Treatment outcome and determinant factors in Ethiopian CML patients with Imatinib resistance and intolerance

A five years retrospective study

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OUTLINE

- Introduction and back ground of the study
- Objectives of the study
- Patients and Methods
- Statistical analysis
- Results
- Discussion
- Conclusion and recommendations

ACKNOWLEDGMENT

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- I am very much grateful for all the help and support I got from the nurses and all the staff at the CML clinic

- I am also thankful for all the support and understanding of our patients

- I also would like to appreciate the staff at the hospital's Patient Chart record room

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Introduction

- Chronic myelogenous leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the dysregulated and uncontrolled production of mature and maturing granulocytes which maintain a fairly normal differentiation.

- The estimated global incidence of CML is 0.6-2.0 cases per 100,000 individuals per year.

- Age adjusted CML incidence rate difference was found among different ethnic sub groups and geographic locations

- Median age at diagnosis of approximately 65 years
  - Low SDI (34 – 39)

Lin Q, Mao L, Shao L, Zhu L, Han Q, Zhu H, Jin J, You L. 1990-2017

- ❖ Tyrosine kinase inhibitors have revolutionized the management of CML in the past two decades and dramatically impacted patient outcomes.
  - 75-80% ; 3%
- ❖ Long term EFS and PFS of patients with CP CML treated with Imatinib 400mg daily is 85-90%.
- ❖ Patients with CML in low income countries tend to present with a more advanced and high risk disease.
  - no enough data to describe the cause
- ❖ unmet clinical need in low SDI countries
  - CHR <70% and CCyR – 50%

Lin Q, Mao L, Shao L, Zhu L, Han Q, Zhu H, Jin J and You L (2020)

- Despite the remarkable success achieved with the introduction of imatinib, development of resistance is still an ongoing obstacle

- Approximately 5% and 20% of newly diagnosed patients do not achieve a complete hematological & cytogenic response respectively.

- During follow-up 20-25% of patients may loose early response

- BCR-ABL1 KD point mutation is most commonly associated with acquired resistance to IM

  Defects of drug influx, accelerated efflux ,

  genomic amplification, clonal evolution

Apperley JF. Part I: Lancet Oncol. 2007;8(11):1018–29

❖ A very important aspect in the treatment of CML with BCR/ABL TKIs is the development of treatment related side effects

❖ Usually tend to be mild and transient, sometimes could be significant or prolonged.

❖ reported in 15-20% of patients on IM therapy

- Dose reductions
- treatment interruptions
- HRQOL
- Treatment adherence
- resistant disease

- Patients with imatinib failure are a challenge in CML care
  - high risk of disease progression
  - close monitoring of molecular response
  - highly sensitive to gaps in drug adherence
  - require expanded and more efficient TK inhibition

- HD imatinib therapy is not usually successful

- Early shift in treatment is associated with a more durable response and surviva.l

Kantarjian H, Pasquini R, Hamerschlak N, Rousselot P, Holowiecki J, Jootar S, et al

- The use of 2nd generation TKIs is now widely practiced
  - newly diagnosed CP-CML
  - Imatinib failure
  - imatinib intolerance
- induced a higher rate , more intense , and an expeditious CCR/MMR
  - CHR – 85-90% (77% retention) ; CCyR – 50%
    - 40% ; 24% (Advanced disease)
- low level of cross intolerance

- Imatinib remains the front line agent of choice in ND CML
  - close cytogenic and molecular monitoring

Cerrano M, Crisà E, Pregno P, Aguzzi C, Riccomagno P, Boccadoro M, Ferrero

- With a little over two decades of experience with imatinib therapy in our center, more than two thousand patients with CML were managed.

- The progressive rise in prevalence of patients failing on and not tolerating front line imatinib therapy motivated us to conduct this study.

- clinical characteristics and treatment outcome of these group of patients has not been adequately studied yet.

- Aiming to provide a single center experience regarding the treatment outcome and important clinical prognostic factors determining the treatment outcome.

Objectives of the study

General Objective

To assess the treatment outcome and determinant factors in Ethiopian CML patients with imatinib resistance and intolerance at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia

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Specific Objectives

- To describe the major initial clinical characteristics of patients with imatinib resistance and intolerance.
- To assess the treatment outcome of patients with imatinib resistance and intolerance at TASH
- To study the major prognostic factors affecting treatment response
- To evaluate the overall survival of patients with imatinib resistance and intolerance at TASH.

PATIENTS AND METHODS

- This study is conducted at the outpatient department of the unit of Hematology in *Tikur Anbessa specialized referral and teaching Hospital.*

- A single centered hospital based five-year retrospective study to assess the treatment outcome and major determinant factors in patients with imatinib resistance and intolerance at TASH

- We reviewed the clinical records and laboratory data available for patients with imatinib failure and intolerance on follow up and treatment in the outpatient unit.

- A structured data collection questionnaire prepared by the investigators in accordance with similar previous studies was used to fill in data obtained from patients and records

- Laboratory data was obtained from electronic data recording of the hospital's laboratory.

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❖ Inclusion Criteria

All CML patients with an imatinib failure and intolerance and on alternative therapy in the study period were included in this study.

❖ Exclusion criteria

- Patients with incomplete laboratory workup on diagnosis and follow up
- Those patients with absent or incomplete clinical data record for analysis
- Duration of treatment less than 06 months for patients with imatinib failure were excluded from the study
  - Patients with advanced phase of the disease

STUDY VARIABLES

❑ Independent Variables

- Age and Sex
- Place of residence
- Phase of CML diagnosis at treatment change
- Baseline prognostic score at diagnosis
- Degree of treatment response to front line imatinib
- Indication for shifting of Imatinib therapy (resistance vs intolerance)
- Presence of baseline BCR-ABL1 KD point mutation at shift of therapy
- Option of treatment given at the time of imatinib intolerance/resistance

❑ Outcome variables

- Degree of best hematologic and cytogenic response
- Duration of retained CHR
- Progression and failure free survival rate
- Overall Survival rate

OPERATIONAL DEFINITIONS

- Advanced or progressive disease is defined according to the 2016 world health organization (WHO) diagnostic criteria for accelerated and blast phase CML.

- Treatment response & failure, in this study, is defined according to the 2020 European leukemia network (ELN) recommendation update on CML treatment milestone assessment and monitoring criteria.

- Imatinib therapy related grade 3 and 4 toxicities requiring treatment alteration were defined based on the national cancer institute (NCI) common toxicity criteria for adverse events version 4.0 (CTCAE v4.0).

STATISTICAL ANALYSIS

- Once data collection was completed, the data was edited and coded for processing and analysis.
- The principal investigator using the SPSS statistical software v27.0 did the data processing and analysis
- Frequency tables and graphs were used to express the results
- Descriptive statistics and coefficients of association , with 95% confidence interval were used to show associations between the study variables
- In all cases, p- value of less than 0.05 was considered as a statistically significant margin of association.

ETHICAL CONSIDERATION

Ethical clearance was obtained from the research ethical review committee at College of Heath Science, Addis Ababa University, Addis Ababa, Ethiopia.

DISSEMINATION OF STUDY RESULTS

After this final report of the study is submitted and presented to the unit of hematology, efforts will be made to disseminate research findings to international medical journals.

RESULTS

Demographic characteristics of Study participants

- A total of 164 patients with the particular diagnosis on follow-up were identified in the study period specified.
- Twenty-nine patients were excluded following our exclusion criteria
- A total of 135 patients were found eligible for inclusion in the final analysis
- Imatinib treatment failure was the indication for alternative therapy in 128 (94.8%); while 7 (5.2%) patients had a diagnosis of imatinib intolerance

Demographic characteristics of patients with imatinib failure

- Out of the 128 patients, on follow-up at our center for imatinib failure, 86 (67.2%) were males and 42 (32.8%) of the participants were females.

- The median age at the initial diagnosis of CML was 35 (IQR 27-42) years.

- The mean age at diagnosis for male and female patients were 36.6 (SD 11.41) and 33.8 (SD 13.0) years, respectively

- 58% of our patients in this cohort were from rural parts of the country while 42% were from the urban areas

- The median age at diagnosis of imatinib failure was 37 (IQR 31-46) years
- The mean age at diagnosis of imatinib failure was higher in males (39.5, SD 10.9 years) than that of females (37.2, SD 13.1 years) in the study (t_{69} =0.98 (-2.35 to 6.99).

- Significant proportion (49/86, 57%) of male patients were in the age group of 30-45 years.
- The age distribution of female patients was fairly proportional across the age groups.

Demographic characteristics		proportion of patients
Total number of patients		**135 (100%)**
Age		
(Years)	Median (M,F)	37 (37,36)
	< 30	28 (21.9%)
	30 - 45	68 (53.1%)
	> 45	32 (25%)
Gender		
	Males	86 (67.2%)
	Females	42 (32.8%)
Residence		
	Rural	74 (58%)
	Urban	54 (42%)

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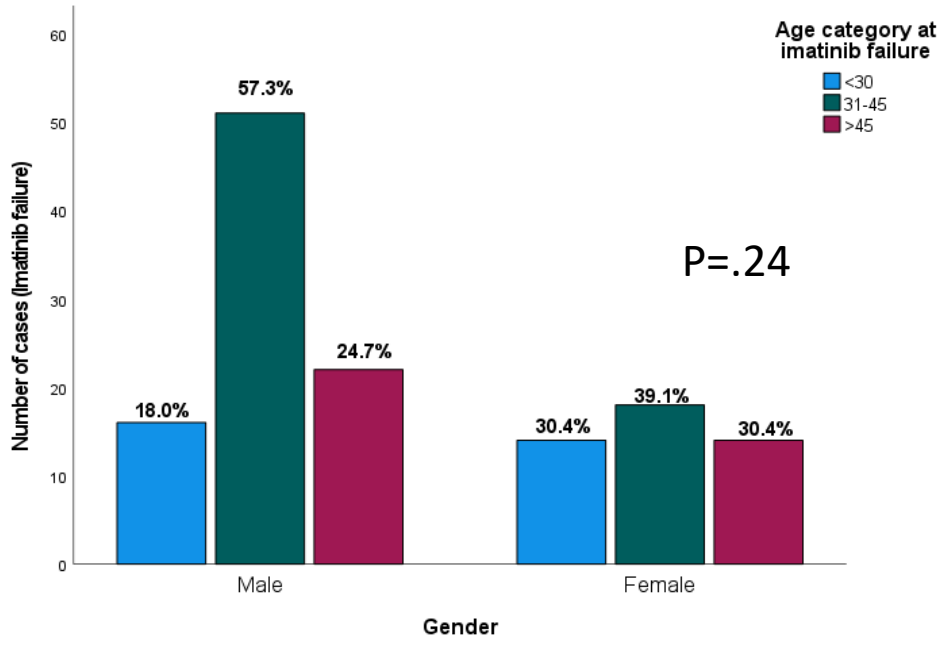
Age category at imatinib failure

