available. Polymorphisms of 4 genes (GSTT1, GSTM1, GSTA1, MDR1 [C3435T]) and mutations of 2 genes (FLT3, NPM1) were analyzed using PCR (GSTT1, GSTM1, FLT3-ITD), RFLP (GSTA1, MDR1 [C3435T]), and direct sequencing (NPM1). Clinico-laboratory data were retrieved from the Asan Medical Center Leukemia Registry. This study included a total of 102 patients who were newly diagnosed as NK AML in the Asan Medical Center, Seoul, Korea between May 1999 and December 2006. Median age of the patients, 63 males and 39 females, was 44 years (range, 15-80). Null genotype of GSTM1 and GSTT1 was observed in 41.2% and 52.0% of the patients, respectively. Genotype of GSTA1 was CC in 75.3% and CT in 24.7%, and C3435T polymorphism of MDR1 gene was CC in 52.2%, CT in 39.1% and TT in 8.7%. FLT3-ITD was detected in 22.8% and NPM1 was mutated in 36.5%. For total patients, the rate of complete remission (CR) was 78.9%, and survival probabilities at 5-year were 39.9% for overall survival (OS), 57.9% for relapse-free survival (RFS), and 42.5% for event-free survival (EFS). Multivariate analyses demonstrated independently significant prognostic factors for clinical outcomes of NK AML as followings: (1) for the induction of CR, no independently significant factor, (2) for OS, age (year, < 60 vs. 60 or more, 45.4% vs. 15.4%, RR 2.710,  $P=0.003$ ) and FLT3-ITD (absent vs. present, 43.1% vs. 30.4%, RR 1.947,  $P=0.025$ ), (3) for RFS, age (year, < 60 vs. 60 or more, 64.7% vs. 11.4%, RR 6.333,  $P<0.001$ ), FLT3-ITD (absent vs. present, 43.1% vs. 30.4%, RR 3.658,  $P=0.002$ ), and uric acid level (mg/dL, < 7.0 vs. 7.0 or more, 61.2% vs. 34.3%, RR 2.833,  $P=0.027$ ), and (4) for EFS, age (year, < 60 vs. 60 or more, 47.8% vs. 9.1%, RR 3.422,  $P=0.003$ ), FLT3-ITD (absent vs. present, 46.0% vs. 31.6%, RR 2.655,  $P=0.005$ ), and C3435T of MDR1 (CC vs. CT/TT, 29.1% vs. 56.3%, RR 0.449,  $P=0.013$ ). In conclusion, mutations of the NPM1 gene did not show significant impact on clinical outcomes in Korean patients with NK AML, whereas presence of a FLT3-ITD mutation was significantly associated with inferior survivals. Clinical significance of genetic alterations in NK AML might be different in different races and the racial differences should be considered before molecular classification is established in NK AML. Keyword: Acute myeloid leukemia, Normal karyotype, Molecular characterization

#### **Leukemia**

#### **Abstract 005**

**Evaluation of Cytopenias occurring in Imatinib treated Chronic Myeloid Leukemia (CML) patients.** T.Roshni Paul, Shantveer G Uppin, Megha S Uppin, Rachel T.Jacob, D.Raghunadha Rao, Senthil Rajappa. Nizam's Institute of Medical Sciences, Hyderabad, India. Email: troshnip@yahoo.co.in

Introduction: Imatinib Mesylate, a Tyrosine Kinase inhibitor, is presently the drug of choice for Chronic myeloid leukemia. During therapy, a few patients develop myelosuppression and present with cytopenias. Aims &

**Objectives:** To study the bone marrow morphology in Imatinib treated CML patients presenting with persistent cytopenias. **Materials & Methods:** The cases were retrieved from the Hematopathology record files, Department of Pathology, Nizam's Institute of Medical Sciences, Hyderabad, India; the study period being January 2008 to June 2009. Cases of CML on Imatinib presenting with grade 2 or more anemia, neutropenia and/or thrombocytopenias with bone marrow studies, were included in the study. The morphology of all cases were reviewed with cytogenetic studies. Follow-up details were obtained from the Medical Oncology records. **Results:** During the study period, 683 Imatinib treated CML patients had bone marrow studies as part of their follow-up investigations. Of these, 60 patients (9%) had some form of persistent cytopenia. The patients ranged from 21 to 75 years of age with a median age of 38 years. The male: female ratio was 1:1. There were 46 patients with = grade 2 anemia, 25 patients with = grade 2 neutropenia and 37 patients with = grade 2 thrombocytopenia. Of these, 20 patients had bicytopenia and 13 cases had pancytopenia. The marrow evaluation revealed morphologic response in 30 patients, persistent marrow disease in 5 patients, marrow hypoplasia in 6 patients, extensive stromal changes including fibrosis in 5 patients, megaloblastic erythropoiesis in 11 patients and disease progression to accelerated or blast crisis in 3 patients. **Conclusions:** Various degrees of cytopenias may occur in few patients of CML on Imatinib therapy. Regular hematologic follow-up is required so that the drug may be stopped or dose modified as per the individual's needs. **Keyword:** Imatinib, Cytopenias, Marrow morphology

#### **Abstract 006**

**Modulation of redox status: synergistic anti-leukemia activity of an HDACI and PEITC.** Yumin Hu, Weiqin Lu, Gang Chen, Yu Jia, Hui Zhang, Peng Huang, Kapil Bhalla, Michael Keating and Guillermo Garcia-Manero. MD Anderson Cancer Center, USA. Email: [yuminhu@mdanderson.org](mailto:yuminhu@mdanderson.org)

Histone deacetylase inhibitors (HDACIs) including suberoylanilide hydroxamic acid (SAHA, vorinostat) have established preclinical and clinical activity in cutaneous T-cell lymphoma (CTLT) and leukemia. A recent phase 1 study suggested that vorinostat, as a single agent has modest clinical activity against human leukemia and that antioxidant gene expression may confer vorinostat resistance. The initial or acquired resistance to HDACIs, which may contribute to their limited benefit, still remains to be a major clinical concern. In present study, by using a pan-HDACI resistant acute myeloid leukemia (AML) cell model HL60/LR, we identified the antioxidant genes associated with HDACI resistance. Acute treatment of vorinostat activated a plasma membrane bound, reactive oxygen species (ROS) generating enzyme NADPH Oxidase (NOX) in various leukemia cell lines. The increase of ROS generation induced translocation of nuclear factor E2-related factor 2 (Nrf2) from cytosol to nucleus, resulting in upregulation of a series of antioxidant genes in response to the ROS stress. Importantly, a majority of these antioxidants are glutathione-associated enzymes. Addition of B-phenylethyl isothiocyanate (PEITC), a natural compound found in cruciferous vegetables and capable of depleting cellular glutathione, significantly enhanced the cytotoxicity of vorinostat in various leukemia cell lines as well as primary human leukemia cells. These results suggest that ROS plays an important role in the action of vorinostat and combination with a redox modulation compound overcomes vorinostat resistance. Such combination strategy may be an effective therapeutic regimen and have potential clinical application. **Keyword:** HDACIs, PEITC, ROS.

#### **Abstract 007**

**Distinct Clinical and Biological Characteristics in Adult AML Patients Bearing IDH1 Mutation.** Wen Chien Chou, Hwei-Fang Tien. National Taiwan University. Email: [wchou@ntu.edu.tw](mailto:wchou@ntu.edu.tw)

Mutations of NADP+-dependent isocitrate dehydrogenase gene (IDH1) have been identified in patients with gliomas. Recently, IDH1 mutation was also found to be a recurrent event in acute myeloid leukemia (AML) by genome-wide screening, but its clinical implications in AML are largely unknown. We analyzed IDH1 mutations in 493 adult Chinese AML patients in Taiwan by polymerase chain reaction and direct sequencing and found 27 patients (5.5%) harboring this mutation. IDH1 mutation was strongly associated with normal karyotype (8.8%,  $p=0.002$ ), isolated monosomy 8 ( $p=0.043$ ), NPM1 mutation ( $p<0.001$ ), and FAB M1 subtype ( $p<0.001$ ), but inversely associated with FAB M4 subtype ( $p=0.030$ ) and expression of HLA-DR, CD13 and CD14 ( $p=0.002$ ,  $0.003$ , and  $0.038$ , respectively). There was no impact of this mutation on patient survival. Sequential analysis of IDH1 mutation was performed in 130 patients during follow-ups. None of the 112 patients without IDH1 mutation at diagnosis acquired this mutation at relapse. In all 18 IDH1-mutated patients studied, the mutation disappeared in complete remission; the same mutation re-appeared in 9 of 11 samples obtained at relapse but could not be detected in the remaining 2. We then designed an allele-specific oligonucleotide (ASO) PCR method which could rapidly detect all

types of IDH1 mutation with 100% specificity and high sensitivity. By this method we detected 1 more patient with IDH1 mutation at diagnosis which was not shown by sequencing method. Moreover, all the relapsed samples from IDH1-mutated patients showed the same mutant signals as those at initial diagnosis by ASO PCR method, including the two which showed loss of the mutant by sequencing, suggesting ASO-PCR is superior to DNA sequencing in the detection of IDH1 mutation. We conclude that IDH1 mutation is associated with distinct clinical and biological characteristics in AML, and has very high stability during disease evolution. The mutation is a potential molecular marker for monitoring of minimal residual disease in IDH1-mutated patients. Keyword: AML, IDH1 mutation.

#### **Abstract 008**

**Clinical features and prognosis of patient with chromosome 5 abnormalities in Korea.** June-Won Cheong. Yonsei University College of Medicine, The Korean Society of Hematology AML/MDS Working Party. Email: [jwcheong70@yuhs.ac](mailto:jwcheong70@yuhs.ac)

**Introduction:** The myelodysplastic syndrome (MDS) associated with isolated 5q- and restricted with marrow blasts less than 5% was called '5q- syndrome'. This unique subtype of low-risk MDS with favorable prognosis is known as good responder of lenalidomide recently and occurs predominantly but not exclusively in middle age to older women in Western countries. In contrast, the patients with other abnormalities in chromosome 5 showed quite different clinical features from those with '5q- syndrome'. The aim of this study was a retrospective evaluation of clinical characteristics and prognostic impact of various factors in Korean patients with abnormalities in chromosome 5 including '5q- syndrome'. **Materials and Methods:** Among 456 patients with MDS diagnosed at 16 hospitals in Korea between 1996 and 2006, 370 patients with available cytogenetic data entered the study. Univariate and multivariate analysis including various prognostic factors were performed. **Results:** On the basis of chromosomal analysis, 93 out of 370 patients (25.1%) showed abnormalities in chromosome 5. The '5q-syndorme' was documented only in 10 patients (2.7%). The deletion of 5q was interstitial, of variable size, but with a predominance for 5q13-33 deletions (34.8%). The female predominance ( $p=0.029$ ) was documented similar to Western country. The anemia was more prominent ( $p=0.003$ ) and macrocytic ( $p<0.001$ ) in '5q- syndrome' than other MDS patients. The erythroid hypoplasia in marrow seemed to be prominent in '5q- syndrome' ( $p=0.149$ ). None of '5q- syndrome' was transformed to leukemia and overall survival was significantly better than other patients. ( $p=0.036$ ). Thirty nine patients (41.9%) had various abnormalities in chromosome other than 5q deletion such as translocation with other chromosome or 5 monosomy. They didn't share the clinical features with '5q-syndorme'. The patients with mosaic chromosomes with isolated 5q- and normal chromosome also showed different clinical outcomes with '5q- syndrome'. **Conclusions:** The incidence of '5q- syndrome' in Korea was lower than that reported in Western countries. The favorable clinical features of '5q- syndrome' were also documented in Korean patients. Patients with isolated 5q- and excess blast (>5%), other abnormalities than isolated 5q-, or mosaic chromosome with isolated 5q- and normal chromosome didn't share the clinical features such as lower rate of leukemic transformation and long survival. **Keywords:** MDS, chromosome 5, 5q- syndrome.

