4015 Efficacy and Safety of Dasatinib in Late Suboptimal Response CML Patients a Its Relation with Lymphocytosis, Lymphocyte Migration and Chemokine Receptor Expression.

Chronic Myeloid Leukemia: Biology and Pathophysiology, excluding Therapy
Program: Oral and Poster Abstracts
Session: 631. Chronic Myeloid Leukemia: Biology and Pathophysiology, excluding Therapy: Poster III
Monday, December 7, 2015, 6:00 PM-8:00 PM
Hall A, Level 2 (Orange County Convention Center)

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INTRODUCTION: In patients with so called “late suboptimal responses” (patient with complete cytogenetic response (CCyR) without major molecular response (MMR) after 18 months of imatinib) , the role of dasatinib has not been evaluated. Dasatinib has unique immunomodulatory effects especially on the proliferation and activation of T- and NK-cells. Yet, how dasatinib affects the migration of lymphocytes is unknown. DASAPOST is the first clinical trial evaluating efficacy and safety of dasatinib in patients with late suboptimal response (now considered as ELN2013 as warning). Another aim

is to correlate new immunological aspects related to dasatinib and its possible correlation with responses.

METHODS: We are presenting results of first 18 patients enrolled in the phase II DASAPOST study (NCT01802450). Main inclusion criteria were patients treated with late suboptimal response by ELN09 (CCyR without MMR after 18 months of treatment. Sokal risk groups were (L/I/H) 22.5%, 50% and 22.5%. All BCR-ABL/ABL (IS) measurements were centralized in an EUTOS laboratory. An exhaustive lymphocyte migration study was done, including immunophenotipying pre and post samples (CD 45, CD3,CD8, CD16, CXCR3, CXCR4, CD56 and CCR7), migration assay (chemokines CXCL10, CCL19+CCL21 and CXCL12) and CXCL10 plasma concentration measured by ELISA.

RESULTS:

- Clinical: Median follow up was 288 days (100-380). Three out of 18 (16%) patients had discontinued dasatinib due to side effects (pancreatitis, pleural effusion and low grade, persistant side effects (fever, arthralgias, anemia and astenia). All patients have been evaluated at 3 months, 17 at 6 months and 11 at 12 months. Cumulative incidences by ITT of MMR by 3 and 6 months were 50% and 81%. Cumulative incidences by ITT of MR4.5 by 3 and 6 months were 18% and 25%, respectively.

- Inmunological: Dasatinib intake induced a significant increase of NK-cells and decrease of percentage of T-cells. Further, it increased CD8+ T cells, while reducing the proportion of CD4+ T-cells among the total T-cells. With the first dose of dasatinib (to), the percentage of CCR7 was lower in CD4+ and CD8+ T-cells in the post-samples. Lymphocyte migration was studied with transwell assays. At t0, post-samples showed a reduced migratory capacity towards the chemokines CCL19 and CCL21 in both CD4+ and CD8+ T-cell subsets. Patients were classified as mobilizers (n=14) or non-mobilizers (n=3) depending on whether they experienced an increase in the absolute lymphocyte counts after the first intake of dasatinib or not, showing different lymphocyte distribution and migratory capacity. In order to study the long term effects of dasatinib, we calculated the fold change (FC) of absolute lymphocyte counts pre- and post-dasatinib intake. Patients were divided into two groups based on whether in the 3 months samples (t3)had a higher (“increase group") or a lower (“decrease group") FC compared with t0. The migratory capacity of these two groups was studied in basal conditions and towards CCL19+CCL21 or CXCL10. We found no differences in basal migration in the “increase “group, while, the basal migration in the “decrease” group was quite promoted at t0 and t3. Further, migration towards CCL19+21 in post-samples is even more inhibited in “increase" patients at t3, whereas in the “decrease" patients the inhibition is diminished. The patients were divided into two groups based on the achievement of MMR at t3. At t0 both patient groups had similar migratory

capacity, however, at t3, responders maintained significantly impaired migratory capacity to CCL19+21, compared with non-responders.

CONCLUSIONS: Our study shows, for the first time to our knowledge, that in patients treated with Imatinib and with late warning responses, switch to Dasatinib induced MMR in 83% of the patients, although 16% discontinued treatment because of toxicity. We reported for the first time that dasatinib has significant effects on lymphocyte migration, and these are associated with early response.

Disclosures: García-Gutierrez: Ariad: Consultancy , Membership on an entity's Board of Directors or advisory committees , Research Funding ; Pfizer: Consultancy , Membership on an entity's Board of Directors or advisory committees , Research Funding ; BMS: Consultancy , Membership on an entity's Board of Directors or advisory committees , Research Funding ; Novartis: Consultancy , Membership on an entity's Board of Directors or advisory committees , Research Funding . Casado: Pfizer: Honoraria , Research Funding ; BMS: Honoraria , Research Funding ; Novartis: Honoraria , Research Funding ; Roche: Honoraria , Research Funding . Sánchez-Guijo: Novartis: Consultancy , Speakers Bureau ; BMS: Consultancy , Speakers Bureau ; Pfizer: Consultancy , Speakers Bureau ; Ariad: Consultancy , Speakers Bureau . Boque: Celgene: Honoraria ; BMS: Honoraria ; Novartis: Honoraria . Muñoz-Calleja: BMS: Research Funding . Steegmann: Novartis: Consultancy , Honoraria , Research Funding , Speakers Bureau ; BMS: Consultancy , Honoraria , Research Funding , Speakers Bureau ; Pfizer: Consultancy , Honoraria , Research Funding , Speakers Bureau ; Ariad: Consultancy , Honoraria , Research Funding , Speakers Bureau .