Age category at imatinib failure

	Frequency	Percent	Valid Percent	Cumulative Percent
<30	28	21.9	21.9	21.9
31-45	68	53.1	53.1	75.0
>45	32	25.0	25.0	100.0
Total	128	100.0	100.0	



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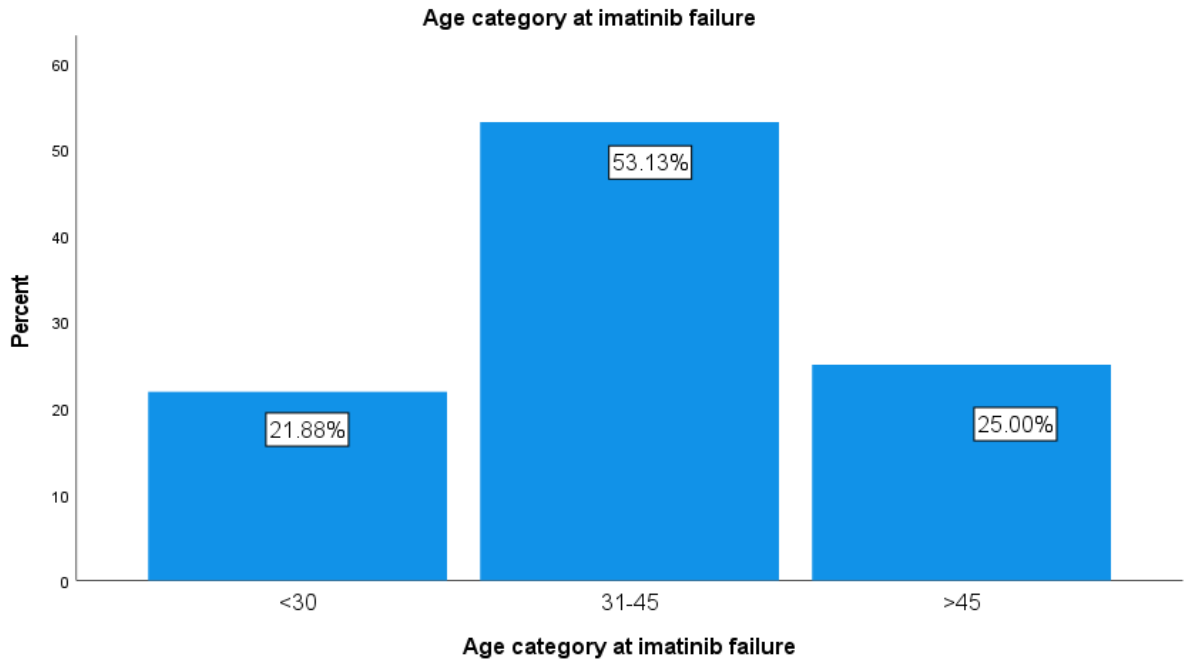

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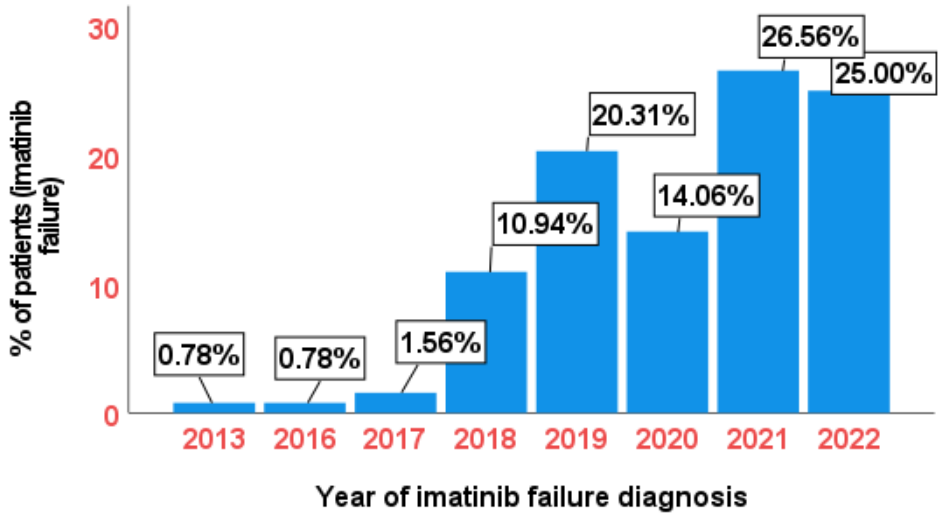
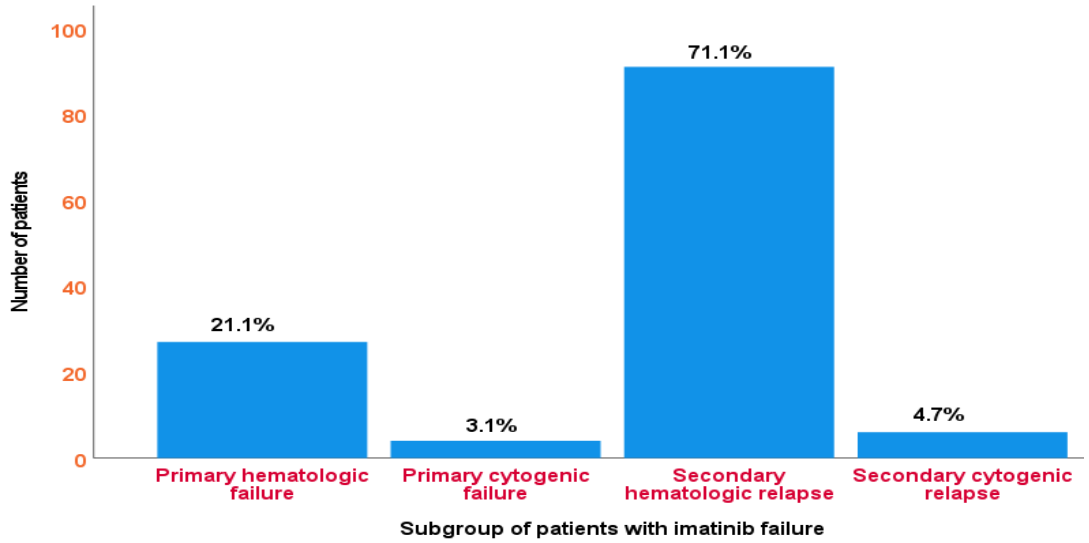
Demographic Characteristics of study participants with imatinib intolerance

- Out of these 7 patients, 3 of them were males and the remaining 4 were females.
- The mean age at diagnosis of imatinib intolerance was 47.4 (SD 23.5)
- The mean age of male and female patients with imatinib intolerance was 20 (SD 33.9) years and 55.7 (SD 11.7) years, respectively
- Five out of the seven patients were either below the age of twenty years or above the age of sixty completed years.

Clinical Characteristics and laboratory features of patients with imatinib failure

- initial diagnosis of CML from the year 2006 to 2021.
- 65.6% of patients were diagnosed with imatinib failure between the years 2020 and 2022.
- The median duration of symptoms prior to presentation was 24 (IQR 12-56) weeks.





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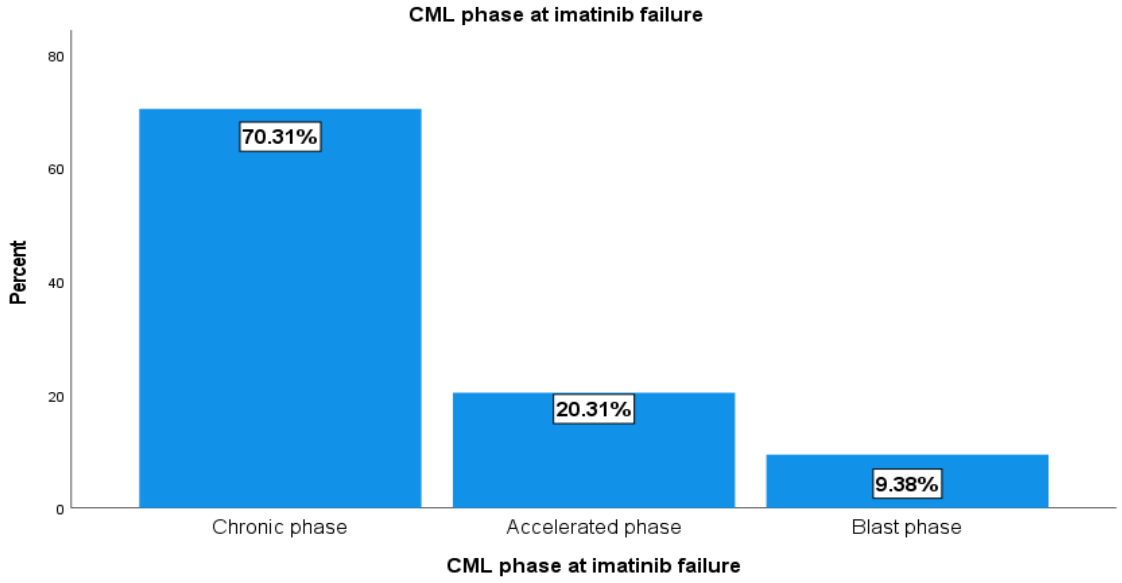
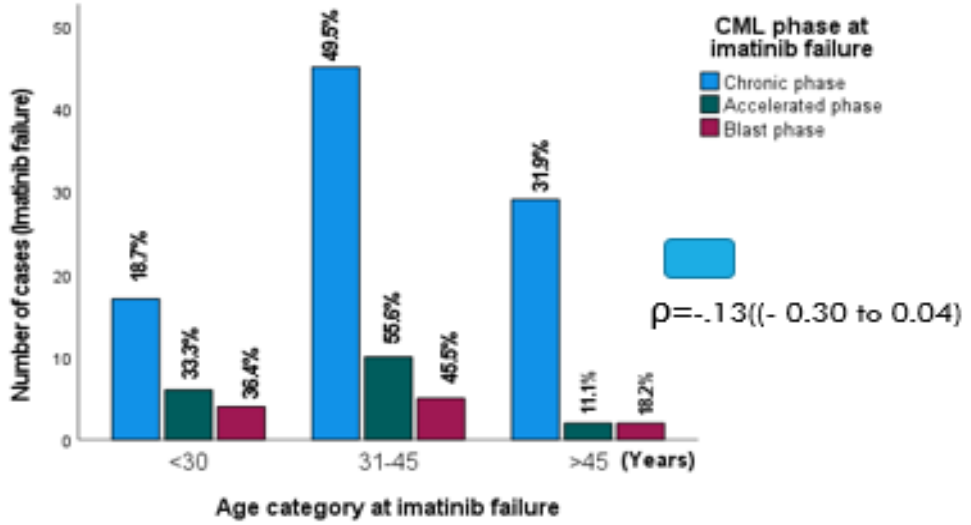
❖At the time of imatinib failure, 90 (70.3%) patients were still in the chronic phase of the disease; while 26 (20.3%) and 12 (9.4%) patients were in the accelerated and blast phases, respectively.