#### **Abstract 009**

**Outcome of consolidation blocks in paediatric acute myeloid leukemia:Tertiary care centre experience**

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**Introduction:** Paediatric AML outcome by and large is dismal, however modalities to improve outcome from time sequential multi-agent chemotherapy to now fortify consolidation blocks is evolving. **Objective:** Notwithstanding the routine practice of treating paediatric AML patients with conventional 3:7 protocol, analysis of 9 paediatric AML patients treated with a protocol(AML-BFM 98) over a period of 3 years. **Materials and Methods:** 9 paediatric AML patients, mean-age 6.5 years, male female ratio 5:4. Induction followed by consolidation blocks. AI (Idarubicin, Cytosine) and HAM (high dose mitoxantrone, cytosine), Intensification, maintenance for one year. **Results:** Out of 9 patients, 1 had early relapse and 8 completed full cycles. Mean duration of neutropenia was prolonged (18-23 days). Febrile neutropenia was managed as per NCCI guidelines. Almost all patients received SDAP 3-4 times and G-CSF was used in four patients. High risk case defined as per protocol as those cases without Auer rods and normal cytogenetics, received early intensification block and had stormy course. There was no treatment related mortality and 1 patient had CSOM persistent during maintenance. Skeletal toxicity was managed by periodic calcium supplementation. **Conclusion:** Experience though based on less number of cases yet given the outcome in majority of cases is fair enough to suggest with a good degree of confidence that at centres where

treatment related morbidity can be managed by good support and care, it is worthwhile to employ protocols having consolidation blocks for management of paediatric AML. Doing so shall contribute towards better outcome. Keyword: AML, Single donor aphaeresis

#### **Abstract 010**

##### **Glutathione S-transferase and Microsomal Epoxide Hydrolase Gene Polymorphisms and Risk of Acute myeloid Leukemia.**

Pradeep Singh Chauhan, Rakhshan Ihsan, Ashwani Kumar Mishra, Bharat Bhushan, Sumita Saluja, Mishi Kaushal, Dharendra Singh Yadav, Abha Soni, Thoudam Regina Devi, Indranil Chattopadhyay, Sunita Saxena, Sujala Kapur. INSTITUTE OF PATHOLOGY (ICMR). Email: [pradeepchauhan23@gmail.com](mailto:pradeepchauhan23@gmail.com)

Introduction: Acute myeloid leukemia (AML) is a very heterogeneous disease with regard to clinical features and acquired genetic alterations. Interindividual and interethnic variation due to environmental exposures and genetic susceptibility in metabolizing enzyme activity may be responsible for the heterogeneity in the occurrence of AML. However, the role of polymorphism of genes involved in the metabolism of drugs and xenobiotics in the occurrence of AML is equivocal. In the current study, polymorphism in GST, EPHX1 and p53 genes were analyzed to find out if their variant alleles could explain the reason for interindividual differences in leukemia risk as a result of exogenous environmental exposures. Aim: The study was done to assess any association between GSTM1, GSTT1, GSTP1, p53 codon 72 and EPHX1 (exon3 Tyr113His and exon4 His139Arg) gene polymorphisms, either separately or in combination, with the likelihood of development of the adult acute myeloid leukemia. Materials and methods: One hundred twenty consecutive adult patients (above 15 years of age) diagnosed with AML at Safdarjang Hospital, New Delhi, India and 202 healthy controls were included in the study. PCR followed by restriction fragment length polymorphism (PCR-RFLP) analysis was done for the EPHX, GSTP1 and p53 codon 72 gene polymorphism. GSTM1 and GSTT1 genotypes were identified by multiplex PCR. Data was analyzed using chi-square test and conditional logistic regression model using STATA software. Results: All the genotype frequencies were within the Hardy–Weinberg equilibrium. No differences were observed in the frequencies of GSTM1, GSTT1, GSTP1, p53 and EPHX1 genotypes between patients with AML and healthy controls. In multivariate analysis, GSTT1 null polymorphism was marginally significantly associated with the reduced risk of AML (OR 0.58 95% CI 0.32-1.05, P=0.074). Decreased risk for AML observed when various genotypic combinations were analyzed, these included GSTM1 (present), GSTP1 (Ile/Ile) and EPHX1 (His113/His113) slowest allele (0.17, 0.04-0.70, P=0.014); GSTM1 (null), GSTP1 (Ile/Ile) and EPHX1 (Tyr113/Tyr113) wild allele (0.27, 0.08-0.87, P=0.029); GSTM1 (null), GSTP1 (Ile/Ile) and EPHX1(Tyr113/His113) slow allele (0.31, 0.10-0.96, P=0.043) and GSTM1 (null), GSTP1 (Ile/Val) and EPHX1(Tyr113/His113) slow allele (0.26, 0.07-0.91, P=0.036). However, in the two risk genotype combination GSTP1 (Ile/val) and EPHX1 (His113/His113exon3) slowest allele was found to be a significant risk factor for AML patients (4.2, 0.99-17.9, P=0.051). Conclusion: Individual with specific combinations of the xenobiotic metabolizing genes might be at risk of developing AML. However, certain combination would confer a protective effect. Keywords: AML, Polymorphism, xenobiotic.

#### **Abstract 011**

##### **Outcome of Acute Promyelocytic Leukemia in Myanmar Treated with ATRA and Anthracycline Based Therapy.**

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BACKGROUND: In Myanmar, acute promyelocytic leukemia (APL) accounts for about 30% of acute myeloid leukemias (AML) in both adult and children. Although it used to be highly fatal from coagulopathy, outcome has improved since 2006 due to availability of all-trans retinoic acid (ATRA) at the Yangon General Hospital and Yangon Children's Hospital which are the main referral centers of the country for adult and children at or under 12 years respectively. METHODS: Hospital records of new APL diagnosed by FAB cytomorphologic criteria from these centers during August 2006 to July 2009 were reviewed for the outcome of treatment among Myanmar children and adults. Genetic analysis was made only for atypical cases to confirm the diagnosis. International Consortium on APL protocol (IC-APL 2006) of American Society of Hematology for developing countries was adopted for Myanmar patients in 2006 and ATRA and anthracycline (daunorubicin or mitoxantrone) have been used for induction and three consolidation courses which are followed by maintenance. Blood products were given according to general transfusion guidelines. RESULTS: During 3 year-period, a total of 103 APL (33 children and 70 adolescence and adults) with mean age of 24.8 years (range 2-69) and male:female ratio of 0.84:1 were admitted to these tertiary hospitals. Early death rate was 35.9% and even higher among adults compared to children (44% vs

18%) and 80% of adults had evidence of coagulopathy at diagnosis. Of 66 patients (27 children and 39 adults) completed induction, 55 (83.3%) achieved morphologic remission where 13 cases (33% of children and 16% of adults) abandoned treatment. There were 9 (13.6%) induction deaths from bleeding or infection and 3 (4.5%) died during consolidation. Relapse rate was 18.2% and 10 of 12 relapse were patients who discontinued maintenance. At the end of the study, 42.4% of 66 APL (33.3% of children and 48.7% of adults) receiving ATRA and anthracycline remained alive and 39.4% had survival beyond 1 year. CONCLUSION: Although survival of APL in Myanmar has improved substantially in recent years, mortality is still high due to late arrival to centers from remote areas, limitations in laboratory and transfusion support and drug supplies and high abandonment. Keywords: acute promyelocytic leukemia, ATRA and anthracycline, adult and children in Myanmar.

#### **Abstract 012**

**Flow Cytometric Analysis of Cell-Surface Ags in the diagnosis of Acute Lymphocytic Leukemia.** Himabindu Mantravad\*, Sushama Belurkar\*, Annamma Kurien\*\*. KMC, Manipal University\*, Melaka Manipal Medical College\*\*, Karnataka, India. Email: [hima002@yahoo.com](mailto:hima002@yahoo.com)

Background: The availability of flow cytometers along with extensive panel of monoclonal antibody reagents for characterizing cell lineage can be made use of to identify and sub classify acute lymphocytic leukemias (ALL). Immunophenotyping can improve the diagnostic precision and refine immunological classification, ensure the selection of the most appropriate therapy for the patients. Aim: To evaluate the usefulness of flow cytometric detection of surface antigens in establishing proper lineage affiliation and its contribution to the diagnosis of ALL. Methodology: A retrospective study of 2 years from August 2007 to August 2009 was done at Kasturba Hospital, Manipal, India to classify ALL based on their surface antigens by flow cytometry. During this period, 34 patients with age ranging from 2 to 89 years were diagnosed as ALL based on morphology. Flow cytometry was done following the standard Lyse wash method for these cases and they were further sub classified based on their surface antigens. Result: Among 34 cases we found 22 B cell lineage ALL, 5 T cell lineage ALL, 6 CALLA + ALL and 1 mixed lineage leukemia. We found that CD19/ CD10, CD3/ CD7 were very sensitive B and T cell markers respectively that were expressed in virtually all cases of B and T cell ALLs. Immunophenotyping led to improvement in diagnostic precision and refinement of immunological classification, ensuring the selection of the most appropriate therapy for the patients studied. Conclusion: Results from this study indicate that cell surface Ags detection was of utmost importance in establishing correct lineage affiliation in cases with equivocal or ambiguous morphologic features and in identifying biphenotypic acute leukemia. In combination with morphology and immunophenotyping, we were able to reliably classify all patients with ALL in our study. Keywords: Flow cytometer, Immunophenotyping, acute lymphocytic leukemia

#### **Abstract 013**

**DZNep, a Polycomb Repressive Complex 2 inhibitor, targets leukemia maintenance in acute myeloid leukemia.** Jianbiao Zhou\*, Chonglei Bi, Kian-Ghee Tay, Shaw-Cheng Liu, Tze-Loong Koh, Qiang Yu\*\*, Wee-Joo Chng\*\*\*. Cancer Science Institute of Singapore\*, National University of Singapore; Genome Institute of Singapore\*\*, Department of Medicine, NUS, Singapore. Email: [csizjb@nus.edu.sg](mailto:csizjb@nus.edu.sg)

Changes of DNA methylation and histone modifications are the landscape of cancer epigenome. Particularly, trimethylation of lysine 27 of histone H3 (H3K27me3) is believed to be a robust, long term repressive chromatin mark. H3K27me3 is mediated by Polycomb Repressive Complex 2 (PRC2), which contains Suz12, EED and EZH2. S-adenosylhomocysteine hydrolase inhibitor 3-Deazaneplanocine A (DZNep) has recently been identified as the first EZH2 inhibitor in breast and colon cancer. Here, we first tested the potential anti-leukemic effect of DZNep. According to the sensitivity to DZNep treatment at 5 microM, MV4-11 and MOLM-14 were very sensitive (>40% of apoptosis). Mono-Mac-1 and TF-1 showed moderate response (>15%, but <40% apoptosis). THP-1 and KG-1 were resistant to DZNep (<10% apoptosis). Combination of HDAC inhibitor, trichostatin A (TSA) and DZNep induced remarkable greater killing of Mono-Mac-1 and THP-1 cells, than the additive effect of single agent. These results suggest a potential powerful treatment for AML by using DZNep in combination with HDACi. FACS analysis of CD11b, a common differentiation mark expressing on granulocytes, was gradually increased after treatment. NBT reducing activity was also dose-dependently increased among the cells treated with DZNep as compared to DMSO control (p< 0.05). Methylcellulose-based colony assay revealed that treatment with DZNep at 0.5 microM, 1 microM and 2 microM decreased the number of AML-CFU7s 72%, 55% and 22% respectively, but minimally inhibited the colony formation of normal samples This differential effect provides the opportunity for DZNep

specifically target LSC, while potentially spare normal HSC. DZNep treatment induced expression a set of well-defined markers of myeloid cell differentiation, including MPEG1, CD86, AMICA1, CTSK, CD93, CNR2, and CD36. Furthermore, TXNIP (thioredoxin interacting protein), a tumor suppressor gene identified in breast cancers, was increased. We validated that DZNep dose-dependently elevated the expression of TXNIP on protein level. Interestingly, microarray analysis also revealed the increasing expression of microRNA 155. DZNep inhibited progression of MOLM-14 tumor xenografts in mice and prolonged survival in a bone marrow engraftment model of leukemia. FACS analysis showed CD11b positive cells were significantly higher in DZNep treated mice than in vehicle controls. Furthermore, Wright-Giemas staining of blood smears showed MOLM-14 cells in the vehicle controls were round and large, with a higher ratio of nuclei/cytoplasm. Their cytoplasm were less light blue and nuclei were round. While, MOLM-14 cells in the DZNep treated group became smaller with less ratio of nuclei/cytoplasm. These morphological changes of MOLM-14 cells, together with the FACS analysis of CD11b, between these two groups clearly support that DZNep could induce leukemia cell differentiation in vivo. Herein, we reported the potent efficacy of DZNep to induce AML cell apoptosis and differentiation in vitro and in vivo. DZNep differentially inhibited LSC and normal HSC. Combination of TSA and DZNep achieved synergistically anti-leukemia effect. These results support the further development of DZNep in treatment of AML alone or in combination with other novel small molecule inhibitors or chemotherapy. Keyword: EZH2, epigenetic therapy, AML

