https://doi.org/10.48047/AFJBS.6.14.2024.11972-11982

African Journal of Biological Sciences

Research Paper Open Access

Retrospective Analysis of Clinico-Epidemiological Data and Treatment Outcome in Patients with Chronic Phase Chronic Myeloid Leukemia

Hossam El-Din Hamdy Zawam[1], Wedad Mohamed Bassam[1], Radwa Refat Mohamed[2*], Sara Ayman Nassar[3]

[1] Associate Professor of Clinical Oncology Faculty of Medicine, Cairo University

[2] MBBch Faculty of Medicine, Cairo University

[3] Lecturer of Clinical Oncology Faculty of Medicine, Cairo University

Corresponding author: Radwa Refat Mohamed.

Article History

Volume 6, **Issue** 14, 2024

Received: 10 July 2024

Accepted: 31 August 2024

Published: 06 September 2024

doi: 10.48047/AFJBS.6.14.2024.11972-11982

Abstract:

Background: Chronic myelogenous leukemia (CML) is a clonal stem cell disorder characterized by increased proliferation of myeloid elements at all stages of differentiation.

Aim: To clarify the benefit of treatment cessation in CML patients by assessing the molecular relapse-free survival (MRFS) in CML chronic phase.

Patients and methods: This retrospective study was carried out at Kasr Al-Aini Center of Clinical oncology and Nuclear Medicine (NEMROCK) during the period from January 2015 to December 2022.

Results: This study shows that using the ELTS score, 66.7% (80) patients were found in the in the low-risk category, 23.3% (28) in the intermediate-risk category, and 10.0% (12) in the high-risk group. This study shows that the event-free survival (EFS) at 4 years was 79.5% at 7 years was 43.5% with second line treatment (95% CI, 58.6-88.0). Other studies shows that Age, gender, baseline ELTS score, duration of TKI, type of TKI used, time to MR4.5, duration of MR4.5 were analyzed as potentially predictive factors for TFR durability. On univariate analysis, overall TKI duration in months and time to DMR at the time of treatment discontinuation was found to be predictive of TFR durability (p=0.011, 0.002 respectively).

Conclusion: The study found that middle-aged patients with chronic Myeloid Leukemia have low-risk ELTS scores, with better outcomes compared to those with intermediate or high-risk scores.

Keywords: CMI; Myeloid; MRFS

1. Introduction

Chronic myelogenous leukemia (CML) is a clonal stem cell disorder characterized by increased proliferation of myeloid elements at all stages of differentiation **(1)**.

More than 95% of CML patients have a chromosomal abnormality, the Philadelphia chromosome which is a reciprocal translocation of the long arms of chromosomes 9 and 22, the t (9;22) (q34; q11). This aberrant chromosome encodes a fusion gene, BCR- ABL **(2)** .

Before the 2000s, treatment strategy for CML was limited to interferon-alpha (IFN-alpha), chemotherapy, hydroxyurea and allogeneic stem cell transplantation which was the most efficient treatment strategy **(3)**.

Later on, the treatment protocol completely changed with the introduction of Imatinib, being the first targeted therapy used in treating CML patients **(4)**.

First-line therapy options are first-generation (Imatinib) and second-generation (Nilotinib and Dasatinib) TKIs. Second-line therapy options consist of second-generation TKIs (Nilotinib, Dasatinib, and Bosutinib) and third-generation TKI, ponatinib, which is also used in third-line therapy as well as for patients with T315I mutation associated with pan-TKI resistance **(5)**.

The aim of this retrospective study was to assess Chronic phase CML treated at NEMROCK in the period from January 2015 to December 2022; Evaluating their demographic features, disease characteristics, molecular response status, and survival rate of chronic phase CML patients treated with different TKIs. In addition, to assess tolerance and compliance of the TKIs.

Furthermore, it aims to clarify the benefit of treatment cessation in CML patients by assessing the molecular relapse-free survival (MRFS) in CML chronic phase. We will, also, try to find any predictive factors for sustained TFR in those patients to enhance the future patient selection criteria to stop their treatment.

