Research Abstracts for 2018 CLIC-I4C Joint Meeting

Abstract Number, Presenting Author (Last, First) – Title

Legend

* = Presenting author

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01

MOLECULAR EPIDEMIOLOGY OF PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA IN BRAZIL. Francianne G Andrade†, Suellen V. Moura Feliciano, Ingrid Sardou-Cezar, Daniela Palheiro Mendes-de-Almeida, Paulo Chagas Neto, Marceli S. Santos, Maria S. Pombo-de-Oliveira *(Pediatric-Hematology-Oncology Program (PHOP) Research Center, National Cancer Institute (INCA), Brazil)*

Background: Acute promyelocytic leukemia (APL) presents well-characterized mechanisms of pathogenesis with distinctive acquired fusion gene. The incidence rate of APL seems to vary among geographic regions, being higher in the Latino population, underlying genetic background that plays a role along with environmental factors. Our aim was to establish the incidence rate of APL among children and adolescents according to hospital-based and population-based cancer registries (PBCR) in Brazil. We also aim to describe the molecular features of APL to provide insight into molecular epidemiology potentially associated with APL development. **Methods**: APL cases (<19 years old) were assessed from a dataset of hospital-based registry from a central laboratory (PHOP, INCA) that is a reference for leukemia diagnostic assistance (2002-2017) and from 18 PBCR in Brazil. Diagnostic algorithm included morphology, immunophenotype, and PML-RARa identified by FISH/RT-PCR. Additionally, FLT3, KRAS, NRAS, and PTPN11 mutations were analyzed. **Results**: In the PHOP-based registries, 149 patients out of 734 myeloid malignancies (MM, 20.3%) were diagnosed with APL, while in the PBCR 45 out of 1.421 (3.2%) MMs were APL. The incidence rate based on PBCR showed that APL was highest in Southeast/South (1.60 per million) compared with other Brazilian regions (0.9 per million). MM rate of unspecified cell-type in PBCRs was about 50% and the coverage of PHOP was estimated in 95% of PBCRs. Patients were similarly distributed among age ranges >2-10 and >10-21 years old (47.3% and 50%, respectively); no sex differences were observed, but a remarkable decrease in Blacks (10.5%) vs. Non-Black (90.5%) was found. PML-RARA was identified in the great majority of cases; RAS mutations were observed in 55% of APLs, including FLT3 (45.2%), NRAS (7.3%), KRAS (2.5%) and PTPN11 (rs61736914, a silent aminoacid substitutions=4.9%). **Conclusions**: APL is the most frequent MM subtype highly associated with FLT3 mutations, reflecting the profile of the disease in Brazil. Future studies should explore these association with environmental exposures.

02

INCREASED PENETRANCE OF ACUTE LYMPHOBLASTIC LEUKEMIA SUSCEPTIBILITY LOCI IN CHILDREN WITH DOWN SYNDROME. Adam J. de Smith†§, Austin L. Brown§, Vincent U. Gant§, ME Scheurer, KM Walsh, N Winick, NA Heerema, AJ Carroll, MJ Borowitz, BL Wood, WL Carroll, EA Raetz, E Feingold, W Yang, M Devidas, CG Mullighan, SP Hunger, C Pui, M Loh, LM Morimoto, T Whitehead, HM Hansen, AY Kang, D Sinnett, P Thompson, JM Birch, JW Taub, ME Zwick, MS Pombo-de-Oliveira, C Metayer, X Ma, BA Mueller, SL Sherman, JL Wiemels, MV Relling, JJ Yang, Philip J. Lupo§, Karen R. Rabin§ *(Department of Preventative Medicine, Keck School of Medicine, University of Southern California, California, USA)*

Down syndrome (DS) is one of the strongest risk factors for acute lymphoblastic leukemia (ALL), the most common pediatric malignancy, as children born with trisomy 21 have an approximately 20-fold increased risk of disease. ALL in children with DS (DS-ALL) is associated with inferior outcomes and unique somatic characteristics, including a high frequency of CRLF2 overexpression. However, the role of inherited genetic variation in DS-ALL is unknown. To this end, we performed the first genome-wide association study (GWAS) of DS-ALL, including four independent case-control studies comprising 542 DS-ALL cases and 1192 DS controls. We carried out genome-wide imputation of autosomal and disomic single nucleotide polymorphisms (SNPs), and combined results from all studies using fixed effects meta-analysis. Genome-wide significant SNPs were identified at four loci previously associated with non-DS ALL, including: rs58923657 near IKZF1 (odds ratio [OR] = 2.02, Pmeta=5.32x10-15), missense SNP rs3731249 in CDKN2A (OR=3.63, Pmeta=3.91x10-10), rs7090445 in ARID5B (OR=1.60, Pmeta=8.44x10-9), and rs3781093 in GATA3 (OR=1.73, Pmeta=2.89x10-8). Case-case analyses comparing the frequency of ALL risk alleles (at IKZF1, CDKN2A, ARID5B, GATA3, CEBPE, BMI1, and PIP4K2A) in DS-ALL versus non-DS ALL (n = 3082 cases) revealed significantly higher risk allele frequencies in DS-ALL cases for SNPs in CDKN2A (OR=1.58, Pmeta=4.08x10-4), GATA3 (OR=1.34, Pmeta=4.38x10-5), and IKZF1 (OR=1.18, Pmeta=0.015). Genetic risk scores (GRS) calculated from the seven susceptibility loci were also significantly higher in DS-ALL cases than in non-DS ALL cases (weighted GRS, P=3.33x10-6), indicating that DS-ALL cases harbor significantly more risk alleles than non-DS cases. Furthermore, among controls without ALL, neither the GRS nor any individual ALL risk alleles were associated with DS status, suggesting that the higher risk allele frequencies in DS-ALL cases represents a larger magnitude of effect for known ALL risk loci in the genetic background of trisomy 21. Finally, shRNA knockdown of IKZF1 in lymphoblastoid cell lines (LCLs) revealed significantly higher proliferation rates in DS LCLs versus non-DS LCLs, as measured by serial counts (P<0.05) and proportion of cells in S-phase (P<0.05). Our results support a higher penetrance of ALL susceptibility loci in the DS population, and may inform surveillance strategies for children with DS who are at the greatest risk of developing ALL.

