odborníků bez výsledného efektu a následnou hrozbou amputace dolní končetiny. Zpočátku s námi pacient moc nekomunikoval, byl uzavřený a smutný. S prvními výsledky naší práce se psychika nemocného zlepšila. Závěr: Cílem příspěvku je vyzdvihnout náročnost péče o maligní ránu a psychiku nemocného u pacienta s DLBCL. Dále příspěvek poukazuje na nezbytnost souhry celého týmu, který se na ošetřování podílel.

2893. EMOCE - JAK S NIMI ZACHÁZET NA ONKOLOGICKÉM PRACOVIŠTI

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Klinická práce na onkologickém pracovišti je náročná v mnoha směrech. Má vysoké nároky na odbornost, znalosti, zručnost. Kromě výkonových a odborných požadavků se od zdravotníků očekává schopnost adekvátně reagovat a orientovat se v emočně náročných situacích tak, aby onkologického pacienta podporovali při léčbě. Syndrom psychického ohrožení se objevuje v nadlimitní, ohrožující a bezvýchodné situaci, kdy je ohrožena psychická a fyzická jednota člověka. Pacient, ať už s nově sdělenou onkologickou diagnózou či v průběhu léčby samotné, se v takovém stavu psychického ohrožení nachází. Onkologická diagnóza je nepříjemný ortel a je třeba, aby pacient realitu nemoci kognitivně a emočně přijal. Tento stav s sebou nese různé afektivní reakce. Je vhodné, aby se uměl s emocemi zkonfrontovat a odžít je. Nejčastější emoce jsou kromě úzkosti a strachu, také i vztek, bezmoc a smutek. Pokud pacient neumí zrale a adekvátně emoce zpracovat nebo pokud zdravotnický personál nevědomě pacientovi nedovolí emoční reakci odžít, pak můžeme očekávat neadaptivní, dysfunkční reakci. Ta se může projevit panickou, agresivní reakcí, útěkovým či regresivním chováním nebo až stavy derealizace. Pokud se tyto emoční a behaviorální projevy zafixují, můžeme očekávat klinické obrazy, které se v MKN 10 diagnostikují jako reakce na závažný stres F43.0, poruchy přizpůsobení F43.2, posttraumatická stresová porucha F43.1. Je tedy s výhodou, pokud pacient na náročné období s onkologickou diagnózou, zareaguje tzv. sympatikovou reakcí, která má podobu akutní stresové reakce s veškerou vegetativními a behaviorálními projevy oproti parasympatikové. Ta se vyznačuje pasivní reakcí, reakcí tzv. mrtvého brouka, kdy není zřejmá žádná emoční či behaviorální reakce. Pacient jakoby ve svém prožívání „ztuhne“ a svoji situaci bere v klidu a s nadhledem. Z pohledu zdravotníka je takový pacient statečný, bezproblémový a rozumný, ale z psychologického hlediska tato skupina pacientů inklinuje k rozvoji syndromu psychického ohrožení, který může vést až k rozvoji disociativních poruch, posttraumatické poruchy, afektivních poruch či k různým typům somatizace potíží. Proto je více než žádoucí, aby zdravotník si byl vědom těchto rizikových faktorů při snaze tlumit emoční reakce pacienta a při snaze „apelovat“ na dospělé chování. Měl by nabídnout bezpečný prostor pro odžití emocí, měl by mít dovednost pacientovi emoce zrcadlit a měl by nabídnout ujištění o „normalitě“ různě projevených reakcí. Obecné pravidlo zní: Mohu reagovat, nesmím však pacienta zatížit a zahltit vlastní emoční reakcí! Každý zdravotník by měl umět pracovat s vlastními reakcemi a reakcemi pacienta s citem, empatií a autenticitou. Tyto kvality by měly patřit do standardů léčebné péče každé sestry či lékaře.