Patients and methods

This retrospective study was carried out at Kasr Al-Aini Center of Clinical oncology and Nuclear Medicine (NEMROCK) during the period from January 2015 to December 2022.The study included all patients presenting in this period. The patient's files were reviewed and extrapolation of data was performed.

Inclusion criteria: Age ≥18 years, diagnosed as CML BCR-ABL fusion gene positive and in Chronic Phase (CP).

Exclusion criteria: Presence of other primary malignancies, patient in accelerated phase and blast phase and received chemotherapy except hydroxyurea, underwent stem cell transplantation and Incomplete medical data.

Methods

In the present study it reviewed 136 patients diagnosed as chronic phase CML treated at NEMROCK in the period from January 2015 to December 2022. Patients with exclusion criteria were excluded from analysis, the only analyzable group with complete data are 120 patients. We reviewed and collected the following Data including: **Demographic Data:** Age, gender. **Baseline patients' characteristics:** Co-morbidities included diabetes mellitus, hypertension, cardiac disease and others, disease related symptoms and splenic size in centimeter below costal margin. **Laboratory evaluation: Complete** blood count with differential, molecular assessment by Q-RT PCR. **Risk classification:** According to ELTS SCORE. **TKI evaluation**: All below mentioned data were checked for first, second and third lines: Type of TKI, dosage and duration of treatment,

response (hematological, cytogenetic and molecular), toxicity, Interruptions (duration and causes) and loss of MMR. **Primary outcomes (Most important measurable outcomes):** Response to TKIs (Hematological and Molecular response)**. Secondary outcome parameters (Other outcomes to be assessed):** Tolerance and compliance of different TKIs, discontinuation of TKI and treatment free remission (TFR) and overall survival was defined as the length of time from the date of diagnosis till the date of last follow up or death. Adverse events were assessed according to common terminology criteria for adverse effects (CTCAE) version 5.0 cancer institute N. common terminology criteria for adverse events (CTCAE) version 5.0; 2017. (cancer institute N. common terminology criteria for adverse events (CTCAE) version 5.0; 2017, 2017).

Statistical Analysis

Data were collected, revised, coded and entered to the statistical package for social science (IBM SPSS) version 27. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using **Chi-square test** and/or **Fisher exact test** when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and non-parametric distribution were done by using **Mann-Whitney test**.

Kaplan Meier analysis was used to assess the relation between overall survival and the other studied parameters using **Log Rank Test. Cox regression analysis** was used to assess the predictors of the probability that the event of interest has occurred at a given time *t.* The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value > 0.05: Non-significant (NS), P-value < 0.05: Significant (S) and P-value < 0.01: Highly significant (HS).

Results

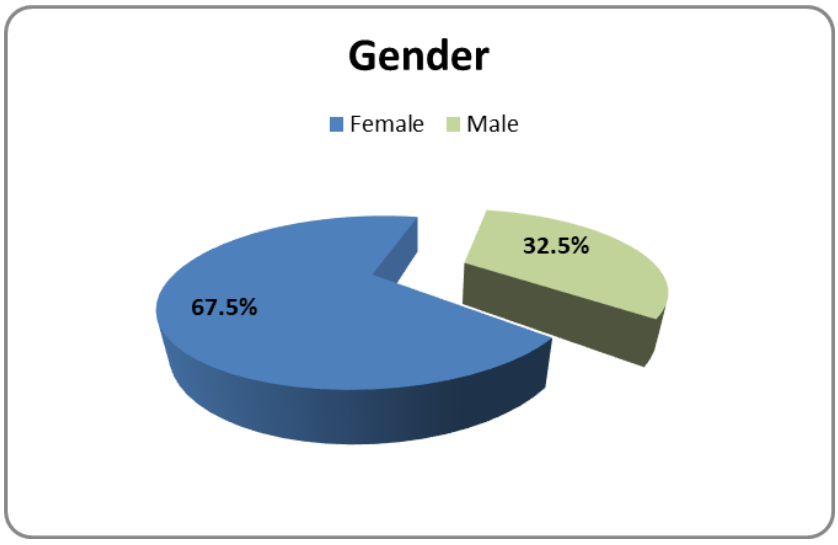

Figure (1): Gender distribution among the studied patients.

