Estudo de biomarcadores preditivos da resistência à inibidores tirosina quinase em paciente com Leucemia Mielóide Crônica

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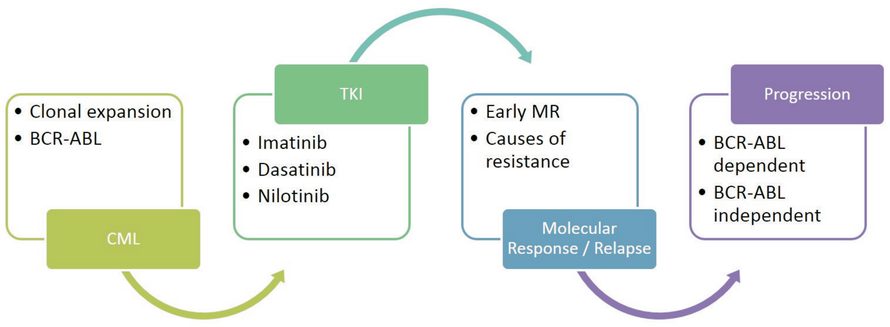
INTRODUCTION



OBJECTIVE

1 - Early molecular response for patients who swtich to 2TKI;
2 - Better characterized patients who switch to 2TKI with <10% BCR-ABL^{IS} ;
3 - Study of causes of resistance in patients who failed to IM;
   a) Compound mutation;
   b) study of mutation in genes associated with leukemia by NGS in patients who progress;
   c) miRnoma – NGS Illumina;

EXPERIMENTAL STRATEGY

Epidemiology	• Rox curve, OS, PFS, FFS; • GraphPad software;
Compound mutation	• PCR • Cloning • Direct Sequencing
Progression	• PGM-NGS
miRnoma	• Illumina - NGS

RESULTS AND DISCUSSION

Halving time – patients who switch to 2TKI

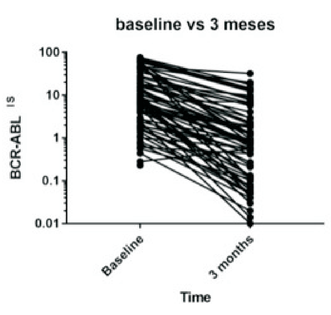


Figure 1: BCR-ABL^{IS} levels at baseline (before switch to 2TKI) and 3 months, each line represent one patient.

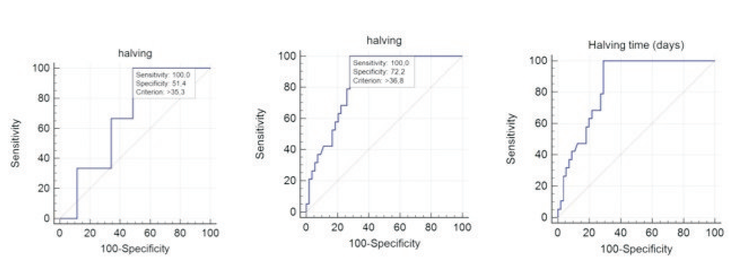


Figure 2: ROC curve with Youden index calculation for halving time of a) OS, b) FFS and c) PFS.

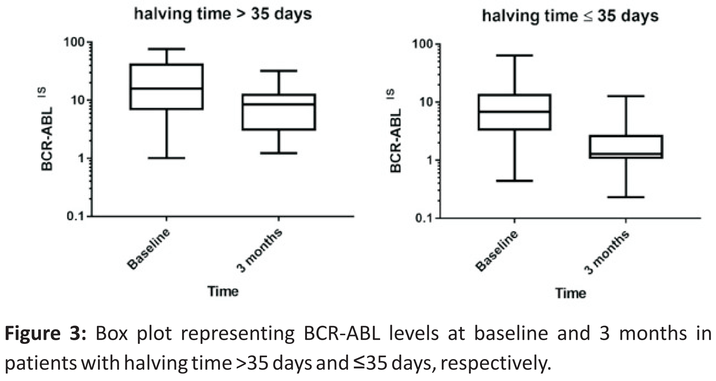


Figure 3: Box plot representing BCR-ABL levels at baseline and 3 months in patients with halving time >35 days and ≤35 days, respectively.

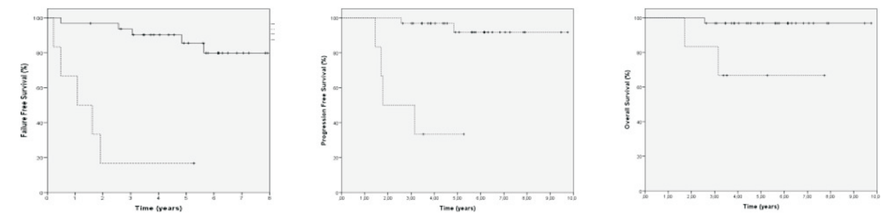


Figure 4: FFS, PFS, OS, respectively in Patients with 1% of BCR-ABL levels at 3 month.