❖ No statistically significant correlation demonstrated between age group (P=0.13), gender (P=0.68), residence (P=0.3) and phase of CML at imatinib failure.





- The baseline risk scores of patients were calculated using the Sokal and ELTS prognostic scores.

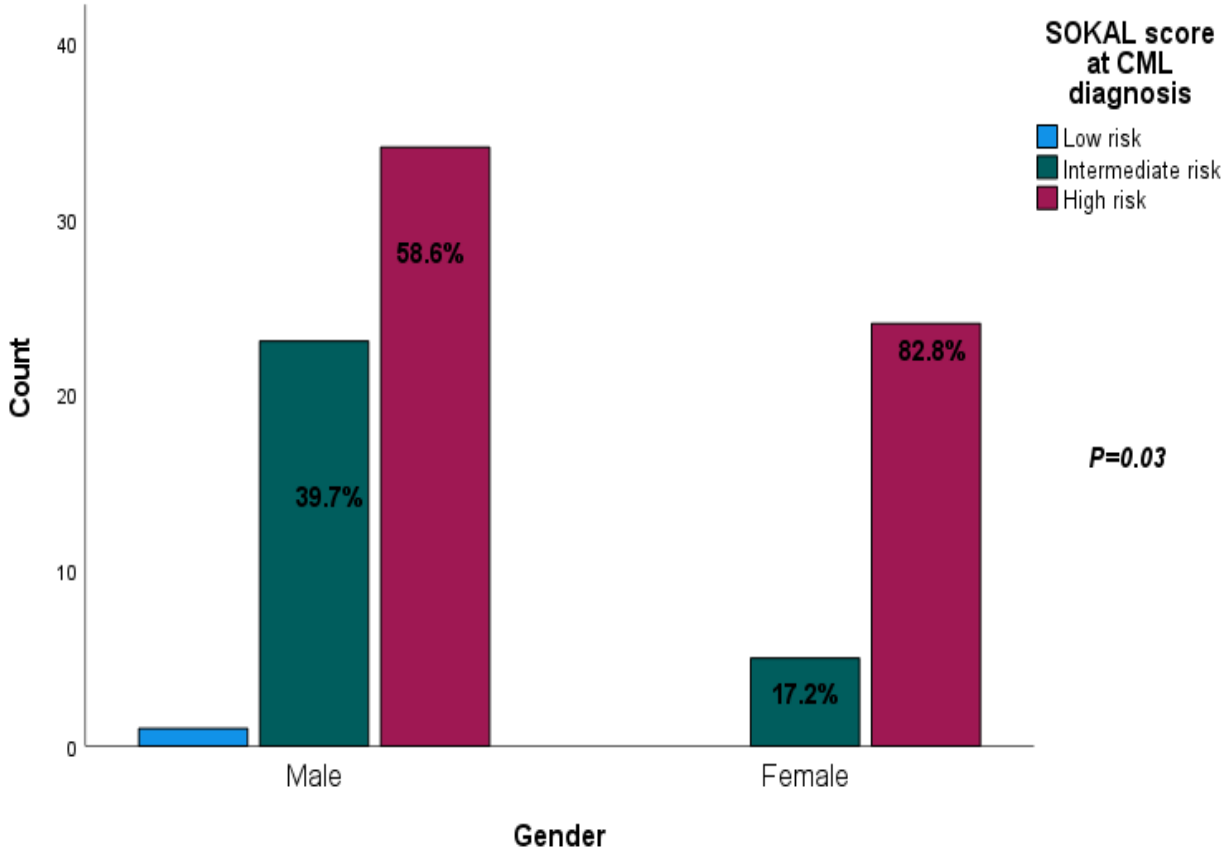
- High and intermediate Sokal scores were reported in 67.5% and 31.3% of patients; and 51.2% & 41.3% of patients according to the ELTS risk stratification system

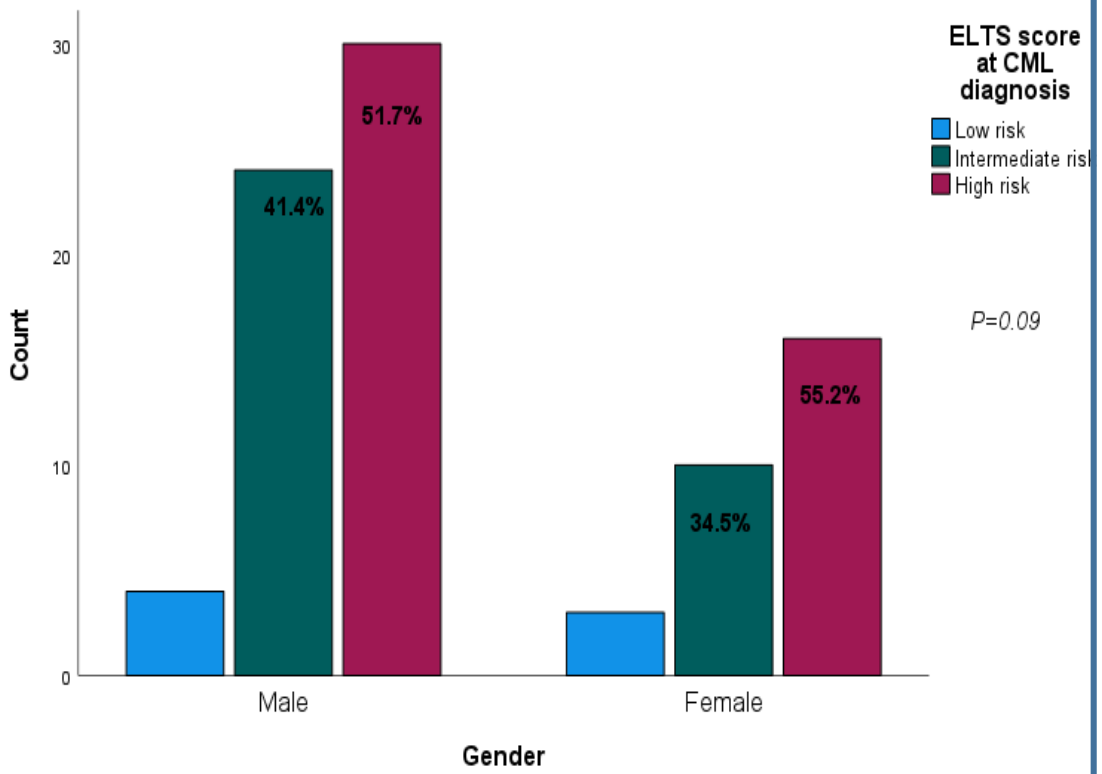
- Female patients with imatinib failure presented at a higher Sokal risk score (82.8%) compared to male patients (58.6%) (P=0.03) (MW NPT)

  - not statistically significant with the ELTS (P=0.95)

- independent sample t-test didn't show any significant difference in duration of symptoms between the genders, $t_{65} = 0.96$ (95.0% CI (-7.7 – 22.2).

Risk scores by gender





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Clinical Characteristics and laboratory features of patients with imatinib failure

- Massive Spleen – 88.9%
- Leukocytosis – 100%
- 19.5% - thrombocytosis
- Anemia – 51.2%

- Leukocytosis - 64.3%
- Platelet abnormal-63.5% (36/26)
- Anemia - 21.4%)

Incident		WBC count (k/ul)	Hgb level (g/dl)	PLT count (k/ul)	Spleen size (c.m ALG)	Blast count (BM) (%)	Basophil count (P) (%)	Q BCR-ABL1 (%IS)
CML diagnosis	Median (IQR)	266.0 (166-388)	9.850 (8.4-11.5)	316.5 (218-316)	12 (9-16)	5 (4-8)	6.5 (4-9)	- -
	Mean (SD)	283.9 (140)	10.0 (2.3)	411.4 (280.6)	12.4 (4.9)	6.5 (5.9)	7.4 (4.6)	- -
	Range	637 (64-701)	10.2 (5.7-15.9)	1745 (55-1800)	22 (3-25)	8 (2-10)	11 (2-13)	- -
Imatinib failure	Median (IQR)	17.2 (5.4 – 38.3)	12.5 (10.5-14)	212 (89-576)	- -	5 (3-8)	6 (4-13)	30.5 (13.5-57.2)
	Mean (SD)	32.3 (47.5)	122.0 (2.6)	396.6 (468.4)	- -	9.9 (15.0)	8.2 (5.4)	37.6 (28.6)
	Range	377.4 (1.6-379)	11.3 (4.5-15.8)	2790 (10-2800)	- -	73 (2-75)	20 (2-22)	98 (2-100)

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- Forty-seven (36.7%) patients had a BCR-ABL1 Kinase domain resistance mutation analysis done.
  - mutations were reported in 22 (46.8%) patients
  - 50% (P) ; 35% (Non P) ; 15% (FS)
  - T315I – 60%/ 30% of total / Non P loop

- 9.7% of patients at initial diagnosis of CML had one or more major comorbidities.
  - 6.7% - HIV/AIDS
  - T2 DM / HBV - 2 patients each

Clinical Characteristics of study participants with imatinib intolerance

- Out of the 7 patients, 4 (57.1%) had a non-hematologic intolerance and 3 (42.9%) had a hematologic intolerance to imatinib.
- All patients were at the chronic phase of the disease
- Most patients had an intermediate to high Sokal and ELTS risk scores at presentation.
- mean spleen size at initial presentation was 11.5 (SD 5.6) c.m
- All but one of the 7 patients had a massive splenomegaly
- 2 patients had an underlying major comorbidity

- mean bone marrow blast and peripheral blood basophil percentages were 4.4 (SD 0.9) % and 8.5 (SD 7.7) %, respectively

- All patients had leukocytosis (mean WBC count of 236 (SD 138.3) k/ul)

- Only 1 patient had thrombocytosis (mean platelet count was 316.0 (SD 142.1) k/ul)

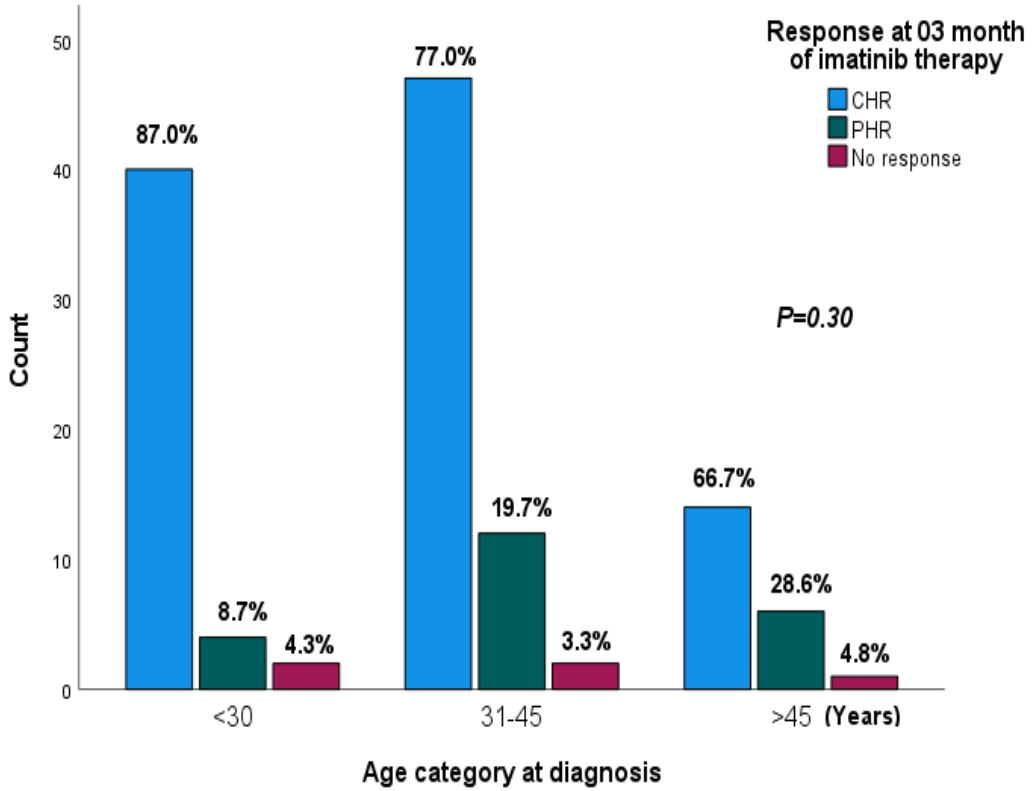
- significant anemia at initial CML diagnosis was reported to be 42.1% (mean hemoglobin level was 10.0 (SD 2.4) g/dl.