Fig 1 shows that Patient's age ranged from 19 to 67 years with a median age 36 years. Male patients were 39 (32.5%) and female patients were 81 (67.5%) with ratio 0.48:1.

Table (1): ELTS Score at diagnosis among the studied patients.

ELTS score	**Low**	80 (66.7%)
	Intermediate	28 (23.3%)
	High	12 (10.0%)

Using the ELTS score, 66.7% (80) patients were found in the in the low-risk category, 23.3% (28) in the intermediate-risk category, and 10.0% (12) in the high-risk group (Table 1).

Table (2): First line TKI response among the studied patients.

		First line		**Test value**	**P-value**	**Sig.**
		Imatinib	**Nilotinib**			
		No. = 109	**No. = 11**			
Hematologic response	No	2 (1.8%)	0 (0.0%)	20.154*	0.09	NS
	Yes	107 (98.2%)	11 (100.0%)			
CHR	Median (IQR)	2(1 – 2)	1(0 – 1)	**-1.973≠**	**0.048**	S
	Range	0 – 4	0 – 1			
PCR at 3 months	Optimal	64 (58.7%)	7 (63.6%)	1.149*	0.284	NS
	Warning/failure	42 (38.5%)	2 (18.2%)			
PCR at 6 months	Optimal	44 (40.4%)	4 (36.4%)	5.466*	0.065	NS
	Warning	52 (47.7%)	3 (27.3%)			
	Failure	4 (3.7%)	2 (18.2%)			
PCR at 12 months	Optimal	42 (38.5%)	7 (63.6%)	**8.719***	**0.013**	S
	Warning	45 (41.3%)	0 (0.0%)			
	Failure	12 (11.0%)	0 (0.0%)			
PCR 18 months	Optimal	61 (56.0%)	7 (63.6%)	2.565*	0.277	NS
	Warning	22 (20.2%)	0 (0.0%)			
	Failure	1 (0.9%)	0 (0.0%)			
PCR 24 months	Optimal	65 (59.6%)	7 (63.6%)	1.610*	0.447	NS

Regarding the major molecular response (MMR), BCR-ABL1IS transcripts ≤0.1% at the 12 month of therapy, nilotinib group had significantly higher frequency of MMR. About 63.5% patients achieved MMR while only 38.5% patients in imatinib group achieved MMR (p = 0.013) (Table 2).

Table (3): Relation between 2nd line type of TKI and 2nd line Major molecular response among the studied patients.

		Second line TKI		Test value	P-value	Sig.
		Nilotinib	Dasatinib			
		No. = 35	No. = 6			
MMR	No	11 (31.4%)	4 (66.7%)	**3.958***	**0.047**	**S**
	Yes	24 (68.6%)	2 (33.3%)			
Loss of MMR	No	12 (50.0%)	2 (100.0%)	1.857*	0.173	NS
	Yes	12 (50.0%)	0 (0.0%)			
Time to MMR in months	Median (IQR)	59.84(54.9 – 70.08)	53.64(13.35 – 93.93)	-0.096≠	0.923	NS
	Range	0.89 – 109.45	13.35 – 93.93			
MMR Duration in months	Mean ± SD	56.36 ± 17.16	23.2 ± 24.32	**2.378•**	**0.039**	**S**

Higher proportion achieved MMR as well as longer MMR duration in the nilotinib group than the Dasatinib. (p=0.047 and 0.039) (Table 3).

Table (4): Event free survival (months) at 2nd line distribution among the studied patients

Total No.	EFS (months)		95% CI		Survival at		
	Mean	S.E	Lower	Upper	1 year	4 years	7 years
267	73.305	7.516	58.575	88.036	92.0%	79.5%	43.5%

Table 4 show that the event-free survival (EFS) at 4 years was 79.5% and at 7 years was 43.5% with second line treatment (95% CI, 58.6-88.0).

Table (5): Molecular relapse-free survival in months distribution among the studied patients.