Compound Mutation

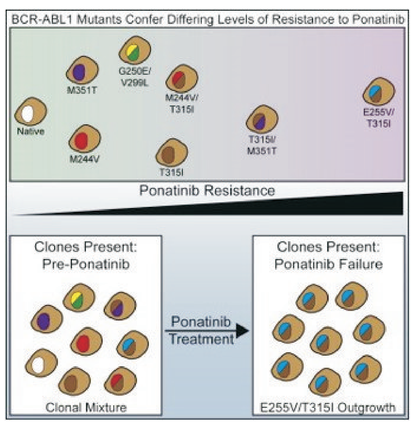


Figure 5: Example f the difference between compound and clonal mutation (Zabrieskie *et al*. 2014).

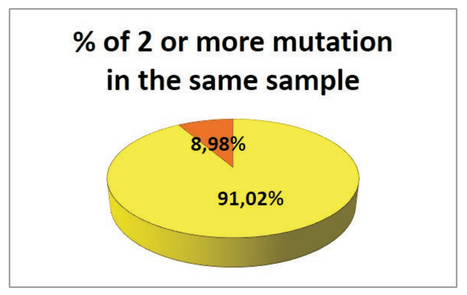


Figure 6: in our cohort the percentage of mutation in the same sample. More than 90% has only one mutation (yellow).

Table 1: results of the mutation analyzed in each clone, by patients.

	clone 1	clone 2	clone 3	clone 4	clone 5	clone 6	clone 7	clone 8	clone 9	clone 10	RESULTADO
26197 (A397P / T315I)	A359P/T315I	A359P/T315I	A359P/T315I	A359P/T315I	A359P/T315I	A359P/T315I	A359P/T315I	A359P/T315I	A359P/T315I	A359P/T315I	Compound
20373 (V268M / E355G)	V268M	V268M	E255G	V268M	E255G	E255G	E255G	E255G	V268M	V268M	Policlonal
20683 (F359V / E450G)	F359V	F359V	E2450G	F359V	E2450G	F359V	E2450G	F359V	E2450G	E2450G	Policlonal
20561 (F317L / E275K)	E275K	F317L	E275K	E275K	F317L	E275K	E275K	F317L	F317L	F317L	Policlonal
20452 (T315I e F359V)	F359V	T315I	T315I	T315I	T315I	F359V	F359V	F359V	T315I	F359V	Policlonal
30245 (L248V / T315I)	L248V	T315I	T315I	L248V	T315I	L248V	T315I	T315I	L248V	T315I	Policlonal
35448 (G250E / M351T)	G250E/M451T	G250E/M451T	G250E/M451T	G250E/M451T	-	G250E/M451T	G250E/M451T	G250E/M451T	G250E/M451T	G250E/M451T	Compound
37557 (F359V / H396R)	F359V/H396R	F359V/H396R	F359V/H396R	F359V/H396R	F359V/H396R	F359V/H396R	-	F359V/H396R	F359V/H396R	F359V/H396R	Compound
41207 (G250E/T315I)	T315I	G250E	T315I	T315I	G250E	T315I	T315I	G250E	T315I	G250E	Policlonal
40514 (F317L / T315I)	F317L	F317L	F317L	F317L	F317L	T315I	T315I	T315I	F317L	F317L	Policlonal
42692 (F359I / E450K)	F359I	E450K	F359I	E450K	E450K	F359I	F359I	E450K	E450K	F359I	Policlonal

Chronic Phase vs Progression - NGS study

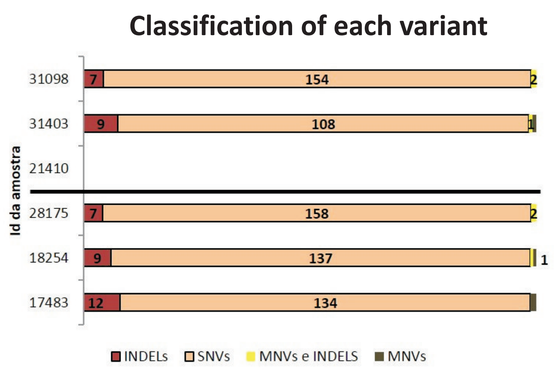


Figure 7: Classification of all variants found in each sample.

gene	alteração nucleotídeo	alteração proteína
TET2	c.5333A>G	p.His1778Arg
DNMT3a	c.2645 G>A	p.Arg882His
TP53	c.385 G>T	p.Arg213Pro

Figure 8: Example of genes found mutated in AP/BC.

CONCLUSION

- The 35 days halving time is a good predictor to better classify patients who failed to IM;, better than this parameters is <1% BCR-ABL^{IS} at 3 months, since was able to discriminate FFS, PFS and OS in those group;

- Patients with compound mutation had worst prognostic comparing to policlonal mutation;

- Mutation in genes other than BCR-ABL can be involved in disease progression

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA