K104903 final report

Title: Relationship of genetic variant-combinations of the innate immune system with disease susceptibility and therapeutic outcome in haematological malignancies

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During the grant period (01.01.2013- 31.12.2017) our research focused on three main aims:

I. Establishing and extending databases of patients with hematologic malignancies [acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), myeloproliferative neoplasm (MPN), multiple myeloma (MM)] and patients suffering from hematologic neoplasms treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT, n=426). Clinical characteristics were collected in collaboration with St. István & St. László Hospital (Budapest).

II. Characterization and monitoring of somatic mutations, other molecular markers. Detailed characterization of the acquired genetic background allows the investigation of the effect of inherited variants in subgroups with more homogenous aetiology. Monitoring by quantitative molecular methods is necessary to describe the depth of response, which is a surrogate marker of treatment outcome.

III. Genotyping of germline variants influencing innate immune system to identify predisposing, predictive or prognostic markers. Predisposing alleles increase disease susceptibility, prognostic markers provide information about the outcome independently of treatment, while predictive markers provide outcome information specifically about different treatment regimens.

Results

II/A. Characterization and monitoring of acquired somatic mutations in AML

Mutations of *isocitrate dehydrogenase 1 and 2 (IDH1/2)* are genetic alterations in AML. We investigated the frequency and prognostic effect of *IDH1/2* mutations in 376 AML patients. *IDH1* and *IDH2* mutations were mutually exclusive, detected in 8.5% and 7.5% of cases, respectively. *IDH1* or *IDH2* mutations were associated with older age, higher platelet count, intermediate karyotype and nucleophosmin (*NPM1*) mutation. Overall survival, remission and relapse rates were not different in *IDH* positive compared to negative patients. *IDH* mutations were associated differently with *NPM1*. Our observations showed that particular amino acid changes affecting *IDH* proteins differentially influence the clinical characteristics and treatment outcome. (*Koszarska, 2013*)

Internal tandem duplications (ITDs) of the fms-like tyrosine kinase 3 (FLT3) gene occur in about 25% of AML patients. We performed a detailed analysis of mutational load and size of insertions in 324 AML patients. *FLT3*-ITD alone did not influence survival. Worse survival was observed in patients with high mutational load. Patients with medium sized *FLT3*-ITD (48-60bp insertions) showed the worst survival. Our novel observation suggested that not only high *FLT3*-ITD load, but also medium-sized ITD represented an adverse prognostic subgroup in AML. (*Koszarska, 2014*)

II/B. Characterization and monitoring of acquired somatic driver mutations in MPN

Since the discovery of the Janus kinase 2 (*JAK2*) V617F mutation in the majority of *BCR-ABL1* negative MPN, further MPN-specific mutational events, notably in *JAK2* exon 12, and thrombopoietin receptor (*MPL*) exon 10 and calreticulin (*CALR*) exon 9 have been identified. Our group was one of the first laboratories in Hungary that incorporated these novel genetic tests in diagnostic panels. We also participated in an international collaboration that aimed standardisation of quantitative molecular techniques in MPN. (*Langabeer, 2015*)

We performed extensive characterisation of MPN patients (n=949) with the detection of mutually exclusive driver mutations in *JAK2*, *CALR* and *MPL* genes. A complex array of molecular techniques (qualitative and quantitative allele-specific polymerase chain reactions, fragment analyses, high resolution melting and Sanger-sequencing) was applied. All 354 patients with polycythemia vera (PV) carried *JAK2* mutations (V617F 98.6%, exon 12: 1.4%). In essential thrombocythemia (ET, n=468), the frequency of V617F was 61.3%, *CALR* 25.2%, and *MPL* mutations 2.1% (n=10), while 11.3% (n=53) were triple-negative. Similar distribution was observed in primary myelofibrosis (PMF, n=127): 58.3% *V617F*, 23.6% *CALR*, 6.3% *MPL*-positive and 11.8% (n=15) triple-negative. The definite molecular diagnostics became available in >90% of MPN cases. (*Krähling, 2014, article in Hungarian*).

In a subset of ET and PMF cases, more detailed comparisons were performed. *CALR*$^+$ patients were younger, had higher platelet counts compared to *JAK2*$^+$ counterparts. In addition, *CALR*$^+$ patients with ET showed lower risk for venous thrombosis. *CALR*$^+$ patients with PMF showed better overall survival compared to the *JAK2*$^+$ or triple-negative cases. *CALR* type 2 mutation occurred more frequently in ET compared to PMF. In ET, *CALR* mutational load was higher than JAK2 mutational load, and increased gradually in advanced stages. We confirmed, that *CALR* mutation is associated with distinct clinical characteristics and extended these observations to relationships between mutation type, load and clinical outcome. (*Andrikovics, 2014*)

The main complication of *BCR-ABL1*-negative MPNs is deep vein thrombosis. Identification of triggers is a major issue in MPN. We evaluated the possible effect of lipocalin 2 expression on thrombotic events in MPN patients. According to our data, lipocalin 2 may be useful in thrombotic risk stratification in MPN. (*Rajnics, 2016*)