03

INCIDENCE OF CHILDHOOD CANCER IN COSTA RICA, 2001 – 2013, IN AN INTERNATIONAL PERSPECTIVE. Friederike Erdmann†, Tengfei Li, George Luta, Joachim Schüz, Ana Maria Mora *(Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France)*

Background: Higher childhood cancer incidence rates, particularly for leukaemia, are reported from high-income countries (HICs) versus lower income countries. However, estimating childhood cancer incidence globally is hampered by lack of reliable data from developing countries, including for Latin America. Costa Rica is one of the few middle-income countries (MICs) with a longer-term nationwide population-based cancer registry, enabling to study high quality incidence data on childhood leukaemia. **Methods**: Data on incident leukaemia in children aged under 15 reported to the National Cancer Registry of Costa Rica between 1999 and 2013 were analysed by leukaemia type, age, gender, and geographical region at diagnosis. **Results**: For the 13-year period a total of 832 children with leukaemia was reported, resulting in an overall age-standardised incidence rate (ASR) of 58.08/million. The male-to-female ratio was 1.2. The highest age-specific rate was observed in children aged 1-4 years (97.7/million). Most frequent leukaemia type was lymphoid leukaemia. With an ASR of 49.1/million the observed rate was among the highest in the world. A very low rate in international comparison was observed for leukaemia in infants, which was largely driven by the low lymphoid leukaemia rate. With respect to geographical differences, substantially higher leukaemia rates were observed in the regions Huetar Atlatica (69.2/million) and Huetar Norte (68.1/million). **Conclusion**: Childhood leukaemia incidence patterns in Costa Rica were closer to those observed in HICs than found in many low and middle-income countries. Further research is recommended to explore which factors may drive the high overall leukaemia rate as well as the low rates observed in infants. Our data suggests applying caution when interpreting geographical variation, as this example of a MIC with established paediatric oncology and a well-functioning cancer registry showed less differences to childhood leukaemia incidence patterns in HICs.

04

DIAGNOSTIC MEDICAL RADIATION EXPOSURE AND RISK OF CHILDHOOD LEUKEMIA: RESULTS FROM AN ITALIAN POPULATION-BASED CASE-CONTROL STUDY. Tommaso Filippini†, Elisa Arcolin, Carlotta Malagoli, Silvia Cilloni, Federica Violi, Lucia Borsari, Marco Vinceti *(Environmental, Genetic and Nutritional Epidemiology Research Center (CREAGEN), University of Modena and Reggio Emilia, Modena, Italy)*

Introduction: In utero exposure to low-dose radiation delivered from medical procedures is a risk factor for childhood leukemia (CL), while findings for postnatal exposure are scarce and still inconsistent. In a population-based case-control study carried out in a Northern Italian province we explored the relationship between post-natal exposures to medical radiation and CL risk. **Methods**: We identified CL cases diagnosed in the Modena province in the period 2004-2013 through the Italian National Childhood Cancer Register and we randomly selected four population controls matched by age, sex and calendar year. For each subject we retrieved detailed information about any medical procedure involving ionizing radiations from birth up to six months prior to the onset of the disease by accessing to databases of the Radiology services of Modena province. We collected information about child age, type, total number, body region and reason of the radiological examination. Finally, we estimated for each study participant the total effective dose (mSv) and the red bone marrow-specific dose (mGy) experienced from birth. **Results**: Using a conditional logistic regression model we found an increased risk of developing CL, especially in children aged 5 or more, in association with experiencing one or more diagnostic tests with ionizing radiation (odds ratio 1.68, 95% confidence interval 0.66–4.29). The risk of CL and particularly of acute lymphoblastic leukemia increased in children who received one or more x-ray test in the first 5 years of life. Risk of CL by increasing total effective dose and red bone marrow-specific dose increased in the highest (>0.035 mSv and >0.0125 mGy) compared to null exposure. **Conclusions**: Our study suggests an increased risk of CL related to early exposure to post-natal medical radiation.