- severe neutropenia and thrombocytopenia were the features.

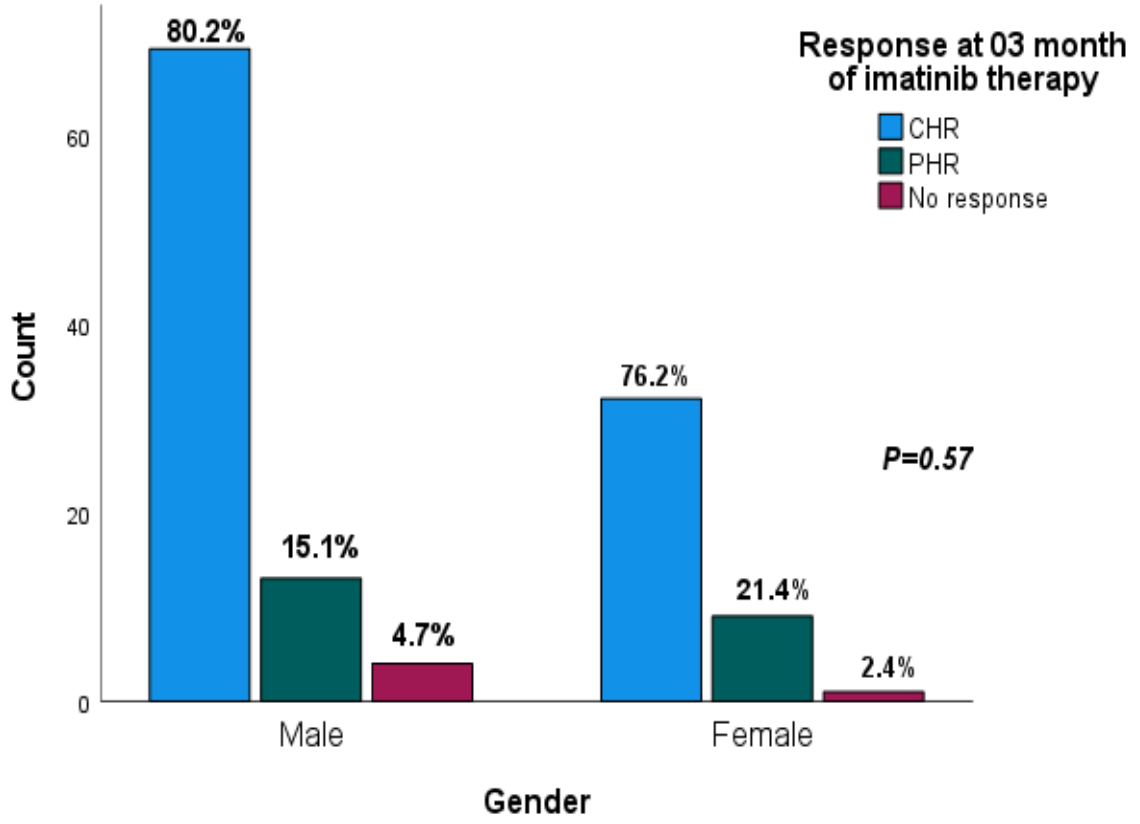
Treatment Outcome and determinant factors of patients with imatinib failure

- The median time gap between initial CML diagnosis and initiation of imatinib was 23 days (IQR 8.5-34.5) days.
- The rate of CHR at 03 months of initial imatinib therapy was 79.7% (102/126).
- The remaining 14.8% (19) and 5.6% (7) of patients had a PHR and no significant response to front line imatinib therapy, respectively.
- only 5 additional patients were able to achieve a CHR past the 03-month mark.
  - mean duration of remission for these late responders was only 9.5(SD 7.1) months
- The remaining 21 (16.4%) patients had no CHR throughout the course of initial imatinib therapy.

Response with age category



Response by gender



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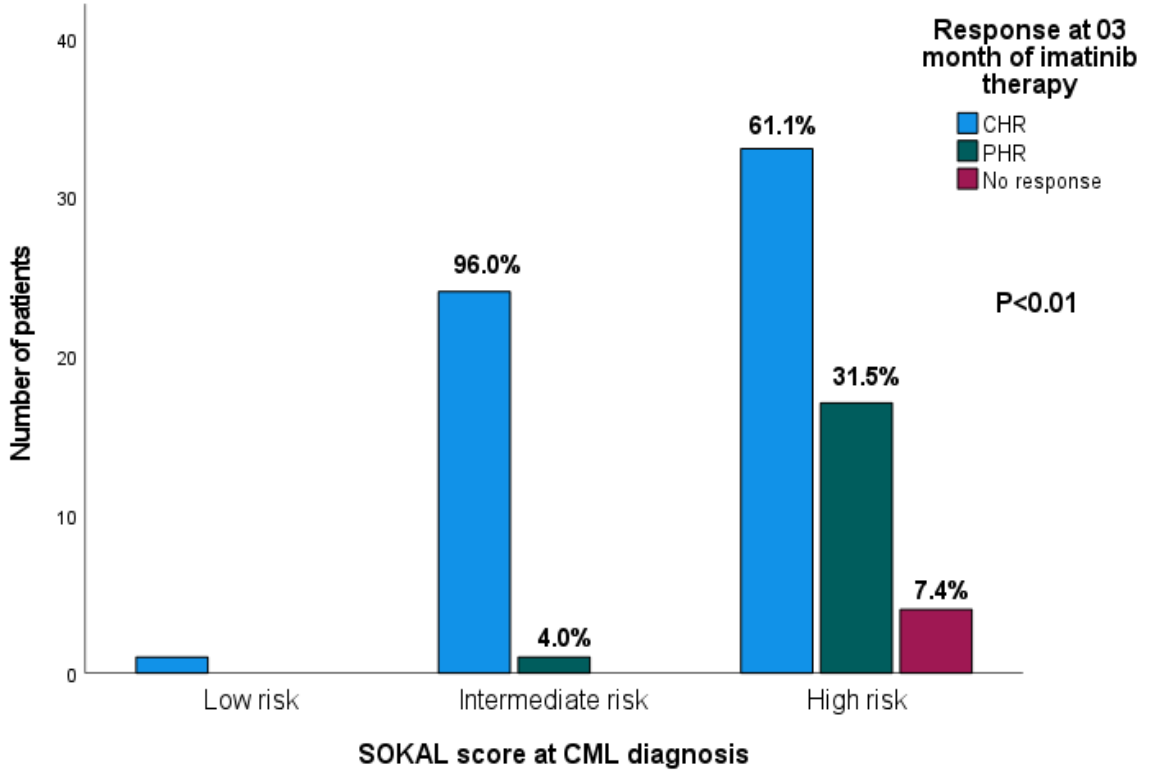
Response by risk score

- Patients with a high sokal risk score at diagnosis had a significantly lower rate (63.2%) of CHR compared to patients with other scores at 03 months (ρ= **- 0.36**; P<0.01)

- ELTS risk score also had a significant negative correlation (ρ = **- 0.23**; P=0.03)



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- The median duration of maintained CHR with initial imatinib therapy was 30.0 (IQR 12-60; Range:2-152) months

- 28.1% of patients failed on imatinib therapy in the first 12 months of initiation of treatment; 38.3% had a documented failure after 36 months of front line imatinib exposure.

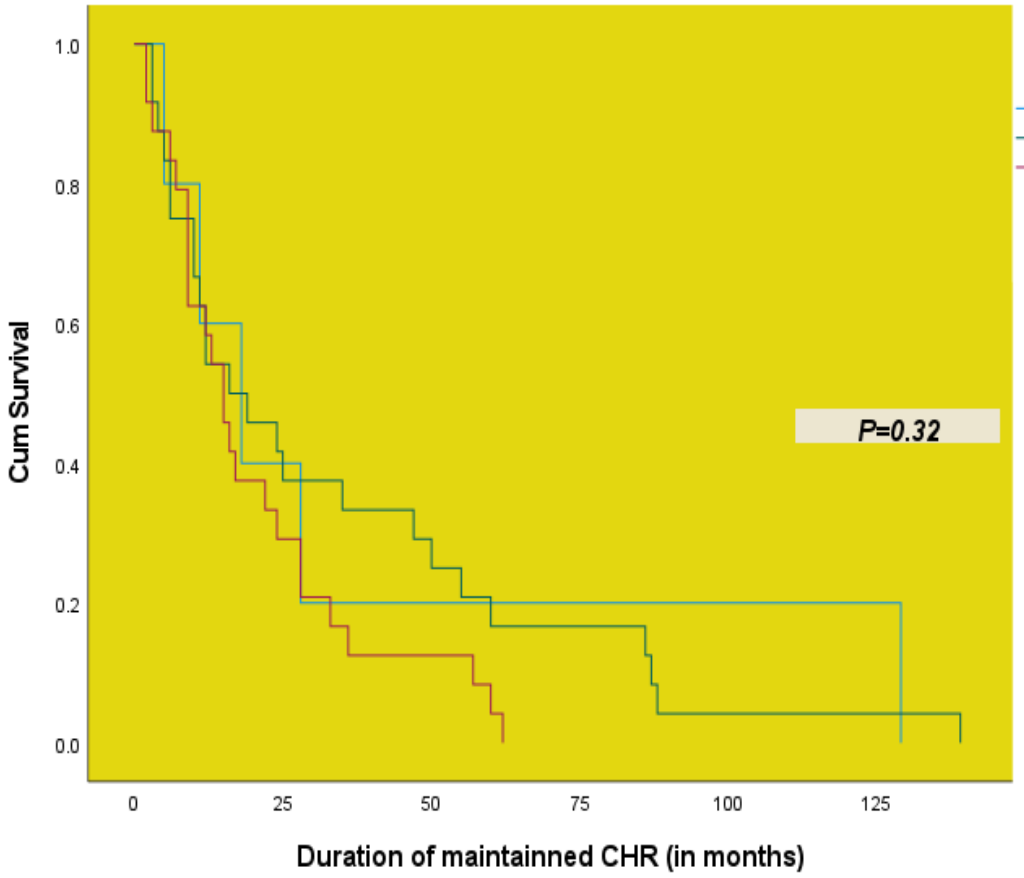
- A significant negative correlation between age at CML diagnosis and duration of remission on imatinib (ρ = - 0.21; P=0.03) was identified.