#### **Abstract 014**

**INFECTIONS ENCOUNTERED DURING MANAGEMENT OF ACUTE LEUKEMIA PATIENTS IN A GENERAL WARD IN EAST INDIA.** Uttam Kumar Nath, Prantar Chakrabarti, Bhaskar Narayan Chaudhuri, Siddhartha Sankar Ray, Rajib De, Ganesh Jaishetwar, Utpal Chaudhuri. Institute of Haematology & Transfusion Medicine, Kolkata, India. Email: [prantar@gmail.com](mailto:prantar@gmail.com)

**BACKGROUND:** Bacterial infections are a major cause of morbidity and mortality in patients with acute leukemia, due to disease-related and/or chemotherapy-induced neutropenia. We work in an institute which is a referral center for benign and malignant hematological disorders in the setting of a tertiary care hospital in Kolkata. Patients with acute leukemias constitute approximately 75% of the total admissions and they are managed in the general ward with no isolation rooms or HEPA filters. All episodes of fever are considered to be due to infection, unless proved otherwise and blood cultures are sent routinely at the onset of fever and repeated as and when necessary. The central venous catheter tip is also sent for bacterial culture when it is removed, if indicated. **METHODS:** We analyzed data on all acute leukemia inpatients managed between 1st August 2008 and 30th November 2009. Rapid culture by BacT/Alert 3D system (Biomérieux) was performed in all samples. Empiric antimicrobial therapy was initiated with cefoperazone + sulbactam / piperacillin+tazobactam / ceftazidime / cefepime, in combination with amikacin as first line therapy and modified if the patient deteriorated or the culture report mandated the change of antimicrobials. The second line gram-negative coverage used was imipenem+cilastatin / meropenem, with/without netilmicin, aztreonam. The gram-positive coverage added to the first line empiric antibiotic therapy was teicoplanin, vancomycin, or linezolid. Metronidazole and clindamycin were used for anaerobic coverage when indicated. The antifungals used as empiric/preemptive antifungal therapy were amphotericin B and voriconazole. Antibiotic prophylaxis with levofloxacin for all neutropenic patients was routinely prescribed, and patients with acute lymphoblastic leukemia (ALL) received cotrimoxazole for prophylaxis against *Pneumocystis jirovecii*. **RESULTS:** A total of 202 blood cultures were sent during the above period, and bacterial isolates were documented in 63 cases (31.2%). Gram negative organisms constituted 61% (38/63) and Gram positive organisms 39% (25/63). Gram positive isolates were *Staphylococcus* (both *Staphylococcus aureus* and coagulase negative staphylococcus) in 84% cases. There were more Methicillin-resistant (MRSA) strains (53%) than Methicillin-sensitive (MSSA). Sixty seven percent of the Coagulase negative *Staphylococci* were methicillin-sensitive. The remaining 16% of Gram positive isolates were Enterococci sensitive to Vancomycin. *Pseudomonas aeruginosa* was the commonest Gram negative isolate (31%), followed by *Escherichia coli* (18%), *Klebsiella pneumoniae* (13%) and *Acinetobacter baumannii* (13%). Enterobacter species was isolated during two episodes, and *Proteus mirabilis* was isolated in 1 episode. Majority of the Enterobacteriaceae (83% isolates) demonstrated Extended Spectrum Beta Lactamase (ESBL) activity. Alarming, multidrug-resistant *Pseudomonas aeruginosa*, sensitive only to Polymyxin B and Colistin, was isolated from a terminal patient with relapsed ALL. *Stenotrophomonas maltophilia* was grown from CVC blood sample culture in 7 consecutive patients with febrile neutropenia over a period of 2 weeks, in January 2009. **CONCLUSION:** Hematologists face a daunting task in

managing acute leukemia patients in resource limited settings with severe multidrug resistant bacterial infections being the rule rather than an exception. Keywords: bacterial infections, febrile neutropenia, acute leukemia

#### **Abstract 015**

##### **Safety and efficacy of ATRA and Arsenic trioxide combination therapy in acute promyelocytic leukemia.**

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Acute promyelocytic leukemia (APL) is now considered as a curable disease. The standard therapy consists of all trans retinoic acid (ATRA) along with an anthracycline with or without cytarabine. The relapse/resistance rates have been in the range of 20-30%. Almost similar success and relapse rates have been seen with single agent arsenic trioxide (ATO). Combination of ATRA with ATO as first line therapy is an attractive treatment options in APL. Both drugs have distinct action on degradation of PML RAR alpha and thus act synergistically. Methods: All newly diagnosed patients with APL were given the option of combination of ATRA and ATO as first line therapy. This therapy was also used in those patients who had poor performance status and also did not give consent for standard chemotherapy. The diagnosis of APL was made by bone marrow examination and PPML RAR alpha detection by RT PCR. ATRA was used in the dose of 25 mg/m<sup>2</sup> (45 mg/m<sup>2</sup> in two patients with therapy related APL) and ATO in the dose of 0.15mg/kg/day until complete hematological remission. Patients were given consolidation with the same therapy after a drug free interval of 4-weeks after bone marrow remission. Consolidation therapy consists of 28 injections of ATO, 5 days per week and ATRA for 6-weeks. A total of 3 consolidation therapies were given each after a gap of one month. Subsequently after documentation of molecular remission, patients were put on maintenance chemotherapy consisting of intermittent ATRA 15 days every 3 monthly, 6-mercaptopurine 50 mg/m<sup>2</sup> daily and methotrexate 20 mg/m<sup>2</sup> weekly for 2-years. RT PCR for PML RAR alpha was done after successful induction, after completion of consolidation and yearly during maintenance therapy. Results: From December 2005 till August 2009, 16 patients (10 males, 6 females) were offered treatment with combination of ATRA and ATO. The median age of the patients was 32.5 years (range 14-70 years). The presenting complaints of the patients were low-grade fever and fatigue with median symptom duration of 25.5 days (range 2-90 days). Baseline median hemoglobin value was 6.7 gm/dl (range 3-12.4 gm/dl). Half of patients had white cell count of more than 10,000 and 94% patients had platelet count of less than 40,000 at presentation. Coagulopathy was present in 63% patients. Out of 16, 14 patients opted for treatment with ATRA and ATO. All patients achieved hematological remission with a median time to bone marrow remission of 56 days (range 27-80 days). One patient died in hematological remission due to undiagnosed central nervous system infection. ATRA syndrome developed in 25% of patients and was managed with injectable dexamethasone. ATRA scrotal vasculitis developed in 2 patients and was managed with temporary interruption of ATRA. No grade III-IV toxicity developed on cardiac or liver functions in any of the patients during entire course. One patient abandoned the treatment after successful induction and he is still in hematological remission. One patient abandoned the treatment after consolidation and she is also in hematological remission. One patient developed hematological relapse during second year of maintenance therapy. Remaining 10 patients are in molecular remission at a median follow-up duration of 14 months (range 4-55 months). Conclusions: Combination of ATRA and ATO produces high rates of successful induction in APL. The therapy is well tolerated without any major side effects. This therapy requires further evaluation in a randomized trial. Keyword: ATRA and Arsenic trioxide, Acute promyelocytic leukemia, combination therapy

#### **Abstract 016**

##### **EFFECT OF IMATINIB ON PLATELET FUNCTION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA.**

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Introduction: Imatinib, an inhibitor of BCR-ABL tyrosine kinase has become the standard-of-care for upfront therapy in chronic myeloid leukemia (CML). Though Imatinib has revolutionized the management of CML and it is well tolerated by most of the patients, it is not entirely free of adverse effects. A number of well known adverse effects are related to Imatinib, like cytopenia, fluid retention, myalgia, GI disturbances. Sometimes, patients on Imatinib complain of bleeding manifestations, which are mostly related to the degree of thrombocytopenia. However, a minority of patients with normal platelet counts show abnormalities in platelet function, which may or may not be related to bleeding manifestations. In this study, we tried to analyze the effects of Imatinib on platelet

function in patients with CML. Materials and Methods: We studied 28 consecutive CML patients on Imatinib therapy and analyzed their platelet function with collagen, ADP, and epinephrine. The median duration of Imatinib therapy before the test was performed was 154 days. We studied their platelet function by chronolog aggregometer and analyzed the results. Although the lowest cut off of aggregation is different with different reagents and instruments, as a convention, we fixed 60% as the lowest cut off for aggregation with different agonists. Result: 18 patients out of 28 (64%) showed altered platelet function. This was consistent with previous findings. Interestingly, those who showed lower than 60% aggregation with ADP, also showed lower aggregation with Collagen. Though ADP (10 uM) induced reduced aggregation, it did not show any deaggregation pattern. No patient recruited in this study with defective platelet aggregation demonstrated with ADP had any history of bleeding manifestations. Only one patient with reduced platelet aggregation demonstrated with collagen and one with both collagen and epinephrine showed bleeding manifestations. As ADP and epinephrine are known to be synergistically coupled and so also epinephrine and collagen, there is a theoretical possibility of an indirect dependency of collagen on ADP induced aggregation. In our study, the patients showing lower aggregation with ADP also showed similar results with collagen confirming the possibility of the collagen ADP dependency. The reduced aggregation by ADP was not followed by any further deaggregation phase and hence, although the thrombus formation was reduced, it was a stable thrombus. This may be the probable cause of reduced bleeding manifestations in patients with altered platelet function on Imatinib therapy. Conclusion: Imatinib can impair platelet function which might not always manifest clinically. Clinicians should carefully follow up their patients in this regard. Keyword: platelet function, chronic myeloid leukemia, imatinib

#### **Abstract 017**

**Acute Biphenotypic Leukemia: A comparison of WHO versus EGIL.** Dass J\*, Dhingra B, Anand H, Rathod N, Pati HP, Mahapatra M, Saxena R. All India Institute of Medical Sciences, New Delhi, India. Email: [drjasmita@gmail.com](mailto:drjasmita@gmail.com)  
Introduction: Acute biphenotypic leukemias (BL)/ Mixed Phenotype acute leukemia (MPAL) are relatively uncommon and constitute <4% of all acute leukemias. They are diagnosed by the EGIL score and are further classified into acute bilineage and acute biphenotypic leukemia depending upon the cell populations expressing various immunophenotypic markers. However, the new WHO2008 classification has introduced a new terminology 'Mixed Phenotype Acute Leukemia' for these cases and redefined the criteria for their diagnosis. Materials and Methods: 270 cases of acute leukemias were diagnosed between January 2009 and November 2009. Till May2009, BL were diagnosed by the EGIL criteria and June onwards, the WHO2008 criteria were applied. A total of nineteen cases diagnosed as BL/MPAL were reviewed. To compare the two classifications all these cases were reviewed by application of both WHO and EGIL criteria. The results were compared. Results: The incidence of BL/MPAL was observed to be 7%. Out of these 19 cases diagnosed as BL/MPAL, 13 cases were diagnosed as MPAL by both the criteria. Six cases diagnosed as BL according to EGIL criteria did not fit into the WHO criteria for MPAL. Following the application of WHO criteria to all the cases, the incidence of MPAL in the studied cases was observed to be 4.8%. Conclusions: The incidence of MPAL at our institution diagnosed with the recent WHO criteria is in accordance with the reported incidence worldwide. The application of WHO criteria is an improvement over the old EGIL criteria for diagnosis of MPAL as it has therapeutic and prognostic relevance. Keyword: biphenotypic leukemia, EGIL, MPAL

#### **Abstract 018**

**HIGH ACTIVITY OF OFATUMUMAB WITH FLUDARABINE AND CYCLOPHOSPHAMIDE IN UNTREATED CLL: PHASE II TRIAL.** William Wierda\*, Thomas Kipps\*\*, Jan Dürig\*\*\*. M.D. Anderson Cancer Center, USA; UCSD Moores Cancer Center, La Jolla, USA, Klinik für Hämatologie Huflandstr Universitätsklinikum Essen, Germany. Email: [wwierda@mdanderson.org](mailto:wwierda@mdanderson.org)