SYMPOSIUM ON ADVANCES IN MOLECULAR HEMATOLOGY 2: STRESSED HEMATOPOIESIS

2918. JAK2 V617F PROGENITORS EXHIBIT INTRINSIC INFLAMMATORY SIGNALING AND PROTECTION AGAINST INFLAMMATION INDUCED DNA DAMAGE

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Recent clinical observations recognize chronic inflammation as an essential component of development and progression of oncogenic JAK2 V617F mutation-positive polycythemia vera (PV) and other Philadelphia chromosome-negative myeloproliferative neoplasm (MPNs). However, much remains to be understood about how inflammatory and oncogene-induced signaling interact in disease initiation and clonal evolution into final burn-out state of fibrosis or neoplastic

transformation. Using induced pluripotent stem cell (iPSC) clones with distinct JAK2 genotypes derived from female PV patient and immunohistochemistry staining (IHC) of patients' bone marrow (BM), we show presence of IFNg and its transcription program to be intrinsic for hematopoietic progenitors with JAK2 V617F mutation. As this potent immunomodulatory cytokine with broad functions has important role in mediating inflammatory response, we hypothesize that IFNg is the key inflammatory cytokine present at the very beginning of JAK2 V617F transformation and driving BM microenvironment remodeling. Our IHC stainings during the course of disease progression, as well as recently published data show continuously increasing expression of inflammatory cytokines TNFa and TGFB1, suggesting their important role in senescent-associated fibrosis of later disease stages. Such observation prompted us to test the effects of IFNg in combination with TNFa and/or TGFB1 on the expression of inflammatory signature in JAK2 V617F-positive progenitors. This treatment spurred more than 100 times fold increase in expression of CXCL10 and CXCL9 specifically in JAK2 V617F progenitors, but not in wild-type progenitors. Both of these chemokines have been previously shown to have important roles in fibrogenesis. As pro-inflammatory cytokines are known to induce high levels of reactive oxygen species (ROS) causing DNA damage, we analyzed DNA damage response (DDR) in PV progenitors in vitro and in vivo. We show that both DDR markers, gH2AX and ATMpS1981, were weakly detectable in PV, with increased trend of gH2AX and ATMpS1981 foci accumulation in later disease stages. The same applied for the presence of oxidative-stress marker 8-Oxoguanine, suggesting involvement of protection mechanisms against inflammation-evoked DNA damage, thus allowing rapid propagation of premalignant clone in inflammatory BM microenvironment and creating a barrier that delays transformation of chronic myeloproliferation to senescence-associated fibrosis. As the main source of DNA damage induced by inflammatory cytokines is mediated by ROS, we have measured activity of ROS-buffering anti-oxidative system. We observed significantly increased intrinsic and inflammation-stimulated activity of most of the tested enzymes (G6PD, glutathione reductase, glutathione peroxidase and 6-phosphogluconate dehydrogenase) in V617F cells, compared to wild-type cells, suggesting metabolic protection against inflammation-induced DNA damage in PV, which might be overrun in later disease stages by gradually increasing cytokine storm. If we take into account recently published function of DNA helicase RECQL5, which acts as a suppressor of replication stress-associated genomic instability in MPNs, addition of our data create a novel model of multi-level protection of premalignant clone in PV, with cooperative interplay between the cell-intrinsic and tissue environment-dependent fail-safe mechanisms that jointly serve as a barrier that delays transformation of chronic myeloproliferation to senescence-like condition in myelofibrosis. Support: GP14-10687P.

2991. GENE VARIANTS OF THE ATM-NFKB-IL6 SIGNALING AXIS: IMPLICATIONS IN PREDICTION OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) RELATED COMPLICATIONS

