EFFICACY OF SWITCHING TO DASATINIB IN CHRONIC MYELOID PATIENTS WITH LATE WARNING RESPONSES TO IMATINIB. STUDY OF THE ASSOCIATION OF RESPONSE TO DASATINIB TO IMMUNOLOGIC STATUS

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Abstract: P609

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Background

European LeukemiaNet (ELN) recommendations (2013) advised closely monitoring for patients with late warning response (patients with complete cytogenetic response without major molecular response after 12 months of treatment). Our trial, DASAPOST, has been the first one evaluating efficacy and safety of dasatinib in patients with late warning responses, and preliminary results have been reported (Garcia-Gutierrez et al, ASH 2016; P5450). Besides, many studies suggest that dasatinib may augment responses due to its immunomodulating effect. Although NK and CD8 cells seem to be involved, the specific mechanism remains to be clarified.

Aims

To evaluate the efficacy and safety of switching change to dasatinib in patients treated with imatinib first line during at least 18 months and having a late warning response, and to study the association between response to dasatinib and immune robustness, both baseline and during the therapy, and dasatinib-induced lymphocyte “mobilization”.

Methods

Phase II, open, multicenter DASAPOST study (NCT01802450). Patients previously treated with imatinib after at least 18 months, with CCyR but without MMR, were included. All BCR-ABL/ABL (IS) measurements were centralized in a EUTOS laboratory. Patients not molecularly analyzed at a given time point were considered as non responders, Lymphocyte counts, subpopulations and migration studies were done at baseline (1st day of dasatinib), and every 3 months, and they were done both previous to the dose, and 2 hours after.

Results

From April 2013 to May 2015, 18 patients were enrolled in 12 centers. Median age was 59 years (39-77). The ratio of men to women was 13/5, and the Sokal risk groups were 48%, 30% and 22% for low, intermediate and high risk, respectively. Median time from diagnosis to switch to dasatinib was 2.6 years (1.6-23) and median time while on imatinib to achieve CCyR 1.4 years (0.2-12). Median exposure to imatinib was 2.4 years (1.6-14). Eight patients (44.4%) obtained MMR at 3 months, and 12 (66.7%) obtained MMR at 6 and 12 months. Of interest 9/18 patients (50%) achieved MR4 by 12 months. There were 3 study discontinuations because of toxicity (16%). Table 1 shows the median number of the most relevant lymphocyte populations in the pre-dose sample at baseline. Table 2 shows that the absolute number of CD8 cells was significantly superior at baseline in those patients having a MMR at 3 months, with a trend in the same direction of absolute lymphocyte count and percentage. There were no significant associations with response when considering CD4 T cells, NK cells, or the degree of mobilization after dasatinib dose either in total lymphocyte numbers or in subpopulations. Besides, lymphocyte number or proportions at 3 or 6 months were not associated with MMR at 6 or 12 months (data not shown).

Table 1

	Lymphocytes Baseline	CD8 Baseline	CD4 Baseline	NK Baseline
N (x 10^9/L)	1.78(0.83-3.24)	0.4(0.15-1.43)	0.68(0.43-1.59)	0,20(0.05-0.77)
Percentage	27.4(14.5-39.2)	32,2(15.4-64.8)	65.4(30.4-82.8)	14.1(2.9-40.3)

Table 2

	MMR 3m	No MMR 3m	p
Lymphocytes Baseline (x 10^9/L)	2.23	1.63	0.051
Lymphocytes Baseline (%)	30.4	23.3	0.053
CD8 Baseline (x 10^9/L)	0.62	0,29	0.037
CD8 3 monthd (x 10^9/L)	0,72	0,49	0.088

Conclusion

Our study shows that in patients treated with imatinib and with late warning responses, switching to Dasatinib induced MMR in 2 out

every 3 patients, and MR4 in half of the patients, with a good safety profile. Contrarily to other group reports, we have not found any significant association between response and lymphocyte mobilization in any point studied. Interestingly, the absolute number of CD8 at baseline was significantly associated with the early obtention of MMR at 3 months, a finding which underscore the prognostic importance of baseline immune status, the relevance of CD8 cells in the antileukemic effect,and which suggest that this quite simple variable must be included in future studies with dasatinib in second line.

Session topic: 8. Chronic myeloid leukemia - Clinical

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