Total N	Molecular relapse-free survival in months		95% CI		Survival at		
	Mean	S.E	Lower	Upper	1 year	2 years	3 years
40	40.361	4.664	31.219	49.504	78.8%	67.2%	51.0%

Table (6) Relation of Molecular relapse-free survival in months with demographic data and clinical presentation among the studied patients

		Total N	No. of Events	Molecular relapse-free survival in months		95% CI		Log Rank test		
				Mean	S.E	Lower	Upper	X^2	P-value	Sig.
Age at Diagnosis	< 35 years	19	9	33.66	4.97	23.93	43.39	0.528	0.467	NS
	≥ 35 years	21	11	43.86	6.30	31.51	56.21			
Age at time of TFR	< 40 years	18	10	32.693	4.64	23.59	41.79	1.01	0.315	NS
	≥ 40 years	22	10	45.113	6.70	31.99	58.24			
Gender	Female	32	16	42.028	5.18	31.87	52.18	1.176	0.278	NS
	Male	8	4	24.409	2.77	18.98	29.84			
ELTS score	Low	23	16	34.759	4.94	25.08	44.44	0.529	0.467	NS
	Intermediate /High	11	4	18.802	2.52	13.86	23.74			
TKI at discontinuation	Imatinib	26	13	42.938	6.13	30.91	54.96	0.179	0.672	NS
	Nilotinib	14	7	33.971	3.88	26.37	41.57			
Overall TKI duration in months	< 70 months	18	9	25.67	4.60	16.66	34.67	**6.055**	**0.014**	S
	≥ 70 months	22	11	48.10	5.48	37.35	58.84			
Time to $MR^{4.5}$	< 38 months	20	10	48.88	5.62	37.87	59.89	**8.633**	**0.003**	HS
	≥ 38 months	20	10	21.696	2.65	16.49	26.90			
$MR^{4.5}$ duration	< 30 months	21	8	53.671	5.98	41.95	65.40	1.525	0.217	NS
	≥ 30 months	19	12	33.106	4.79	23.72	42.49			

Age, gender, baseline ELTS score, duration of TKI, type of TKI used, time to $MR^{4.5}$, duration of $MR^{4.5}$ were analyzed as potentially predictive factors for TFR durability. On univariate analysis,

overall TKI duration in months and time to DMR at the time of treatment discontinuation was found to be predictive of TFR durability (p=0.011, 0.002 respectively) (Table 5,6).

Table (7): Final outcome among the studied patients.

		Total No. = 120
$MR^{4.5}$	No Yes	47 (39.2%) 73 (60.8%)
Time to $MR^{4.5}$ in months	Median (IQR) Range	35.05 (23.9 – 63.02) 4.6 – 95.87
$MR^{4.5}$ duration in Months	Median (IQR) Range	32 (21 – 49) 2 – 85
Loss DMR (BCR-ABL1 ^{IS} transcripts)	Median (IQR) Range	0.05 (0.04 – 0.1) 0.04 – 78
TFR	No Yes	80 (66.7%) 40 (33.3%)
Last BCR-ABL1 ^{IS} transcripts	Median (IQR) Range	0.09 (0 – 0.33) 0 – 78
Status	Alive Dead	110 (91.7%) 10 (8.3%)
OS (months)	Median (IQR) Range	92.22 (74.4 – 108.26) 10.68 – 183.72
Relapse on 1st line	No Yes	57 (66.3%) 29 (33.7%)
EFS on 1st line (months)	Median (IQR) Range	68.5 (46.03 – 82.45) 4.5 – 148.34
Relapse on 2nd line	No Yes	14 (53.8%) 12 (46.2%)
EFS on 2nd line (months)	Median (IQR)	57.58 (40.41 – 72.3)

Discussion

This study shows that Patient's age ranged from 19 to 67 years with a median age 36 years. Male patients were 39 (32.5%) and female patients were 81 (67.5%) with ratio 0.48:1.

The age range of patients in our study was between 19 and 67 years, with a median age of 36 years. This median age is notably younger compared to studies in Europe (55 years) and America (66 years) as indicated **Tardieu et al. (6)**.However, our study age was comparable to previous Egyptian reports **ElNahass et al. (7).** Likewise, studies conducted in Pakistan by. **Syed et al. (8)** and in Nigeria by **Oyekunle et al. (9)** reported median ages of 38 years and 37 years for patients with Philadelphia-positive CML, respectively. Furthermore, a study in Mexico by **Ylescas-Soria et al. 10** reported a median age of 40 years for CML patients. This could be a result of Egypt's population pyramid, which leans towards a younger and expanding demographic.