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Introduction Acute and chronic Graft-versus-Host Disease (aGVHD/cGVHD) – donor's immunocompetent cells mediated adverse reaction damaging target organs and tissues of HSCT recipients and conditioning regimen-related gastrointestinal toxicity (RR-GIT) as result of chemo(radio)therapy preceding grafting represent the most frequent causes of non-relapse mortality and morbidity in allografted patients. ATM-NFkB-IL6 axis links DNA-damage response (DDR) with inflammatory signaling. We hypothesize that analysis of germline genetic variation of genes implicated in DDR and senescence-associated inflammatory signaling could provide a tool for prediction of HSCT-related complications. Patients and Methods In a single-center study, we analyzed 109 patients allografted between 2009-2015 for: AML (41%), MDS/MPN (19%), ALL (17%), CLL (8%), NHL (6%), CML (4%), and other hematological disorders (5%). The median age of the cohort was 50 (20-63) years. Patients were allografted after myeloablative (14%), non-myeloablative (20%) and reduced intensity/toxicity (66%) conditionings from HLA identical donors (matched-related 40%). GVHD prophylaxis was done by solo cyclosporine-A (76%) or cyclosporine-A and mycophenolate mofetil (20%) or low-dose methotrexate (4%). Patients were genotyped for 5 single-nucleotide polymorphisms (SNPs) (rs4585 T/G, rs189037 A/G, rs227092 T/G, rs228590 C/T, and rs664677 T/C) of the ATM gene,

2 SNPs (rs3774937 C/T, rs3774959 A/G) of the NFKB1 gene and 1 SNP (rs1800795 G/C) of the IL6 gene. SNP genotyping was performed with Sequenom MassARRAY platform using allele-specific MALDI-TOF mass spectrometry assay (Sequenom, San Diego, USA). Primers were designed using the Sequenom SNP Assay Design software version 3.0 for iPLEX reactions. Logistic regression was used in the study with significance level set to 0.05. Results During the post-transplant neutropenic period 78 recipients (72%) suffered from RR-GIT. Grade I/II and III/IV were documented in 48 (44%) and 30 patients (28%), respectively. Thirty-three patients (30%) developed aGVHD. Grade I/II and III/IV were observed in 20 (18%) and 13 recipients (12%), respectively. Twenty-seven of 91 evaluable patients (30%) developed cGVHD and extensive form was observed in 14 patients (15%). The type of conditioning, ATM gene haplotypes (rs4585*T, rs189037*A, rs227092*T, rs228590*C, and rs664677*T), female sex, and EBMT score were associated with RR-GIT grade III-IV [OR=3.0, 95%CI(1.8–5.1) p=0.004; OR=9.7, 95%CI(2.0–47.0), p=0.006; OR=2.4, 95%CI(1.0–5.6), p=0.05; OR=2.1, 95%CI(1.4–3.2), p=0.0001, respectively]. The effect of the ATM haplotype was maintained after accounting of the above mentioned risk factors in the multivariate analysis (p=0.006). Patients homozygous for NFKB1 gene haplotypes (rs3774937*T, rs3774959*G) were at lower risk for aGVHD (OR=0.12, 95%CI [0.03-0.52], p=0.005). Furthermore, patients homozygous and heterozygous for NFKB1 gene protective haplotype (haplotype carriers) had significantly less cGVHD (OR=0.1, 95%CI [0.02-0.58], p=0.01 and OR=0.13, 95%CI [0.02-0.74], p=0.02, respectively). Moreover, patients homozygous for both protective haplotypes suffered from the extensive form of cGVHD less frequently (p=0.04). We have not confirmed any significant impact of the IL6 gene SNP on aGVHD and/or cGVHD. Conclusions This is the first report addressing ATM-NFkB-IL6 signaling in HSCT setting. Based on our preliminary data ATM--NFkB-IL6 signaling merits further investigation which may bring new information for patients' pre-transplant risk assessment. Supported by IGA_LF_2016_001

3002. A NOVEL MUTATION OF RIBOSOMAL PROTEIN S7 IN THREE FAMILY MEMBERS WITH MARKEDLY DIFFERENT SEVERITY OF DIAMOND-BLACKFAN ANEMIA IN A SINGLE FAMILY