Introduction: Chemoimmunotherapy with CD20 monoclonal antibody (mAb) is an effective frontline treatment for fit patients with chronic lymphocytic leukemia (CLL). Ofatumumab is a human mAb that binds a unique epitope encompassing both the large- and small-loop on CD20. The recent international pivotal study of single-agent ofatumumab demonstrated high overall response rates (ORR) in fludarabine-refractory CLL. We conducted an international, randomized, parallel-group, Phase II trial with two doses of ofatumumab combined with fludarabine and cyclophosphamide (O-FC) in patients with CLL; efficacy and safety were evaluated. Methods: Previously untreated patients (N=61) with active CLL (NCI-WG criterion) were randomized to ofatumumab 500 (Group A) or 1000 mg (Group B) on Day 1, combined with fludarabine (F) and cyclophosphamide (C) (25 and 250 mg/m squared

intravenously daily, respectively; Days 2–4 Course 1, Days 1–3 Courses 2–6) every 4 weeks for 6 courses; first ofatumumab dose was 300 mg (both groups). Dose reduction was allowed for FC only. Premedication for ofatumumab was paracetamol and antihistamine prior to each infusion and glucocorticoid prior to infusions 1 and 2. Growth factors and anti-infective prophylaxis were not mandated. Primary endpoint was complete response (CR) rate (1996 NCI-WG criteria) in each group, measured from start of treatment until 3 months after the last infusion, and evaluated by an Independent Review Committee. Safety evaluations included investigator-reported adverse events (AEs) and deaths. Follow-up continues for time-to-event endpoints. Results: Pretreatment characteristics were as follows: median age 56 years (range, 38–73); Rai stage III–IV in 46%; bulky (>5 cm) lymph nodes in 16%; median serum  $\beta$ 2-microglobulin level 4 mg/L (range, 1.8–11.5); median ALC  $89 \times 10^9/L$  (range, 3–307); 17p del in 13%; 11q del in 16%; unmutated IGHV in 41%. CR rate was 32% for Group A and 50% for Group B; ORR was 77 and 73%, respectively. Overall, 64% of patients received all 6 courses of O-FC; CR rate and ORR among these patients was 55% and 92%, respectively. Median progression-free and overall survival have not been reached with the short median follow-up of 8 months. All infusion-related reactions on day of ofatumumab infusion were grade 1–2 events. During treatment until 30 days following last dose, most common (>10% of patients) grade 3–4 AEs assessed by investigators were infections (n=11) including febrile neutropenia (n=6), and hematologic AEs including neutropenia (n=29), anemia (n=8) and thrombocytopenia (n=9); Grade 3–4 hemolytic anemia was reported in 3 patients (Group A, n=2; Group B, n=1). In Group A, a patient died 50 days from last dose during follow-up (febrile neutropenia). In Group B, a patient died 19 days from last dose during treatment (dyspnea; etiology unknown) and another patient died 186 days from last dose (neutropenia following alternative treatment for progressive CLL). Conclusions: The O-FC regimen is highly active in previously untreated CLL and may offer a new chemoimmunotherapy option. The AEs were manageable with no unexpected toxicities. The 1000 mg ofatumumab dose is currently being evaluated in combination with chemotherapy in other studies for patients with CLL. Keyword: ofatumumab, chronic lymphocytic leukemia, untreated patients.

#### **Abstract 019**

#### **HIGH RESPONSE RATES WITH OFATUMUMAB IN FLUDARABINE-REFRACTORY CHRONIC LYMPHOCYTIC**

**LEUKEMIA.** William Wierda, Anders Österborg, Thomas Kipps. MD Anderson Cancer Center\*, USA; Karolinska University Hospital\*\*, Stockholm, Sweden; UCSD Moores Cancer Center\*\*\*, La Jolla, CA, USA. Email: [wwierda@mdanderson.org](mailto:wwierda@mdanderson.org)

Background: Patients with fludarabine-refractory chronic lymphocytic leukemia (CLL) who are also refractory to alemtuzumab (FA-ref) or less suitable for alemtuzumab due to bulky (>5 cm) lymphadenopathy (BF-ref) have poor outcomes with available salvage regimens (overall response rate [ORR] 23%; median overall survival [OS] 9 months [1]). Ofatumumab is a new human monoclonal antibody that binds a distinct epitope encompassing both the large- and small-loop on the CD20 molecule, close to the cell membrane. Ofatumumab has been shown to induce rapid and efficient killing of B cells through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. We report results of the planned interim analysis of an international pivotal trial of ofatumumab in patients with FA-ref and BF-ref CLL, including outcomes by prior rituximab (RTX) exposure.

Methods: Patients received 8 weekly infusions of ofatumumab followed by 4 monthly infusions (Dose 1, 300 mg; Doses 2–12, 2000 mg). The primary endpoint was ORR (1996 NCI-WG criteria) over the 24-week treatment period assessed by an Independent Review Committee (IRC). Secondary endpoints included progression-free survival (PFS), OS and adverse events (AEs).

Results: In 59 patients with FA-ref, the ORR was 58%; median PFS and OS were 5.7 and 13.7 months, respectively. In 79 patients with BF-ref CLL, the ORR was 47%; median PFS and OS were 5.9 and 15.4 months, respectively. In addition to NCI-WG responses, improvements (maintained for  $\geq$ 2 months) in disease-related symptoms, physical findings and blood parameters were observed in a large proportion of patients. Both ORR and median PFS were similar in the prior RTX and no prior RTX subgroups (Table). In FA-ref and BF-ref patients refractory to fludarabine in combination with RTX and cyclophosphamide (n=16 in each group), ORR was 50 and 44%, respectively. Infusions were well tolerated; transient grade 1 or 2 infusion-related reactions occurred in approximately 60% of patients, which subsided during the course of treatment. The most common grade 3 or 4 AEs (occurring between first infusion and up to 30 days after last infusion) reported by investigators to be related to ofatumumab were infections (FA-ref, 12%; BF-ref, 8%) and neutropenia (FA-ref, 14%; BF-ref, 6%). Conclusions: Single-agent ofatumumab shows high ORR and improves disease-related symptoms and physical findings with a favorable safety profile in heavily pretreated patients with FA-ref and BF-ref CLL. Importantly, ofatumumab was effective in

the majority of patients previously treated with RTX, particularly in RTX-refractory patients. 1. Tam C, et al. Leuk Lymphoma. 2007;Oct;48(10):1931–1939. Keyword: Ofatumumab, chronic lymphocytic leukemia, fludarabine-refractory

<b>Table. Efficacy outcomes by prior RTX exposure</b>						
<b>Prior RTX</b>	<b>FA-ref (N=59)</b>			<b>BF-ref (N=79)</b>		
	<b>N</b>	<b>ORR, % (95% CI)</b>	<b>Median PFS, mo (95% CI)</b>	<b>N</b>	<b>ORR, % (95% CI)</b>	<b>Median PFS, mo (95% CI)</b>
<b>Any prior RTX*</b>	35	54 (37, 71)	5.5 (3.7, 8.0)	43	44 (29, 60)	5.5 (3.8, 6.4)
FCR <sup>†</sup>	16	50 (25, 75)	4.6 (2.3, 6.4)	16	44 (20, 70)	5.6 (2.1, 6.6)
<b>No prior RTX</b>	24	63 (41, 81)	7.1 (4.8, 8.7)	36	50 (33, 67)	6.4 (4.0, 8.0)

\*Patients received one or more prior RTX-containing regimen at any time before study entry; includes patients who received FCR; <sup>†</sup>Patients refractory to fludarabine in combination with RTX and cyclophosphamide (FCR), with or without mitoxantrone, as qualifying therapy

## Lymphoma

### Abstract 020

**CLINICOPATHOLOGICAL CHARECTERESTICS OF T CELL NON HODGKIN'S LYMPHOMA – OUR EXPERIENCE OVER 1 YEAR.** Anup J Devasia, Syed Nazarulla, Cecil Ross, Rekha Pradeep. Institution: St Johns Medical College, Banglore, India. Email: [dranupjdevasia@gmail.com](mailto:dranupjdevasia@gmail.com)

**INTRODUCTION** T cell NHL is a relatively uncommon malignancy, accounting for approximately 12% of lymphomas. Although its incidence is higher in Asia, its clinical course, presentation and prognostication in South India is not well defined. **METHODS** We performed an analysis of consecutive cases of T cell NHLs diagnosed and treated in the department of Medicine & Haematology at our tertiary care centre for the last 1 year. **RESULTS** There were a total of 47 NHLs, out of which 14 cases (30%) were T cell NHL. The mean age at diagnosis was 35.79 with a male predisposition. The most common histopathological variant was Peripheral T cell lymphoma- unclassified(n=10), while there were 2 cases of Anaplastic large T cell lymphoma and one each of cutaneous T cell lymphoma and extra nodal T cell lymphoma. 10 patients completed 6 cycles of CHOP, out of which 5 showed a favourable initial response. 2 patients developed CNS relapse and one developed ALL. **DISCUSSION** T Cell NHL is not uncommon in India and is an aggressive disease with widespread dissemination. The initial response was favourable among 50% of patients who had completed the initial cycle of chemotherapy. Our results indicate the need for large scale studies with long term follow up in Indians with T cell NHL. Keyword: lymphoma, response, relapse

### Abstract 021

**Multicenter phase II study of the rituximab-CycLOBEAP in diffuse large B-cell lymphoma with analysis.**

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Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma, accounting for approximately 30% of all new patients. The addition of rituximab to CHOP regimen has been found to improve the outcome of DLBCL. However, it dose not provide a satisfactory treatment outcome in the high-risk group according

to the international prognostic index (IPI). We administered the CycLOBEAP (cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin, prednisolone) regimen to patients with DLBCL, and previously reported its safety and efficacy. The CycLOBEAP regimen was administered over a total period of 12 weeks, in which the dose intensities of cyclophosphamide, doxorubicin, and vincristine are equal to or higher than those in the CHOP regimen, and bleomycin were added to the CHOP regimen. The results showed that 106 (80%) of the 121 patients achieved complete response (CR), the 5-year overall survival (OS) rate was 72%, and the 5-year progression-free survival (PFS) rate was 62%. Therefore, relatively good results were obtained. Here, we report the results of a multicenter phase II study of the R-CycLOBEAP regimen. This was a prospective, single-arm phase II trial in the Adult Lymphoma Treatment Study Group (ALTSG) in Japan. Patients were enrolled in the study between April 2004 and March 2008. Patients aged between 15 and 60 years who were in the low-intermediate, high-intermediate, or high risk groups, were eligible for this study. The CycLOBEAP regimen was administered over a total period of 12 weeks. Rituximab 375mg/m<sup>2</sup> was given every 2 weeks. There were 101 eligible patients. A CR was achieved in 96 patients (95%). The 5-year OS rate was 85% and PFS rate was 76%. When the patients were divided according to the IPI or revised IPI, the 5-year OS and PFS rates did not significantly differ among the risk groups. We next examined survival curve of the patients with DLBCL in whom soluble interleukin-2 receptor data were available. The 5-year survival rates for the high (>2000 IU/ml) and low soluble interleukin-2 receptor groups (<2000 IU/ml) were 60 and 94%, respectively, with PFS values of 64 and 81%. Lymphoma tissue was analyzed by immunohistochemistry for biomarkers of CD5, CD10, BCL2, BCL6, MUM1, and nm23-H1. CD5, CD10, BCL2, BCL6, and MUM-1 had no prognostic impact with R-CycLOBEAP. As for nm23-H1 expression in DLBCL in the present study, the 5-year OS of the nm23-H1-positive group was 65% and that of the nm23-H1-negative group was 97%, indicating that the nm23-H1-positive group showed significantly poorer prognosis. The 5-year PFS of the germinal center B-cell (GCB) group was 80% and that of the non-GCB group was 74%, showing no significant difference. Univariate analysis showed that the stage, presence of B symptoms, number of extranodal lesions, and soluble interleukin-2 receptor were significant prognostic factors, and in multivariate analysis, the soluble interleukin-2 receptor was a significant independent prognostic factor. Grade 4 neutropenia was observed in 91 patients and thrombocytopenia in 9 patients. The addition of rituximab to CycLOBEAP therapy may enhance the effect of CycLOBEAP therapy for DLBCL. Keyword: diffuse large B-cell lymphoma, rituximab-CycLOBEAP, nm23

#### **Abstract 022**

**Activation of Multiple Oncogenic Pathways in Natural Killer / T-cell Lymphoma.** Siok-Bian Ng, Viknesvaran Selvarajan, Gaofeng Huang, Jianbiao Zhou, Mark Law, Andrew Feldman, Manual Salto-Tellez, Wee-Joo Chng. National University Health System, Singapore. Email: [siok\\_bian\\_ng@nuhs.edu.sg](mailto:siok_bian_ng@nuhs.edu.sg)