This study shows that Using the ELTS score, 66.7% (80) patients were found in the in the low-risk category, 23.3% (28) in the intermediate-risk category, and 10.0% (12) in the high-risk group.

The risk group distribution of the patients in our study showed predominance of low ELTS risk group (66%) and lower proportion of high ELTS risk (10%). This is in accordance with other studies as **Specchia et al. (11)**

However, **Elbedewy & Elashtokhy. (12)** demonstrated a different distribution, with a lesser percentage of low-risk patients at 45.5%, and a higher proportion classified as intermediate risk at 46.7%, with 7.8% of patients categorized as high risk.

This study shows that regarding the major molecular response (MMR), BCR-ABL1IS transcripts ≤0.1% at the 12month of therapy, nilotinib group had significantly higher frequency of MMR. About 63.5% patients achieved MMR while only 38.5% patients in imatinib group achieved MMR ($p = 0.013$).

In our study, at 12 months of treatment, BCR-ABL1≤ 0.1% was observed in 42.4% of patients receiving imatinib which is considered optimal responders by the ELN 2020 guidelines **Hochhaus et al. (5**). This result is close to results of IRIS study in which the major molecular response (MMR) rate in 553 patients in the imatinib arm increased from 24% at 6 months to 39% at 12 months **Deininger et al. (13).** Machado et al. investigated 60 patients who had received imatinib as first or second line therapy and found this level of response in 40% of the patients **Machado et al.14**

This study shows that Higher proportion achieved MMR as well as longer MMR duration in the nilotinib group than the Dasatinib. (p=0.047 and 0.039).

Another real-life report by **Tiribelli et al. (15)** investigating second-line treatment in 163 CML patients found similar rates of MMR, 60%, for both nilotinib and dasatinib groups (p=ns). A comparable median time to achieve molecular response, PFS, and overall survival (OS) was noted However, in our study, higher proportion achieved MMR and durable MMR duration were noted in the nilotinib group than in dasatinib group (p=0.047 and p=0.03). This could be attributed to the very small number of patients received second line dasatinib (14%) in comparison to those received nilotinib (85%) in our study.

This study shows that the event-free survival (EFS) at 4 years was 79.5% at 7 years was 43.5% with second line treatment (95% CI, 58.6-88.0).

Shah et al.16, in 670 patients, reported MMR incidence with second line TKI at 7 years of 46%; in our smaller series, we reported MMR in 63.4% of cases with median follow up 55 months. However, they reported also an EFS and OS of 42% and 65%, respectively. This is similar to our outcomes where EFS at 7 year was 43.5%.

These studies shows that Age, gender, baseline ELTS score, duration of TKI, type of TKI used, time to $MR^{4.5}$, duration of $MR^{4.5}$ were analyzed as potentially predictive factors for TFR durability. On univariate analysis, overall TKI duration in months and time to DMR at the time of treatment discontinuation was found to be predictive of TFR durability (p=0.011, 0.002 respectively).

For patients attempting treatment free remission (TFR), the median age at the time of TKI discontinuation was 40 years (31.5 – 50.5). This result is similar to **Samra et al. (17)** median age for the study population was 36.5 years. However, the median age of another Egyptian study population was 51 years for the treatment free group **Nafea. (18**). The median age of patients in the STIM trial was 63 years (range 29-80) **F.-X. Mahon et al. 19**, 61 years in the STIM 2 study.

Baseline ELTS score was low in 23 (57.5%), intermediate in 11 (27.5 and high in 6 (15.0%) similar to Gabriel Etienne,50.0 % were low risk, 30.6 % intermediate risk, 13.3 % high risk and 6.0% unknown status **Etienne et al. (20)**.