II/C. Monitoring of CML

During the time period of the current grant, our group participated in an international research in relation with the improvement of the molecular follow up of *BCR-ABL1*$^+$ CML as the Hungarian reference laboratory. Detection of *BCR-ABL1* transcripts by quantitative PCR (QPCR) has been proven to be a sensitive molecular diagnostic method to measure leukemic-cell burden in CML. The initial standardization process covered the range of 1-4 log reduction of *BCR-ABL1* expression. Recommendations for deep molecular responses (DMR below 4-log reduction) were recently defined. Our laboratory participated in three external quality controls to harmonize DMR assessment and in two trials for external reference materials: plasmid calibrator (*White, 2015)* and secondary reference panel (*Cross, 2016)* Our laboratory organised the standardization in Hungary (*Andrikovics, 2013*; Andrikovics, *2017, in press, articles in Hungarian*).

The concomitant occurrence of two diseases (*BCR-ABL1*$^+$ CML and *JAK2*$^+$/*CALR*$^+$ MPN) in the same patient has been reported as an extremely rare event. We performed a comprehensive genetic analysis of sequential samples obtained from 7 patients with concurrent BCR-ABL1 and *JAK2* V617F or *CALR* mutations. Further 10 genes frequently mutated in MPNs were analysed by next generation sequencing. The quantitative analyses of the mutations suggested that driver mutations occurred in different clones in 5/7 cases. Additional somatic mutations were identified in 4 cases (*DNMT3A*, *ASXL1*, *TET2*). (*Bödör, 2016 abstract*) Since our poster presentation, further 11 cases have been identified in four laboratories in Hungary. Detailed description of cases and the review of the literature will be included in our collaborative publication (*Bödör; J Mol Diagn; manuscript in preparation*)

III/A. Genotyping of germline variants in relation to HSCT

With the help of our database, our clinical partners summarized the 2548 haematopoietic stem cell transplantations (HSCT) performed during 1993-2015 in Szt. László Hospital, Budapest with a more detailed discussion of the 425 allogeneic HSCT (allo-HSCT) between 2007-2013. (*Bátai, 2017, article in Hungarian*)

The role of human leukocyte antigen (HLA) in allo-HSCT outcome is unarguable. We investigated the association of HLA-A,-B and-DRB1 alleles with overall survival (OS) in 186 patients undergoing allo-HSCT for lymphoid malignancies. Analyses confirmed better OS for HLA-DRB1∗04 carriers compared with non-carriers (confined to male patients). Donor gender also affected outcome. Combined analyses showed the best survival among male HLA-DRB1∗04 carriers transplanted from female donors. Our observation highlighted, that in contrast to general favour of male donors, HLA-DRB1∗04 carriers with lymphoid malignancies could benefit from HSCT with female donors. (*Balassa; 2018*)

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a feared complication of allo-HSCT. We studied the frequency, clinical associations and prognostic effect of TA-TMA, in 425 allo-HSCT patients. The cumulative incidence of TA-TMA was 19% (80/425). The majority of TA-TMA patients (83%) also suffered from acute graft versus host disease (aGvHD). As a novel risk factor we identified HLA-DRB1*11 carriership. Among patients with TA-TMA, the outcome of HLA-DRB1*11 carriers was significantly better compared to non-carriers. (*Balassa, 2015)*

In another study we compared HLA diversity (HLA-A; -B and -DRB1) in the Hungarian population (voluntary bone marrow donors, n=2404) with surrounding European populations (Austria, Croatia, Czech Republic, Romania and Serbia). In addition the Hungarian Gypsy Minority population (n=186) was compared with two other Gypsy cohorts (Spain Andalusia Gypsy and India North Gujarat). This was the first comprehensive investigation of HLA distribution in Hungary. (*Inotai, 2015)*

Perfect HLA match is an important factor for successful HSCT. Null alleles represent a significant risk for aGvHD or graft failure. C*04:09N is defined as „common" null allele, coded by a single nucleotide substitution outside the regions routinely sequenced. Typing 6076 unrelated Hungarians, the haplotypes, that presumably contain this null allele, were present in 107 chromosomes (0.9%), but none of them carried C*04:09N allele. Our results highlight the importance of local data for genetic traits and have implications for the routine histocompatibility testing. (*Bors, 2015*)

Recognition of recipient's HLA-C2 group alleles by the activating killer immunoglobulin like receptor (KIR), KIR2DS1 on donor natural killer (NK) cells may lead to increased graft versus leukaemia effect in allo-HSCT patients. In patients with myeloid malignancies (n=314), recipients with HLA-C2 group allele (rC2) showed improved OS if transplanted with KIR2DS1 positive donor (dDS1) compared to those without one or both of this genetic attribute. KIR genotyping might have an influence on donor selection before allo-HSCT. (*Bors, 2015 abstract; Tordai, 2018; under submission*)