Extranodal nasal-type Natural Killer/T-cell lymphoma (NKTCL) is a distinct clinicopathologic entity most commonly affecting Asians and Central and South Americans, and characterized by a clonal proliferation of NK or T cells with a cytotoxic phenotype. There is a strong association with Epstein-Barr Virus. The tumor is aggressive with patient usually surviving short duration even with chemotherapy. We performed the first comprehensive genome-wide gene expression profiling (GEP) of extranodal nasal-type Natural Killer/T-cell lymphoma (NKTCL) using formalin-fixed paraffin embedded (FFPE) tissue (n=25) and NK cell lines (n=5) and compared the results to the GEP of normal NK cells using the Illumina DASL whole genome array, with the objective of understanding the oncogenic pathways involved in the pathogenesis of NKTCL and to identify potential therapeutic targets. Quantitative-PCR validation of the GEP findings revealed over-expression of candidate genes BIRC5 (survivin), EZH2 and STMN1 in NK cell lines compared to normal NK cells, consistent with the GEP data. We then extracted a list of genes that are differentially expressed between NKTCL and normal NK cells and tissue controls. We then subjected this list of genes to pathway and network analysis using Metacore. This revealed a significant enrichment for cell cycle related genes and pathways. Furthermore, the network analysis results demonstrated a pro-proliferative and anti-apoptotic phenotype in NKTCL characterized by activation of Myc and nuclear factor kappa B (NF-KB), and deregulation of p53. This was further corroborated using immunohistochemistry on tissue microarray of NKTCL (n=33, including all cases with GEP performed). We observed a significant percentage of NKTCL showing overexpression for c-Myc (45.4%), p53 (87.9%) and NF-KB p50 (67.7%) on immunohistochemistry. Notably, overexpression of survivin was observed in 97% of the cases. Based on our findings, we propose a model of NKTCL pathogenesis where deregulation of p53 together with activation of MYC and NF-KB, possibly driven by EBV LMP-1, result in the cumulative upregulation of survivin. When KHYG and NKYS cell lines were treated with a compound IDR E804 which inhibited survivin, there is significant inhibition of cell growth as assessed by MTS assay and induction

of apoptosis as measured using Annexin V staining by flow cytometry. This suggests that compounds inhibiting survivin may be a potentially useful novel therapeutic approach in NKTCL. Keyword: Survivin, MYC, NFkB, p53, Natural Killer / T-cell lymphoma

#### **Abstract 023**

##### **Bendamustine in the treatment of relapsed / refractory lymphoid malignancies: The SGH's Experience**

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Background : Indolent lymphoid malignancies are generally incurable and run a remitting/ relapsing course. Patients will eventually succumb to these diseases and new therapies are needed to improve the clinical outcomes of these patients. Bendamustine (B) is a purine analog/alkylator hybrid that has demonstrated clinical activity in relapsed indolent non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) patients. It has yet to be registered in South-East Asia. Aim : We sought to evaluate our initial experience in using B in our patients and assess the associated efficacy and toxicity. Clinical characteristics including patient's age, histological diagnosis, number of prior treatments, total cycles of treatment with B and the adverse effects with B were analyzed. Patients and methods: Patients with relapsed/refractory lymphoid malignancy after at least 1 prior treatment were included. Bendamustine is used as single agent or in combination with other agents. Results: We identified 7 treated patients (2 CLL, 2 mantle cell lymphoma, 1 MM and 1 marginal zone lymphoma) who have been treated with B salvage regimes. B is dosed at 90mg/m<sup>2</sup> in all patients. The most frequently used regime is Rituximab plus B. The median age of patients is 62 years (range 44-72) . The median number of prior therapies is 3 cycles (range 1-7). Three patients are still receiving ongoing B treatment. Six patients have shown response to initial treatment after 2 cycles, with 1 patient achieving a complete response so far. The patient with MM unfortunately succumbed to severe tumor lysis syndrome and hence his response could not be ascertained. The median duration of hospitalization for B treatment so far is 3 days. The most common adverse events are neutropaenia (40%) and thrombocytopenia (60%). However these were mild and there was no morbidity recorded due to the toxicity. Conclusion : Our experience with B is encouraging. This is consistent with the newly published data. Patients with multiply relapses are showing good responses to treatment, independently of the underlying histology. B is well tolerated and highly effective in this cohort of Asian patients. Updated data will be presented at the meeting. Keyword: Bendamustine; relapse/ refractory lymphoid malignancy

#### **Multiple Myeloma**

#### **Abstract 024**

**Sequential VAD (vincristine, adriamycin, dexamethasone) and VTD (bortezomib, thalidomide, dexamethasone in newly diagnosed multiple myeloma.** Sung-Soo Yoon\*, Hye-Jin Kim\*\*, Jae-Hoon Lee\*\*\*. Seoul National University Hospital\*, Seoul Bohun Hospital\*\*, Gachon University Gil Hospital\*\*\*. Email: [ssysmc@snu.ac.kr](mailto:ssysmc@snu.ac.kr)

Background: Incorporation of novel agents has resulted in improved response rate and reduced side effect in multiple myeloma. It suggested the possibility as induction chemotherapy in newly diagnosed multiple myeloma. Methods: Patients are planned to receive 2 cycles of VAD (vincristine 0.4mg D1-4, adriamycin 9mg/m<sup>2</sup> D1-4, dexamethasone 40mg D1-4, 9-12 every 3 weeks), and VTD (bortezomib 1.3mg/m<sup>2</sup> D1, 4, 8, 11, thalidomide 100mg daily, dexamethasone 40mg D1-4, 9-12 every 3 weeks). High dose melphalan (200mg/m<sup>2</sup>) is used as a conditioning regimen for ASCT. Bortezomib (1.3mg/m<sup>2</sup>) as a maintenance treatment is administered weekly x 4 times every 6 weeks for 4 cycles after ASCT. Response was assessed by the International Myeloma Working Group uniform response criteria with additional category of near CR. Adverse events were graded by the NCI-CTCAE, Version 3.0. Results: Total 71 patients were enrolled, and efficacy could be assessed in 59 patients. After 2 cycles of VAD, RR was 67.8%. After VTD, RR was more increased with 96.6% (CR and near CR 27.1%). Especially, 7 patients with poor prognostic cytogenetics all responded after VTD. So far, autologous stem cells were successfully collected in all 42 patients with a median CD34+ count of 6.49x10<sup>6</sup>/kg (range, 0.6-44.7x10<sup>6</sup>/kg) except one patient. After autologous stem cell transplantation (ASCT), 30 patients completed bortezomib maintenance, and rate of CR and near CR was 70%. The median follow-up duration was 34.6 months, and median time to response was 1.6 months. Median TTP and OS were not reached. Grade 3, 4 hematological toxicities were not increased after VTD (anemia 3.2%, neutropenia 4.8%, and thrombocytopenia 1.6%), and incidence of grade 3 peripheral neuropathy after VAD was lower (1.4%) than VTD (6.4%). After low-dose aspirin prophylaxis, grade 3 deep vein thrombosis was observed in

one patient, but it was not related with thalidomide. Conclusions: The sequential VAD and VTD induction therapy in newly diagnosed multiple myeloma was effective, even in patients with poor prognostic cytogenetics with tolerable toxicity profiles, and it did not prejudice stem cell collection. VTD could have contributed to increased RR and minimized side effects as an induction therapy. Keyword: myeloma, velcade, transplantation

#### **Abstract 025**

**Suppression of Alox5 gene is involved in DZNep induced apoptosis in multiple myeloma cells.** Zhigang Xie, Chonglei Bi, Lip Lee Cheong, Shaw Cheng Liu, Jianbiao Zhou, Qiang Yu, Wee Joo Chng

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The 3-Deazaneplanocin A (DZNep), one of S-adenosylhomocysteine (AdoHcy) hydrolase inhibitors, has shown antitumor activities in a broad range of solid tumors and acute myeloid leukemia. It was found that DZNep effectively depletes EZH2 levels and inhibits trimethylation of lysine 27 on histone H3. Here, we examined its effects on multiple myeloma (MM) cells and found that, at 500 nM, it potently inhibited growth and induced apoptosis in 2 of 8 MM cell lines (8226, H929, KMS11, KMS12BM, KMS18, MM1S, OPM-2 and U266). We then attempted to identify molecular mechanisms of sensitivity to DZNep. RNA from un-treated and DZNep treated cells was profiled by Affymetrix HG-U133 Plus 2.0 microarray and genes with a significant change in gene expression were determined by significance analysis of microarray (SAM) testing. ALOX5 was the most down-regulated gene (5.8-fold) in sensitive cells and was expressed at low level in resistant cells. The results were corroborated by qRT-PCR. Western-blot analysis indicated ALOX5 was highly expressed only in sensitive cell line H929 and greatly decreased upon DZNep treatment. Furthermore, down-regulation of ALOX5 by RNA interference can also induce apoptosis in H929. Since it was reported ALOX5 can regulate IL-6 mRNA level, we also determined IL-6 and IL-6R expression by qRT-PCR. As expected, IL-6 and IL-6R mRNA levels were decreased (>2-fold) in H929 upon DZNep treatment. May-Grunwald-Giemsa staining demonstrated that treatment with DZNep also dose dependently induced nuclear and cytoplasmic morphologic features of apoptosis in H929. These findings in vitro warrants further investigation of DZNep for the treatment of MM in vivo. Keyword: Multiple Myeloma, Alox5, DZNep

#### **Abstract 026**

**Multiple Genetic Events Converge on MYC Activation in MGUS to Myeloma Transformation.** WJ Chng, G Huang, SB Ng, M Chesi, PL Bergsagel, R Fonseca. National University Health System, Singapore

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Multiple myeloma (MM) is an incurable bone marrow cancer. Events mediating transformation from the pre-malignant monoclonal gammopathy of undetermined significance (MGUS) to MM is unknown. We analyzed 2 gene expression datasets generated on the Affymetrix U133 platform. The test set consisted of 22 MGUS and 101 MM (GEO Accession GSE6477) and the validation set 50 MGUS and 351 MM (GEO Accession GSE2658 and GSE5900). The gene expression profiles of MM were compared to MGUS using gene-set enrichment analysis. Genes over-expressed in MM were enriched for cell cycle, proliferation and MYC activation gene-sets. We dissected the relationship between MYC and cell cycle, and identified a MYC activation signature dissociated from proliferation. We validated our MYC signature in publicly available mouse and human cell line gene expression dataset (GEO Accession GSE3151 and GSE3158 respectively), showing specific expression of our MYC signature in cell lines forced to express MYC but not when over-expressing other oncogene such as E2F, HER2. In these analyses, we noted that tumors with RAS mutation also consistently express this signature. Applying this signature to the test dataset, we showed that MYC is activated in 60% of myeloma but none of MGUS. This pattern is reproduced in an independent validation dataset. In order to validate the hypothesis that RAS mutation may also lead to the MYC activation signature, we correlated RAS mutation with MYC activation as measured by a MYC index calculated from the median expression of genes that constitute the MYC activation signature, and showed that almost all cases with RAS mutation have a high MYC index. Together with samples with very high expression of MYC mRNA corresponding to those with MYC translocations, these 2 mechanisms account for 67% of cases with MYC activation. To further confirm MYC activation, we performed immunohistochemistry using a validated MYC antibody together with CD138 double-staining. We can clearly identify CD138 positive plasma cells with and without nuclear MYC expression and found that nuclear expression of MYC, a marker of MYC activation, correlated strongly with the MYC signature, therefore providing clear evidence that MYC activation is present in majority of newly diagnosed MM but not in MGUS. MYC activation is not very well correlated with proliferation as assessed by the plasma cell labeling index. Among newly diagnosed myeloma patients with plasma cell labeling index less than

1, those with nuclear MYC expression have significantly shorter survival than those without (Median survival 77.7 months versus 37.9 months, log-rank p-value 0.04). Multiple pathways converge on MYC activation, which is a common transforming event in MM associated with poor prognosis. MYC nuclear staining by IHC can be a useful clinical surrogate. Targeting MYC can be a chemoprevention strategy. Key Word: MYC; prognosis; MGUS

#### **Abstract 027**

**Vinorelbine plus cyclophosphamide for stem cell mobilization in patients with multiple myeloma.** Michelle LM Poon, Lip Kun Tan, Belinda Tan, Yee Mei Lee, Te Chih Liu, Chin Hin Ng, Shir Ying Lee, Eng Soo Yap, Wee Joo Chng, Teck Guan Soh, Liang Piu Koh. Institution: Adult Stem Cell Transplant Program, Department of Hematology-Oncology, National University Cancer Institute, Singapore, Singapore. Email: [poonlm@hotmail.com](mailto:poonlm@hotmail.com)

