Title: ATHEROTHROMBOTIC RISK ASSESSMENT DURING TYROSINE KINASE INHIBITORS TREATMENT IN CHRONIC MYELOID LEUKEMIA PATIENTS: NEW INSIGHT?

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Introduction: Peripheral Arterial Occlusive Disease (PAOD) has been reported in chronic myeloid leukemia (CML) patients (pts) treated with second generation Tyrosine Kinase inhibitor (TKI) nilotinib (NIL). To explore potential underlining mechanisms, we investigated genetic and biochemical traits associated with vascular events, in CML pts treated with TKIs.

Methods: 110 CML pts, 58 on imatinib (IM) and 52 on NIL (median treatment time 84 mos, range 12-180, and 56 mos, range 3-228, respectively), all in complete cytogenetic response, were studied. Pts were screened for PAOD a/o other atherothrombotic episodes and evaluated for: traditional cardiovascular risk factors (TCRF) (Diabetes Mellitus, Dyslipidemia, Blood Pressure, Body Mass Index, Smoke, Familiarity); sCD40L, Endogenous Thrombin Potential (ETP); oxidized LDL (oxLDL) level; IL6, IL10 and TNFα pro/anti-inflammatory cytokines network; intron 4 IVS4-14 A>G polymorphisms of OLR1 (rs3736235), encoding for the oxidized LDL receptor 1 (LOX1) to evaluate the distribution of genotypes AA (cardiovascular low risk), AG and GG (cardiovascular high risk).

Results: The distribution of classical risk factors showed a slight prevalence of dyslipidemia in the NIL cohort. Similarly, the presence of 3 or more TCRF was more frequent in the NIL group. In the IM cohort 3/58 (5%) pts experienced an atherothrombotic event (1 PAOD, 2 carotid occlusion major than 50%), while in the NIL cohort 14/52 (27%) atherothrombotic events were documented (9 PAOD, 5 acute coronary syndrome) (p= 0.00011).

LOX-1 polymorphism was evaluated in all 110 pts and genotype frequency respected the Hardy-Weinberg equilibrium with other populations of ancestral Caucasian origin. However, when considering the genotype frequency according to TKI treatment, we found a slight excess of homozygotes A/A in the IM group and a significant excess of homozygotes G/G in the NIL treated cohort. Interestingly the homozygotes G/G clustered in the NIL sub-group with history of atherothrombotic events during treatment.

Multivariate analysis showed that once corrected for age, sex, BMI and each applicable, biochemical and genetic data available at the moment of event recording or clinical observation if event-free; the single influencing risk factor was the G/G homozygosis for IVS4-14A/G of OLR1 in the NIL group (Fig.1). No significant influence was detected for each single traditional risk factor, despite the slight increase of dyslipidemic subjects in the NIL group (Fig.1). Furthermore, the clustering of 2 or ≥3 TCRF was not associated with the increased risk of cardiovascular events during treatment with both TKIs (Fig. 1).

In addition, we found significant differences in many biochemical parameters evaluated: oxLDL, sCD40L level and ETP were significantly higher in NIL vs IM treated group, while IL10 level, inversely related to ox-LDL, sCD40L and ETP, was significantly lower.

Discussion: Our data suggest no influence of classical risk factors in atherothrombotic risk during TKI treatment, while an unbalance of pro/anti-inflammatory cytokines network observed in NIL

pts, together with genetic pro-atherothrombotic predisposition conferred by LOX1, may have a role in the increased incidence of vascular events. With the ultimate intent to achieve a "personalized" TKI treatment, we are conducting a prospective study, in newly diagnosed CML pts treated front line with any TKIs, in order to identify a genetic/biochemical tool able to early detect pts at potential increased atherothrombotic risk.