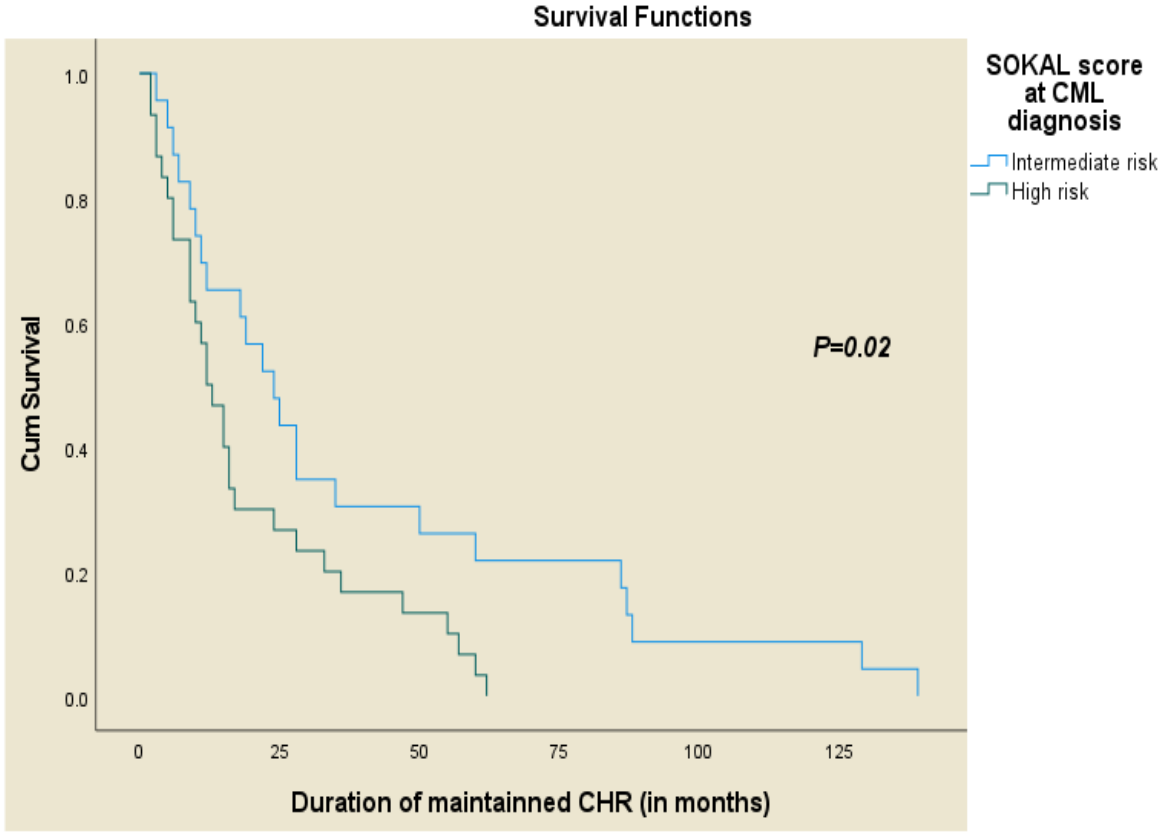
- A significant negative correlation was also identified between the Sokal score and duration of response (ρ= -.26; P= .04); but not with the ELTS score (ρ= -.08; P = .52) at diagnosis.

- No significant difference in the duration of remission between male and female patients, t_{54} = -.84 (-21.9 to 8.6).

- The negative correlation between the duration of symptoms prior to diagnosis and the period of maintained CHR was not statistically significant (ρ = - 0.17; P=0.19).

Maintained CHR by risk scores





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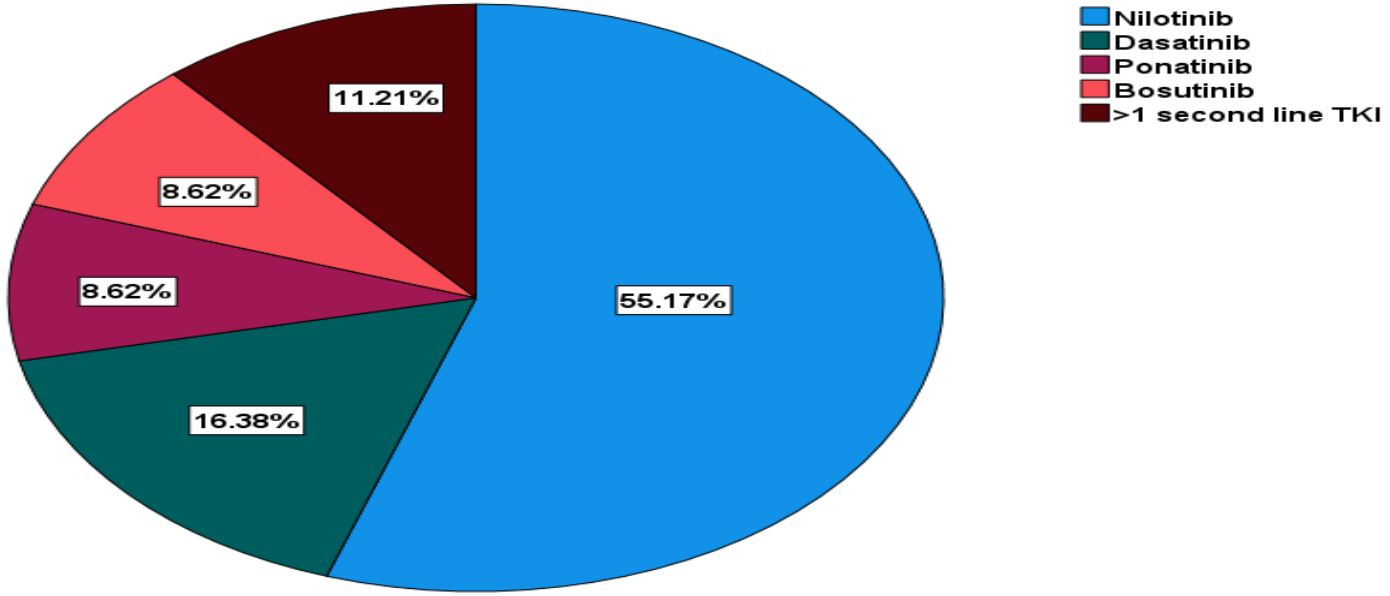
- At the diagnosis of imatinib failure, 116 (90.6%) patients were shifted to alternative second line TKI; and the remaining 12 (9.4%) patients were managed only with high dose imatinib therapy.

- The median time gap from the diagnosis of imatinib failure to second line TKI initiation was much longer (8 months, IQR 5-15.5) for the 37 patients for whom a high dose imatinib trial was made in between, as compared to the remaining 79 (2 months, IQR 1-4) for whom treatment was swiftly shifted.

- The negative correlation detected between this time gap and duration of remission on second line therapy was not statistically significant, r= -.05 (95.0% CI -.52 to .42).

- Four different second and third line TKIs were used for our patients with imatinib failure or intolerance
- Nilotinib and dasatinib were the two most commonly used agents; accounting for 55.2% and 16.4% of patients with imatinib failure
- 11% of patients were given more than one alternative TKI.



- The rate of CHR at 06 months of second line TKI for patients with imatinib failure was 66.4%.

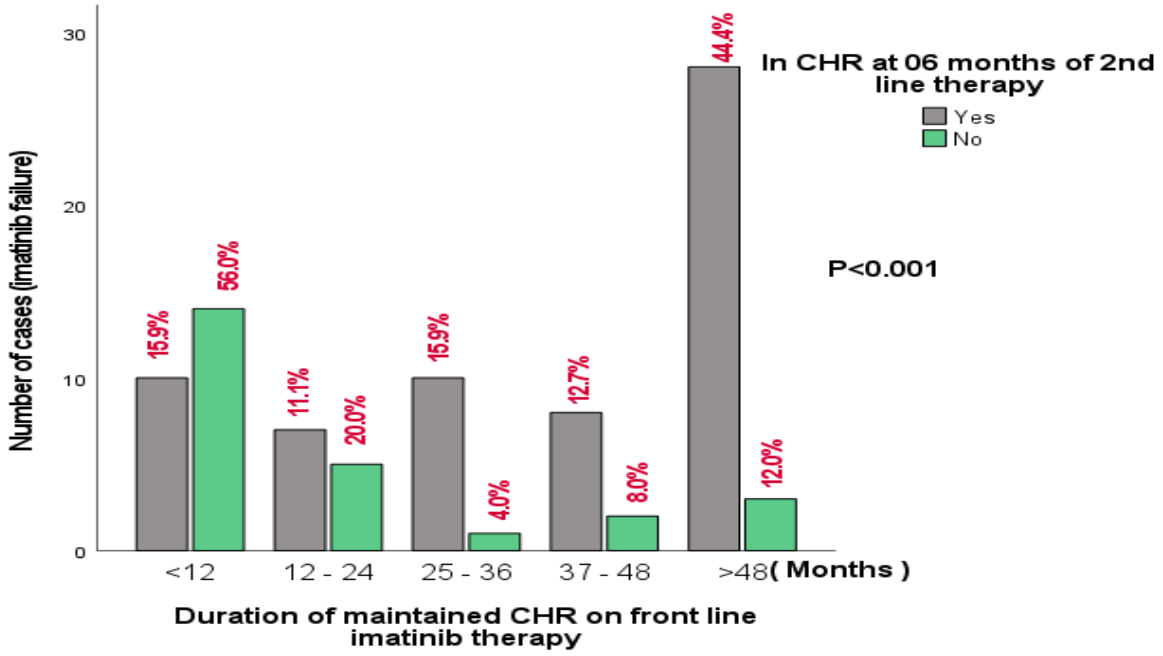
- CHR at 06 months for patients in chronic (81), accelerated (23), and blast phases (12) were 71.6%, 55.6% and 50.0%, respectively.

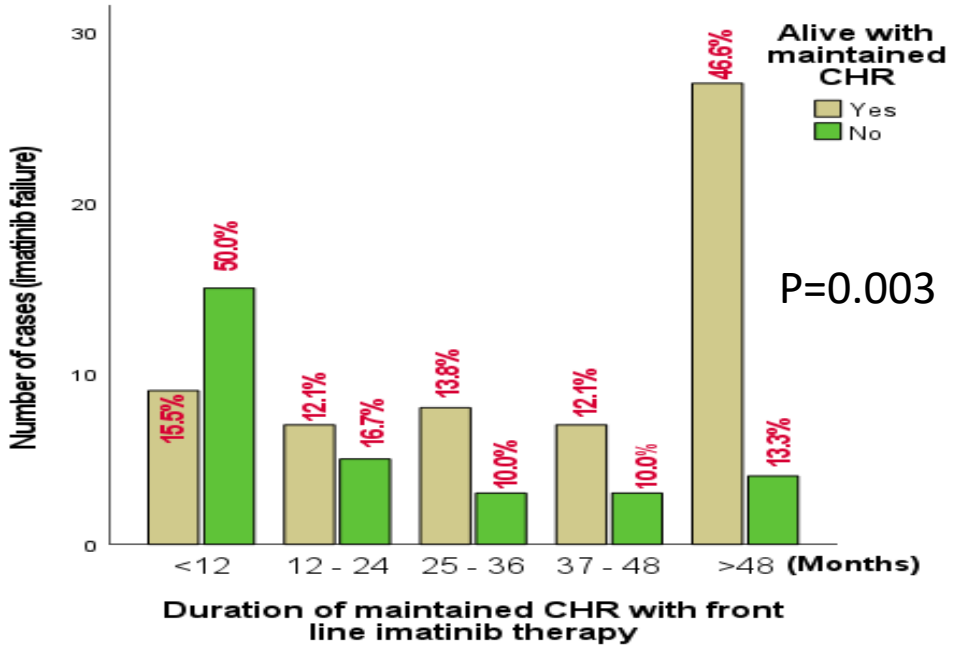
- After a median duration of treatment of 33 (IQR 23-49) months on second line TKI, 60.0% of our patients, in this cohort, were alive with retained CHR

- 66.7%, 43.5% and 41.7% of patients were alive with maintained CHR.

- No significant difference between M/F patients in terms of hematologic response (P=0.66); or duration of maintaining early CHR (*P=0.23*).

- The median duration of maintained CHR for all patients during the follow-up period was 24 (IQR 12-41; Range: 2 - 87) months.
- Longer durations of initial hematologic remission on imatinib are positively correlated with the rate of CHR at 06 months & proportion of alive patients in CHR following second line therapy (P=0.003).





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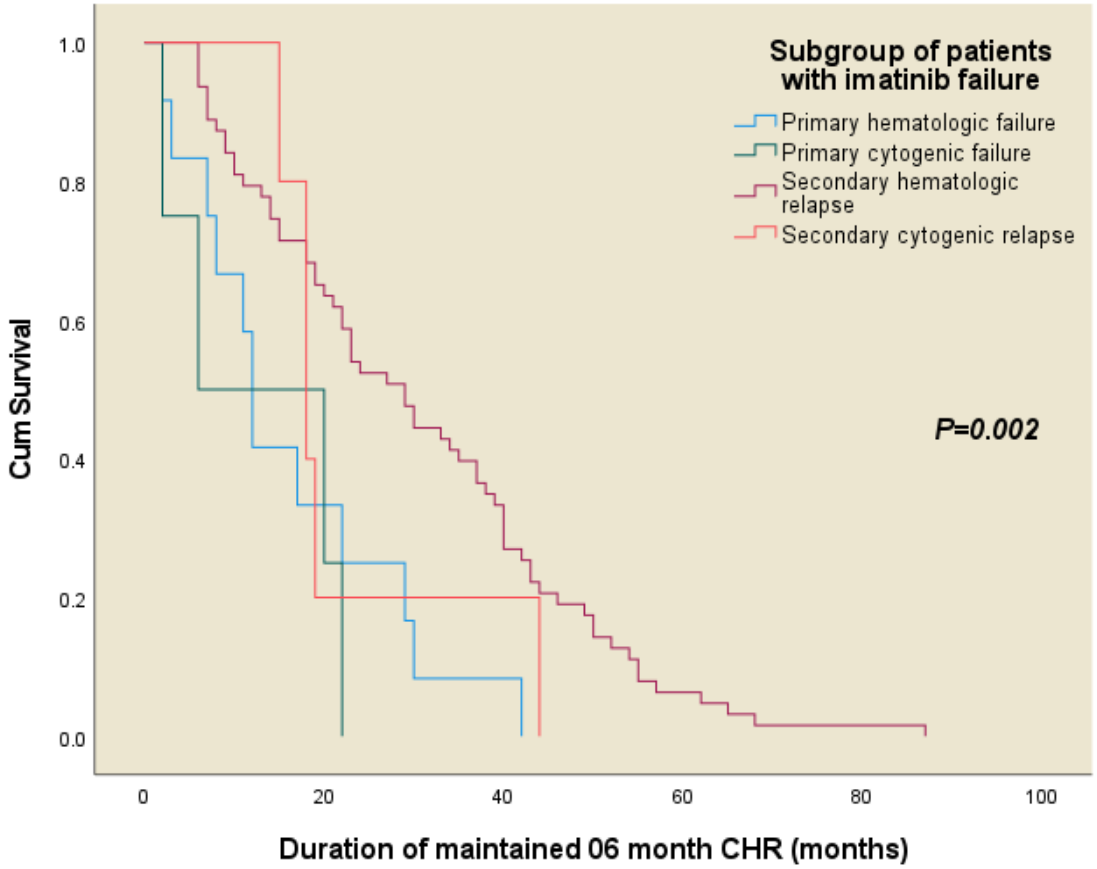
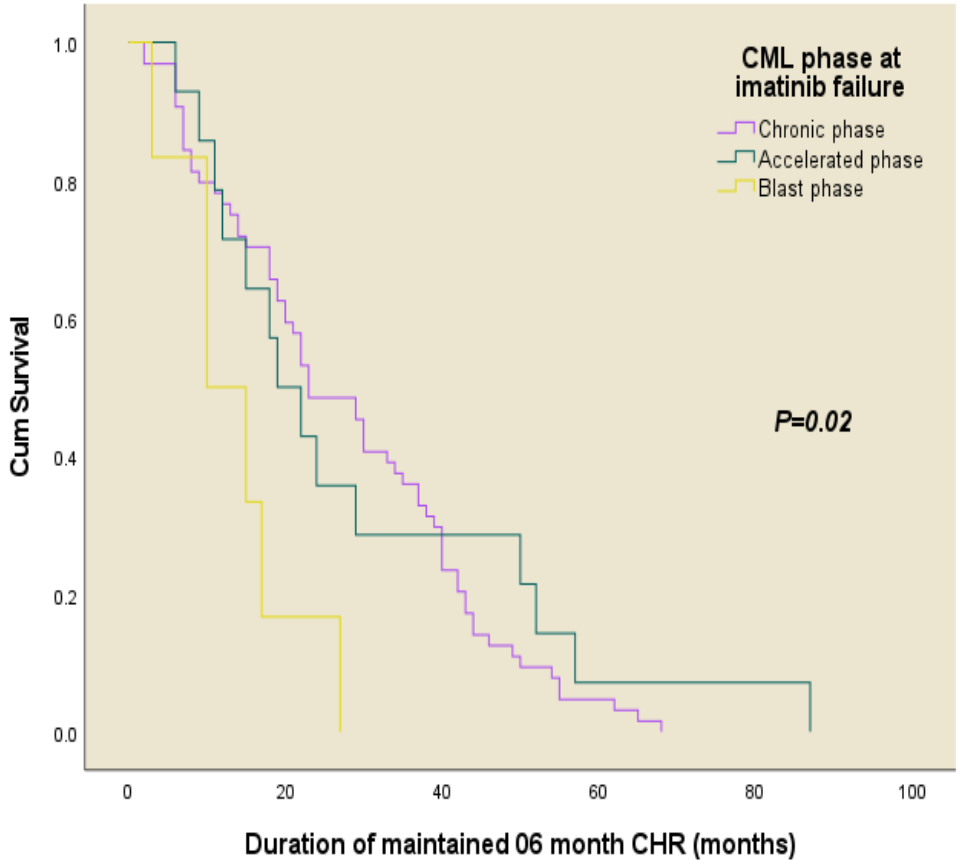
Maintained response (Determinants)





- Significant proportion (37/49, 75.5%) of patients on high dose imatinib were shifted to one of the second line TKIs.

- The rate of CHR at 06 months for the group of patients given HD imatinib (49) was 64.6%.

- After a median duration of treatment of 25 (IQR 14.0 – 35.2) months, 56.3% of patients were alive with maintained CHR

- The median duration of retained CHR was 18.5 months (Range: 2 – 37 months). ($t_{82 = -1.69 (-14.9 \text{ to } 1.2)}$; $P=0.09$)

- 29% of patients treated with high dose imatinib registered no significant hematologic response

- The baseline Sokal and ELTS scores failed to predict CHR at 06 months (*P=0.10; P=0.82*, respectively); and the degree of best treatment response (*P=0.28, P=0.95*, respectively)

- The Presence of major comorbidities did not significantly affect the duration of remission on second line TKIs *(P=0.57).*

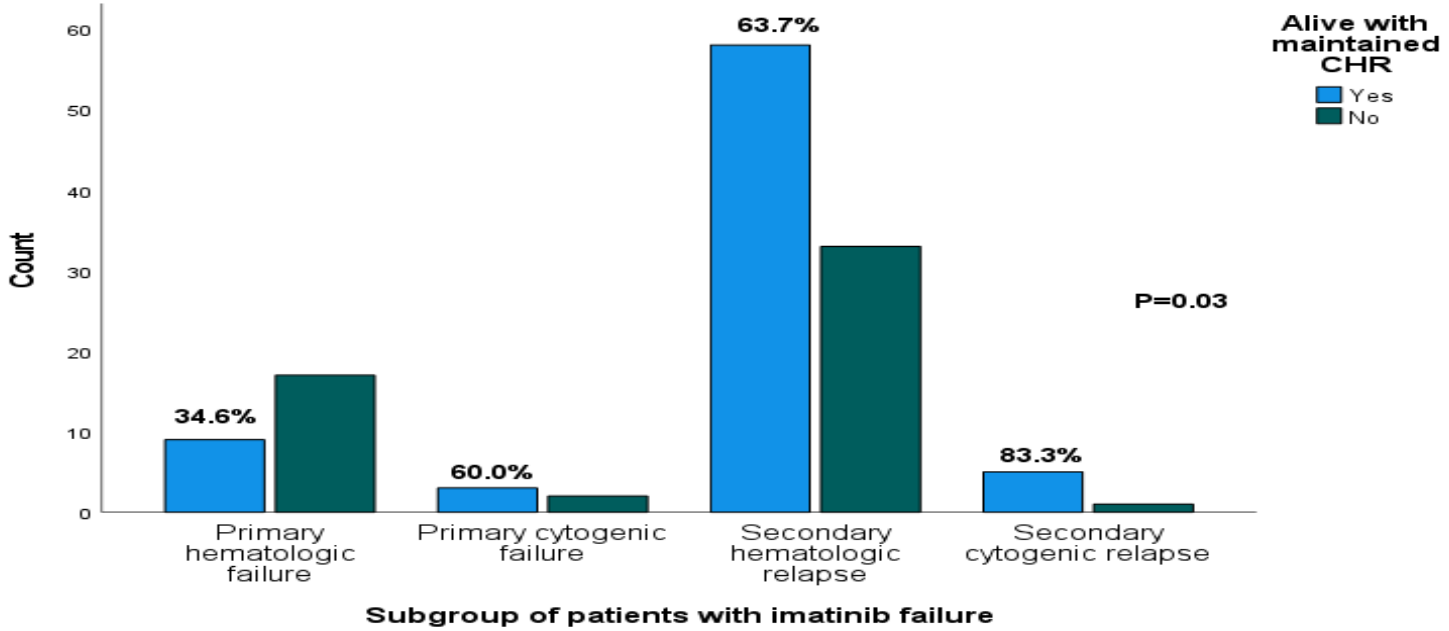
- The median duration of maintained CHR for patients in chronic, accelerated and blast phases were 26 months (IQR 13-42; Range 2 – 68) months, 19 months (IQR 11-51; Range 6 – 87 months) and 12.5 months (IQR 8.2-19.5; Range 3-27) months, respectively.

- Fewer number of Patients from the advanced phase of the disease were in CHR at 06 months (p=0.19); and were alive with CHR at the time of analysis (P=0.09).

- Presence of +ve KD mutation had no significant association with the rate of CHR at 06 months (P=0.72), duration of maintained CHR (*P = 0.98*). or chance of being alive with CHR (P=0.75) at the time of analysis.

- No significant correlation between the duration of response
  - age of patients at imatinib failure ((ρ = - 0.05; P=0.65).
  - qBCR-ABL1 level at treatment failure (ρ = 0.20; P=0.12).

- Significantly less number of patients with primary hematologic failure were alive with CHR than patients with secondary hematologic or cytogenic relapse (P=0.03).
- better rate of CHR at 06 months of second line TKI (P=0.08) for the later group.



- The median PFS and OS of patients in the study were not reached.

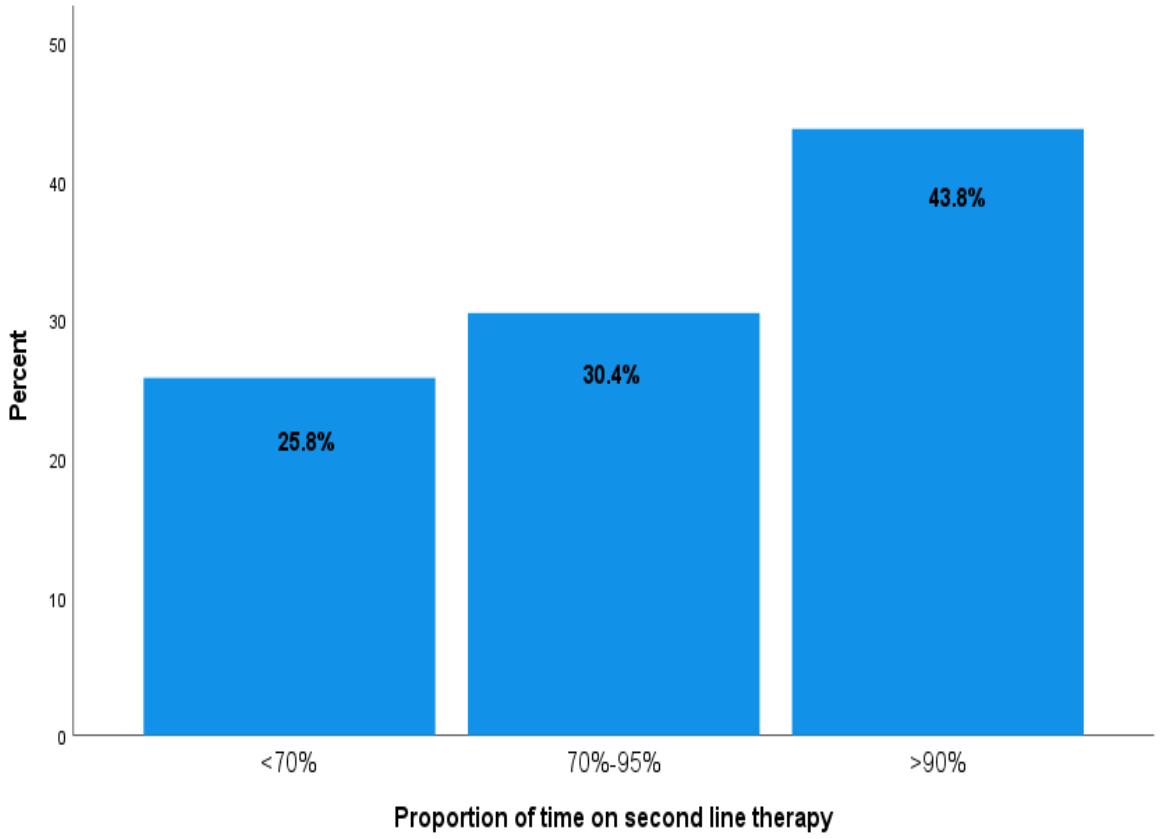
- For patients in chronic phase of the disease, only 8 (9.9%) patients progressed to an advanced phase; and only 3 (3.7%) patients were lost to follow-up

- 87% and 75% of patients in accelerated and blast phases of the disease were still on treatment & follow-up.

❖ Adherence to alternative therapy after the diagnosis of imatinib failure or intolerance was also assessed by MPR.

Proportion of time on second line therapy					
		Frequency	Percent	Valid Percent	Cumulative Percent
	<70%	33	25.8	25.8	25.8
	70%-95%	39	30.5	30.5	56.3
	>90%	56	43.8	43.8	100.0
	Total	128	100.0	100.0	

Patients with high treatment adherence and compliance did significantly better than others in achieving CHR at 06 month of therapy (P<0.01) and being alive with CHR at the final data cut off point (P<0.01).



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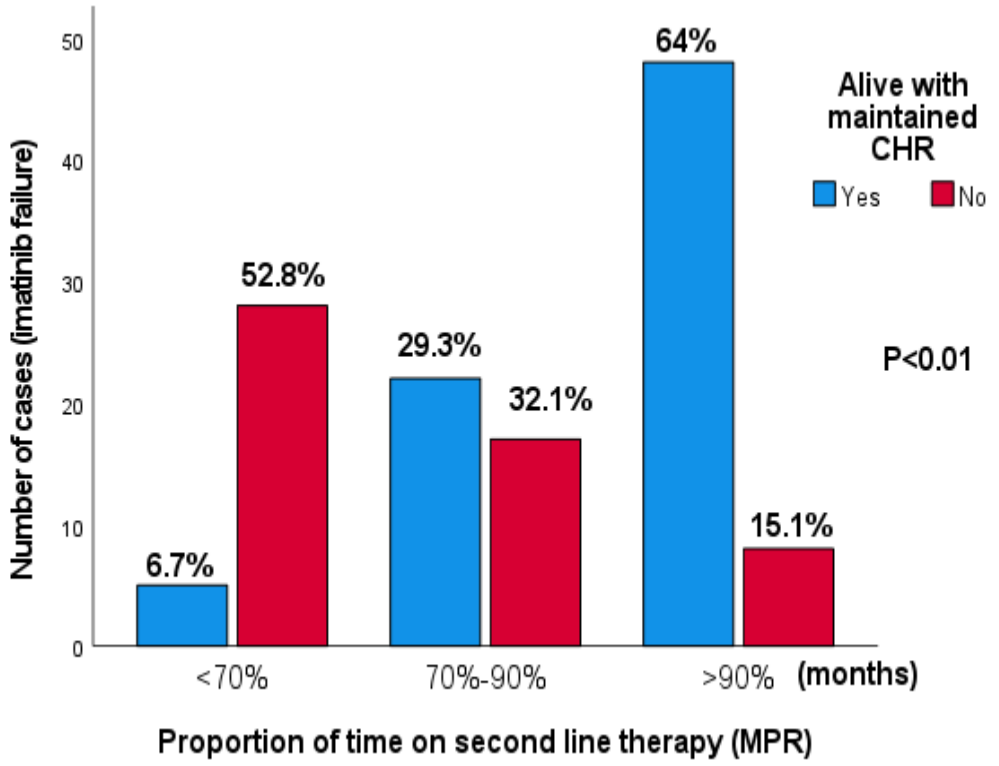
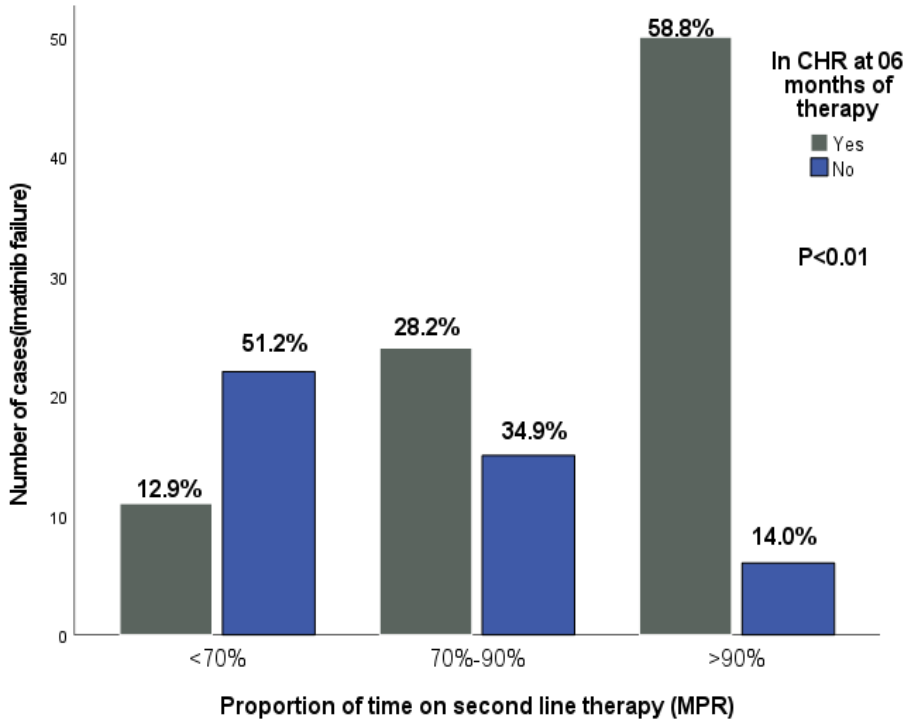
Treatment outcome by adherence





Treatment Outcome and determinant Factors of patients with imatinib intolerance

- Seven patients on follow-up developed hematologic and non-hematologic intolerance to imatinib between the year 2018 and 2022.
- All patients were in chronic phase of CML and treatment for all patients was expectedly changed to an alternative TKI
- Dasatinib was the most commonly used (57.1%) second line TKI followed by nilotinib (28.6%)
- There was no documented significant cross intolerance to subsequently chosen second line TKI
- comparable degree of adherence to patients with imatinib failure.

- The rate of CHR at 6 months of treatment for patients with imatinib intolerance was 71.4%.

- After a median duration of follow-up of 31 (IQR 23-47) months, 6/7 (85.7%) of our patients were alive with maintained CHR

- The median duration of maintained CHR on second line TKI was 32 months (IQR 11-47; Range 6-54) months.

- No significant association with patient age at diagnosis (P=0.64), gender (P=0.21), presence of comorbidities (P=0.49) and Sokal risk score at diagnosis (P=0.35).

- More patients with non-hematologic imatinib intolerance were in CHR at 06 months of second line TKI as compared to patients with hematologic intolerance (P=0.05).

- At the final data cut off point, all patient with imatinib intolerance were on alternative therapy; and were progression free.

In CHR at 06 months of therapy					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	5	71.4	71.4	71.4
	No	2	28.6	28.6	100.0
	Total	7	100.0	100.0	

Alive with maintained CHR					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	6	85.7	85.7	85.7
	No	1	14.3	14.3	100.0
	Total	7	100.0	100.0	

Statistics			
		Duration of followup of after imatinib failure (months)	Duration of followup of o second line (months)
N	Valid	7	7
	Missing	0	0
Mean		35.00	32.71
Median		31.00	27.00
Std. Deviation		16.361	16.204
Minimum		13	12
Maximum		63	60
Percentiles	25	23.00	22.00
	50	31.00	27.00
	75	47.00	46.00

Statistics		
Duration of maintained 06 month CHR (months)		
N	Valid	5
	Missing	2
Mean		29.60
Median		32.00
Std. Deviation		19.047
Minimum		6
Maximum		54
Percentiles	25	11.00
	50	32.00
	75	47.00

Questions ?
Comments ?

DISCUSSION

- This retrospective cohort study was conducted with the intention of acquiring a local data regarding the demographic, clinical characteristics and treatment outcome of patients with the imatinib failure and intolerance.

- The progressive rise in prevalence of patients failing on and not tolerating front line imatinib therapy motivated us to study the clinical features of this group of patients taking the subsequently introduced second and third line TKIs in our center.

- This study also intended to identify important prognostic and predictive markers of response in both group of patients.

- Out of the 128 patients, on follow-up at our center for imatinib failure, 86 (67.2%) were males and 42 (32.8%) of the participants were females (M: F ratio 2:1).

- This ratio is unlike similar other studies which reported a comparable M:F ratio in patients at the time of imatinib failure diagnosis.

- Patients with imatinib failure in our study were found to be younger (Median: 37 years) than the western population.

- the median age at imatinib failure in most studies is between the age of 50 and 55 years

Shah NP, Kantarjian HM, Kim DW, Réa D, Dorlhiac-Llacer PE, Milone JH, et al

- ❖ Significant proportion (58%) of our patients were referred from the rural areas of the country.
- ❖ Due to delayed presentation (41 vs 33 weeks) and diagnosis, majority (79.6%) had a high Sokal risk score at initiation of imatinib.
- ❖ Only 10-15% of patients from developed regions have a high Sokal score at CML diagnosis.
- ❖ The median duration of symptoms prior to presentation was 24 weeks and only a single patient was diagnosed incidentally

- significantly less than the proportion of CML patients from high SDI countries diagnosed incidentally at routine medical check-up

Efficace F, Baccarani M, Breccia M, Alimena G, Rosti G, Cottone F, et al

- High prevalence of major comorbidities in patients with imatinib failure was not identified on our patients. (9.7%).

- The high proportion of marked leukocytosis (Median 266k/ul), massive splenomegaly (Median 12c.m) and high Sokal/ELTS (67.5%/51.2%) scores noticed in our patients were similar to other studies having high proportion of patients with delayed CML diagnosis and referral.

- Female patients with imatinib failure had a significantly higher Sokal risk score at CML diagnosis

- Forty-seven (36.7%) patients had a BCR-ABL1 Kinase domain resistance mutation analysis done at imatinib failure; and point mutations were reported in 22 (46.8%) patients

  - similar proportion of patients from western CML treatment centers.

Saußele S, Krauß MP, Hehlmann R, Lauseker M, Proetel U, Kalmanti L, et al.

❖ 79.7% of our patients with imatinib failure had a reported CHR at 03 months of imatinib therapy.

- comparable between male & female patients; and among the different age groups at CML diagnosis.

❖ A high sokal and ELTS risk scores at diagnosis had a significantly lower rate (63.2%) of CHR

- conforms with results from other previous studies which looked in to the significance of risk score stratifications.

❖ The vast majority (91, 71.1%) of our patients with imatinib failure had a secondary hematologic relapse

❖ The median duration of maintained CHR with initial imatinib therapy was 30 months.

- significantly shorter than reports from patients with imatinib failure in western treatment centers.

❖ Older patients and patients with a high Sokal score had a significantly shorter duration of response prior to imatinib failure.

Hochhaus A, Baccarani M, Deininger M, Apperley JF, Lipton JH, Goldberg SL, et al

❖ CHR at 06 months of second line TKI in patients in chronic (81), accelerated (23), and blast phases (12) were 71.6%, 55.6% and 50.0%, respectively

- comparable to the responses obtained with similar second line TKIs, across the phases of the disease, in other Non transplant treatment centers.

❖ After a median duration of treatment of 33 months on second line TKI, 60% of our patients, in this cohort, were alive with retained CHR

❖ The median duration of maintained CHR for all patients during the follow-up period was 24 months

- also comparable with similar other studies assessing durability.

Cortes JE, Khoury HJ, Kantarjian HM, Lipton JH, Kim DW, Schafhausen P, et al

- In concordance with previous similar studies, the initial duration of hematologic response to imatinib positively correlated with both the achievement of early response and maintained hematologic response.

- patients with primary hematologic failure did poorly with alternative therapy in terms of the rate of early hematologic response and maintained duration of response

- only few number of patients will have a delayed CHR.

- confirms the predictive nature of early and durable response to imatinib in the subsequent efficacy of alternative therapy at the time of imatinib failure.

- Advanced Patient age and disease phase at imatinib failure were the other negative predictors of durability of early hematologic response to second line TKIs.

Hochhaus A, Kantarjian HM, Baccarani M, Lipton JH, Apperley JF, Druker BJ, et al

- ❖ The KD point mutation status failed to predict hematologic response to second line TKIs in our patients

- ❖ This is in contrary to studies reporting the negative impact of presence of KD mutations on hematologic response and PFS.

- ❖ High dose imatinib therapy for patients with imatinib failure in this study showed a comparable rate of CHR at 06 months of therapy; but responses were non-durable. and hence 75.5 % of patients were shifted to second line TKIs.

- ❖ Only 56.3% of patients on high dose (600mg QD) imatinib were alive in CHR at the time of analysis.

- consistent with studies which compared high dose imatinib to dasatinib therapy at the time of imatinib failure.

Bengió RM, Riva ME, Moiraghi B, Lanari E, Milone J, Ventriglia V, et al

Jabbour E, Kantarjian HM, Jones D, Shan J, O'Brien S, Reddy N, et al

- We evaluated patients' treatment adherence using the MPR and 74.2% of our patients had an intermediate to high degree of adherence to second line TKIs.

- In accordance with similar previous studies, patients with a high (>90%) medication adherence had a significantly better sustained hematologic response to second line TKIs.

- After a median duration of follow-up of 24 months, the PFS and OS of patients on chronic phase of the disease were 90.1% % and 96.3%, respectively.

- Survival rate of our patients with imatinib failure is comparable to patients from the western states on second line TKIs

De Almeida MH, Pagnano KBB, Vigorito AC, Lorand-Metze I, De Souza CA
Giles FJ, Abruzzese E, Rosti G, Kim DW, Bhatia R, Bosly A, et al

- ❖ Seven patients with imatinib intolerance, all in the chronic phase of the disease, taking second line TKIs, were included in this study.
- ❖ No incidence of cross intolerance between imatinib and other TKIs.
- ❖ Adherence to therapy was comparable to patients with imatinib failure
- ❖ The rate of CHR at 06 months of treatment was 71.4%.
- ❖After a median duration of follow-up of 31 months, 85.7% of our patients were alive with maintained CHR.

  - durability is consistent with previous reports in patients with imatinib intolerance from other treatment centers in high SDI countries.

Khoury HJ, Goldberg SL, Mauro MJ, Stone RM, Deininger MW, Bradley-Garelik MB, et al

❖ Patients with non-hematologic imatinib intolerance did better in terms of achieving an early CHR at 06 months of therapy.

- supported by few studies which compared the outcome of sub group of patients with imatinib intolerance.

❖ At the time of analysis, all patient with imatinib intolerance were on alternative therapy; and were free of disease progression.

Khoury HJ, Goldberg SL, Mauro MJ, Stone RM, Deininger MW, Bradley-Garelik MB, et al.

CONCLUSION

- ❖ Patients with imatinib failure in our set-up were predominantly male; and found to be much younger than patients from the western population.
  - Public health impact.

- ❖ Significant proportion of our patients were referred from the rural areas of the country with delayed presentation and diagnosis

- ❖Responses with second line TKIs in patients with imatinib failure were comparable to the responses obtained with similar agents, across the phases of the disease, in other treatment centers

- ❖ Duration of FFS on initial imatinib, age of patients at imatinib failure, degree of adherence to therapy and phase of CML at imatinib failure were important predictors of durable hematologic response in our patients.

- ❖ High dose imatinib following failure of standard dose therapy with imatinib led to non-durable response.

- ❖ Survival rate of our patients with imatinib failure and intolerance is comparable to reports from western treatment centers

- ❖ Imatinib intolerance, in our set-up, was more diagnosed in the extremes of age.
- ❖ well tolerated alternative therapy with no significant cross intolerance with second line TKIs
- ❖ Patients with non-hematologic imatinib intolerance did better in terms of achieving an early CHR

RECOMMENDATIONS

- Decentralized oncologic diagnostic and treatment centers are urgently needed.
- Solutions for occasional interruptions of TKIs.
- Using HD imatinib should be discouraged particularly in patients with overt hematologic failure or relapse.
- Efforts being made in introducing a regular cytogenic and molecular treatment response monitoring needs to be continued.
- Facilitation of efforts under way (? Here and there) to introduce HSCT service in our set-up.
- Follow-up studies enrolling more number of patients and targeting molecular responses with longer duration of follow-up need to be carried on.

STRENGTH AND LIMITATIONS

Strength

- Conducted in the largest and the most recognized tertiary referral hospital
- a five-year study period
- included all patients managed in the study period
- provides a new local practical knowledge

Limitations

- difficulty in obtaining patients' medical records
- Incomplete clinical and laboratory data
- low number of patients were able to have a BCR-ABL1 transcript level done

THANK YOU !!!