Introduction: High dose cyclophosphamide is a commonly used regimen for the mobilization of patients with multiple myeloma. However, it is commonly associated with a variable time to mobilization, as well as infective complications. A new mobilization regimen of intermediate dose cyclophosphamide and vinorelbine has been reported recently to be safe, effective and highly predictable for patients with myeloma. Since 2006, our institution has used this new regimen in the mobilization of patients with myeloma. Our study aims to compare the collection data using this new regimen with a historical control mobilized with high dose cyclophosphamide. Patients and Methods: Fifteen patients (median age, 57 years) with multiple myeloma, were mobilised using a combination of vinorelbine (VNB) (25 mg/m<sup>2</sup> day 1) plus cyclophosphamide (Cy) (1.5 g/m<sup>2</sup> day 2) and granulocyte colony stimulating factor (GCSF). Results were compared to those achieved in 10 previously diagnosed patients (median age, 54 years) mobilized with high dose Cy at 4 g/m<sup>2</sup>. The two patient populations were comparable in terms of age (median age 57 years vs 54 years, p= 0.48), and number of prior chemotherapy regimens (5 cycles vs 5 cycles, p= 0.24). Results: Overall, 14/15 patients receiving VNB-Cy (93.3%) mobilized, as opposed to 8/10 (80%) in the controls (p=0.32). Median number of days from chemotherapy to mobilization was shorter for VNB-Cy patients (9 vs 13.5 days, p<0.05), and the predictability of the first day of mobilization was higher with the VNB/ Cy group (median Day 9, range 7- 9 days) as opposed to the high dose Cy group (median Day 13.5, range 10 – 16). The number of days of apheresis needed was similar between both groups ( 2 vs 2 cycles, p= 0.22). Median number of CD34+ cells collected was 13.15 X 10<sup>6</sup>/ kg for VNB-Cy patients and 10.2 X 10<sup>6</sup>/ kg for controls, p=0.38. No VNB-Cy patient experienced infective complications as opposed to 2 patients in the high dose Cy arm. The costs of mobilization with VNB-Cy was estimated at \$4208 per patient, as compared to \$4688 with high dose Cy. Conclusions: Vinorelbine, cyclophosphamide and GCSF appears to be a safe, effective and highly predictable mobilization regimen for patients with multiple myeloma. Keyword: Myeloma Mobilisation Stem cells

#### **Transplant**

#### **Abstract 028**

**Reduced-intensity conditioning stem cell transplantation for patients with young and low-risk MDS.** Kim YJ, Lee SE, Cho BS, Eom KS, Kim HJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS. The Catholic University of Korea. Email: [yoojink@catholic.ac.kr](mailto:yoojink@catholic.ac.kr)

Reduced-intensity conditioning (RIC) regimen has made allogeneic hematopoietic stem cell transplantation (SCT) more feasible in older or debilitated patients with MDS. The low risk of acute toxicity and long-term sequelae after RIC-SCT make this approach appealing to young patients devoid of significant comorbidities. Consecutive 14 patients with intermediate-1 MDS with an age 50 or younger received RIC-SCT and their transplant outcomes were compared with historical control who received conventional myeloablative SCT (C-SCT). RIC regimen consisted of fludarabine (150mg/m<sup>2</sup>) and intravenous busulfan (6.4mg/kg) and ATG was added for unrelated setting, while C-SCT regimen was 1.2 Gy total body irradiation and cyclophosphamide (120mg/kg). Pre-transplant characteristics were similar except patient sex and source of graft. The median follow-up duration of survivors after C-SCT and RIC-SCT was 91 (range, 72-147) and 63 (range, 47-92) months. Primary engraftment was achieved in all, but 1 in RIC-SCT suffered from secondary graft failure. Acute GVHD (grade II-IV) developed in 32% (C-SCT) and 21% (RIC-SCT), meanwhile chronic extensive GVHD occurred in 56% and 62% among evaluable patients, respectively. Overall survival between two groups were significantly different (C-SCT 54.5% vs RIC-SCT 92.9%, p=0.03), but event-free survival (54.5% vs 70.7%), relapse rate (11.6% vs 23.8%), rate of transplant-related mortality (28.7% vs 7.1%) were not. For relapsed patients, donor lymphocyte infusion (DLI) was given to 2 patients in C-SCT but failed to induce remission, meanwhile 3 relapsed patients in RIC-SCT achieved complete remission

after DLI, azacitidine, and second transplantation, respectively. The differences of treatment outcomes for relapsed patients, in addition to lower TRM, may attribute to the survival benefits after RIC-SCT. Although there are several limitations in this study, such as small number of patients, differences in transplant period and supportive care, these results suggested that RIC-SCT could be considered for lower-risk MDS who are young and devoid of comorbid clinical conditions. Keyword: MDS, stem cell transplantation, reduced-intensity conditioning

#### **Abstract 029**

##### **Cyclosporine, Mycophenolate Mofetil and Methotrexate as Post Grafting Immunosuppression after Nonmyeloablative Allogeneic Stem Cell Transplantations Conditioned with Fludarabine and Low-Dose Total Body Irradiation**

Michelle LM Poon<sup>1\*</sup>, Lip Kun Tan<sup>1</sup>, Belinda Tan<sup>1</sup>, Yee Mei Lee<sup>1</sup>, Te Chih Liu<sup>1</sup>, Chin Hin Ng<sup>1</sup>, Shir Ying Lee<sup>1</sup>, Eng Soo Yap<sup>1</sup>, Wee Joo Chng<sup>1</sup>, Teck Guan Soh<sup>1</sup>, Liang Piu Koh.<sup>1</sup> <sup>1</sup>Adult Stem Cell Transplant Program, Department of Hematology-Oncology, National University Cancer Institute, Singapore, Singapore. Email: [poonlm@hotmail.com](mailto:poonlm@hotmail.com)

**Introduction:** Nonmyeloablative (NM) hematopoietic cell transplantation (HCT) has extended the potential curative treatment option of allografting to patients in whom it was previously contraindicated due to advanced age or comorbidity. Graft-versus-host disease (GvHD), however, remains one of the major impediments to long term remission. Recently, our group has introduced a modified post grafting immunosuppression by adding methotrexate (MTX) onto the standard mycophenolate mofetil (MMF)/cyclosporin (CsP) for NMHCT recipients, with significant reduction in severe GvHD and non relapse mortality (NRM), thereby conferring favorable survival in patients receiving NMHCT. The current study is initiated to assess the feasibility and efficacy of similar approach in the setting of single institution with additional patient accrual.

**Patients and Methods:** Twenty-nine patients (median age, 47 years) with hematological diseases, who were poor candidates for a conventional myeloablative transplantation, receiving NM conditioning with fludarabine 90 mg/m<sup>2</sup> and total body irradiation (TBI) 200-cGy, followed by filgrastim-mobilized peripheral blood stem cell transplant from HLA identical (n=27), or matched unrelated (n=2) donors. Diagnosis include leukemia/MDS (n=19), lymphoma (n=2), ALL (n=1), myeloma (n=5) and CML (n=2). All patients were given CSP, MMF and short course of MTX as post-grafting immunosuppression. **Results:** The median times to neutrophil ( $\geq 500$ /mL) and platelet recovery ( $\geq 20,000$ /mL) were 20 and 13 days, respectively. Myelosuppression was moderate with neutrophil counts not declining below 500/mL in 5 (17%) patients, and with more than half of the patients not requiring any blood or platelet transfusion. Non-relapse mortality was low with only 2 transplant related death occurring within the first 1 year. Overall, 12 (41%) patients had grade 2-4 acute GvHD, with only 6 (21%) patients experiencing grade 3-4 acute GVHD. Extensive chronic GVHD was observed in 2 of 24 evaluable patients (8.3%). Relapse-related death occurred in 6 (21%) patients. At median follow-up of 55 months (range, 35-72 months), the 5-year probability of overall and progression-free survival were 59% and 44%, respectively. **Conclusions:** The addition of MTX onto the CSP and MMF as post grafting immunosuppression offers the possibility of further optimization of GvHD control in patients receiving NMHCT, with encouraging survival. **Keyword:** Immunosuppression Transplantation

#### **Abstract 030**

##### **Experience of Allogenic Hematopoietic stem cell transplant stem cell transplant in non-HEPA filtered single rooms.** Niranjana Rathod, Bhavana Dhingra, M Mahapatra. All India Institute Of Medicine, New Delhi, India. Email: [drniranjanrathod@gmail.com](mailto:drniranjanrathod@gmail.com)

Background-Hematopoietic Stem Cell Transplant (HSCT) is conventionally performed in HEPA filtered room as patient has to pass through critical period of 1-2 weeks of severe neutropenia. This reduces potential bacterial and fungal infections which would have significant impact on early transplant related mortality. Aim of study- To evaluate short and long term outcome of HSCT performed in various hematological patients, in non-HEPA filtered single rooms. Methodology- We reviewed medical records of 69 HSCT performed in non-HEPA filtered single rooms, over last 5 years, at our institution retrospectively with respects to different variables and analyzed systematically. G-CSF was given to all from D+1. Antibacterial and antifungal prophylaxis was administered along with conditioning, and at the onset of fever, systemic antibiotics were started. Antifungal agents were added if fever persisted for 3 days. Results-We present our single centre experience of 69 allogenic stem cell transplants performed over period of last 5 years. All these transplants were performed in non-HEPA filtered single room.

Source of stem cells were PBSC-59, BM-9, Combined-1. The indications were SAA-32, CML-10, AML-8, ALL-5, Biphenotypic AL-2, Thalassemia-9, and MDS-3. The median age was 24 years (range 2.2-46) with 15 females and 54 males as participants. Median time for neutrophil engraftment was 10 days (range 8–17). Fever occurred in 62 (89.85%) for a median of 5 days (range 1–38), Systemic antibiotics were used in 88.4% and antifungal in 51.5% cases. The 30-day mortality was 3(4.34%), and 100-day mortality was 6 (8.69%). After day 100, there were eighteen fatalities (26.08%) due to chronic GVHD-6, relapse-2, graft rejection-2, infections like disseminated tuberculosis-1 and aspergillosis-3, VOD-2, platelet refractoriness leading to IC bleed-2. Conclusion- Our experience suggests that allogeneic HSCT can be safely performed in non-HEPA filter rooms in India. Keyword: HEPA, Allogeneic transplant

### **Abstract 031**

**Hematopoietic Stem Cell Transplant in Aplastic Anemia: Single Institution Experience.** Niranjan Rathod, Jasmita Dass, M Mahapatra. All India Institute Of Medicine, New Delhi, India. Email: [drniranjanrathod@gmail.com](mailto:drniranjanrathod@gmail.com)  
Background- Hematopoietic Stem Cell Transplant (HSCT) is the most effective therapy for Aplastic Anemia (AA). Use of cyclosporine as Graft Versus Host Disease (GVHD) prophylaxis has improved outcome over period of years. Age, severity of AA is most important predictors of survival in AA. However, In India due to significant time delay between diagnoses to HSCT, alloimmunisation is very important factor in outcome. Aim of study- To evaluate short and long term outcome of HSCT in patients with severe aplastic anemia in Indian settings. Methodology- We reviewed medical records of 32 HSCT performed over last 5 years, at our institution retrospectively with respects to different variables and analyzed systematically. Fludarabine/ATG/Cyclophosphamide conditioning regimen was used in all. G-GSF was given to all from D+1. Antibacterial and antifungal prophylaxis was administered along with conditioning, and at the onset of fever, systemic antibiotics were started. Antifungal agents were added if fever persisted for 3 days. Results-We present our experience of 32 transplants performed in 30 patients with severe aplastic anemia over period of last 5 years. All these transplants performed in non-HEPA filtered single room. Out of these, 22 were males and 10 females. Median age of patients was 25.5 years (9-37). In 30 out of 32 patients PBSC was used as source for transplant as compared to 2 patients with BM as source. Median Time from diagnosis to transplant - 10.5 months (1-65) with median number of blood transfusions- 31.5 (3-106). Fever occurred in all patients requiring initiation of antibiotics. Antifungal were used in 15 (46.8%). Median Day of Neutrophil Engraftment - 10 (8-17) and that of platelet engraftment- 15.5 (10-33). There were 3 secondary graft failures, 1 of which was successfully transplanted again from same donor. 8 patients and 9 patients developed acute and chronic GVHD respectively. 7 out 9 of chronic GVHD patients had acute GVHD proceeding to it. The 30-day mortality was 1(3.12%), and 100-day mortality was 3 (10%). After day 100, there were seven fatalities (26.5%) due to chronic GVHD-3, graft rejection-1, infections like disseminated tuberculosis-1 and aspergillosis-1, platelet refractoriness leading to IC bleed-1. In these patients who died, median time from diagnosis to transplant was higher at 14 months (3-60) compared to 8 months (1-65), and median number of Blood transfusions was also higher at 85 (50-92) compared to 23(3-106). Conclusions-Our experience suggests that allogeneic HSCT can be safely performed in non-HEPA filter rooms in India for treatment of aplastic anemia. Time to transplant from diagnosis and number of blood transfusions are significantly associated with poor outcome. Acute GVHD is most important risk factor for chronic GVHD. Uncontrolled Infections and GVHD are two most important risk factors determine poor outcome. Keyword: Aplastic anemia, transplant

### **Abstract 032**

**An analysis of the charges associated with peripheral blood hematopoietic progenitor cell mobilization, collection and cryopreservation in patients with lymphomas undergoing autologous stem cell transplantation.** Ken t H. Walters, Veronica Smith, Beverly Rhodes, Richmond Thompson, Muzaffar Qazilbash, John McMannis, Amin Alousi, Marcos De Lima, Partow Kebriaei, Sergio Giralt, Issa Khouri, Richard Champlin, Uday Popat, and Chitra Hosing. MD Anderson Cancer Center, Houston, TX, USA. Email: [kwalters@mdanderson.org](mailto:kwalters@mdanderson.org)  
Peripheral blood hematopoietic progenitor cells (HPC) may be mobilized with cytokines alone or with chemotherapy followed by cytokines. The yield of stem cells is higher and the failure rate is lower with chemomobilization compared to cytokines alone. Although a cell dose of 2 million CD34+ cells/kg is considered adequate, some authors have shown that patients who receive < 5 million CD 34+ cells /kg have higher resource utilization after transplant (longer hospitalization, more antibiotic use, more transfusions etc). The purpose of this study was to analyze the charges associated with HPC chemomobilization. PATIENTS AND METHODS: We

analyzed 149 patients with non-Hodgkin's (N=101) and Hodgkin's (N=48) lymphomas who underwent HPC mobilization at our institution for autologous transplantation between 1/03 and 12/04. Data was collected from the departmental database and patient charts. The retrospective chart review was approved by the IRB. Patients who collected < 2million CD34/kg in 4 leukapheresis procedures were called failures. The estimated charges were divided into pre apheresis, apheresis, and post apheresis costs. (Source: Cleverly and Associates, CY06 data based on national average of hospital claims submitted to CMS by CPT/HCPCS code). Medication costs were obtained from [www.drugstore.com](http://www.drugstore.com). RESULTS: A total of 133 patients underwent chemomobilization, 16 patients were mobilized with cytokines alone (NA 2 patients). The most commonly used chemotherapy regimen was ifosfamide, etoposide, with or without rituximab (98 patients). The average in patient stay for chemotherapy administration was 6 days (range, 3-28). A total of 24 patients required readmission for complications of chemotherapy (22/24 patients were readmitted for fever/infections). The median hospital stay during readmission was 5 days (range, 1-12). The number of days on G-CSF was 14 days (range, 8-34). All patients received IV hydration while in the hospital and were discharged on prophylactic oral antibiotics (antibacterial, antiviral, and antifungal) to be continued till ANC > 500/mm<sup>3</sup>. The median time on oral antibiotics was 9 days (median 0-16). Patients who were successful mobilizers, the average number of apheresis procedures required to reach a target stem cell dose of 5 million/kg was 2 (range, 1-7). In this group of patients who received ifosfamide and etoposide chemomobilization only 3 patients failed to mobilize adequate HPC on the first attempt. However of the total of 149 patients, 30 patients failed to collect adequate HPC on the first attempt. Of those 12 patients underwent a BM harvest (at a cost of \$2389/harvest), 4 were re mobilized with chemotherapy (only 1 mobilized successfully), 4 patients underwent an allogeneic transplant (\$250,000 to 500,000/transplant) and 3 patients underwent an autologous transplant with suboptimal cell dose (all had prolonged time to engraftment and 1 patient needed an allogeneic transplant for graft failure). Average pre apheresis charge per patient was \$1800 (clinic visit, laboratory evaluation, insertion of central venous catheter, and chest x-ray to check placement). The average charge for chemotherapy administration, hospitalization, prophylactic antibiotics and G-CSF was \$ 36453 (not including rituximab). This is an underestimation as it does not include the costs associated with supportive care, intravenous fluids, readmission etc). The post apheresis charges were \$ 2493. These charges also do not take in to account the professional fees and hospital overheads which varies from one institution to the other. CONCLUSIONS: Although in this present analysis we may have underestimated the actual costs associated with HPC mobilization, the costs are still considerable. Accordingly, the financial implication for transplant centers where reimbursement charges are DRG (disease related group) or case rate based is significant. Interventions that may reduce the failure rate or reduce the number of apheresis procedures required to reach a target dose without increasing the toxicity may reduce the costs associated with transplant especially in patients who do not require chemotherapy for treatment of their primary disease. Newer agents like plerixaflor may have lower toxicity and may improve the HPC yield. Keywords: mobilization, cost analysis, transplant

### **Abstract 033**

**Should we incorporate anti-thymocyte globulin in matched sibling donor hematopoietic stem cell transplant? Experience learnt from matched unrelated donor transplant.** Su-Peng Yeh. China Medical University Hospital, Taiwan. Email: [supengyeh@gmail.com](mailto:supengyeh@gmail.com)

At China Medical University Hospital, bone marrow transplantation (BMT) has been used to treat patients since 1998 and is now the only center actively doing HSCT in central Taiwan. The transplant activities increased rapidly after 2002 when peripheral blood stem cell transplantation (PBSCT) was approved by the government and the cost was reimbursed by the national insurance. After that, PBSCT almost totally replaced BMT in allogeneic transplant. For the prevention of graft-versus-host disease (GVHD), we routinely added anti-thymocyte globulin 6-8mg/kg (rabbit ATG, Gemzyme) to standard Cyclosporine and short course Methotrexate for HSCT using matched unrelated donor (MUD) from 2003. Besides, ATG was also routinely used in the conditioning treatment of patients with severe aplastic anemia. There were 135 patients received allogeneic transplantation in this period, with 100 patients using HLA-matched sibling donor (MSD) and 35 using MUD. There is no significant difference in age, disease status before HSCT, incidence of female donor, and incidence of sex-mismatched transplant between these 2 groups. The use of ATG was associated with a much higher incidence of CMV reactivation (66.7% vs 28%, p=0.012) but not CMV infection-related death, and also a much lower incidence of extensive chronic GVHD (8.9% vs 56.7%, p < 0.001). The use of ATG did not increase the incidence of relapse death (53.3% vs 54.8% of all deaths), but was associated with a trend of lower GVHD-related death (6.7% vs

23.8%) and higher infection-related death (20% vs 2.4%;  $p=0.09$ ). The overall outcome is similar between these 2 groups with 5-year overall survival of 45%. Our data suggest that the use of ATG can significantly reduce the incidence of extensive chronic GVHD. The higher incidence of CMV reactivation can be effectively managed by careful monitor and early pre-emptive anti-viral treatment. This result is consistent with another 2 transplant centers at Northern Taiwan (National Taiwan University Hospital and Sun Yet-Sen Cancer Center). The high incidence of extensive chronic GVHD is a serious problem in our recipients of allogeneic PBSCT using MSD and standard protocol for GVHD prophylaxis (Cyclosporine and short course Methotrexate). The efficacy of ATG in preventing GVHD had been extensively studied in unrelated donor transplant; however, studies in related donor transplant were few and small-scale only. Although the long-term efficacy and optimal dosage of using ATG to prevent GVHD in matched related donor transplant remain to be confirmed, we are now planning to initiate a clinical trial of incorporating low dose ATG to allogeneic PBSCT using MSD in Taiwan.

## Miscellaneous

### Abstract 034

**Hematological malignancies in HIV: Experience of single tertiary care centre of North India.** Aman Sharma, Ravinder Sachdeva, Ajay Wanchu, Pankaj Malhotra, Surjit Singh, Subhash Varma. PGIMER, Chandigarh, India. Email: [amansharma74@yahoo.com](mailto:amansharma74@yahoo.com)

Background: HIV significantly increases the risk of developing cancer during ones life time especially since HAART has prolonged the survival of these individuals. Almost 1/3rd of HIV infected individuals are likely to develop cancer at some stage in their illness. India has the second largest number of HIV/AIDS individuals in the world, but studies done in the area of HIV related hematological malignancies are still few. Aim: To study the frequency and type of hematological malignancies in HIV individuals. Materials and Methods: This retrospective study analyzed HIV infected individuals with hematological malignancy. The study included all HIV infected individuals enrolled in the Immunodeficiency clinic of the department of Internal medicine, Post Graduate Institute of Medical Education & Research, Chandigarh, India, from April 2004 to September 2009. Analysis of records of each selected patient was carried out to obtain the clinical history, presentation, investigations, treatment and follow up details. Results: Fifty one hundred HIV infected individuals got enrolled in the immunodeficiency clinic during five years. Hematological malignancy was noted in fourteen individuals (0.3%). Non-Hodgkins lymphoma was diagnosed in 9/14 (64.2%) patients, 3/14 (21.4%) were diagnosed with Hodgkin's lymphoma and one each (7.1%) had acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML). Mean CD4 cell count of these 14 individual was 132 cells/ $\mu$ l. Thirteen patients were not on antiretroviral therapy (ART) prior to the diagnosis of hematological malignancies. Remaining one patient was on ART for nine years before diagnosis of diffuse large B cell lymphoma. Conclusion: Non Hodgkin lymphoma formed the most common hematological malignancy in HIV infected individuals. Keyword: HIV, Hematological Malignancies, North India

### Abstract 035

**Chronic Myeloproliferative Disease in Young – An Indian Experience.** Tahlan A\*, Chauhan S, Mahajan S, Palta A. Government Medical College & Hospital, Chandigarh. Email: [tahlananita@yahoo.co.in](mailto:tahlananita@yahoo.co.in)

Introduction: Chronic myeloproliferative diseases (CMPD) are not so commonly seen in young persons (age less than or equal to 45 years). Aims & Objectives: This study was undertaken to look at the occurrence of CMPD in young, along with clinical and haematological profile. Methods: The present study was carried out at Government Medical College & Hospital, Chandigarh, India. Records of all patients from 2003 to 2007 with diagnosis of CMPD were reviewed. Inclusion criteria were patients with diagnosis of CMPD and age less than 45 years. Exclusion criteria were age more than 45 years and/or those with age less than 45 years but did not fully satisfy criteria of CMPD. Results: A total of 60 patients with CMPD were reviewed out of which 32 (53.3%) fulfilled the criteria. Mean age of presentation was 32.3 years (range 8-45 years). Males outnumbered the females (56.2% vs. 43.7%) Chronic myeloid leukemia (78.12%) was the most common CMPD followed by chronic idiopathic myelofibrosis (12.5%), and hypereosinophilic syndrome /chronic eosinophilic leukemia (9.37%). Fever was the most common presenting symptom. Splenomegaly and hepatomegaly were present in 78.1% and 43.7% patients respectively. Mean haemoglobin was  $9.19 \pm 2.92$  g/dl, mean white blood cell count was  $184 \pm 1.72 \times 10^9$  /l and mean platelet count was  $2.78 \pm 1.73 \times 10^9$  /l. Conclusion: Rate of myeloproliferative disorders is higher in young persons than what has been previously reported. Also they are associated with higher incidence of Splenomegaly, anaemia and

leukocytosis.: A prospective analysis of a large cohort of young MPD patients is needed to determine the biological and clinical significance of these observations. Keyword: myeloproliferative disorders, young patients, chronic myeloid leukemia

#### Abstract 036

**Asparaginase induced coagulopathy: Does prophylactic component support help.** Aleemjan, Sheikh Aejaz, Vinod Gupta. SKI MS, India. Email: [aleem\\_maleem@yahoo.co.in](mailto:aleem_maleem@yahoo.co.in)

L-Asparaginase forms backbone of leukemia protocols. Therapy has been associated with various forms of toxicity in particular hypersensitivity and coagulation abnormalities. Asparaginase therapy is associated with depletion of Antithrombin III and fibrinogen. Literature emphasises thrombosis more than haemorrhage. Cerebro vascular symptoms appear in two forms, either increased or normal coagulation factors, in particular fibrinogen. Thrombotic cases develop by low ATIII and fibrinogen levels while in haemorrhagic cases these levels could be normal. Herein, we portray two recent cases A and B seen over a period of 3 months. A) 12 YEAR OLD BOY, B-cell ALL with myeloid coexpression on UKALLXII protocol (Phase I induction), developed focal seizures with secondary generalisation during asparaginase phase. Imaging suggested thrombotic event (Fig 1). Hypofibrinogenemia (0.66) with deranged PT, Aptt (25,43 sec.) respectively and a positive D-Dimer. B) 11 year old female child MPAL (Mixed Phenotype acute leukemia) on Modified BFM 90 protocol developed focal seizures with secondary generalisation during asparaginase phase. Serial Imaging suggested thrombotic event (Fig2). (undetectable) with PT, aPTT near normal Hypofibrinogenemia. Anticoagulation with fondiprinux (factorX inhibitor) and Warfarin overlap coupled with component support (FFP/Cryoppt.) was employed and possibly made the difference. Though statistically not significant yet in the backdrop of debate, whether prophylactic FFP/Cryoppt. should be routinely employed, we believe in high risk cases, on the basis of morphology, markers like ours it does have a role. Monitoring Fibrinogen levels affordable and available easily than ATIII, could prognosticate.

