JAK2-UNMUTATED ERYTHROCYTOSIS IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA DURING TYROSINE KINASE INHIBITORS

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INTRODUCTION

Erythrocytosis is rare in CML and, in some cases, is associated with coexistence with polycythemia vera (PV). We report several cases of erythrocytosis in chronic phase CML (CP-CML) without confirmed PV

METHOD

Retrospective non-interventional study of CP-CML patients receiving TKI who developed erythrocytosis. Under our observation there are 9 male patients with CP-CML receiving tyrosine kinase inhibitors (TKI) who developed erythrocytosis. Erythrocytosis was defined by the World Health Organization in 2016 with threshold of Hgb/Hct levels >16.5 g/dL/49%[1]. This retrospective study was approved by the Ethics Committees of ANMRC in accordance with the Declaration of Helsinki. All patients signed informed consent. To exclude PV JAK2V617F mut, JAK2 mut in 12 exon was performed. Erythropoietin level and bone marrow sample analysis were also performed. To evaluate the secondary causes of erythrocytosis the following diseases were excluded: renal artery stenosis (CT or sonography exam), cardiovascular diseases (ECHO), P50, spirometry, testosterone level, congenital erythrocytosis (VHL, HIF1a expression), non-canonical JAK2mut (863bp, 11-15 exons) [2]

PATIENTS

At the time of erythrocytosis onset median age was 46 (range, 20-55) yrs, median time of TKI treatment was 159 (range, 67–214) mos (table 1).

Table 1. Patient characteristics af the time of erythrocytosis

Charactreristics	Age, years	Previous TKI, n	TKI	Response	Time from last TKI to erythrocytosis	Smoking	Anabolic steroids/EPO doping/Diuretics
Patient 1	20	1	Nilotinib 400mg BID →Ponatinib 45 mg	CHR	11 mos	No	No/No/No
Patient 2	48	2	Nilotinib 400mg BID→Asciminib 40mg BID	MR2	4 mos	No	No/No/No
Patient 3	42	2	Ponatinib 45mg QD	MMR	14 mos	Yes	No/No/No
Patient 4	51	2	Ponatinib 15mg QD	MR4	22 mos	No	No/No/No
Patient 5	55	2	Ponatinib 30mg QD	CHR	11 mos	Yes	No/No/No
Patient 6	42	2	Ponatinib 45mg QD	MR4	3 mos	No	No/No/No
Patient 7	28	3	Ponatinib 15mg QD	MR2	23 mos	Yes	No/No/No
Patient 8	52	4	Ponatinib 15mg QD	MMR	8 mos	Yes	No/No/No
Patient 9	46	0	Bosutinib 500mg QD	MR5	61 mos	Yes	No/No/No

RESULTS

- Median time from last TKI to erythrocytosis was 11 (range, 3–61) mos. At the last visit erythrocytosis was sustained in all patients except 1 who underwent stem cell transplantation
- Median time of follow-up was 41 (range, 17–103) mos
- All patients had a mean increase of Hgb 1.8 (range, 0.4-4.2) g/dL during TKI therapy. Median peak Hgb and Hct was 17.9 (range, 16.6–20.4) g/dL and 54.1 (range, 50.7–62.4) %, respectively (Figure 1-3)
- There was no evidence of EPO-producing tumors, renal artery stenosis or another renal disorders, as well as cardiac or pulmonary diseases
- Phlebotomies* were performed in 2 cases. No skin or microvascular symptoms, nor major thrombotic events were observed
- No evidence of EPO-producing tumors, renal artery stenosis or another renal disorders, as well as cardiac or pulmonary diseases (table 2)

Table 2. Secondary cause exclusion study characteristics

Charactreristics	Pathology of bone marrow	Erythropoietin, mIU/ml (range, 2.59-18.5)	Testosterone, pg/ml (range, 8.64-29.00)	P50 venous mmHg (range, 24-32)	MetHb, % (range, 0-1.5)	JAK2^{V617F}mut/JAK2 ^{12ex} mut	Non-canonical JAK2mut (11-15 ^{ex})	VHL expression	HIF1a expression
Patient 1	ND	2.19	14.2	27.9	0.5	Neg/Neg	Neg	NS	NS
Patient 2	ND	5.48	17.82	ND	ND	Neg/Neg	Neg	ND	ND
Patient 3	Hypercellular, Erythrokaryocytes decreased, MF3, Coll2, OS0	3.56	14.66	28.3	0.5	Neg/Neg	Neg	NS	NS
Patient 4	Hypocellular	12.61	12.46	26.8	0.8	Neg/Neg	Neg	NS	NS
Patient 5	Normocellular	32.39	20.93	24.5	0.8	Neg/Neg	Neg	NS	NS
Patient 6	ND	6.51	20.5	30.1	0.6	Neg/Neg	Neg	ND	ND
Patient 7	ND	4.59	23.85	27.3	1.2	Neg/Neg	Neg	NS	NS
Patient 8	ND	6.08	18.81	ND	0.9	Neg/Neg	Neg	ND	ND
Patient 9	ND	5.93	18.09	31.7	0.8	Neg/Neg	Neg	NS	NS

NS – not significant, ND – not done, Neg - negative

Figure 1. Comparison of median hemoglobin before and during TKI treatment

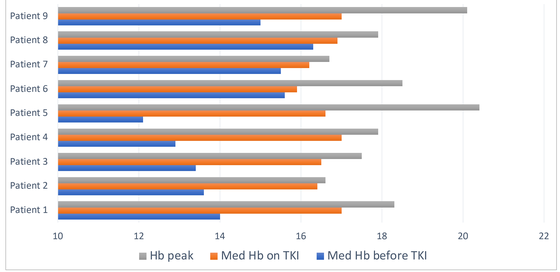


Figure 2. Dynamics of hemoglobin level during TKI treatment

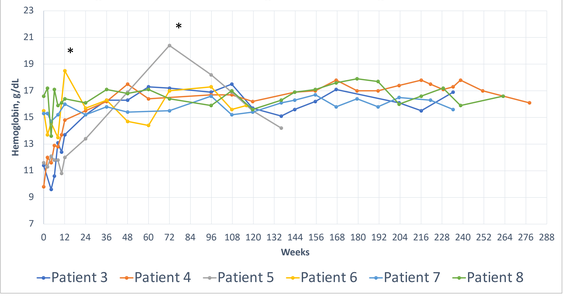
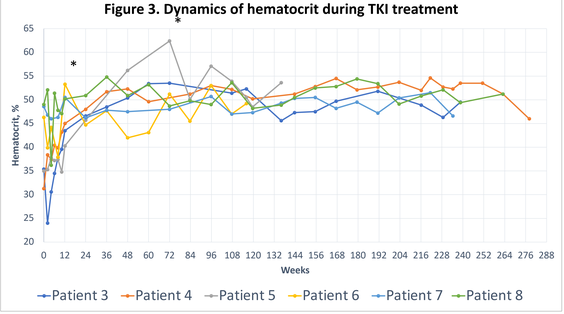


Figure 3. Dynamics of hematocrit during TKI treatment



* Phlebotomy

CONCLUSIONS

We reported erythrocytosis of unknown origin in CP-CML patients. Whether erythrocytosis might be related to TKI therapy is disputable and should be further investigated

REFERENCES

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