Kinetics Of CITED2 Gene Expression In Chronic Myeloid Leukemia Patients

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Background

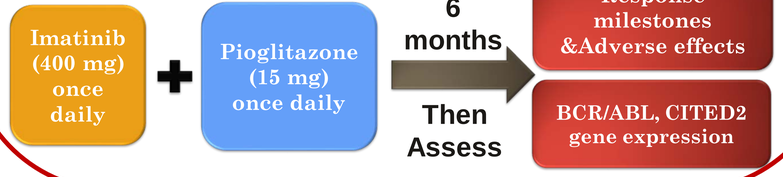
In CML, BCR-ABL1 oncoprotein induces overexpression of STAT5 and its target genes for example CITED2 gene. This gene is involved in regulating the proliferation and quiescence states of leukemic stem cells (LSCs). Recently, studies reported that adding pioglitazone (PPARγ agonist) to imatinib may decrease the transcription of both STAT5 and CITED2 gene, eliminate the quiescent LSCs (resist TKIs) and ameliorate the patients' response.

Objectives

The primary objective is to clarify the value of combining pioglitazone with imatinib to downregulate the CITED2 gene aiming to eradicate the LSCs in CML treatment.

Materials & Methods

In a context of a clinical trial (approved by the ethical Committee of the Faculty of Medicine Mansoura University MD/17.12.30), eligible denovo patients of philadelphia +ve CML chronic phase (N=26) were treated with imatinib 400 mg combined and pioglitazone 15 mg daily for 6 months after having their consent.



Results

The study group included 15 males (57.7%) and 11 females (42.3%) with a mean age of 43.2 years. At 6 months 65.4% and 23% of the patients had response ≥ CCyR and ≥ MMR respectively (figure 1). The most frequent complaints (figure 2) among patients were increased body weight and edema ($p < 0.001$).

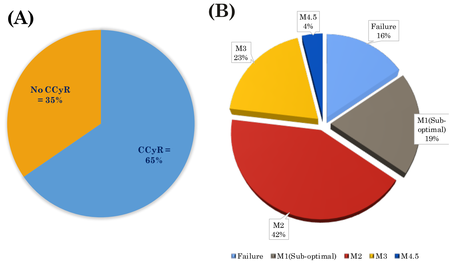


Figure 1: (A)Percentage of patients achieving CCyR at 6 months. (B) percentage of patients achieving different levels of molecular response

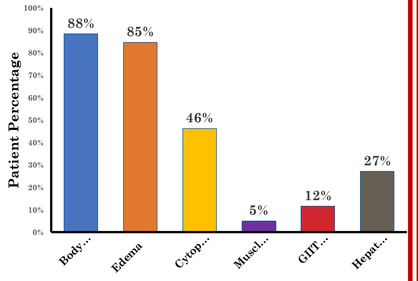


Figure 2: Percentage of patients complaining of different adverse effects

Their median BCR-ABL gene expression before treatment was 79% (range = 0.63-380) that decreased to 3.65% (range = 0.05-20) and 0.750 % (range = 0.002-46) on 3rd ($p=0.04$) and 6th months ($p=0.05$)post-treatment. The median of CITED2 gene pre-treatment and post-treatment expression levels were: 276.3 (range= 1-241221.7) and 2.6 (range= 0.006-86475.3) with a significant decrease in expression *($p=0.005$)* after the combined treatment (figure 3).

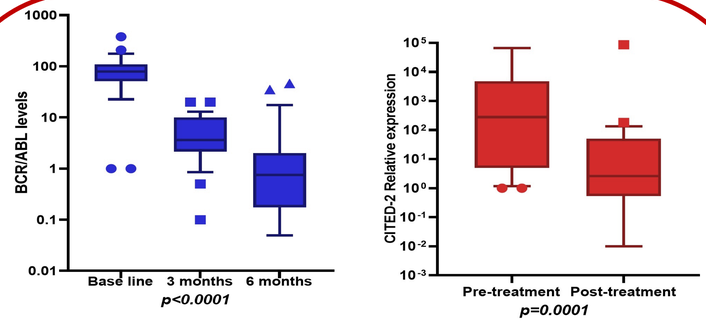


Figure 3: (A) The difference between BCR-ABL gene expression levels (baseline, 3 months and 6 months). (B) The difference between CITED2 relative gene expression levels pre and 6 months post-treatment.

Conclusion

- Pioglitazone in combination with imatinib improved the patients' molecular response and downregulate the expression of both BCR/ABL and CITED2 genes.
- Longer follow up is planned and needed to confirm the safety and efficacy of such combination therapy (whether it can effectively induce more deep molecular response among the patients or not).

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