The median duration of TKI therapy before discontinuation in our study was 87 months (range 44-128), which slightly aligns with the duration observed in the TWISTER study (70 months), though it surpasses that of the STIM 1 study (58.8 months) and falls short of the median in the EURO-SKI study (96 months). Across all these studies, including ours, a minimum TKI duration of 36 months was required **Ross et al.21, Mahon et al. 19, Saussele et al.22.**

Regarding the median period to achieve $MR^{4.5}$ (deep molecular response), our study recorded 38.5 (with a range of 4 – 88) months, which differs from the TWISTER study (30 months), the STIM Study (36 months), and the EURO-SKI study (64 months). It is similar to median duration of $MR^{4.5}$ found in Khazaal et.al, 37.5 months and in Samra et.al, 41 months **Khazaal et al. (23), (Samra et al. (17).**

The molecular relapse-free survival was 67% at 2 years. This is comparable to KID study where median follow up was 27 months and TFR rate was 59% at 2 years **Zang et al. (24)**.

Conclusion and recommendation

Our study revealed that patients with Chronic Myeloid Leukemia (CML) in the chronic phase, were primarily middle-aged individuals, with a slight female predominance and low-risk ELTS scores. Comorbidities such as diabetes mellitus and cardiac disease were associated with worse overall survival. Additionally, a correlation was observed between the ELTS prognostic risk score and treatment response, indicating that individuals with a low-risk score tended to have better outcomes compared to those with intermediate or high-risk scores. Patients received nilotinib as second line TKI had higher MMR rates although the size of our sample was limited. Ceasing TKIs in appropriately selected patients with stable Major Molecular Response (MMR) for a minimum of two years appears to be a safe strategy, with negligible impacts on survival or quality of life, and potential economic advantages, particularly in resource-limited settings. Nonetheless, meticulous patient selection and strict follow up are imperative for achieving favorable outcomes.

References

1. Champlin RE, Golde DW. Chronic myelogenous leukemia: recent advances.
2. Goldman JM, Melo JV. Chronic myeloid leukemia—advances in biology and new approaches to treatment. New England Journal of Medicine. 2003 Oct 9;349(15):1451-64.
3. Sahin F, Saydam G, Cömert M, Uz B, Yavuz AS, Turan E, Yönal İ, Atay H, Keltikli E, Turgut M, Pehlivan M. Turkish Chronic Myeloid Leukemia Study: Retrospective Sectional Analysis of CML Patients. Turkish Journal of Haematology: Official Journal of Turkish Society of Haematology. 2013 Dec 5;30(4):351-8.
4. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine. 2003 Mar 13;348(11):994-1004.
5. Hochhaus A, Gambacorti-Passerini C, Abboud C, Gjertsen BT, Brümmendorf TH, Smith BD, Ernst T, Giraldo-Castellano P, Olsson-Strömberg U, Saussele S, Bardy-Bouxin N.

Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: primary results of the phase 4 BYOND study. Leukemia. 2020 Aug 1;34(8):2125-37.