05

MATERNAL INFECTION DURING PREGNANCY AND CHILDHOOD LEUKAEMIA IN THE OFFSPRING: A SYSTEMATIC REVIEW AND META-ANALYSIS. Jian-Rong He†, Rema Ramakrishnan, Jane E. Hirst, Audrey Bonaventure, Stephen S. Francis, Ora Paltiel, Siri E. Håberg, Stanley Lemeshow, Sjurdur Olsen, Gabriella Tikellis, Per Magnus, Michael F G Murphy, Joseph L. Wiemels, Martha S. Linet, Terence Dwyer *(Nuffield Department of Women's and Reproductive Health, University of Oxford, UK; Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China; The George Institute for Global Health, University of Oxford, Oxford, UK)*

Background: Strong evidence suggests that a substantial fraction of childhood leukaemias originate in utero, and maternal infection is potentially a contributor to this risk. While many individual epidemiologic studies have previously examined the association of maternal infection during pregnancy and childhood leukaemia risk in the offspring, no systematic review has been conducted. **Methods**: In this systematic review and meta-analysis (PROSPERO number, CRD42018087289), we searched PubMed and Embase from inception up until 16 January, 2018. We included human studies that reported associations of at least one measure of maternal infection during pregnancy with acute lymphoblastic leukaemia (ALL) or all childhood leukaemias (CL) in the offspring. We conducted random-effects meta-analyses to pool odds ratios (OR) of any infection and specific type of infection on ALL and CL. **Findings**: We identified 2,072 records; 20 studies (ALL, n=15; CL, n=14) reported in 32 articles were included. Any infection during pregnancy was associated with higher risk of ALL (OR [95% confidence interval], 1.63 [1.14, 2.33]) and CL (1.36 [1.01, 1.84]) in offspring. Influenza during pregnancy was associated with higher risk of ALL (3.64 [1.34, 9.90]) and CL (1.77 [1.01, 3.11]). Varicella (10.19 [1.98, 52.39]) and rubella (2.79 [1.16, 6.71]) infections were also associated with higher risk of CL. **Interpretation**: Maternal infection during pregnancy may be associated with higher risk of childhood leukaemia. Future studies with larger sample sizes, including a greater collection of prospective evidence, and more accurate methods for infection measurements (e.g. biospecimens or medical records) are needed to confirm these findings.

06

GESTATIONAL RISK FACTORS IN PEDIATRIC CANCER. A COHORT STUDY IN TAIWAN. Julia E Heck*, Hsin-Yun Tsai, Chung-Yi Li, Beate Ritz, Onyebuchi A. Arah, Pei-Chen Lee *(Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, California, USA)*

Background: The incidence of childhood hepatic and germ cell tumors is higher in Taiwan, while the incidence of lymphomas, renal tumors, and central nervous system cancers is lower than in other developed nations. Taiwan has unique cancer risk factors such as much higher adult male than female smoking, betel quid use (particularly in aboriginal communities), endemic hepatitis B, low maternal overweight, and low rates of high birthweight. Still, there are few epidemiologic studies from Asian countries. Our study aimed to examine demographic and gestational risk factors for pediatric cancers in a Taiwanese cohort. **Methods**: We included all children born in Taiwan 2004-2014 for whom there were birth records and included 1900 cancer cases and 2,077,137 controls. We used multivariable adjusted logistic regressions to estimate associations between gestational factors and childhood cancer. **Results**: Greater parity of □2 older children was related to AML [odds ratio (OR)=2.01, 95% confidence interval (CI): 1.05, 3.84), central nervous system tumors (OR=1.69, CI: 1.04, 2.75) and neuroblastoma (OR=1.97, CI: 1.16, 3.35). Hepatoblastoma was more likely in very low birthweight (<1500g; OR=21.99, CI: 10.8, 44.78), very preterm birth (<33 weeks gestation; OR=20.29, CI: 10.5, 39.23), plural pregnancies (OR=3.73, CI: 1.69, 8.23), and both small- (OR=2.05, CI: 1.06, 3.98) and large- (OR=2.15, CI: 1.04, 4.41) for-gestational-age children. Acute lymphoblastic leukemia (ALL; OR=0.56, CI: 0.35, 0.90) and non-Hodgkin lymphoma (NHL; OR=0.56, CI: 0.32 -0.98) cases were less likely among small-for-gestational-age children. Germ cell tumors were more common among children born in rural areas (OR=1.62, CI: 1.01, 2.58). **Conclusions**: We observed point estimates for the associations between high birthweight and childhood cancer similar to those reported in meta-analyses of ALL, AML, NHL, and central nervous system tumors, despite the lower rates of high birthweight in Taiwan. Hepatoblastoma risk from fetal growth and plural pregnancies, and findings for varying risk with parity, were similar to that reported elsewhere.