High frequency of *BTK* and *PLCG2* mutations in chronic lymphocytic leukemia patients on Ibrutinib therapy

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Background and objective

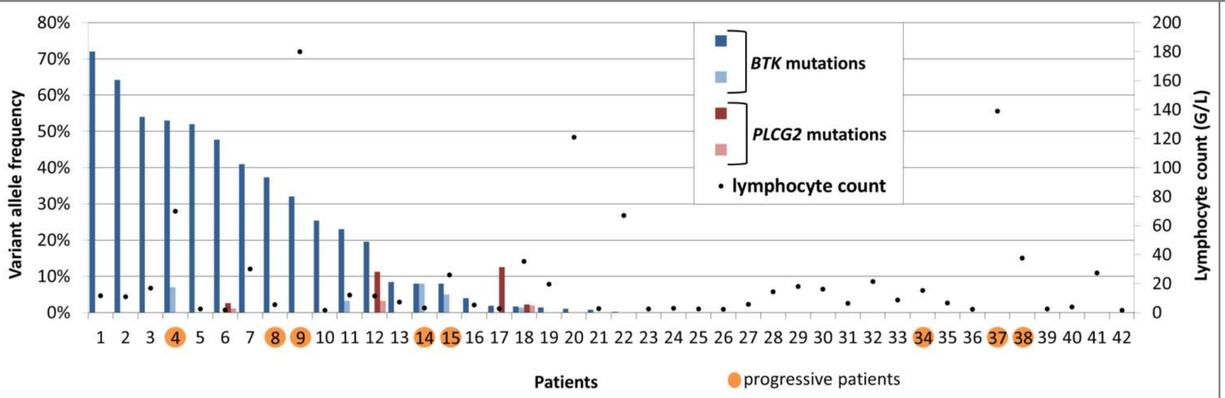
- Targeted therapies such as the BTK inhibitor Ibrutinib profoundly changed the management of patients with CLL.
- *BTK* or *PLCG2* mutations seem to be an important molecular mechanism underlying disease progression on Ibrutinib therapy, with a high frequency in resistant patients [1].
- However, only limited data are available regarding *BTK* and/or *PLCG2* mutations in patients on Ibrutinib without evidence of disease progression [2,3].

The objective of the study is to analyze the CLL genetic profile of patients on Ibrutinib after at least 3 years of treatment.

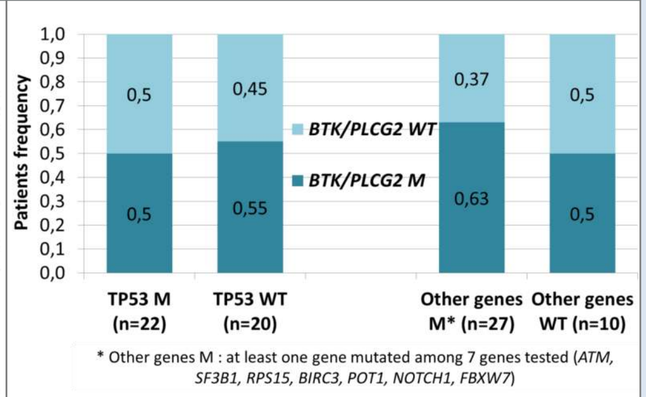
Patients and methods

- 70 CLL patients with relapsed refractory CLL and/or *TP53* alterations on Ibrutinib therapy for several years (median 3 years).
- *BTK*, *PLCG2, ATM, SF3B1, RPS15, BIRC3, POT1, NOTCH1, FBXW7* mutations were investigated by NGS in 42 patients with a CLL cell count >0,5G/L.

Results

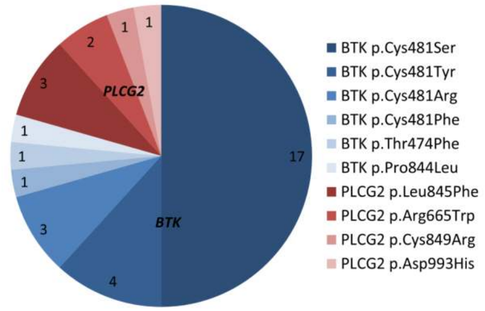


- 22/42 patients (52%) showed at least one mutation of *BTK* and/or *PLCG2*, with no correlation between variant allele frequency (VAF) and lymphocyte count.
- Among progressive patients, 5/8 harbored mutations (VAF ranged from 5 to 53%, median 32%).
- Among non-progressive patients, 17/34 harbored mutations (VAF ranged from 0.2 to 72%, median 20%).



* Other genes M : at least one gene mutated among 7 genes tested (*ATM, SF3B1, RPS15, BIRC3, POT1, NOTCH1, FBXW7*)

- There was no significant difference in the frequency of *BTK* and *PLCG2* mutations according to the mutational status of *TP53* or of the other genes analysed.



- We identified a total of 27 mutations in *BTK* and 7 in *PLCG2*, with a co-occurrence of several mutations (up to 4) in 36% cases (8/22).
- Mutations of *BTK* were mostly located in the cysteine 481 hotspot, with 4 different mutations: p.C481S (c.1442G> C or c.1441T> A), p.C481R and p.C481Y, with a combination of 2 mutations in 5/22 patients.
- We identified 4 different mutations in *PLCG2* : p.L845F, p.D993H, p.R665W and p.C849R, with a combination of 2 mutations in 3/4 patients.

References

1. Woyach, J. A. et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N. Engl. J. Med. 370, 2286–2294 (2014).
2. Woyach, J. A. et al. BTKC481S-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 35, 1437–1443 (2017).
3. Landau, D. A. et al. The evolutionary landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy. Nat. Commun. 8, 2185 (2017).

Discussion and conclusion

Mutations of *BTK* and *PLCG2* are frequent on Ibrutinib therapy, among patients with sustainable response to Ibrutinib.

→ Follow-up will determine if all these mutations are predictive of disease progression.

Mutations of *PLCG2* and *BTK* identified among progressive patients are frequently subclonal.

→ Further studies are needed to determine the mechanism by which these mutations can lead to progression.

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