6. Tardieu S, Brun-Strang C, Berthaud P, Michallet M, Guilhot F, Rousselot P, Sambuc R. Management of chronic myeloid leukemia in France: a multicentered cross-sectional study on 538 patients. Pharmacoepidemiology and drug safety. 2005 Aug;14(8):545-53.
7. ElNahass YH, Assem MM, Saber MM, Abdalla SK, Mahmoud HK, ElRefaey FA. Prognostic impact of Additional Chromosomal Abnormalities in Egyptian Chronic Myeloid Leukemia Patients. Open Access Macedonian Journal of Medical Sciences. 2020 Jul 20;8(B):623-30.
8. Syed NN, Usman M, Adil S, Khurshid M. Additional chromosomal abnormalities in Philadelphia-positive chronic myeloid leukemia. Hematology/oncology and stem cell therapy. 2008 Jul 1;1(3):166-70.
9. Oyekunle AA, Bolarinwa RA, Oyelese AT, Salawu L, Durosinmi MA. Determinants of Overall and Progression-Free Survival of Nigerian Patients with Philadelphia-Positive Chronic Myeloid Leukemia. Advances in hematology. 2015;2015(1):908708.
10. Ylescas-Soria J, de la Torre-Lujan AH, Herrera LA, Miranda D, Grimaldo F, Rivas S, Cervera E, Meneses-García A, Leon-Sarmiento FE, Prada D. Prognostic factors for overall survival in patients with chronic myeloid leukemia treated with imatinib at the National Cancer Institute–Mexico, from 2000 to 2016. Cancer medicine. 2019 Jun;8(6):2942-9.
11. Specchia G, Pregno P, Breccia M, Castagnetti F, Monagheddu C, Bonifacio M, Tiribelli M, Stagno F, Caocci G, Martino B, Luciano L. Prognostic factors for overall survival in chronic myeloid leukemia patients: a multicentric cohort study by the Italian CML GIMEMA network. Frontiers in Oncology. 2021 Aug 26; 11:739171.
12. Elbedewy TA, Elashtokhy HE. The utility and applicability of chronic myeloid leukemia scoring systems for predicting the prognosis of Egyptian patients on Imatinib: retrospective study. J Leuk. 2016;4(210):1-9.
13. Deininger M, O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, Radich JP, Hatfield AK, Mone M, Filian J, Reynolds J. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. Blood. 2009 Nov 20;114(22):1126.
14. Machado MP, Tomaz JP, Lorand-Metze I, Souza CA, Vigorito AC, Delamain MT, Bendit I, Pereira NF, Pagnano KB. Monitoring of BCR-ABL levels in chronic myeloid leukemia patients treated with imatinib in the chronic phase: the importance of a major molecular response. Revista brasileira de hematologia e hemoterapia. 2011; 33:211-5.
15. Tiribelli M, Bonifacio M, Binotto G, Iurlo A, Cibien F, Maino E, Guella A, Festini G, Minotto C, De Biasi E, De Marchi F. Excellent outcomes of 2G-TKI therapy after imatinib failure in chronic phase CML patients. Oncotarget. 2018 Mar 3;9(18):14219.
16. Shah NP, Rousselot P, Schiffer C, Rea D, Cortes JE, Milone J, Mohamed H, Healey D, Kantarjian H, Hochhaus A, Saglio G. Dasatinib in imatinib-resistant or-intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. American journal of hematology. 2016 Sep;91(9):869-74.
17. Elsafty MH, Samra MA, Elgammal M, Fattah RA. Treatment-free remission after stopping tyrosine kinase inhibitors in patients with chronic myeloid leukemia in chronic phase achieving major molecular response. Drug Invention Today. 2019 Nov 1;11(11).

18. Nafea DA, Nazer AA, Khalaf MH, Omara S. Treatment Free Remission Assessment after Discontinuation or dose Reduction of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia Patients. International Journal of Research and Reports in Hematology. 2022 May 4;5(2):89-98.
19. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, Legros L, Charbonnier A, Guerci A, Varet B, Etienne G. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. The lancet oncology. 2010 Nov 1;11(11):1029-35.
20. Etienne G, Dulucq S, Bauduer F, Adiko D, Lifermann F, Dagada C, Lenoir C, Schmitt A, Klein E, Madene S, Fort MP. Incidences of deep molecular responses and treatment-free remission in de novo CP-CML patients. Cancers. 2020 Sep 4;12(9):2521.
21. Ross DM, Branford S, Seymour JF, Schwarer AP, Arthur C, Yeung DT, Dang P, Goyne JM, Slader C, Filshie RJ, Mills AK. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. Blood, The Journal of the American Society of Hematology. 2013 Jul 25;122(4):515-22.
22. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, Janssen JJ, Mayer J, Koskenvesa P, Panayiotidis P, Olsson-Strömberg U. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. The Lancet Oncology. 2018 Jun 1;19(6):747-57.
23. Jummaa AK, Khalaf AA, Hasson HM, Dawood QM, Qasim ZR. Treatment-free remission in chronic myeloid leukemia (CML): experience of Basra Hematology centre. Onkologiairadioterepia. 2022 Feb 1;16(2):17-9.
24. Zang DY, Lee WS, Mun YC, Do YR, Oh S, Lee SE, Choi SY, Kim DW. Long-term follow-up after treatment discontinuation in patients with chronic myeloid leukemia: the Korean Imatinib Discontinuation (KID) study. Blood. 2018 Nov 29; 132:4252