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We present here the case of three women suffering from macrocytic anemia with markedly different severity, in whose a new mutation of gene coding for ribosomal protein S7 (RPS7) was identified. However, severe anemia with the need of repeated transfusions was diagnosed in the youngest female patient at newborn age only. She had normal birth weight, no physical anomalies were found. Until one year of age, she was transfusion-dependent. She showed a good response to steroids, and has been steroid-dependent for the last 10 years (intermittent low dose). The mother and older sister were examined within the family genetic counseling. Interestingly, they were diagnosed with mild macrocytic anemia, however, never required any treatment. In all three women, increased erythrocyte adenosine-deaminase (e-ADA) was proved with the highest levels in the patient and lowest in her mother, respectively (5.29±0.340, 4.18±0.150, 3.20±0.218 IU/g Hb, reference range: 0.8-2.5IU/g Hb). So far, only five RPS7 mutations clinically associated with DBA were published, all of them in splice sites. We found novel heterozygous nonsynonymous mutation g[3580153G>T] in exon 6 of the RPS7 gene leading to V134F substitution in all three women. Subsequently, this mutation was confirmed by Sanger sequencing method on both gDNA and cDNA levels. Furthermore, role of the RPS7 V134F mutation was established on the cellular model. MRC-5 fibroblasts (deficient for RPS7) were transiently transfected with plasmid construct carrying WT and V134F RPS7 cDNA. Mutant but not WT transfectants exhibited altered protein synthesis, nucleolar and ribosomal stress, consistent with previously reported cellular phenotypes in DBA patients. Patients described previously for the RPS7 mutations in splice sites showed milder form of DBA compared to our V134F patient and similarly had only minimal physical anomalies. Our DBA patient is to the best of our knowledge the first case identified with pathogenic heterozygous nonsynonymous mutation of RPS7 gene and demonstrates the importance of complex diagnostics and validation of sequence alterations in suspect DBA individuals. Grant support: Czech Science Foundation (GA15-13732S) and Ministery of Health of the Czech Republic (AZV 16-32105A).

2985. CHROMATIN DEFECTS INDUCED UPON KNOCKOUT OF MAJOR CHROMATIN REMODELING FACTOR ISWI ATPASE SMARCA5 IN MOUSE ARE SENSED VIA P53 PATHWAY AND BLOCK CELL CYCLE PROGRESSION

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Chromatin structure is a major prerequisite of proper developmental processes. Chromatin structure is established, maintained and disrupted by SWI/SNF2 superfamily of ATP-dependent helicases. Sensing of irregularities of chromatin structure is not fully understood. Subfamily of ISWI ATPases has been proposed to regulate developmental processes although the particular mechanisms of its activity were elusive. We herein utilized conditional deletion of major ISWI member, Smarca5, in murine early thymic progenitors. Phenotype of Smarca5 mutants is not indicative of being mediated via defective T-cell receptor (TCR) rearrangement or dysregulation of gene repair. Smarca5 deficiency resulted in proliferation defect together with activation of DNA damage pathway. Production of double Smarca5-/- Trp53-/- mutants partially restored proliferation blockade but neither rescued developmental disruption of the thymocyte development nor aggravated lymphomagenesis in the Trp53-/- mutants.

SYMPOSIUM ON ADVANCES IN MOLECULAR HEMATOLOGY 3: STATE OF THE ART INVITED LECTURE

3003. DNA DAMAGE RESPONSE, AGING AND CANCER: MECHANISMS AND OPPORTUNITIES FOR TREATMENT

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Abstrakt sdělení není k dispozici.

KONFERENCE OŠETŘOVATELSTVÍ 2

2983. VÝBĚR OPTIMÁLNÍHO ŽILNÍHO VSTUPU S OHLEDEM NA SPECIFIKA HEMATOLOGICKÉHO A HEMATOONKOLOGICKÉHO PACIENTA

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Hematologie a hematoonkologie jsou obory, které využívají dominantně parenterální formu léčby, a proto je správný výběr žilního přístupu stěžejní pro optimální aplikaci léčiv. Využíváme přitom vstupů krátkodobých, střednědobých i dlouhodobých. Volba žilního přístupu je výsledkem rozvahy, hodnotící charakter a délku podávané léčby, vlastnosti pacienta a stav žilního systému. V případě indikace centrálního přístupu nejčastěji volíme mezi klasickou centrální kanylou (netunelizovanou), tunelizovanou centrální kanylou, PICC (centrální kanylou zaváděnou z periferie) a portem. Každý z těchto druhů vstupů má své výhody i nevýhody, a to nejen při inzerci, ale především při dlouhodobém používání, kdy je pacient obecně vystaven vyššímu riziku komplikací, a to především infekčních a trombo-