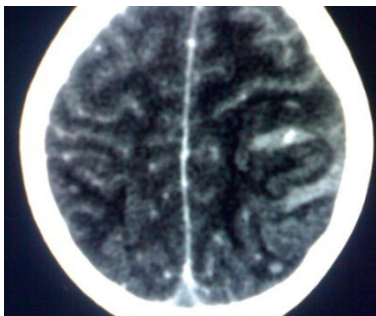


FIG 1

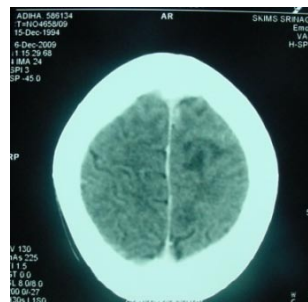


FIG2

#### References:-

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#### Abstract 037

**A STUDY OF IRON STATUS IN CHILDHOOD LYMPHORETICULAR MALIGNANT DISORDERS.** Pankaj C Vaidya\*, Bhanu Kiran Bhakhri\*\*, Ram Kumar Marwaha\*\*\*, Amita Trehan\*\*\*, G Grewal\*\*\*. LTMMC & GH, Sion\*, Mumbai; Safdarjung Hospital\*\*, New Delhi; APC, PGIMER\*\*\*, Chandigarh, India. Email: [dr\\_pcv@rediffmail.com](mailto:dr_pcv@rediffmail.com)

Background: Children with malignant disorders experience varied grades of anemia which could significantly impact the quality of life, morbidity, mortality and therapy outcome. There is scant information regarding iron deficiency in children with malignant disorders. Purpose: We report here the findings of a study designed to prospectively evaluate iron status in children with lymphoreticular malignancies. Patients and Methods: The prospective study was carried out in the Division of Hematology-Oncology of the Advanced Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India from January 2003 to June 2004. Previously untreated children with lymphoreticular malignancies who fulfilled the inclusion criteria were recruited. Patients who had received iron in the preceding 4 weeks and those who had defaulted therapy were excluded. Age matched controls were enrolled from follow-up and growth monitoring clinics. At presentation, details of blood component therapy and hematinics were recorded. Prior to initiating chemotherapy, CBC, reticulocyte count, platelet counts, MCV, MCHC, MCH, RDW, serum iron, TIBC, serum ferritin and bone marrow iron store detected by Perl's stain (not done in controls), were done. All the investigations were repeated after completion of remission induction therapy i.e. 5-6 weeks after initial presentation. Results: Anemia was documented in 80% of children with lymphoreticular malignancies. Iron deficiency was an important etiological factor; microcytosis was observed in 71.4% of cases, at presentation. Increased RDW and TIBC were indicators of iron deficiency. In the majority of cases therapy resulted in significant improvement towards normalization of deranged hematological parameters. This phenomenon could be attributed to enhanced quantity and quality of erythropoietic activity and red cell transfusions. Conclusion: The observation suggests that therapeutic iron supplements are not indicated in the majority of children on therapy for malignant disorders. Various hematological and body iron status parameters, should be assessed on a case to case basis. Keywords: Anemia, iron deficiency, iron status, lymphoreticular malignancies, blood transfusion

#### **Abstract 038**

**Hematological Malignancies: What Kills Them?** Gaurav Prakash, Sameer Bakshi, Vinod Raina. All India Institute of medical sciences, New Delhi, India. Email: [drgp04@gmail.com](mailto:drgp04@gmail.com)

BACKGROUND: Cancer directed chemotherapy regimen, over last few decades, have evolved significantly in spectrum, effectiveness, usage and safety. There is parallel improvement in cancer treatment outcome and management of therapy-related complications. In spite of these advancements, inpatient deaths in oncology centers are common occurrence with majority dying due to advanced disease. However, a considerable number of patients die during course of treatment and many of these deaths may be related to cancer treatment. We aimed to analyze all deaths in a calendar year in our oncology center for distribution of causes of death in hematological malignancies with emphasis on neutropenic deaths. Majority of data on causes of death in cancer patients is in the clinical trial setting. This study describes causes of death in patients of hematological malignancies who received standard treatment and care in day to day practice, outside the context of clinical trial. METHODS: From January 2008 to December 2008 data of all deaths in patients of hematological malignancies were retrieved from medical record section and analyzed for cause of death, type of malignancy, status of malignancy at the time of death, type of therapy received and nature of infections in neutropenic deaths. RESULTS: Total 107 deaths were recorded in hematological malignancies in one year duration amongst inpatients. Out of which 65(60%) were cases of acute leukemia, 29(27%) were cases of lymphoma (all subtypes) and 13(12%) were cases of multiple myeloma. Median duration of hospital stay prior to death was 7 (1-90) days. Sepsis/Multi Organ Dysfunction Syndrome was commonest immediate cause of death 71/107[66%] followed by progressive malignancy and hemorrhage in 11/107[10.3%] cases each. Only 9/107(8.4%) patients died with controlled cancer. Rest all deaths were in patients with uncontrolled malignancy (either progressive/refractory disease or partial responders). 82/107[76.6%] deaths occurred within 30 days of any form of anticancer therapy of which 77 deaths were after chemotherapy and other 5 were after hematopoietic stem cell transplant. Among these early deaths, 44/82 [53.7%] were febrile neutropenic deaths, with commonest site of infection in lungs followed by skin and subcutaneous tissue. Microbiologically documented septicemia (positive blood culture) was found in 17/44 (38%) neutropenic deaths of which majority were due to gram negative septicemia with Klebsiella and E.coli being most common organisms. CONCLUSIONS: It is important to audit mortality data on regular basis as this can provide valuable insight in hospital practice and help to improve health care delivery. Accurate mortality record keeping is another important aspect as variable practices in reporting cancer deaths may have implication on cancer mortality epidemiology. As a result, this may not reflect actual scenario. Keywords: mortality audit, cancer deaths, febrile neutropenia

#### **Abstract 039**

**Helicobacter pylori Infection: Association with Blood Group, Demographics and Life style.** Bilawal Ahmed\*, Arif Valliani\*, Ali Khuwaja\*\*. Dow University of Health Sciences\*, Aga Khan University\*\*, Pakistan. Email: [bilawal.ahmed@hotmail.com](mailto:bilawal.ahmed@hotmail.com)

Background: It is well known that blood group antigens are related to the development of peptic ulcer and gastric carcinoma. Infections due to H. Pylori are one of the most widespread in the world. Its intensification in the individual populations is strongly related to economic conditions. Developing countries (Asia, Africa, Central and South America, Eastern Europe) are at high risk, due to people living in poor socioeconomic conditions. This study sought to determine the relationship between H. pylori and ABO blood groups, age, gender, smoking and life style.

Methods: Cross-sectional prospective study was conducted at endoscopy suit in Public Sector Hospitals of Karachi from Sep 2008- Nov 2008. All the symptomatic patients coming for upper GIT endoscopy were included in this study. Results: Biopsy for histopathology was taken from 558 patients out of them 222 (39.8%) were males with age range 18-65 years. Age group of 21-40 years was found to be related with H.pylori infection. Out of 558 patients 216 (38.7%) were turned out H.pylori positive with a significant male preponderance ( $p < 0.05$ ).

Distribution of ABO blood groups in H. Pylori group was A= 66/216 (30.5%), B= 12/216 (5.5%), AB= 6/216 (2.7%) and O= 132/216 (61.1%) which is statistically significant ( $p < 0.05$ ). Rh factor was also related to H.pylori infection ( $p = 0.514$ ). H.pylori could not be related with smoking ( $p = 0.075$ ). Excessive tea consumption was related to H.pylori infection. Conclusion: This study demonstrates that H. pylori infection can be related to ABO blood group, age, gender and even lifestyle. People of blood group O are more prone to develop H.pylori infection related gastritis, ulcers, and even perforations, so they should be cautious against transmission of H.pylori infection. Although there was no correlation found with smoking in this study, other studies have shown otherwise. We suggest that there is a need for making aware people to promote healthy life style, especially after knowing their own health condition and demography. Keyword: Helicobacter pylori ABO blood groups

#### **Abstract 040**

**Comparative Trial on Maintenance of Sterile Atmosphere By Microfibre vs Ayurvedic Incense.** Vinod Kumar Bhardwaj, Deepak Dube, TP Sahu. Peoples College Of Medical Sciences, Bhanpur; Gandhi Medical College; Jawahar Lal Nehru Cancer Hospital Bhopal, India. Email: [drvkbharadwaj3344@hotmail.com](mailto:drvkbharadwaj3344@hotmail.com)

A clinical trial is in progress to compare the effect of Ayurvedic incense with microbial free laminar air flow in maintenance of microbial free atmosphere during the management of immunocompromised patients while on chemo therapy and radiation for solid malignant tumours and leukaemias. Smokes produced by burning roots, stems and seeds of plants and cow dung in various intensity is being practised in India for purifying atmosphere particularly in religious functions. The paper will discuss safety and economy of this method in maintaining sterile atmosphere. Keywords: Sterile atmosphere, immunocompromised status, laminar

#### **Abstract 041**

**Title: Adult T cell Leukemia / Lymphoma ...a case report.** Sheila Das, Anna Mani. Christian Medical College, Ludhiana, India. Email: [dasskus@yahoo.com](mailto:dasskus@yahoo.com)

66 year old Sikh male admitted with fever, cough and constipation for 15 days on examination generalised erythematous skin rash was observed, which the patient said had appeared in the last 8 - 10 days. Hematologic parameters were as follows Hb - 8.7 gm%, TLC -  $425 \times 10^3$ /mL, Plts -  $25 \times 10^3$ /mL ESR - 07 mm/hr, coagulation parameters were normal. Peripheral blood film and bone marrow showed numerous medium to large lymphoid cells with nuclear convolutions and few "flower cells". Immunophenotyping:- Lymphoid cells were CD4+, CD5+ & CD7+. A diagnosis of ATLL was considered. Further details of clinical investigation and lab parameters will be presented. Keywords: ATALL, CTLL, cutaneous lymphoid malignancy

#### **Abstract 042**

**POEMS syndrome : case report.** Amaylia Oehadian, Trinugroho Heri Fadjar, Rachmat Sumantri

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POEMS syndrome is defined by the presence of a peripheral neuropathy (P), a monoclonal plasma cell disorder (M), and other paraneoplastic features, the most common of which include organomegaly (O), endocrinopathy (E), skin changes (S). Not all features of the disease are required to make the diagnosis.

We report a case of POEMS syndrome in a 50-year-old female who presented with weakness, abdominal swelling and history of red cell transfusions. Because of the hepatosplenomegaly (Schuffner VII) we diagnosed her as chronic myelocytic leukemia (CML) or myelofibrosis. Her peripheral blood smear did not show granulopoiesis maturation from myeloblast nor leukoerythroblastic features which was characteristic of CML and myelofibrosis. We found also anemia, peripheral motoric neuropathy and hyperpigmentation at her legs. The protein electrophoresis showed monoclonal gammopathy on  $\gamma$ 2 globulin. Bone marrow examination showed normal plasma cells. There was no lytic or sclerotic lesion on skull and tibia x-ray. The echocardiography showed pulmonary hypertension, pulmonary regurgitation, right and left ventricle hypertrophy with normal ejection fraction (50%).

She was treated with melphalan 10 mg/m<sup>2</sup> (day 1-4) and prednisone 60 mg/m<sup>2</sup> (day 1-4) every 6 weeks with packed red cells transfusion. After 3 cycles the monoclonal protein was reduced from 35.5% to 26.1% (normal 2-5%) without changes in her spleen size. Until now she continued on melphalan and prednisone treatment. Although POEMS syndrome is a rare disease, it should be considered in patient with hepatosplenomegaly, especially if accompanied by peripheral neuropathy. Keywords : POEMS syndrome, plasma cell , peripheral neuropathy