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Incidence of BTK mutations in chronic lymphocytic leukaemia treated with BTK inhibitors in a single UK institution

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INTRODUCTION

The development of Bruton tyrosine kinase inhibitors (BTKi) has dramatically changed the outcome of patients with chronic lymphocytic leukaemia (CLL), nevertheless some patients still expressed progression. In this setting mutations, involving BTK and PLCG2, have been detected.[1-3] These alterations seem to play a crucial role in BTKi resistance, although data on their incidence, clinical impact and patients' outcome are limited.

AIM

- Analyse clinical features of patients treated with BTKi, identify discontinuation of therapy and response to BTKi
- Identify relapsed/refractory disease (R/R) and perform sequencing for BTK and PLCG2 mutations
- Investigate the differences between R/R patients with and without BTK and PLCG2 mutations

METHOD

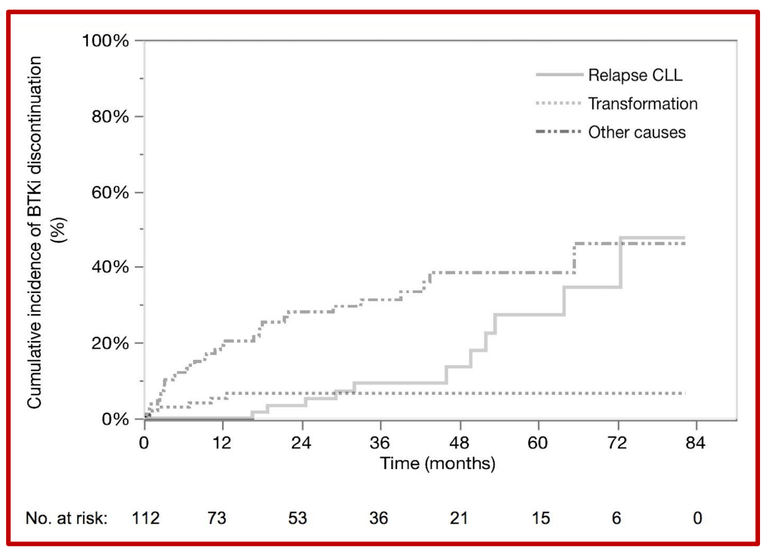
- Retrospective analysis of 115 patients with CLL, treated with BTKi at St James's University Hospital between October 2012 and November 2019, collecting data on clinical characteristics of patients, BTKi discontinuation and response
- Sequencing for BTK (on exon 15) and PLCG2 (exons 19-20) mutations in progressive disease, when material was available. Mutations were considered positive in case of at least 5% of minor allele fraction and 100X read depth of nucleotide variants
- Analysis of clinical characteristics of patients with and without BTK and PLCG2 mutations

RESULTS

Characteristics of population:

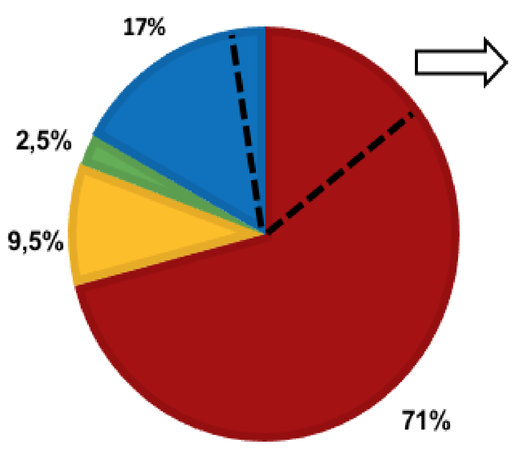
- Median age 68y (42-87), 77% male
- High-aggressive population: 56.5% unmutated IGHV, 29% del17p/TP53 mutation
- FISH: 10% trisomy of 12, 33% del13q, 25% del11q
- 73% R/R CLL, 27% treatment naïve

Cumulative incidence of BTKi discontinuation for relapse, transformation and other reasons



36-month BTKi discontinuation rate of 43.6%

TYPE OF BTKI USED (%)



In 17 patients ibrutinib was associated with:
- rituximab (1)
- obinutuzumab (8)
- venetoclax (8)
Three patients received acalabrutinib + obinutuzumab

Incidence of progression was **18.3%** (95% CI, 10.6-29.7), with 21 R/R patients

At 36 months OS was 72.8% (95% CI, 62.8-80.9) and PFS was 69.6% (95% CI, 58.3-78.9)

Tested **12** out of 21 **R/R** cases for sequencing
- **Cys481 BTK mutations in 5 cases**
- **No PLCG2** mutations detected

Performed sequencing on other **21** patients, still responding to BTKi, **without** any positive result

Characteristics of patients with BTK mutations

Case	Age (y)	Prior therapy	FISH	IGHV	BTKi	TTP (months)
1	63	FCR, Alemtuzumab	17p-	UMUT	I	75.3
2	58	FC+BEAM-Alemtuzumab + Allo-SCT, FCR, BR	11q-	UMUT	I	82.3
3	48	-	17p-	UMUT	I	73.4
4	65	Fludarabine, FCR	13q-	Nd	A	49.4
5	51	FC, BR+Allo-SCT	17p-, 11q-	UMUT	I	62.3

Compared R/R patients with and without BTK mutations:
- Cases with BTK mutation had a **longer exposure time to BTKi** (72.5 months, 56.8-79.2) than those without mutation (35.8 months, 16.5-52.0, p 0.0052)
- Difficult to compare outcome due to small sample size

CONCLUSIONS

- **Although BTKi improved outcome of CLL patients, some of them still progressed**
- **BTKi discontinuation occurred and its timing correlated with the reason of interruption**
- **Mutations have been identified with different BTKi, both in untreated and R/R disease and their occurrence might depend, at least in part, on BTKi exposure**
- **BTK and PLCG2 mutations play an important role in BTKi resistance, but other mechanisms contribute to drug resistance**

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