P981 NEXT GENERATION SEQUENCING (NGS): AN IMPORTANT TOOL TO CHARACTERIZE MYELOPROLIFERATIVE DISEASES IN CHILDREN

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Background:

Mutations in the JAK2, MPL and CALR driver genes are reported in over 90% of adults with BCR-ABL1-negative chronic myeloproliferative neoplasms (MPNs) and in 22-40% of children, where inherited forms, such as familial erythrocytosis (FE) and hereditary thrombocytosis (HT), are common. Next Generation Sequencing (NGS) is useful to identify clonal markers, other than those found using standardized methods.

Aims:

This study was carried out in order to: a) confirm the results obtained in our preliminary experience, using NGS in a larger number of children and adolescents with myeloproliferative diseases (MPDs); b) identify non-canonical driver and/or non-driver mutations in patients (pts) with MPDs; c) evaluate long-term outcome of disease in different subgroups of pts.

Methods:

86 pts (46 male, 41 female; median age at diagnosis: 15 years) with a BM evaluation, molecular analysis for driver mutations for MPN (JAK2V617F, JAK2 exon 12, CALR, MPL), and genes involved in the FE (HIF2α) and HT (MPL), were studied in NGS.

Results:

Driver mutations were found in 52/87 pts (60%) (16 JAK2V617F, 10 CALR, 21 MPLS505N, 2 MPLV501A, and 3 HIF2α). A 44-NGS gene panel providing diagnostic information in myeloid malignancies and in rare inherited erythrocytosis/thrombocytosis were performed in 71/86 pts (82.5%), 28 of them (39.5%) without any mutations. The 44-NGS gene panel detected non canonical driver mutations in 5/28 (18%) triple negative pts, and additional non canonical driver mutations in 2 JAK2V617F and CALR type 2 pts. Overall, driver mutations were found in 61/86 (71%) of pts. The NGS panel revealed 28 additional functional non-driver mutations (12 mutations in 5 genes of the signaling group, 5 mutations in 2 genes of the mRNA splicing group, 6 mutations involving the ASXL1 gene of the histone modification group, and 5 mutations involving 2 genes of the DNA methylation group) in 29 pts, 16 of them with no driver mutations.

Pts with acquired MPNs were retrospectively classified according to the WHO 2016 criteria; pts with HIF mutations and/or anamnestic criteria of familial erythrocytosis were considered as FE, pts with MPLS505N, or MPLV501A mutations were defined as HT (Table1). One or more non-driver mutations were found in 17/37 (46%) TE, 4/15 (26.5%) PV and mPV, 6/9 (66.6%) FE pts, and in 0/23 HT pts. During follow-up, 20 pts (12 ET, 5 HT, 2 PV and 1 pre-PMF) presented progressive splenomegaly, after a median of 120 months; in addition, 10 (6 ET, 3 HT, and 1 pre-PMF) of them developed a ≥2 BM fibrosis, after a median of 188 months. Considering driver mutations, 8/20 pts were JAK2V617F mutated, 5 had CALR mutations, and 5 were MPLS505N mutated; 2 pts were wild type. One or more additional non-driver mutations were present in 3/5 CALR, and in 3/8 JAK2V617F mutated pts. Overt MFI developed in 3 pts, 2 of them needed hematopoietic stem cell transplantation. Two pts developed a malignant neoplasia. Six (7%) pts, 3 MPLS505N, 2 JAK2V617F, and one wild type, without thrombophilic abnormalities, experienced a
thrombotic event. All pts are alive after a median time of 15 years from initial diagnosis.

Summary/Conclusion:

In our experience, the use of a 44-gene NGS panel enabled us to identify non canonical driver, and functional non-driver mutations, in addition to those detected by conventional methods, in about 90% of pediatric pts with acquired and familial MPDs. Additional clonal mutations have been identified in two thirds of FE pts, but none in HT pts. Interestingly, the development of BM fibrosis was observed in pts with HT, but not in FE group.