The role of cytokines in aGVHD is well established and many of the involved cytokines signal through the Janus kinase pathways. We assessed the association of recipient and donor *JAK2* 46/1 haplotypes and allo-HSCT outcome in a cohort of 124 AML patients. Both, recipient and donor 46/1 haplotypes significantly affected aGVHD development, furthermore the influence of the haplotypes seemed to be additive. We observed significantly less relapses among haplotype carriers, but OS did not differ. Our findings suggest that recipient and donor *JAK2* 46/1 haplotypes might be involved in the regulation of aGVHD. *(Balassa, 2017)*

Transforming growth factor B1 (*TGFB1*) is an inflammatory cytokine, which play a pivotal role in the development of aGvHD. W investigated the role of *TGFB1* -1347C>T polymorphism in the outcome of 419 allo-HSCT patients. We did not find any association between recipients' TGFB1 genotype and HSCT outcome, but donor's *TGFB1* genotype influenced OS, and the frequency of severe aGvHD in myeloablative conditioning. (*Meggyesi, 2017; abstract*).

Further polymorphisms of *NOD2*, *TLR2*, *TLR4*, *NFKB1*, *CTLA4*, *SUFU*) have been genotyped in our HSCT cohort, statistical analyses, manuscript preparations are in progress.

Besides haematological disorders, we investigated polymorphism of the innate immunity in other diseases like spontaneous bacterial peritonitis (SBP) in liver cirrhosis. According to our data, advanced disease stage and prior history of SBP were the major risk factors of subsequent bacterial infections. Pattern recognition receptor genetic profile (*NOD2*, *TLR2* and *TLR4*) was not able to predict the long-term disease course in cirrhosis. (*Dinya, 2017*)

III/B. Genotyping of germline variants in relation to MM

Nuclear factor kappa B1 (*NFKB1*) plays an important role in myeloma, and bortezomib works through this pathway. We analysed the effect of *NFKB1* -94ins/delATTG polymorphism in 135 myeloma patients treated with bortezomib-based front line chemotherapy. The median progression free survival (PFS) was significantly longer in patients with homozygous insertion genotype compared to carriers of the deletion allele (902 vs. 639 days). This difference was even more prominent in the more favourable prognosis subgroups (younger age, low international prognostic score, low risk cytogenetics), and proved to be significant in multivariate analysis, too. *NFKB1* -94insATTG homozygous patients benefit more from bortezomib-treatment than patients carrying the deletion allele. (*Varga, 2015*)

Proteasome subunit beta type 1 (*PSMB1*) rs12717 polymorphism, was recently reported to influence response to bortezomib-based therapy in follicular lymphoma. We analysed the prognostic impact of the same polymorphism in 211 MM cases, and performed in vitro experiments to look into its functional consequences. Patients carrying the variant G allele showed significantly shorter PFS with a pattern suggestive of a gene-dose effect (PFS CC: 26.4, CG: 22.3, and GG:16.4 months). In vitro analyses demonstrated significantly reduced protease activity in proteasomes of GG compared with that of CC individuals. Bortezomib exhibited a lower inhibitory capacity on the caspase- and trypsin-like activity of proteasomes from GG

individuals. Our results show that carriership of *PSMB1* minor allele is predictive for suboptimal response with bortezomib. *(Varga, 2017)*

Fibroblast growth factor receptor 1 oncogene partner N-terminal like gene (*FOPNL*) rs72773978 polymorphism was identified as an adverse prognostic factor in MM. In our MM cohort (n=373), *FOPNL* polymorphism showed differential prognostic effect that depended on the treatment applied. (*Kiss; 2018*)

III/B. Genotyping of germline variants in relation to MPN

The germline telomerase reverse transcriptase (*TERT*) rs2736100_C variant was identified as a susceptibility factor for solid tumours and MPN. *TERT* rs2736100_C showed an increased allele frequency in *BCR-ABL1* MPN patients (63%, n=584) compared to controls (49%, n=400). Combined *TERT* and *JAK2* hetero- or homozygosity conferred even higher risk for MPN. Adverse survival was noted in *TERT* carrier PV patients due to higher probability of solid tumours (44% vs 5%). *TERT* carriers had increased risk of solid tumours independently from cytoreductive treatment. (*Krahling, 2016*)

Further publications, not tightly linked to the topic of the NKFIH grant was acknowledged the grant support *(Bors, 2015; Reményi, 2016)*. To summarize the publication activity of the reporting period, our group accomplished 19 international and 4 Hungarian publications, 3 abstracts in relation to the scope of the current grant.

Publications:

International publications in relation to NKFIH 104903 grant (17 articles, 3 abstracts):

Andrikovics H, Krahling T, Balassa K, Halm G, Bors A, Koszarska M, Batai A,Dolgos J, Csomor J, Egyed M, Sipos A, Remenyi P, Tordai A, Masszi T. Distinct clinical characteristics of myeloproliferative neoplasms with calreticulin mutations. Haematologica. 2014 Jul;99(7):1184-90.

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